PULMONARY TUBERCULOSIS IN THE ELDERLY: DIAGNOSTIC CRITERIA AND ITS EPIDEMIOLOGY IN OLD AGE HOMES.

BY

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ABSTRACT

The majority of today's elderly people were primarily infected with Mycobacterium tuberculosis at a time when no effective chemotherapeutic treatment was available. With the progressive decline in cell mediated immunity that accompanies aging, the potential to reactivate a dormant lesion, or to be re-infected increases. The latter particularly applies in areas of high density living e.g. homes for the elderly. The incidence of pulmonary tuberculosis in whites in South Africa is very similar to that in industrialized countries (approximately 16/100 000). In a survey of old age homes in East London (South Africa) involving 809 white subjects the prevalence rate was found to be 1403/100 000; clusters were found in individual homes where up to 10% of residents had tuberculosis. The age specific incidence in the community for whites was 86/100 000, and in homes for the aged the incidence in 648 elderly subjects followed for 2 years was 1080/100 000. It is concluded that the elderly living in high density accommodation constitute a high risk group for the development of the disease.

The diagnosis of pulmonary tuberculosis in the elderly may be complicated by the high prevalence of atypical radiographic changes, difficulty in obtaining sputum, and the high false-negative rate of the tuberculin skin test. Thus the value of haematological and biochemical abnormalities in 93 elderly tuberculotics, 113 elderly non-tuberculotics and 264 young tuberculotics were investigated. The results in the elderly tuberculotic patients were: Normochromic normocytic anaemia (70%), leucocytosis (55%), thrombocytosis (33%), rapid ESR in 90%,

lymphopenia (22%) and monocytopenia (37%); hyponatraemia (60%), hypokalaemia (42%) and hypoalbuminaemia (83%), serum bilirubin (20%) and alkaline phosphatase, aspartic transaminase and lactic dehydrogenase are elevated in approximately 2/3 of patients. In comparison with the younger group (mean age 48 years) with cavitating tuberculosis, the prevalence of elderly patients (with generally mild and non-cavitating disease) with elevated bilirubin, alkaline phosphatase and liver enzymes was approximately 50% higher. When the results of liver enzyme elevations in the elderly tuberculotics were compared retrospectively with elderly patients with non-tuberculotic destructive lung disease, the former group had significantly higher values. The sensitivity (76%), specificity (48%) and positive predictive value (60%) suggest that liver enzyme abnormalities may provide useful contributory data in the non-invasive diagnosis of pulmonary tuberculosis in the elderly.

The chest radiographs in 93 consecutive cases of bacteriologically proven pulmonary tuberculosis showed infrequent apical involvement (7%), with the most frequent abnormality being opacification of the middle and lower zones of the lungs; half the cases had a pleural reaction. Cavitation occurs in only 1/3 of patients, and was sited equally in the apical zones and in the mid and lower zones. These findings contrast with the pattern of cavitating apico-posterior disease commonly seen in reactivated tuberculosis in younger adults.

A series of 21 patients was studied to compare the yield of sputum smear examination with sputum culture for M. tuberculosis. Sputum production in non-cavitating disease was found to be infrequent

and unpredictable and the number of bacilli is usually scanty. Repeated Culture of sputum for M. tuberculosis is required to improve the likelihood of obtaining a positive bacteriological diagnosis. On the basis of this study at least 4 negative sputum cultures are required to exclude the disease.

In a study of 10 patients the impact of 4-drug therapy on the viability of M. tubercle in their sputum was assessed. Viable tubercle bacilli continue to be excreted in patients with cavitating pulmonary disease on treatment for up to 9 weeks. It is suggested that patients with cavitating disease should probably not be allowed to return to high density accommodation for the elderly until their sputum is clear of acid fast bacilli on sputum smear examinations.

The usefulness of using annual tuberculin skin reaction (Mantoux) tests as a screening procedure was evaluated in 648 residents in old age homes. The criteria for further investigation for pulmonary tuberculosis was either recent conversion to positive (reaction equal to 10 mm or more) or a year-on-year increase of greater than 12 mm, or any reaction > 20 mm. 206 subjects were identified as "possibly having the disease" and of these the diagnosis of pulmonary tuberculosis confirmed in 13 cases. 10/13 patients had Mantoux reactions of greater than 20 mm and 3/13 between 10 mm and 19 mm. As a result of this study the recommendation is made that a yearly Mantoux test is a useful screening procedure, and will help identify a population who should be further investigated with chest radiographs and sputum cultures.

ACKNOWLEDGEMENTS

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OVERALL PLAN

PULMONARY TUBERCULOSIS IN THE ELDERLY: DIAGNOSTIC CRITERIA AND ITS EPIDEMIOLOGY IN OLD AGE HOMES.

1. INTRODUCTION

This Thesis addresses the problem of pulmonary tuberculosis in the elderly. The investigation was partly undertaken at the Frere Hospital, East London, and also involved the homes for the elderly in that city.

The introduction provides a background which directs the reader to an appreciation of the epidemiological trends of the disease worldwide, nationally and locally. The pathogenesis, clinical features and diagnostic principles are outlined with special emphasis on those aspects peculiar to the elderly.

1.1 OBJECTIVES OF THE STUDY

In first world countries the incidence of pulmonary tuberculosis is highest in the geriatric population and in particular in homes for the elderly. There are scarce reports on the clinical, radiological, or systemic manifestations of the disease in this age group, and some of these are conflicting. This is a systematic survey which investigates these issues.

The investigations for this thesis are divided into 3 parts.

PART I (a) DIAGNOSTIC STUDY (b) MONITORING STUDY

PART II PREVALENCE STUDY

PART III INCIDENCE STUDY

PART I

Subjects for the study of sputum examination drawn from all homes comprising a total of 1275 residents at any time between June 1987 - September 1989.

PART II

1st Prevalence Study

February 1987 - June 1987 from 12 homes with a population of 1000.

PART III A

2nd Prevalence Study

July 1988 - June 1989 from all registered old age homes with a population of 1275.

PART III B

Incidence Study

July 1989 - June 1990 using the same population as in Part III A. 648 subjects of the original sample were studied in this year.

PART I (a) DIAGNOSTIC STUDY

It is accepted that the presentation of tuberculosis in the elderly may be atypical, and the diagnosis may be difficult. In order to validate and ensure the practicability of the diagnostic criteria to be used in Part II and III a prospective survey of the clinical, radiological, and pre-treatment systemic manifestations (haematological and biochemical parameters) in approximately 100 geriatric patients with proven pulmonary tuberculosis is described. The haematological and biochemical changes were compared to those found in adults of all ages with severe pulmonary tuberculosis.

The cornerstone of diagnosis is the demonstration of acid fast bacilli in the sputum. In cavitating pulmonary disease this presents no problem as the smears are usually repeatedly positive and cultures not required. However in non-cavitating disease the smear method is insensitive and cultures are mandatory. There is no information on the pattern of sputum positivity in these cases or how many sputa need to be examined before the diagnosis can safely be excluded. Therefore a cohort of approximately 200 residents of old age homes who had a productive cough had systematically repeated cultures of their sputa until a diagnosis of tuberculosis was made or excluded. This gave an indication of the prevalence of the disease in this particular group,

and established the pattern of excretion of bacilli.

PART I (b) MONITORING STUDY

It is widely considered safe practice to allow people on treatment for cavitating disease back into the community, and not insist on isolation of these patients. However the elderly living in institutions are at particular risk for becoming infected [1] and excretors of viable bacilli may constitute a hazard. The presence of culture positive mycobacteria in sputum was investigated in 10 geriatric patients with cavitating disease on treatment. Weekly smears and cultures were done until the sputum reverted to culture negative. This allowed correlation of smear and culture conversion, and indicated the period of excretion of culture viable bacilli.

PART II PREVALENCE STUDY

It has been reported from the United States where the incidence of pulmonary tuberculosis in the general population is approximately 15/100,000, that the elderly in old age homes are at particular risk.[1] In South Africa, the incidence of pulmonary tuberculosis in blacks and "coloreds" (mixed race) varies between 350 and 600/100,000 and in whites approximately 15/100,000. The hypothesis to be

tested was that there would be a much higher prevalence of the disease in local old age homes than in the general population. Therefore a cross sectional study of the residents of old age institutions in East London (approximately 1000 subjects) was undertaken. The diagnostic criteria already tested in Part I (a) were used, and included radiography, sputum for both smear and culture, Mantoux and Elisa testing. In addition the role of the Elisa test in this group was tested to determine its positive and negative predictive value.

PART III INCIDENCE STUDY

Part I and Part II are considered to be a prelude to this part of the study which investigated the incidence of tuberculosis in most of the elderly in old age homes in East London. All residents in registered old age homes were informed personally in writing of the aim of the study and what would be required.

Participation was on a voluntary basis. An initial Mantoux test was performed and repeated if negative within a fortnight to exclude anergy (page 44). Subjects were monitored for a two year period. New incoming residents during this period were entered and tested as soon as possible. Yearly Mantoux testing was done, and subjects who had a conversion of the Mantoux from negative to positive or

an increase greater than 12 mm in successive Mantoux tests or with a reaction of 20 mm or more were requested to produce sputum for culture. In addition all residents who had a productive cough for three weeks or more had sputums submitted for tuberculosis culture. If these were positive chest radiographs were taken of the subjects.

This provided figures for the incidence of pulmonary tuberculosis in the elderly living in residences. It also established the beneficial value of monitoring for the disease, and validates the monitoring and diagnostic proposals made at the conclusion of the prevalence study (part II).

1.2 HISTORICAL

Tuberculosis has been known to affect mankind from neolithic times. Lesions of spinal tuberculosis have been found in skeletons of neolithic man (C. 4000 B.C.) and Egyptian mummies dating from 3700 B.C.[2] There is a written description of tuberculosis in the Rig Veda which was written more than 3500 years ago.[3] It is postulated that the disease spread to man when animals were first domesticated during this period. This proposal is not unreasonable as Mycobacterium tuberculosis has one of the widest host ranges of all pathogenic bacteria and causes disease in many feral and domesticated animals.[4,2] On

another continent the writers of the Hindu Upanishads (C.1500 B.C.) described the disease as both the King of Diseases, and the Disease of Kings. This implied comment on the distribution of the disease which traverses all social, age and class barriers is as pertinent today as it was then. The disease has been known by a number of names over the centuries, some of which are still in use. Hippocrates spoke of Phthisis and much later the terms consumption, scrofula, and struma were used.

In the days before treatment of any kind was known, the mortality must have been horrendous, and even in the latter part of the 17th Century the eloquent English evangelist and author John Bunyon referred to it as "The Captain of all of these men of death".

The turning point in the understanding of the pathogenesis of the disease, and indeed the beginning of a new concept of infectivity in general, was when Robert Koch observed and isolated the causative organism of tuberculosis in man and cattle. These "acid fast" bacilli were named Mycobacterium tuberculosis and M. bovis respectively. Apart from making this monumental microbiological breakthrough Robert Koch made the observation in 1891 that the inoculation of viable tubercle bacilli into the skin of sensitised animals led to an ulcerative reaction which he believed destroyed the bacillus. Severe reactions resulted from this and as can be expected in the light of current

knowledge it is not beyond belief that some patients succumbed to a systemic infection. Nonetheless in observing this reaction, he laid the foundations for the discovery of cell mediated hypersensitivity, and the subsequent development of the tuberculin test as used in the Heaf or Mantoux methods.

1.3 EPIDEMIOLOGY

1.3.1 MORTALITY

It is difficult to find reliable figures of the epidemiology of the disease during the 18th and 19th Century. It is known that in the 18th century in North America, figures for death from "consumption" accounted for 18% of all causes, and this had risen in the first decade of the 19th century to 25%.[5] In large American cities the death rate from pulmonary tuberculosis at the beginning of the 19th century was over 400/100 000, and the proportion of all deaths attributed to tuberculosis ranged from 14% to 30%. However in the past 40 years the death rates for all ages have decreased significantly. In 1954, '64 and '74, the death rates were 10,2, 4,3, and 1,7 per 100 000 respectively.[5] Similar figures are applicable to the United Kingdom. Interestingly, although the overall number of deaths from the disease has decreased, this does not apply in the U.K.

the disease has decreased, this does not apply in the U.K. to the very old,[6] where the number of deaths due to TB has remained fairly constant. (Fig. 1). Adjustments of the denominators (as a reflection of changing population demographics) are required to make a valid comparison between these age groups.

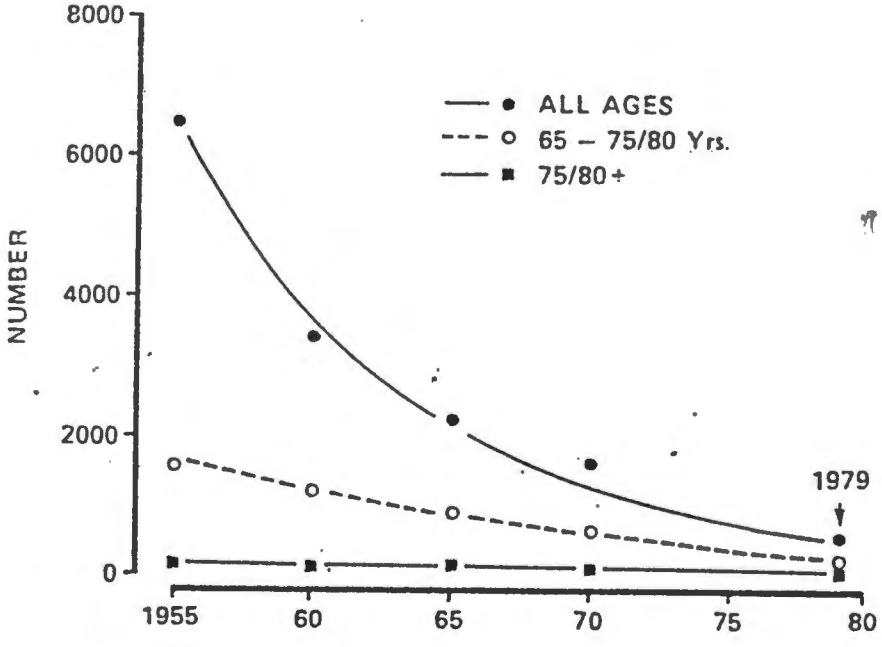


Fig. 1

Total deaths from tuberculosis (England and Wales)[6]

Africa are at best crude but are conservatively given as 7% of all deaths.[7] This is most certainly an under reporting. In a hospital based study, 11% of deaths in a Department of Medicine were due to acute secondary TB. When this figure was combined with deaths due to the consequences of secondary disease e.g. cor pulmonale, respiratory failure, bronchiectasis etc. 31% of deaths in black hospital patients were due to the disease or its sequelae.[8]

1.3.2 MORBIDITY

In the United States the incidence of pulmonary tuberculosis has decreased in the general population since the bad days of the 1900's to a crude morbidity rate of 9.3/100 000 in 1985.[9]

	Rate (per 100,000)	Cases
1954	49.3	79,775
1964	26.6	50,874
1974	14.4	30,122
1985	9.3	22,201

Table 1

Tuberculosis cases in the United States. It should be noted that the total number of cases shows a progressive decline.

In the age specific category of over 65, the case rate has been highest compared to a generally falling incidence amongst the younger population.[10] A similar trend has been found in the United Kingdom, and it is generally accepted that the geriatric population has the highest increase in cases of tuberculosis of any age group.[6]

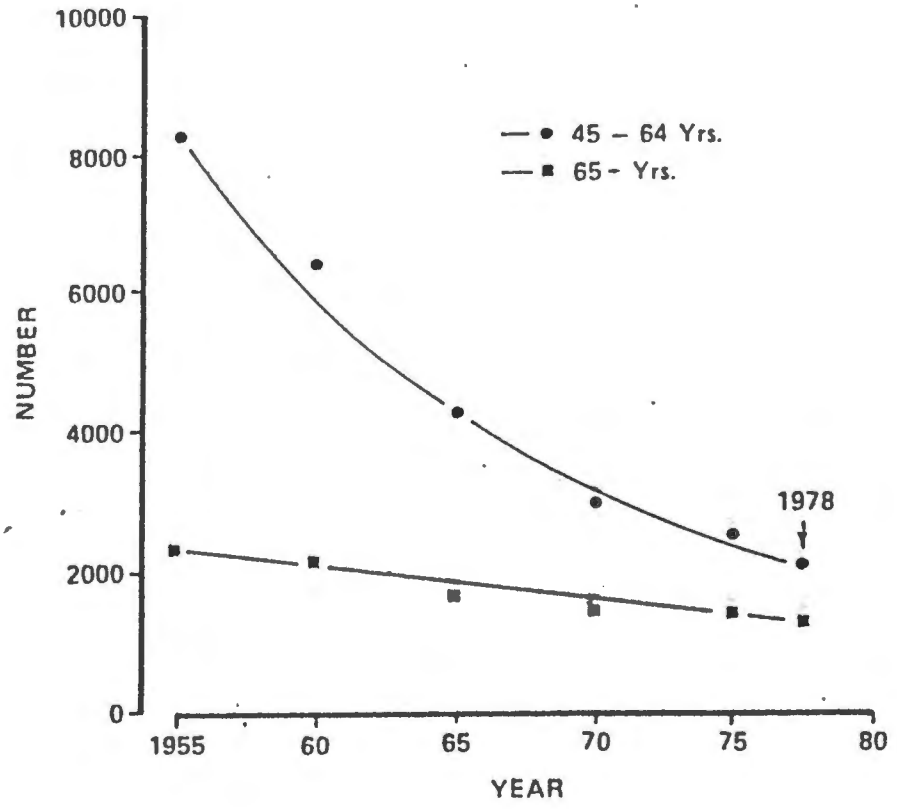


Fig. 2

New cases of respiratory tuberculosis (England and Wales).[6]

1.4 NATIONAL AVERAGE

Pulmonary tuberculosis in South Africa began to make its impact towards the latter part of the 19th century. In 1886, the South African gold mining industry developed and rapid industrial development took place. Much of the mining expertise was imported from Britain and many of these miners had been exposed to tuberculosis and were undoubtedly partially responsible for importing the disease into the country. A combination of poor working conditions with a high exposure to silica dust which renders miners more susceptible to tuberculosis and proximity to a non-immune black community who had had little or no exposure to the disease brought about the beginning of an explosion of tuberculosis in South Africa.[11] [12] Today, poised on the threshold of the 21st century the situation is comparable with the unbridled disease which rampaged through Europe and the Americas 200 years ago. [13] In 1986 the R.S.A. national incidence rate for the disease was 161/100 000 notifications.[14] However this is believed to represent a third to one half of the actual number of new cases.[15] The graphs 3-7 and Tables 2-4 which follow show the incidence rates of the disease in South Africa over the last 40 years and the racial, regional and provincial differences. They are derived from figures supplied by the Department of National Health and Population Development and by courtesy of its Director of Epidemiology Dr H.G.V. Kustner.

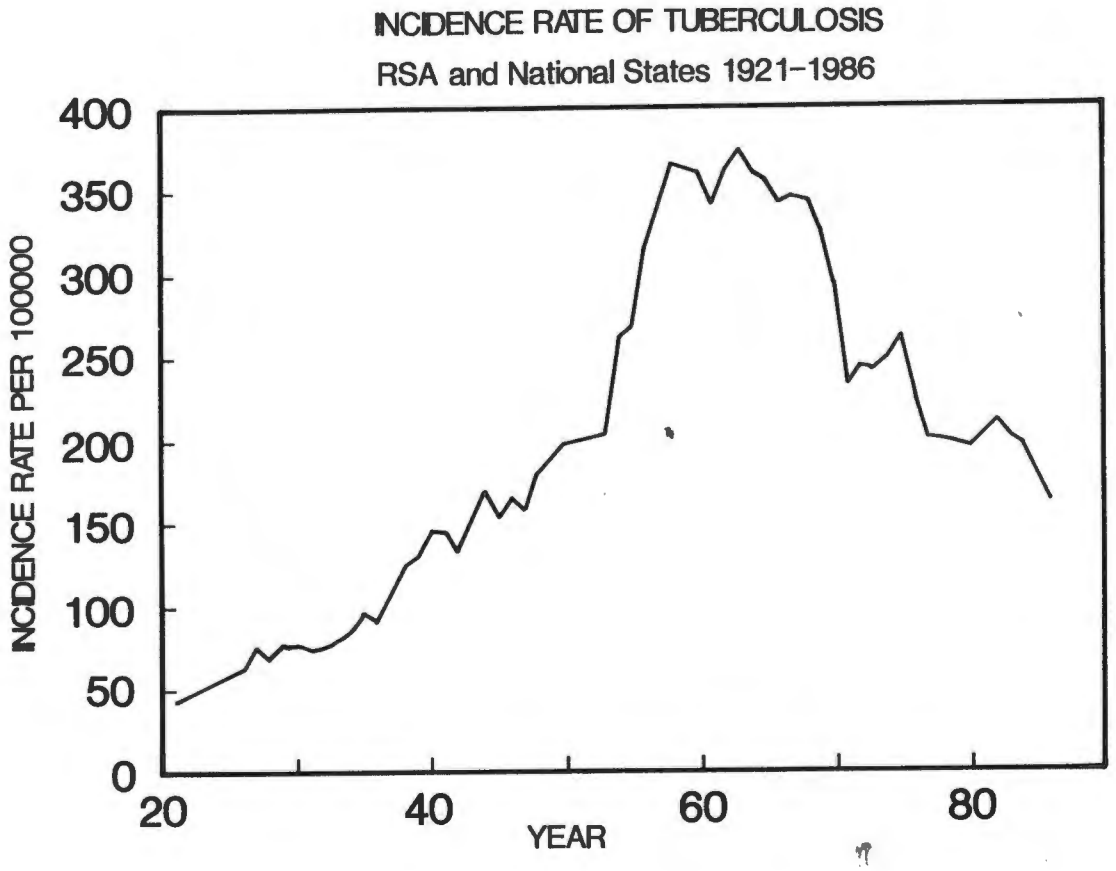


Fig 3.

The incidence rates per 100,000 show a gradual incline up to 1950, and then a rapid increase, plateau and decline over the next twenty years. Whether this represented a real phenomenon or a reflection of the inaccuracies of the data collection has been widely debated, and is not known. It is however an indictment on the tuberculosis control programme in that the overall incidence in 1986 (total population 34,050,000) is the same as in 1950 (total population 13,310,000)'s and the denominator (the quanta of "100,000") has increased by 256%. This means that the total number of notified cases has increased two and half fold in this country during this period whereas in the U.S.A. the total number of cases has decreased (See Table 1, page 9).(Data from Department of National Health and Population Development).

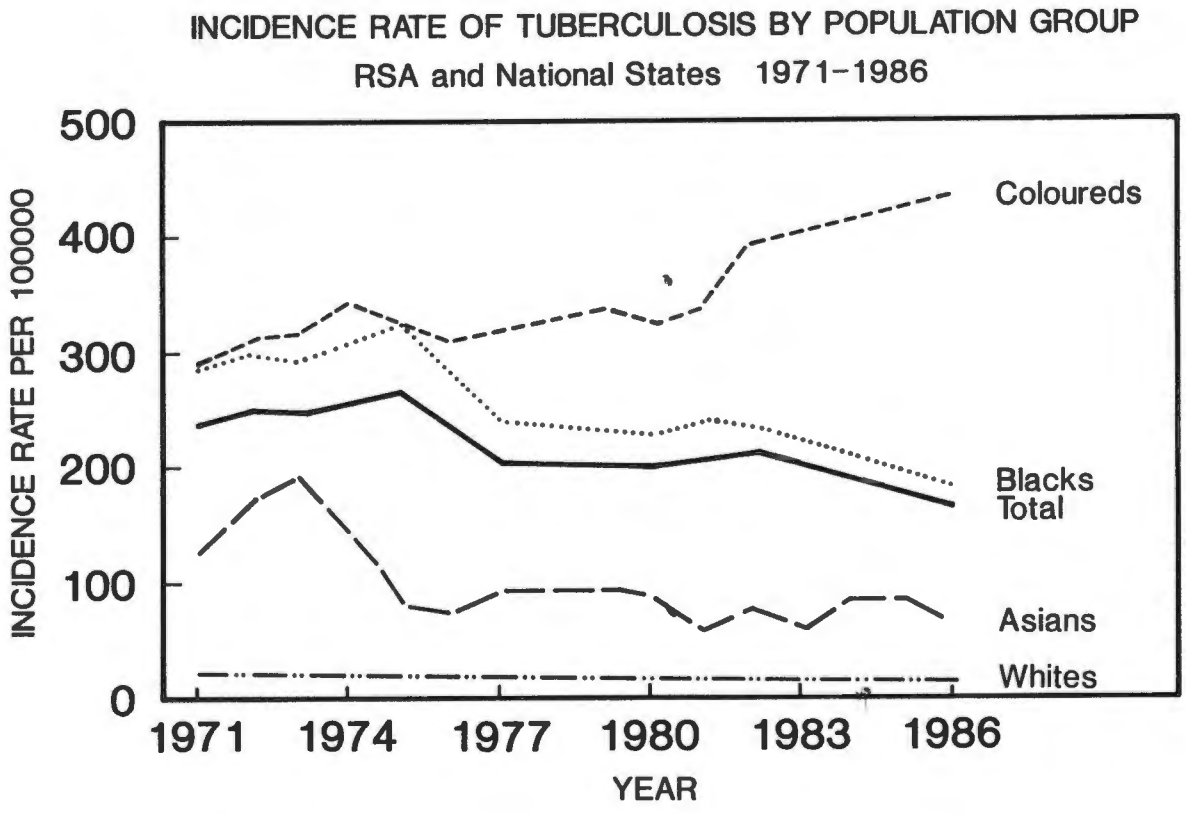


Fig 4.

The incidence for the various population groups shows important differences. The incidence for whites has remained virtually unchanged at approximately 16/100 000. However when the age specific rates are examined it is clear that there is a higher incidence in those over 65 years, thus keeping a parallel trend with the U.S.A. and U.K. (Fig. 2, Table 5). The rates in "coloureds" (*) show an alarming increase since 1980. This is mainly regional, and confined to the Western Cape. (Data from Department of National Health and Population Development).

(*) These investigations were not designed to examine the notion that differences in racial susceptibility to tuberculosis exist, the investigations here reported reflect to a large measure the differences in socio-economic status associated with racial groups. References to racial classification in this thesis are used for the purpose of identifying population groups that are most at risk. Statistics that are reported in the context of "race" are largely derived from population groups that have been classified as "white", "coloured", "black" or "Asian" in terms of the Government's Population Registration Ace (1950) which uses skin pigmentation and cultural origin as its major criteria. At its inception 10 categories existed in terms of the Act including "White", "Cape Coloured", "Malay", "Indian", "Chinese", "Griqua", "Black", "Other Coloured" and "Other Malay". The grounds on which these classifications are made are most sorely tested when individuals apply for reclassification:. the criteria are recognised to be arbitrary. The effects of being accorded any particular classification in the R.S.A. are wide-reaching, such that it is possible to generalise that ethnic classification is the best indicator of socio-economic status (SES), on a spectrum: Black, Coloured, Malay and White. In the biological sciences all indicators of SES (infantile mortality rate, measles attack rate, life expectancy, kwashiorkor) conform to the aforementioned notion. So, too for the prevalence of pulmonary tuberculosis.

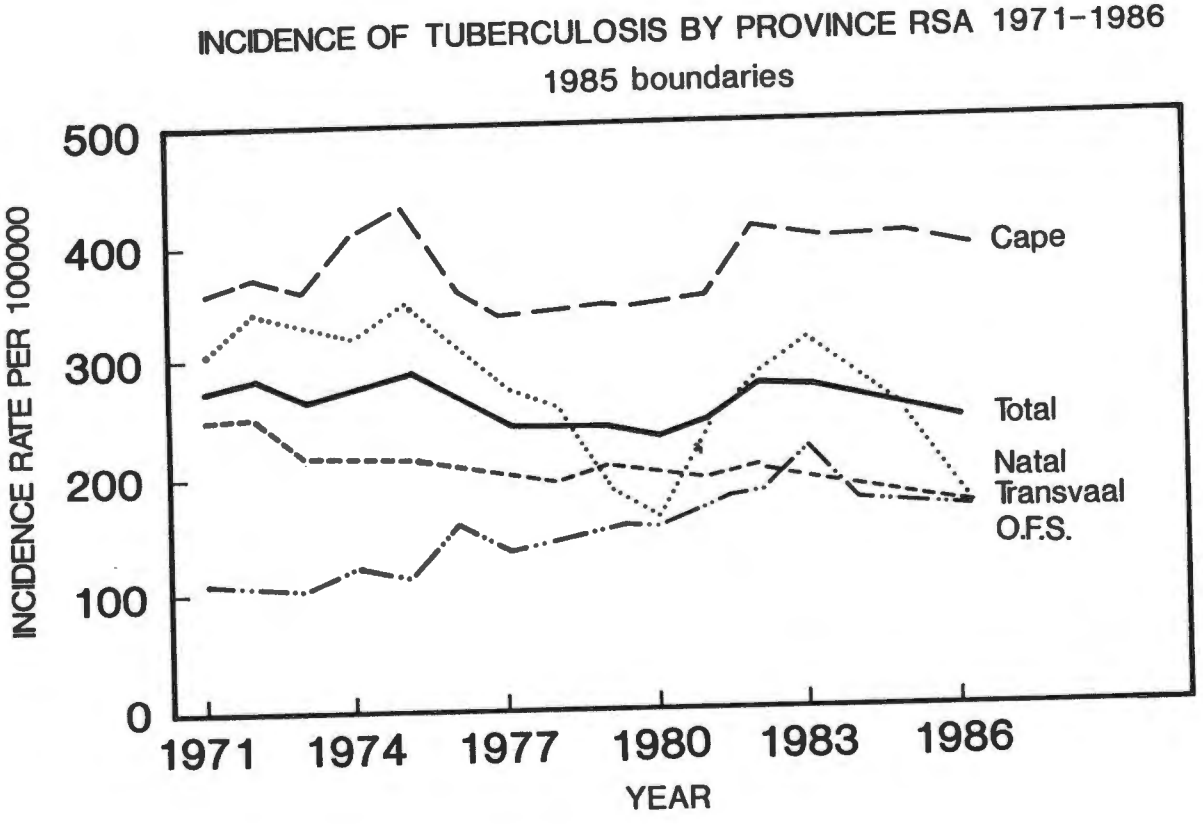


Fig 5.

The provincial overall incidence rates show that the Cape has the highest incidence of all provinces. This is in some measure due to the high incidence amongst the Western Cape Coloured and Black population, but as can be seen from Fig. 6 the incidence amongst Whites in the Cape is also higher than the rest of the country. (Data from Department of National Health and Population Development).

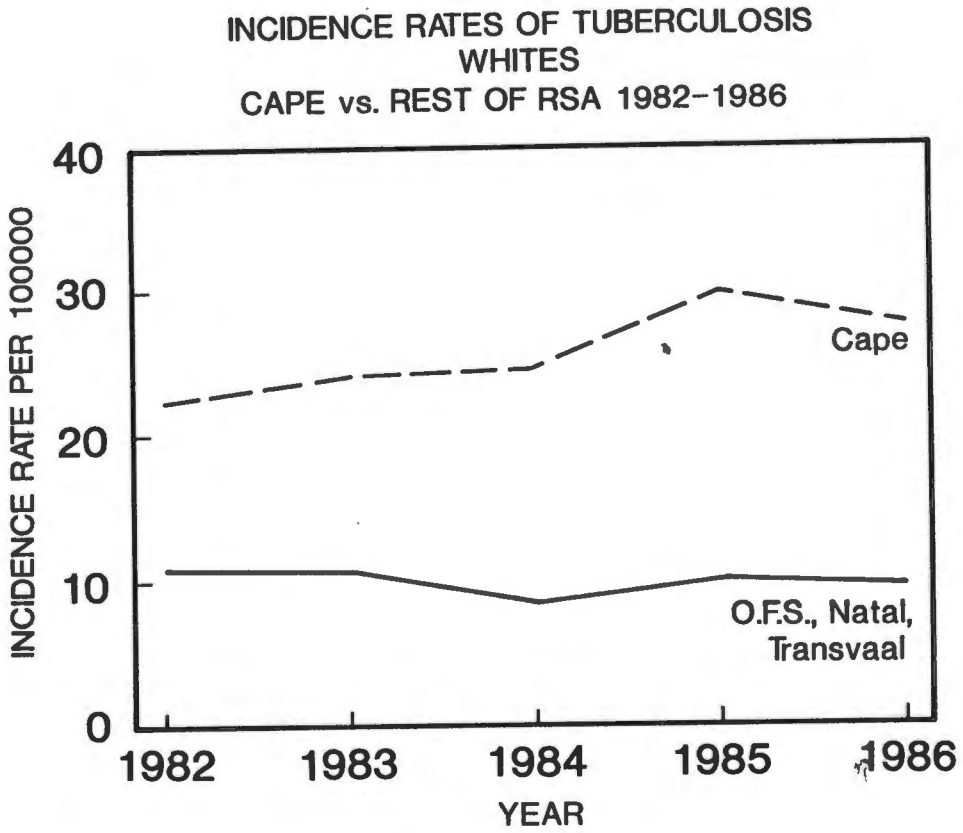


Fig 6.

Whether the higher incidence rates amongst Whites results from a higher exposure to the disease or due to some other factor is not known. (Data from Department of National Health and Population Development).

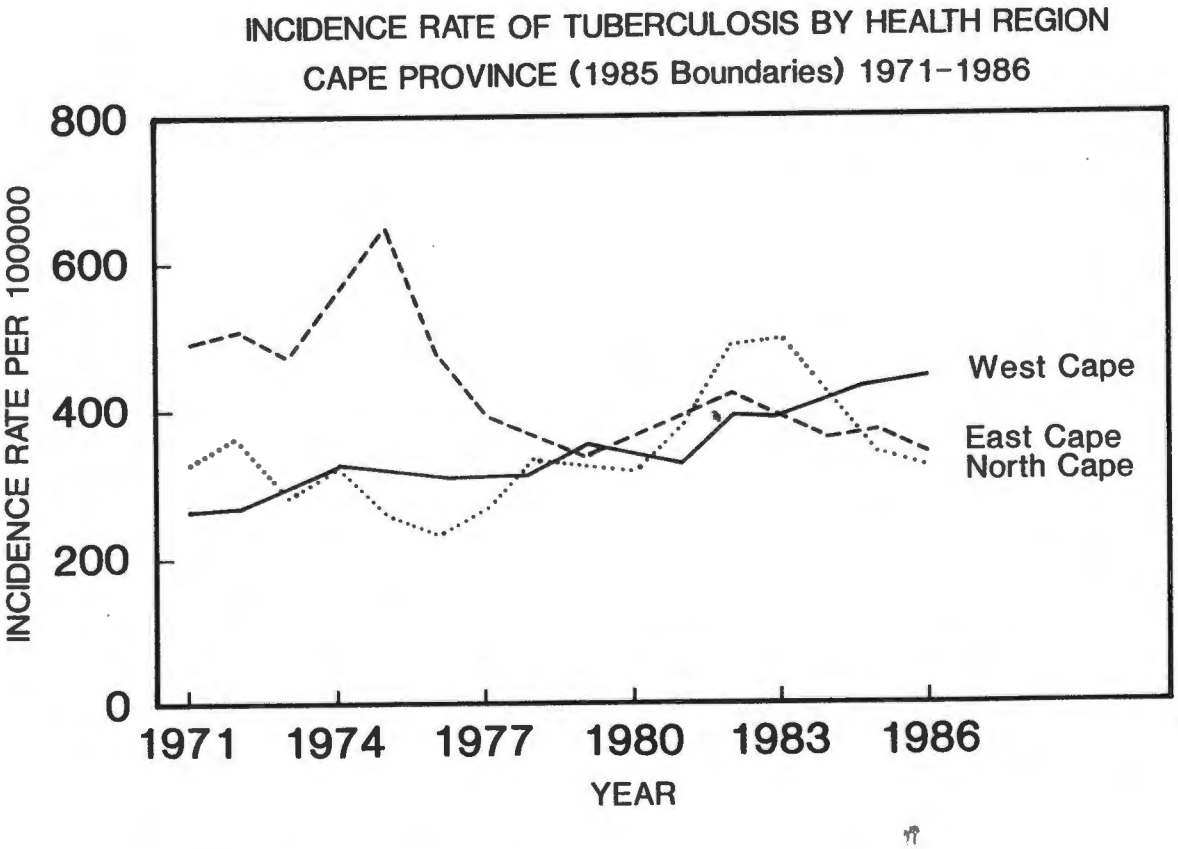


Fig 7. Within the boundaries of the Cape Province there are three health regions. Since 1977 the incidence rates in all three (apart from 1981 and 1982 in the North Cape) have been similar. (Data from Department of National Health and Population Development).

The explanation of the sharp increase and rapid decrease in notification in the Eastern Cape in 1975 is not known. It was postulated that this region may be influenced by figures from the neighbouring independent states of Ciskei and Transkei. However as is seen in Table 2, the rise in the East Cape in 1975 is parallelled by the numbers in Ciskei and Transkei thus making the postulate unlikely.

Year	East Cape	Ciskei	Transkei	Total
1971	7 563	344	8 956	16 863
1972	7 759	526	10 255	18 540
1973	7 462	595	9 659	17 716
1974	8 824	727	9 597	19 148
1975	10 328	1 784	10 242	22 354
1976	7 736	1 929	6 926	16 591
1977	6 791	1 106	6 104	14 001
1978	6 274	1 275	6 007	13 556
1979	5 932	1 564	4 232	11 728
1980	6 200	2 318	4 512	13 038

Table 2

The rise in numbers in 1975 in the East Cape are paralleled by similar increased in the neighbouring states of Ciskei and Transkei. (Data from Department of National Health and Population Development).

In order to see whether coding errors might have crept in, we compared the figures for the East, Western and Northern Cape (Table 3). The rise in 1975 was confined to the East Cape and, there was no sudden dips in either of the other areas making this postulate unlikely.

Year	Region			
	E. Cape	W. Cape	N. Cape	Total
1971	7563	5914	1953	15430
1972	7759	6106	2154	16019
1973	7462	6724	1686	15872
1974	8824	7569	1766	18159
1975	10328	7576	1577	19481
1976	7736	7250	1469	16455
1977	6791	7275	1456	15522
TOTAL	137293	203904	36961	378158

Table 3

TB cases in the Cape, 1971 to 1977. The similarity of the figures in 1975 from the Western and Northern Cape contrast to the surge in the Eastern Cape in that year. (Data from Department of National Health and Population Development).

Finally the returns from the local authorities in the Eastern Cape region were examined to see whether there was a sudden change in notifications (Table 4)

Region	Year 1973	1974	1975	1976	1977	Total
Aliwal North	359	363	384	200	141	1447
Albert	1	2	14	12	10	39
Barkly East	19	39	93	0	0	151
Cathcart	24	40	55	20	23	162
Queenstown	192	357	694	489	484	2216
East London	1358	2549	3220	2109	1548	10784
King Williams Town	61	69	580	212	27	94
Cradock	97	96	130	112	80	515
Graaf-Reinet	77	70	89	79	58	373
Humansdorp	160	237	274	194	128	993
Eastern Cape District	226	40	294	13	16	589
Port Elizabeth	2484	2247	2619	2091	2247	11688

Table 4

The increase in the number of notifications from 12 out 44 local authorities in the East Cape. The returns from the local authorities not included were those with no significant change in the pattern of notifications. (Data from Department of National Health and Population Development).

Therefore the explanation for the sporadic increases in this region in 1975 seems to be partly due to a real scattered increase in cases over a wide area of the region.

1.5 AGE SPECIFIC RATES

The overall incidence of the disease in whites is shown to be higher in the Cape (Fig.6) compared to the rest of the country. This is particularly so in age specific rates for the Eastern Cape where in 1986 the numbers are shown in Table 5. (The reason for choosing 1986 was because this year followed the 1985 census and hence the denominator was as accurate as possible, and it coincided with the start of the project).

	R.S.A.			EASTERN CAPE		
	MALES	FEMALES	COMBINED	MALES	FEMALES	COMBINED
WHITE	25	6	13	83	21	83
COLOURED	692	218	410	665	237	418

Table 5

PTB notification in 1986 per 100,000 for population over 65 years old. (Data from Department of National Health and Population Development).

It is notable that the age specific rates for coloureds is the same in the Eastern Cape as it is in the rest of the country, in contrast to the marked increase for whites living in this region. The figures for blacks are unreliable in that approximately 40% of cases seen in East London are from Ciskei and Transkei. These figures are not included by the Department of National Health and Population Development in the Eastern Cape figures, and hence no meaningful comparison is possible.

1.6 RATES IN EAST LONDON

	White	Coloured
1985	9 (17/100 000)	76 (345/100 000)
1986	15 (28/100 000)	96 (432/100 000)
1987	21 (39/100 000)	136(620/100 000)
1988	14 (26/100 000)	138(591/100 000)
1989	26 (48/100 000)	148(620/100 000)

Table 6

Total PTB notifications for the city of East London. The figures for blacks are omitted because they are not reliable. The reason for this is that an unknown number of patients living in the neighbouring states of Ciskei and Transkei give an East London address in order to gain access to the local medical facilities, and thus the statistics are heavily skewed. The ages of the subjects are not recorded by the local authority and so age specific rates are unobtainable.(Data from Department of Health, Municipality of East London).

1.7 PULMONARY TUBERCULOSIS IN OLD AGE HOMES

Whilst the increased incidence in the elderly has been widely acknowledged, it was in 1980 that attention was drawn to the fact that the incidence was even higher in the elderly living in nursing homes.[1] In 1985, Stead from the U.S.A. reported that 147 out of 21,144 residents in institutions for the elderly had TB.[1] This gives a rate of 695/100 000 compared to approximately 10/100 000 in the general population. This situation was similar in the United Kingdom.[6] Given that the general incidence of disease in these areas is so low, and that it is so high in South Africa (+- 200/100 000) it would be reasonable to assume that the disease in the elderly in old age homes might be very much higher than in the U.S.A. This hypothesis is tested in this thesis.

PATHOGENESIS OF PULMONARY TUBERCULOSIS

2.1 PRIMARY INFECTION

Primary infection with the mycobacterium can occur at any age. It usually presents in childhood but 14% of cases reported by Bates occurred in adults.[16] The inhaled bacillus usually lodges peripherally in the mid or lower zones of the lung where air flow is at its greatest. It is transported across the alveolar membrane probably by means of monocytes where it multiplies within the tissue of the lung. The immediate local response (Fig. 8) is that of a cellular inflammatory infiltrate comprising leukocytes, lymphocytes, fibroblasts, tissue macrophages and plasma cells associated with a humoral component involving complement, interleukins, kinins, prostaglandins and immunoglobulins. Thus the pathological picture is that of an inflammatory cellular infiltrate associated with oedema. This may be seen on the chest radiograph as a diffuse opacification (inflammatory oedema) (Radiograph 1, page 33) which may be nodular in parts reflecting early granulomata formation.

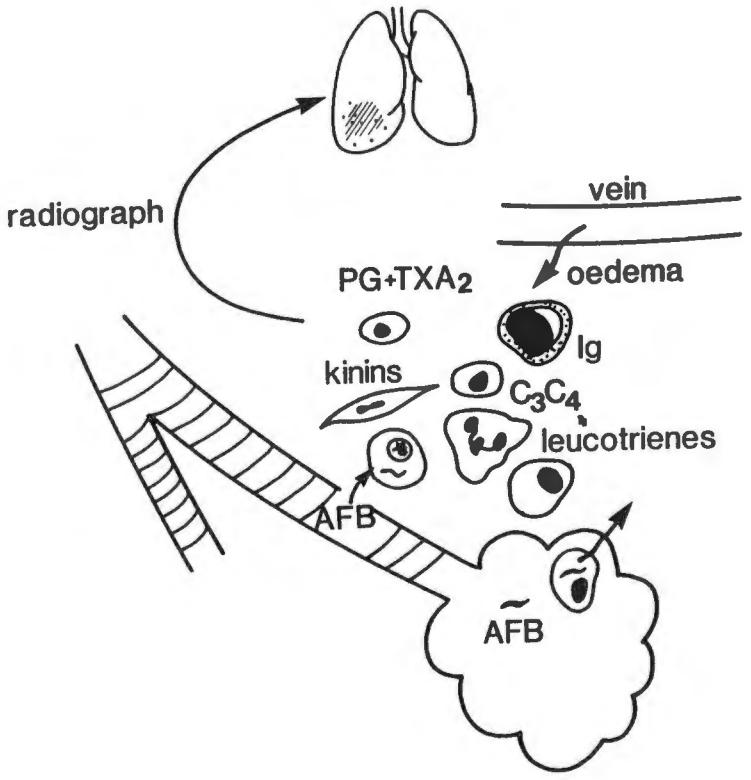


Fig 8.

This scheme depicts the progress of events in the early part of the inflammatory response. The bacilli are transported across the bronchiole/alveolar cell wall engulfed by macrophages, phagocytes, monocytes and polymorphonuclear cell. A cellular response by fibroblasts, lymphocytes and plasma cells ensues. The humoral response involving complement (C3C4) prostaglandins (PG) plus thromboxane (TXA2), immunoglobulins (Ig), kinins and leucotrienes causes further local cellular involvement, and oedema with fluid entering the intratissue space from the veins. This provides the explanation of the early radiographic changes depicted which show patchy opacification and later scattered nodules if granulomata form (Fig 10).

The scheme in Fig. 9 shows how the multiplication of bacilli involves local lymphatics spreading the infection to local regional lymph nodes (para-tracheal and hilar) with consequent enlargement of these nodes and possible calcification (1). This may be seen on radiographs (Radiograph 3,4, page 35). The nodular involvement is an intermediate stage in blood stream invasion and dissemination. Concomitant with this is access to the venous return to the heart (2), which also results in a bacillemia, disseminating the tubercle bacillus throughout the body. The primary pulmonary parenchymal and sub-pleural primary inflammatory response may undergo necrosis and discharge of contents into the pleural space. This results in a pleural reaction with fluid effusing into the space and subsequently pleural thickening (3).

The bacilli in the bloodstream lodge in various organ sites, with a predilection for the apex of lung, cortex of kidney, growing ends of the long bones, and meninges - but may be found in all tissues. These small foci of infection are usually contained within macrophages where they may remain as small granulomatous areas enclosed by an active cell-mediated response.

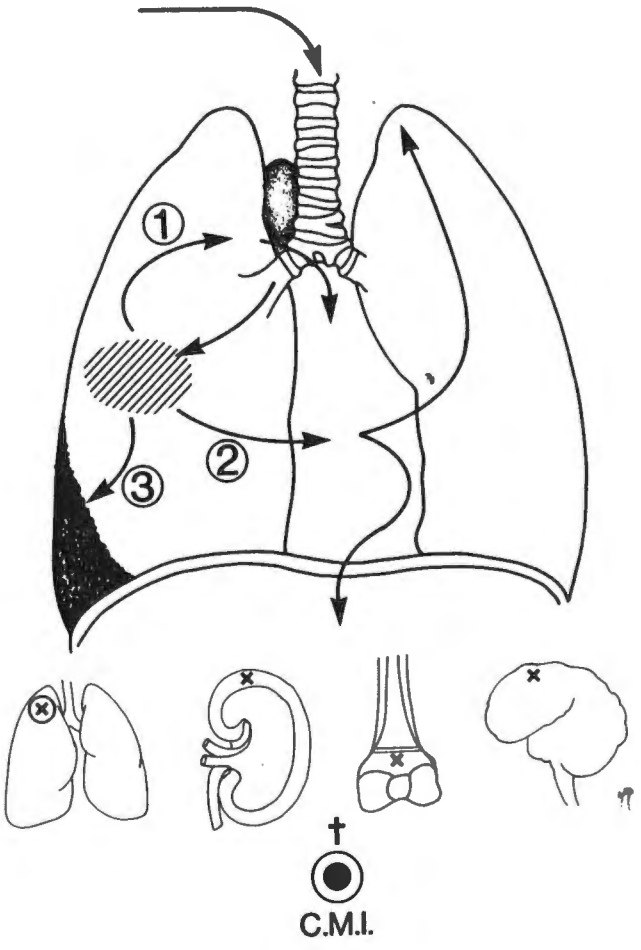


Fig. 9

The early pathogenesis of the infection. For explanation, see text. (C.M.I. = cell mediated immunity).

At the time of the primary infection the CD4 cells in the lymph nodes proliferate in response to the bacterial antigen and give rise to a cohort of specifically sensitised lymphocytes. These cells enter the blood stream after several weeks and circulate for many months or years. It is this cell-mediated (Type 4, in Gell and Coombs' classification) hypersensitivity reaction which forms the basis of the tuberculin test. Plasma cells are also sensitised which respond by producing humoral antibodies. These are not thought to have any protective affect.

In 90% of cases the primary infection is contained in a granuloma containing viable organism which remain dormant. The granuloma becomes fibrosed and may calcify. However between 5% and 15% of the primary infections progress into clinically significant tuberculous disease within 5 years (the majority within the first two years) and another 3% to 5% develop the disease in later life. [17] What determines this breakdown is not entirely clear but a number of factors play a part. This includes the number of organisms involved, the virulence of the organism, and the immune status of the host. A formula proposed by Rich[18] summarises the position whereby

$$T = \frac{V \times N \times H}{R(N+A)}$$

[where T = destructiveness of the lesion, V = the virulence, N = numbers of bacilli, H = hypersensitivity of the

individual, R = resistance (N = natural, A = Acquired)][17]

If the disease in the primary stage progresses, the cellular inflammatory response is enhanced and the tissue macrophages coalesce resulting in the formation of Langhans giant cells. This granulomatous reaction increases in size, and possibly due to both the detriment of the blood supply and tumour necrosis factor release, necrosis takes place. This lesion, characteristic of tubercular infection, is cheesy in consistency and appropriately termed "caseous necrosis". The inflammatory reaction may invade three potential portals of systemic spread, namely discharge of the caseous material into (a) bronchus (b) artery (c) vein.

(a) Discharge of the caseous necrotic material containing viable mycobacterium into the bronchus results in endobronchial spread to areas both local and distant in the lungs (Fig.10). A tuberculous bronchopneumonia results.

(b) If the arteries are involved then the bacilli associated with the necrotic material discharge into the artery and is deposited in an area subtended in the lung which the artery supplies (Fig.10). This results in a segmental area of inflammation with subsequent granulomata and nodularity showing on radiograph. However spread down a segment of bronchioles would

result in a similar picture.

(c) If the discharge occurs into a vein then wide-spread dissemination and bacillemia occurs with the resultant miliary spread involving lung and other organs(Fig.10), radiograph 2.

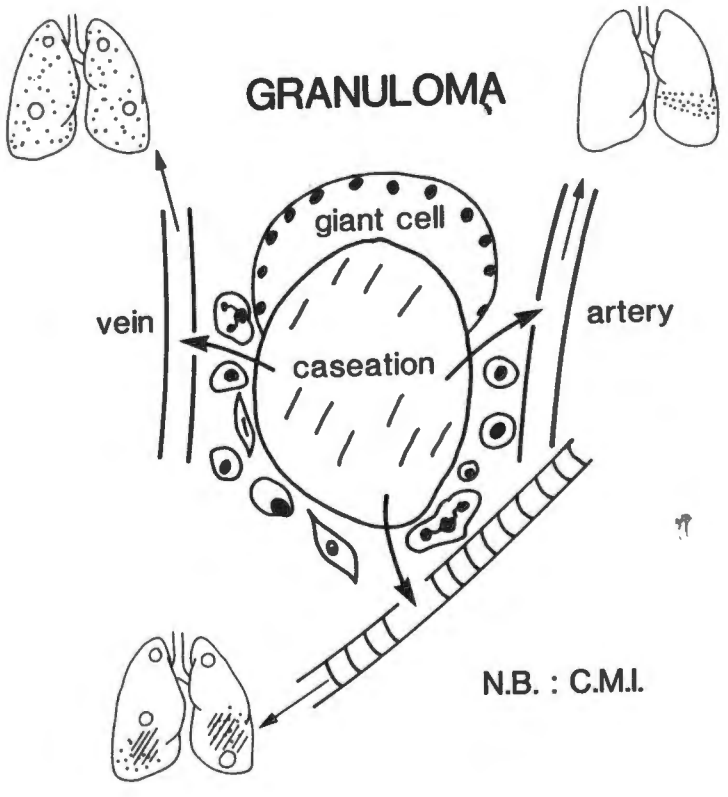


Fig 10.

This scheme depicts the events that may follow breakdown of the granuloma, discharge of its caseous material and hence the formation of cavities. The portal of exit (vein, artery or bronchus) plays a part in determining the radiographic pattern. It is important to note that this is the result of an active cell mediated immunity (C.M.I.).

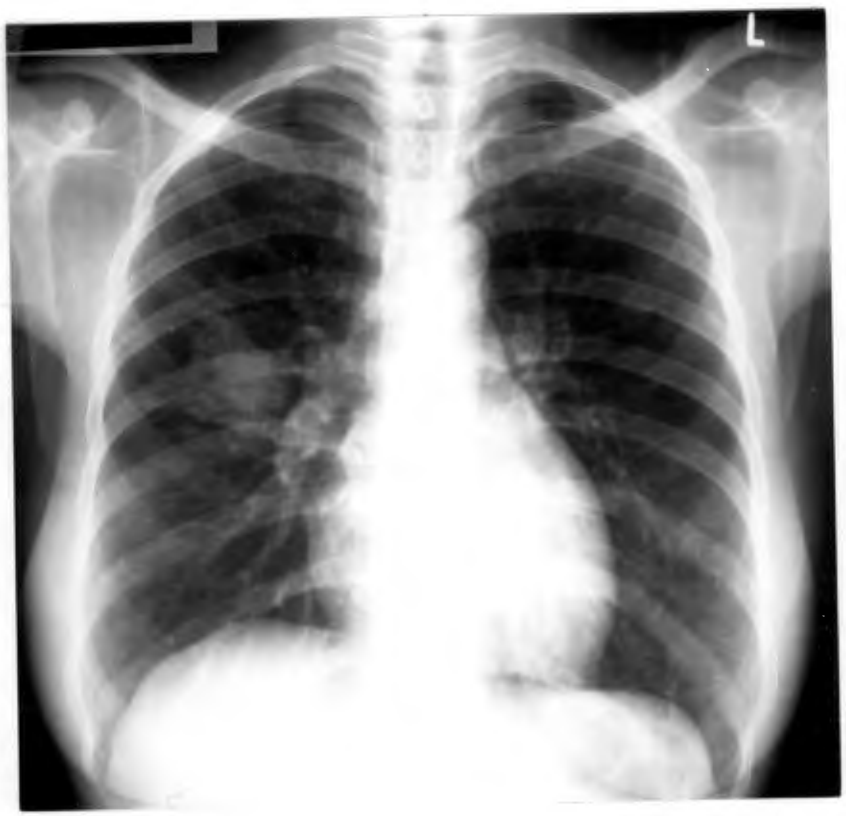
2.2 SECONDARY OR REACTIVATED T.B.

The lesion containing viable bacilli remains dormant in the sites of spread already mentioned and may, many years later, become reactivated. Approximately 90% of the reactivation occurs in the lungs and this usually in the apices of the upper lobes. The factors which are responsible for the breakdown of these areas are not known, but include a reduction in cell mediated immunity due either to disease (e.g. carcinoma, diabetes), drugs (corticosteroids, immunosuppressives, alcohol), old age, and nutritional deficiencies. Undoubtedly reinfection may also be responsible. Whatever the initiating factor however, the clinical picture that is seen in the secondary or re-activated tuberculosis differs considerably from the primary picture. Here apical inflammation, cavitation, and a fibrotic interstitial and an apical pleural reaction is common (Radiograph 5,6). There may be endogenous spread to lower portions of the same lung, or to the opposite side. Furthermore miliary nodularity may be either a generalised form such as has been described in the primary condition (Radiograph 2), or nodules seen in segments of the lung presumably on the basis of arterial invasion (Radiograph 7). Basal pleural effusions are rare (See Radiograph 6). Although it is the apices of the upper lobes which are generally involved apical involvement of the lower lobes may

be involved in approximately 10% of cases (Radiograph 8,9).

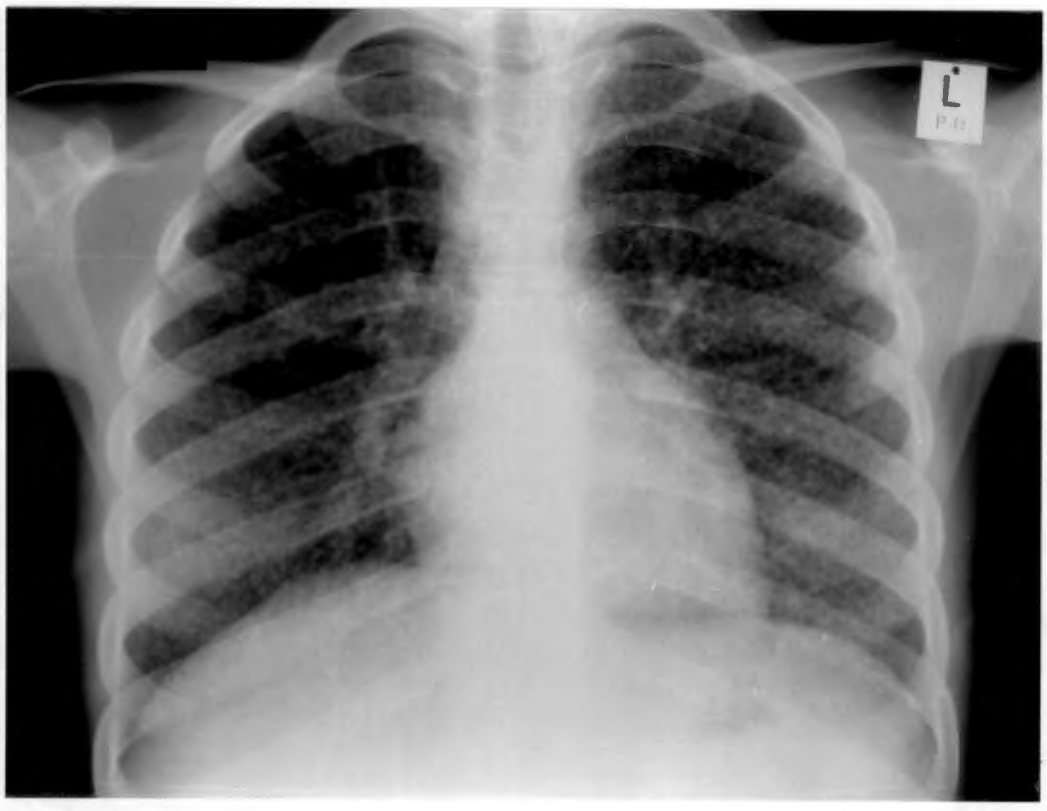
Untreated, this disease is generally progressive, and results in gross destruction of lung tissue (Radiograph 10).

Despite its evident capacity to destroy lung tissue a number of patients with TB are capable of spontaneously arresting the disease, probably by means of a well functioning cell-mediated reaction. Such patients may be seen with destroyed lungs but without any evidence or history of active disease. However relentless progression is usual and patients die of inanition and cachexia, secondary infection, cor pulmonale, haemoptysis and respiratory failure.



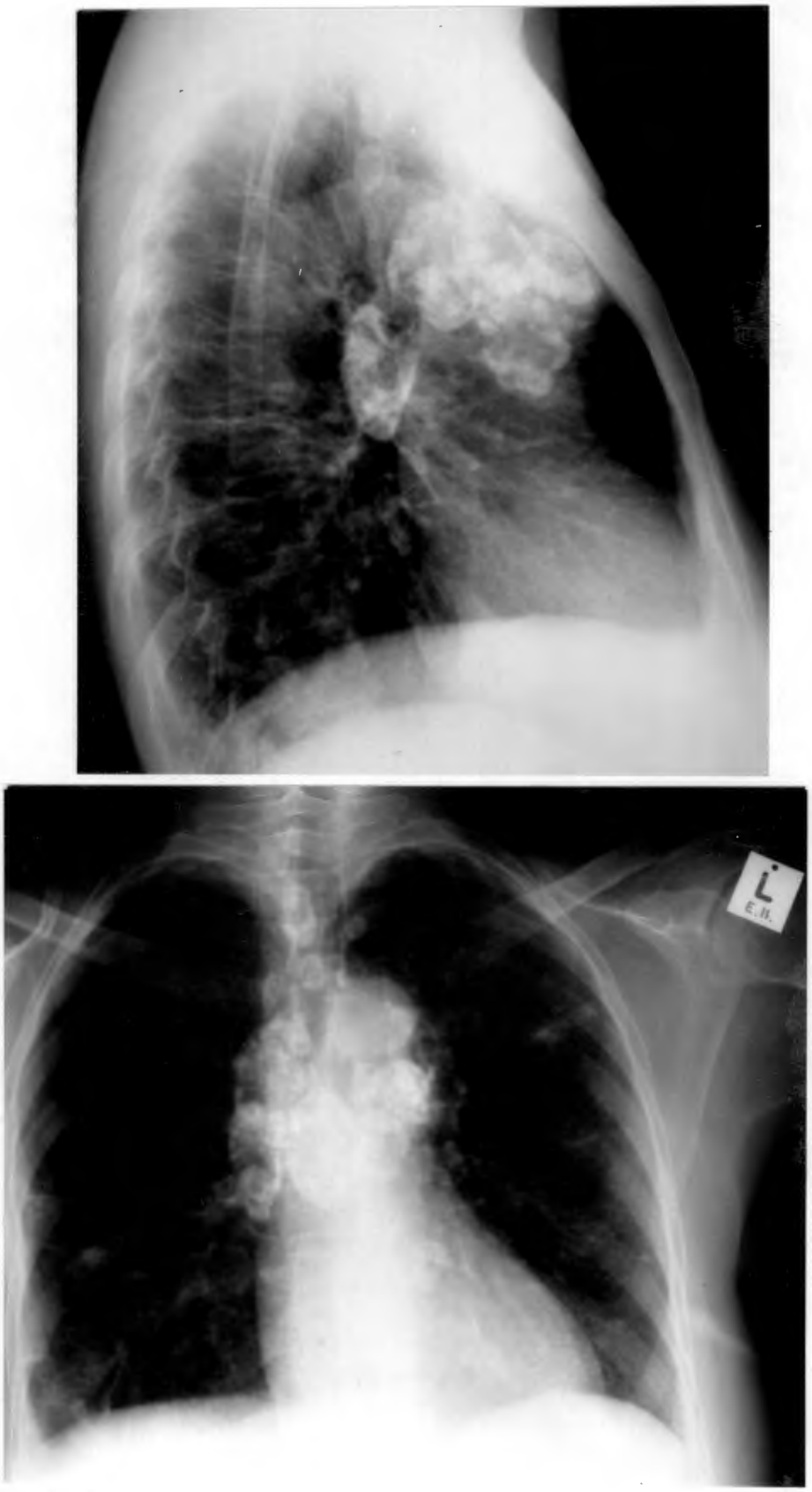
Radiograph 1

A mid zone opacity with hilar enlargement in a 30 year old female. Tubercle bacilli were obtained from endobronchial lavage and brushings.



Radiograph 2

Miliary tuberculosis.

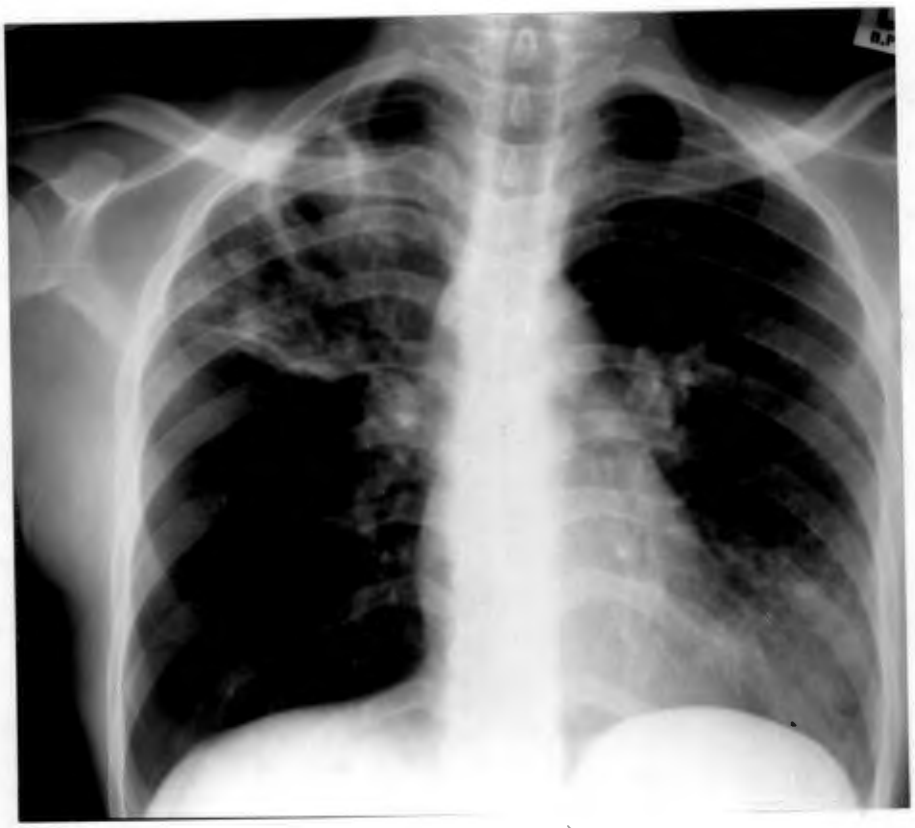


Radiograph 3 & 4

Hilar and peritracheal gland calcification in a 50 year old male. There is a right sided pleural reaction and non-specific shadowing at the left base.

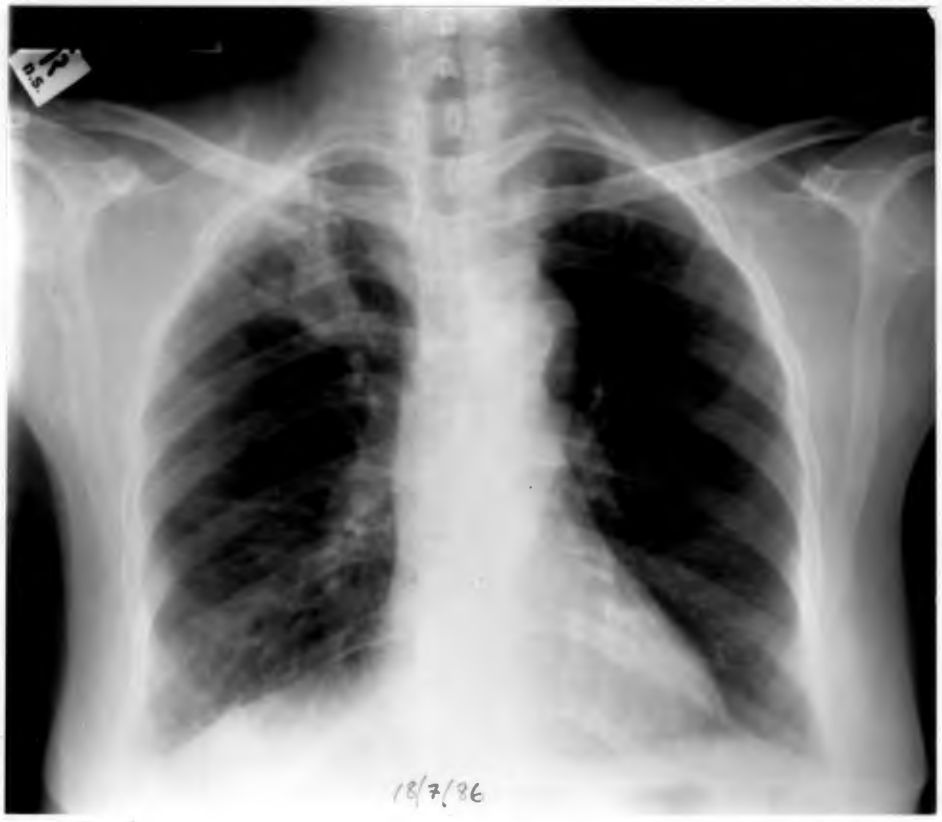
Radiograph 3 & 4

Hilar and paratracheal gland calcification in a 50 year old male. There is a right sided pleural reaction and non-specific shadowing at the left base.



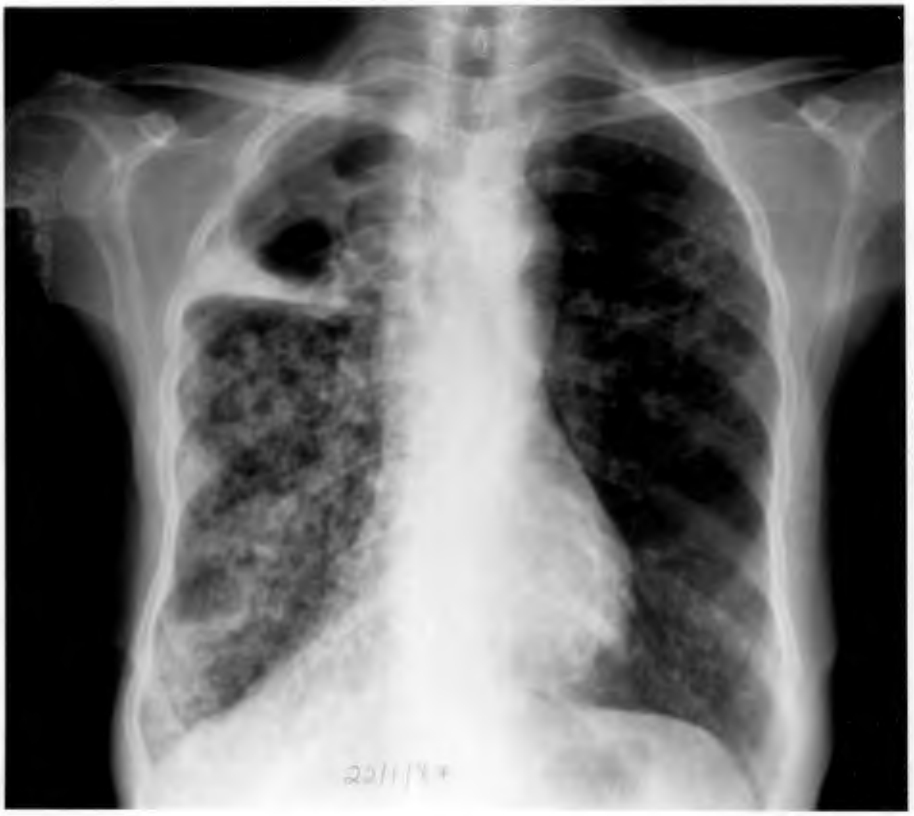
Radiograph 5

Classical apical opacification, with denser fibrotic changes and cavitation in the right apex. There is contralateral spread to the left base which shows a diffuse infiltrate consistent with inflammation.



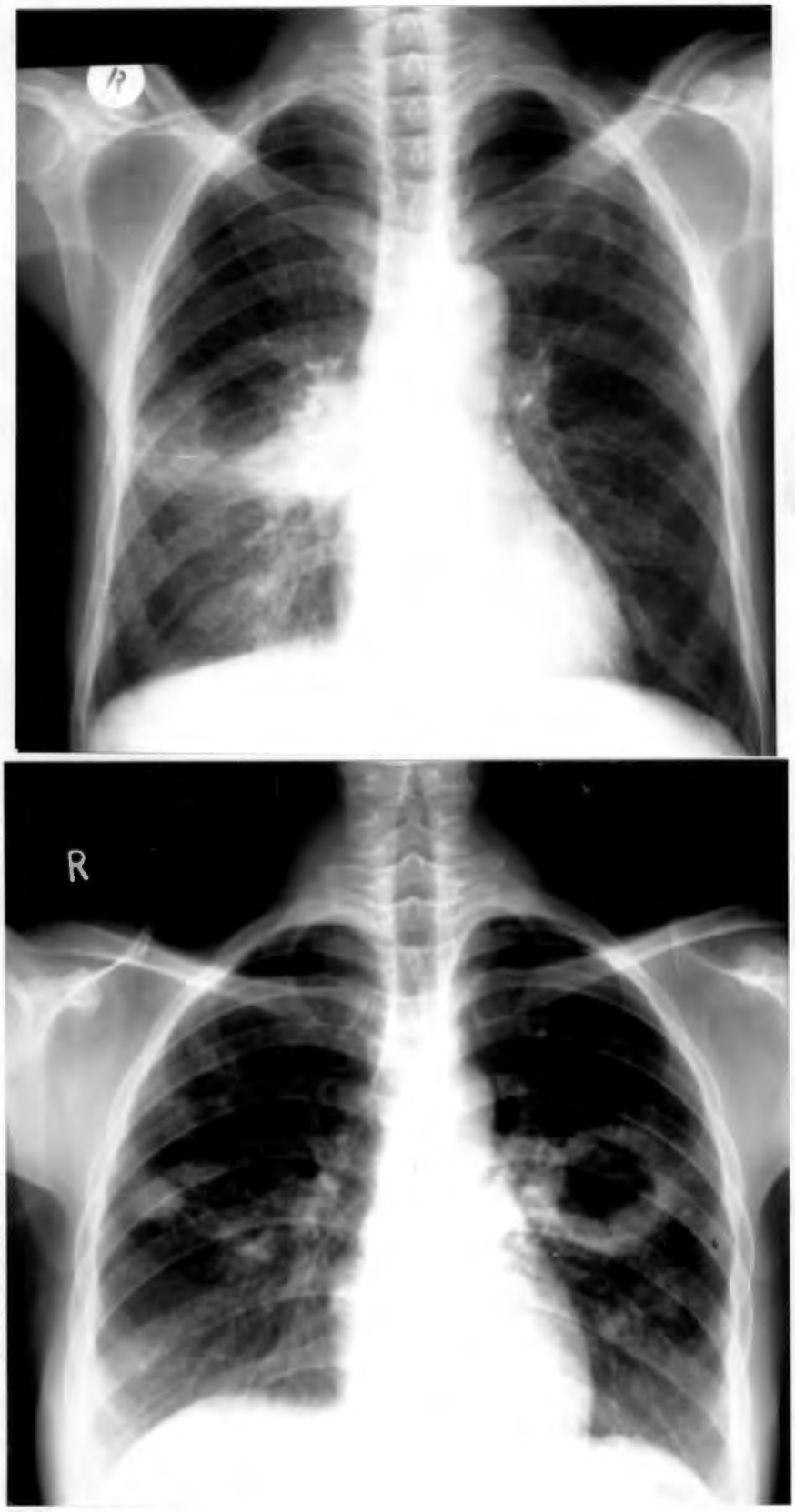
Radiograph 6

Apical changes as for 5 with ipsilateral right basal inflammation and a small basal pleural reaction. This latter feature is not common in reactivated disease.



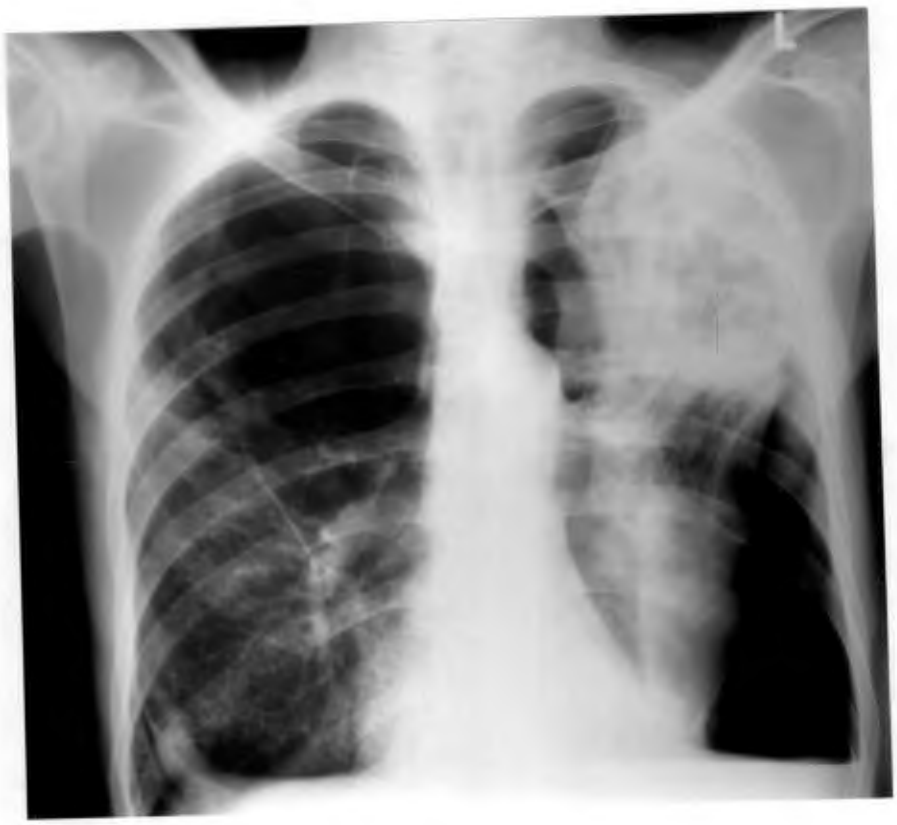
Radiograph 7

This is the same patient as in 6, but taken 5 months later. The patient had absconded. The apical cavities and fibrosis are accompanied by widespread cavities in the right lower lobe. There is segmental nodularity in the left mid and lower zones.



Radiograph 8/9

The apical segments of the lower lobes are involved with cavitating disease in approximately 10% of cases.



Radiograph 10

The devastating result of late diagnosis and inadequate therapy. The left lung is completely destroyed as is the right upper lobe. What little functioning lung is left is found in a fibrotic right lower lobe which contains large bullae.

INVESTIGATIONS

INDEX

PART I

INVESTIGATIONS

3. DIAGNOSIS

3.1 INTRODUCTION

There are four major criteria in the diagnosis of pulmonary tuberculosis in its reactivated phase. These are the detection of acid fast bacilli (AFB), radiographic appearances, the reaction to PPD (i.e. the Mantoux reaction), and histology. The culturing of M. tuberculosis in sputum or in tissue is the gold standard against which the other tests are evaluated for sensitivity and specificity.

3.1.1 ACID FAST BACILLI in the sputum. These can be detected either by the cheap, easy to perform, and reliable smear method, or by demonstrating the bacilli on sputum culture. In the presence of cavitating disease, the bacilli are numbered in the hundreds of millions, and there is usually no problem in detecting these on sputum smear. However where the cavities may be invisible on radiograph, and the infection mainly confined to the intra-tissue phase, bacilli are scanty (10^4/gram tissue) and cultures need to be performed.[19] This may be time consuming and is expensive.

In the elderly population, obtaining sputum is often difficult. Approximately 40% of patients are unable or unwilling to produce sputum. Because it is an essential component of the diagnosis it also needs to be determined whether it is a cost effective method of screening for the disease.

3.1.2 RADIOGRAPHY

The radiographic features in younger adults have already been described comprising apical cavitation, confluent opacification reflecting an inflammatory response, with apical pleural and interstitial fibrotic changes. Hilar gland enlargement is not usually apparent at this stage for poorly understood reasons, probably relating to altered responses in the setting of cellular hypersensitivity. It is also possible that previous inflammation, fibrosis and calcification during the primary phase prevents enlargement. Opacification and cavitation may be seen elsewhere in the lungs particularly in the lower lobes. Nodularity is frequently seen and may be either diffuse or localised. This is a reflection of granulomatous response to endogenous endobronchial infection or vascular spread (See Fig. 10 and Radiograph 7).

The radiographic findings in the elderly tuberculous patient may be different from that of the primary or

reactivated secondary disease. There are a number of studies which have described some of the atypical features found in adults with reactivated disease [20] [21] [22] [23] [24] [25] but none of these address the changes in the elderly. There are three reports comparing radiographic features of reactivated disease in young adults and the elderly. Two found no difference in the frequency of atypical findings[26] [27]. (See page 70) In the third, Katz et al performed a retrospective study in patients with pulmonary tuberculosis and compared the radiographic features in 27 men over 60 years old with 52 younger men. They showed that the elderly had significantly less cavitations, and were more likely to present with lower lobe infiltrates.[28] As no systematic survey of the radiological changes in the elderly exists, a prospective survey to elucidate the matter was undertaken.

3.1.3 HYPERSENSITIVITY RESPONSE TO THE PURIFIED PROTEIN DERIVATIVE

For diagnostic testing in adults the Mantoux reaction is the most widely used. This consists of an intra-dermal injection into the skin of the forearm so that a small bleb is raised. The material is a purified protein derivative (PPD) which is extracted from tubercle bacilli and acts as an antigen in a Type 4 hypersensitivity reaction. The result of this is an erythematous response with a central

area of induration and it is the latter which is measured in the greatest transverse diameter. It has become conventional to use 5 tuberculin units (TU) and to read the test at 72 hours.

A positive result (greater than 10 mm) is an indication that there has been, or is, an infection present. It is not an indicator of disease, and in fact approximately a quarter of patients with the disease will not have a positive reaction. It is rather an indicator of infection. Reasons for false negativity include old age, drugs (corticosteroids), immunosuppressants, current bacterial infections, viral infections, chronic organ failure (e.g. kidney, liver), malignancies, and a poor nutritional state. In addition the test material is of variable potency; is subject to temperature degradation, and faulty technique of injecting the substance is not uncommon.

In the elderly the phenomenon of anergy is a confounding factor in making a diagnosis. This absence of an expected delayed hypersensitivity reaction is a result of complicated cellular and humoral processes with both stimulatory and suppressor control mechanisms.[29] Because of this it has been advocated that people in this age group who react negatively to PPD should be challenged with a second Mantoux test within a week. A positive reaction is an indication of a booster reaction and 6% - 10% of individuals may show this phenomenon. It is important that the booster

phenomenon should be sought for because later positive reactions might be taken to indicate a newly acquired infection, whilst it is simply a booster response following the initial test.

Although a positive result (greater than 10 mm) does not necessarily indicate active infection it is conventional to regard an indurated area of greater than 20 mm with great suspicion, and any ulceration which occurs indicates a need for an active search for the disease. Furthermore a conversion from negative to positive over a period of time (e.g. 1 year) will reflect a recent infection, as will an increase in size of the Mantoux reaction of 12 mm or more. [30] Thus the Mantoux reaction is an important adjunct in the diagnosis of tubercular disease, but in itself is insufficient to make that diagnosis.

However, it has been used for many years as a monitor of infection, and it needs to have its part in identifying an at-risk group within the population for whom further investigations would be necessary to exclude disease.

3.1.4 ELISA TEST

An enzyme linked immunoabsorbent assay (ELISA) which would enable serological diagnosis of TB would be a major advance in the diagnosis of the disease. There have been early encouraging reports using varying antibody reactions, and

recently Waddee et al published their results using a sonicated mycobacterium [31] and claimed good diagnostic ability. This technique had not been tested before in the elderly, and hence its investigation as a diagnostic tool was included in the present study.

3.2 CRITERIA FOR DIAGNOSIS OF PULMONARY TB

The relative weights that can be ascribed to the different diagnostic tests have been quantitated by Escreet and Cowie, and this scheme has proved to be a valuable yardstick.[32] It has a major advantage in that it prevents over diagnosis of the disease in cases with minimal radiographic or non-specific changes. This is of particular importance where it is anticipated that the radiographic appearances may be unusual. The strictness of the criteria are such that there is a danger of underdiagnosis in a high prevalence community, but it was considered important for this study that an unequivocal diagnosis was essential if evaluation of other abnormalities (e.g. radiographic, haematological etc.) were to be meaningful. These authors' criteria which are required to make the diagnosis were met in all cases of pulmonary disease reported in this study. The summarised scheme is as follows.

DIAGNOSIS OF PULMONARY TUBERCULOSIS

CATEGORY	SUBCATEGORY	SCORE
Chest radiograph	1.Lesion(s) in upper or lower lobe apical segment(s).	
	A.Infiltration or scarring with cavitation.	5
	B.Non-confluent infiltration or scarring without cavitation.	3
	2.Lesion(s) elsewhere in the lung (not apico-posterior).	
	A.With cavitation	2
	B.Without cavitation	1
	3.Diffuse lung lesions	
	A.Miliary	3
	B.Non-miliary	2
	4.Pleural lesion(s)	
	A.Pleural effusion(s)	3
	5.Lesion(s) in upper or lower lobe apical segment which is new or enlarging and shows no sign of resolution on a 2-month follow-up radiograph	5
Sputum	1.Direct positive for AFB*	
	A.Once	3
	B.Twice	7
	C.Three times	10
	2.Culture positive for mycobacterium tuberculosis	
	A.Once	7
	B.Twice	10
Tuberculin test	1.Heaf grade 3	2
	2.Heaf grade 4	4
Histology	1.Lung, liver or lymph node	
	A.Epithelioid/giant cell granuloma	5
	B.Granuloma with necrosis	7
	C.Granuloma with AFB*	10
	2.Pleura	
	A.Epithelioid/giant cell granuloma	10
Therapeutic clinical trial	1.Radiological improvement after 2 mo. of treatment as compared with the chest radiograph after 1 mo. of treatment.	3

NOTE: A total score of 10 is required for the diagnosis of active pulmonary tuberculosis, but only 1 score may be used from each category.

(*Acid-fast bacilli resembling Myco. tuberculosis).

If the Mantoux test (5 TU bio-equivalent is used, the following scores apply: (i) 0-9mm..0: (ii) 10-19 mm..2: and (iii) > 19 mm..4.)

3.3 THE HAEMATOLOGICAL AND BIOCHEMICAL CHANGES IN ADULTS WITH SEVERE PULMONARY TUBERCULOSIS

In order to assess the relative value of abnormal haematological and biochemical parameters in the elderly, it would be necessary to compare those values with that of an adult population of all ages suffering from pulmonary tuberculosis. Unfortunately no comprehensive survey exists which describes their prevalence and severity apart from one report [33] which describes some haematological features (anaemia 17%, leucocytosis 10%, leukopenia 10%, eosinophilia 14% and monocytosis 32%). Unfortunately it seems as though all forms of tuberculosis were included in this study, including miliary disease. Furthermore it is not clear whether the changes were due to tuberculosis or accompanying diseases. There is no mention of red cell indices or the platelet count. Other studies report haematological and/or biochemical changes in limited detail, as part of case reports, or as information incidental to the main object of the investigation. [34] [35] [36] [37] [38] There is no comprehensive survey for any of these changes in pulmonary tuberculosis.

This study was undertaken to establish the frequency and severity of biochemical and haematological abnormalities in severe pulmonary TB in adults and to relate them to the clinical features, iron, vitamin B12 and folic acid status and to the morphological appearance of the bone marrow. A

further objective was to monitor common haematological quantities during treatment and to establish whether any relationship existed between these indices and response to treatment. The study described in this chapter forms the basis for testing the hypothesis that TB in the elderly manifests haematological and biochemical features which are different from those in younger adults.

MATERIALS AND METHODS

Patients

The study group consisted of black South Africans admitted consecutively to the Department of Medicine, Frere Hospital and the South African National Tuberculosis Association (SANTA) Hospital, East London, South Africa with the diagnosis of pulmonary TB. The diagnosis was made according to the criteria proposed by Escreet and Cowie (page 48), and all cases were judged to be severe in that they had cavitating lung disease on chest radiography. 80% of patients complained of cough, 21% of haemoptysis, 70% of weight loss and 61% were pyrexial on admission. The treatment regimen was rifampicin, streptomycin, pyrazinamide and isonicotinic hydrazide.

Haematology

Full blood counts were performed on a Coulter S Plus II counter. Blood smears were stained by the May-Grunewald-Giemsa method and a manual differential count was carried out on 100 cells. Erythrocyte sedimentation rate (ESR) was measured by the method of Westergren. A bone marrow aspirate and biopsy was done on patients with any one of the following abnormalities: anaemia (Males: haemoglobin < 13,0 g dl. females:haemoglobin < 11,0.0 g dl.). Thrombocytopenia (platelets < 150 x 10^9/l), thrombocytosis (platelets > 400 x 10^9/l) or leucopenia (white cells < 4.0 x 10^9/l) or leucocytosis (white cells > 11.0 x 10^9/l). Marrow aspirate smears were stained by the May-Grunewald-Giemsa method and with Perl's reagent to assess marrow iron, which was scored by an experienced haematology pathologist according to the method of Gale et al.[39] The trephine biopsy was stained with haematoxylon and eosin and for reticulin.

Biochemistry

Serum ferritin was measured by a radioimmunoassay technique using an Amersham kit and vitamin B12, folic acid and red cell folic acid levels were measured with a Becton-Dickinson kit. Serum sodium, potassium, calcium, urea, creatinine, total protein, albumin, inorganic phosphate, uric acid,

bilirubin, alkaline phosphatase, aspartate transaminase and lactic dehydrogenase were measured by a SMACII analyser.

Bacteriology

Sputum was collected on admission and at two-weekly intervals. It was smeared, stained by the Ziehl-Neelsen method and examined for acid-fast bacilli by an experienced technologist in the Frere Hospital Bacteriology Laboratory.

Statistical analysis

The contingency correlation of the relevant haematological biochemical and clinical independent variables were analysed using 2 x 2 Chi tables. Differences in mean values were analysed by Student's T-test.

RESULTS

Two hundred and sixty-four patients were studied between June 1986 and July 1987 (117 males and 147 females). Mean age was 48 years (Table 7). One hundred and thirty-six consecutive patients were observed at monthly intervals for three months while on treatment for tuberculosis; at each visit full blood count, ESR, body weight and results of sputum examination were recorded.

	Male N = 117		Female N = 147	
Age				
10 - 19	10	7%	4	3%
20 - 29	22	15%	24	21%
30 - 39	30	20%	17	15%
40 - 49	34	23%	17	15%
50 - 59	20	14%	13	11%
60 - 69	18	12%	26	22%
>70	13	9%	13	11%

Table 7

Age distribution of the population studied.

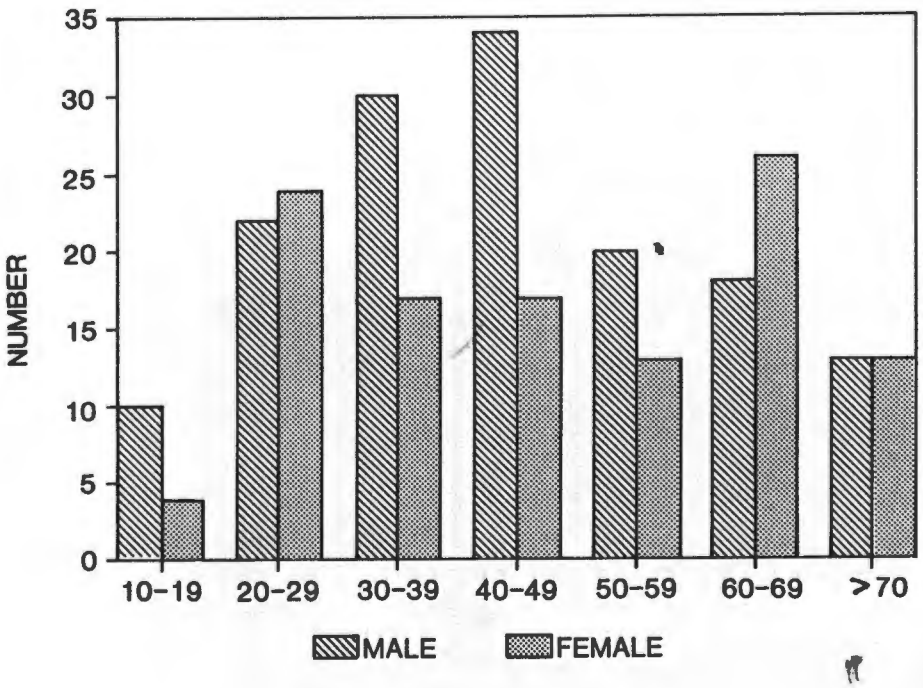


Fig. 11

Age distribution of males and females.

Haematology

Full blood count results are shown in Table 8. 60% of patients were anaemic; this was more frequent in males than females. In 95% of cases the anaemia was normochromic and normocytic. A minority were macrocytic (4%) or microcytic (1%). Of the total number of patients, 18% were macrocytic, 14% microcytic and 68% normocytic. There were no patients with neutropenia, increased eosinophils or basophils.

	Hb(male) (g/dl)	Hb(female) (g/dl)	Mean cell volume (fl)	Mean cell haemoglobin (pg)	Red cell distribution width	White cell count ($x10^9/l$)	Neutrophils ($x10^9/l$)	Lymphocytes ($x10^9/l$)	Monocytes ($x10^9/l$)	Platelets ($x10^9/l$)	ESR (mm/h)
Normal values	13-16	11-14	77-96	27-33	15	4-11	2.0-6.5	0.95-3.38	0.50-0.80	150-400	30
Mean	11.5	11.0	83	29	16.0	10.6	8.057	2.50	0.51	422	74
Median	11.8	11.0	85	28.9	15.8	9.7	7.28	2.32	0.46	405	76
SD	2.35	2.16	1.6	5.6	2.6	5.0	4.52	1.10	0.37	167	35
Percentage above upper limit	2	2	12	1	67	40	57	23	29	52	80
Percentage below lower limit	72	45	12	25	-	2	0	17	50	1	-

Table 8

Full blood count and ESR at presentation.

The normal values are unpublished figures established by the local hospital laboratory for the population served by it.

Bone marrow aspiration and trephine biopsy were performed on the first 37 consecutive patients with peripheral blood abnormalities. The most common finding in the marrow aspirates was a mild plasmacytosis (51%), increased iron stores (81%) and decreased numbers of iron-containing normoblasts (65%). Five aspirates showed megaloblastic maturation; of these two had macrocytic red cell indices. None of these patients had abnormally low levels of vitamin B12 although one had a reduced serum folic acid level. No further significant abnormalities were seen in the trephine biopsies; in particular no granulomata were seen. The small amount of information obtained from these procedures did not justify any further aspirations or biopsies on ethical grounds.

	Ferritin (ng/ml)	B_{12} (pg/ml)	Serum folate (ng/ml)	Red blood cell folate (ng/ml)
Mean	428	987	4.0	283
Median	500	869	3.7	240
SD	127	519	2.8	165
Reference Range	14-230	160-970	1.5-16.9	120-860
Percentage in range	6	43	86	83
Percentage above range	94	57	-	-
Percentage below range	-	-	14	17

Table 9

Analysis of the levels of ferritin, vitamin B_{12}, folate and red cell folate.

Biochemistry

The most notable changes were hyponatraemia (43%) hypoalbuminaemia (72%), and raised alkaline phosphatase, ASPT and LDH values in 37,28 and 54% of patients respectively (Table 9).

Iron or vitamin B12 deficiency was not seen, although ferritin and B12 levels were increased in 94 and 57% respectively. The serum and red cell folic acid levels were normal in most patients (Table 9).

	Na^+ (mmol/l)	K^+ (mmol/l)	Ca^+ (mmol/l)	Urea (mmol/l)	Creatinine (µmol/l)	Total protein (g/l)	Albumin (g/l)	Inorganic phosphate (mmol/l)	Uric acid (µmol/l)	Bilirubin (µmol/l)	Alkaline Phosphatase (u/l)	ASPT (u/l)	LDH (u/l)
Normal	135 – 145	3.5 – 5.0	2.25 – 2.63	2.5 – 6.7	44–106	60 – 80	35 – 50	0.94 – 1.45	120 – 450	0–20	30–115	7–40	100–225
Mean	135	4.1	2.24	4.32	82	61.3	31.0	1.21	278	7.4	116	36	263
Median	136	4.2	2.35	3.80	76	71.0	32.0	1.18	241	5.0	97	29	242
SD	4.25	0.73	0.51	2.39	37	27.9	6.9	0.84	173	7.4	67	38	135
Percentage above range	0	19	–	8	10	20	0	11	3.2	5	37	28	54
Percentage below range	43	8	14	17	0	10	72	11	6	–	–	–	–

Table 10

The biochemical profile. The calcium level has been adjusted according to the albumin concentration.

Haematological results during treatment

One hundred and thirty-six consecutive patients were followed for three months. The results are shown in Table 11. By the end of the third month, when the sputum of 95% of patients had become negative for acid-fast bacilli, mean haemoglobin level had increased from 11.0 to 12.3 g/dl ($p<0.001$), there was a decrease in the mean white cell count ($p<0.001$), the mean ESR ($p<0.001$) and the mean platelet count ($p<0.002$). Mean body mass increased ($p<0.001$) (the statistical analysis was by paired test). There was correlation between sputum conversion and improvement good in all the parameters measured (Table 11).

	Hb (g/l)		Leucocytes ($x10^9$/l)		Platelets ($x10^9$/l)		ESR (mm/h)		Weight (kg)		Cumulative percentage converted
Acid-fast bacilli	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	
Pretreatment baseline	10.7	-	11.6	-	453	-	91	-	47.6	-	0
Treatment for											
1 month	11.3	11.4	13.5	9.8	460	412	92	75	48.7	49.9	23
2 months	11.4	12.3	11.7	9.7	440	374	97	60	51.1	51.0	66
3 months	10.8	13.1	16.3	8.6	505	326	90	47	49.5	54.3	95

Table 11

The relationship between sputum conversion (negative for acid-fast bacilli) and mean values for haemoglobin (Hb), leucocytes, platelets, erythrocyte sedimentation rate (ESR) and weight. Persistance of abnormal values of these indices is associated with excretion of tubercle bacilli (acid-fast bacilli positive).

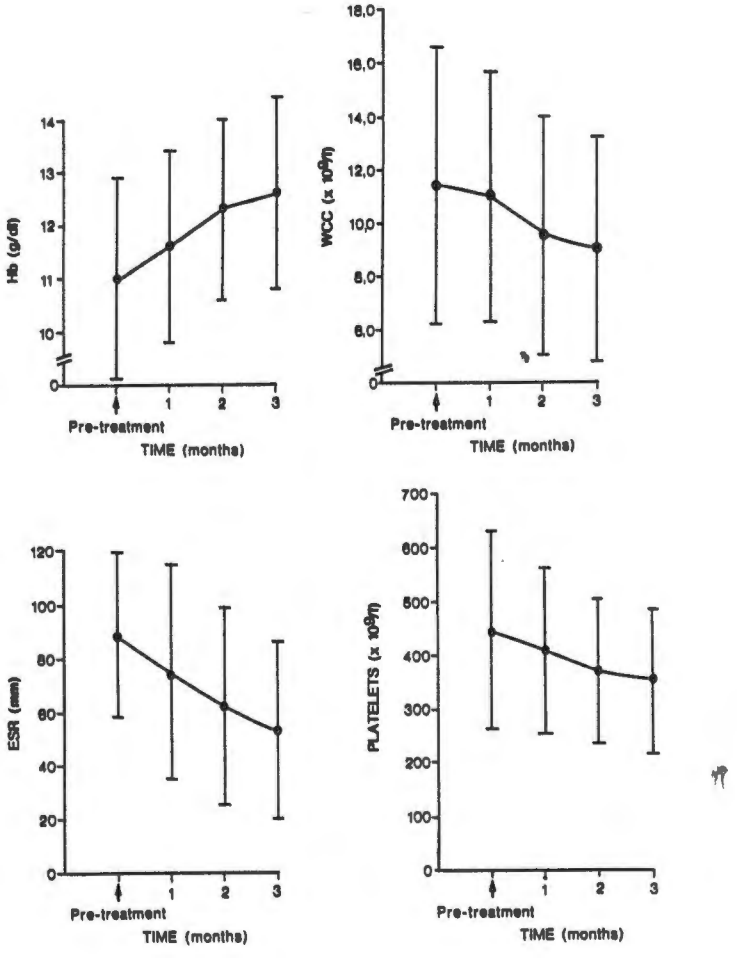


Fig. 12

The levels of haemoglobin (Hb), white cell count (WCC), erythrocyte sedimentation rate (ESR) and platelets before treatment and their return to normal values. The differences between the means of the levels before, and those three months after, treatment are all significant at the 1 per cent level.

Correlation studies

There is always concern that when multiple comparisons are made that spurious association may result. However there was a significant correlation between platelet count and ESR ($p=0.01$), and between elevated platelet count and a history of weight loss ($p=0.01$). Anaemia correlated significantly ($p=0.02$) with both loss of weight and hypoalbuminaemia. These associations are biologically plausible. There was unexpectedly no correlation between leucocyte count and either fever or ESR, and the serum albumin level did not correlate with loss of weight. All these variables were considered as categorical as opposed to continuous.

CONTINGENCY COEFFICIENTS

	LEU	Hb	MCV	RDW	PLA	ESR	NEU	COUGH	HAEM	WTLOSS	FEVER	ALB	Na
LEU	1.000	0.038	0.222 x	0.137 xx	0.153	0.144	0.002	0.137	0.037	0.134 xx	0.006	0.152 xx	0.281
Hb		1.000	0.320 xx	0.280 xx	0.162	0.137	0.022	0.161	0.070	0.228	0.076 xx	0.260	0.067
MCV			1.000	0.310	0.120	0.160	0.108	0.182	0.056	0.046	0.211	0.126 xx	0.125
RDW				1.000	0.041	0.078	0.008	0.061	0.033	0.036	0.029	0.270	0.029
PLA					1.000	0.303 xx	0.133	0.029	0.070	0.204 xx	0.110	0.052	0.044
ESR						1.000	0.100	0.034	0.081	0.010	0.086	0.032	0.082
NEU							1.000	0.029	0.042	0.028	0.015	0.092	0.013
COUGH								1.000	0.179	0.252	0.244	0.195	0.064
HAEM									1.000	0.008	0.013	0.101	0.096
WTLOSS										1.000	0.137	0.116	0.115
FEVER											1.000	0.017	0.040
ALB												1.000	0.015
Na													1.000

Table 12 Contingency co-efficients of all the variables. (LEU = leucocytes, Hb = haemoglobin, MCV = mean cell volume, RDW = red cell distribution width, PLA = platelets, ESR = Erythrocyte Sedimentation Rate, NEU = neutrophils, HAEM = haemoptysis, WTLOSS = weight loss, ALB = albumin, Na = sodium) (x = 0.05 xx = 0.01)

DISCUSSION

Anaemia was common, although it was unclear why more males were affected. The majority had normocytic, normochromic red cell indices, probably reflecting an anaemia of chronic disorders. Red cell anisocytosis, revealed by an elevated mean red cell distribution width was frequent, unlike the series of Bessman et al.,[40] although in agreement with other studies which found that this index does not help to discriminate iron deficiency anaemia from the anaemia of chronic inflammation. [41] [42]

The prevalence of leucocytosis was somewhat greater than that reported in other studies, whether with disseminated or pulmonary TB. [33] [34] [37] [43] [44] This was largely the result of a neutrophilia, although lymphocytosis and monocytosis were seen in a small number of patients. The prevalence of lymphopenia (17%) and monocytopenia (50%) is similar to the findings of Venter [37] which he correlated with severity of disease.

Thrombocytosis was a striking feature in just over half the patients and was significantly correlated with ESR and loss of weight. This confirms a recent report where it was further shown that there was associated increased platelet aggregability and decreased survival. [45]

The majority of patients had elevated ESR at presentation, which decreased significantly in those whose

sputum became negative for acid-fast bacilli. While not a diagnostically discriminating feature, [32] ESR nevertheless appeared to be a useful monitor of progress of the disease in that it showed a significant slowing (Fig. 11) coincident with sputum conversion.

The elevated levels of serum ferritin seen in almost all patients is probably due to its behaviour as an acute phase reactant. This is borne out by results of the bone marrow iron stains which showed, that the majority had increased iron stores with very scant sideroblasts. The concentrations of ferritin are similar to those reported previously in inflammatory conditions, [46] and Bantu siderosis is unlikely as this condition is now rarely seen in our community (personal observation).

The normal folate stores in the majority differ from those reported from some earlier series [34 47] where folate deficiency was found in over a third of the patients. The findings of Markannen et al [48] however were similar to this one. As in other studies, no correlations between folate levels, degree of macrocytosis or megaloblastic marrow changes were noted. The elevated levels of vitamin B12 in more than 50% of patients has not been reported. There was a significant correlation between the raised level of vitamin B12 and leucocytosis ($p=0.005$), presumably because the resultant elevation in R-binders leads to an increased concentration of vitamin B12. [49]

The progressive rise in haemoglobin during treatment in the majority of patients is the expected response in an anaemia of chronic disorders, since haematinics were given only to those with folic acid deficiency. This significant rise was accompanied by a similar gain in body weight and a significant decrease in platelet and leucocyte count (Fig. 12), all of which correlated closely with conversion of the sputum to acid-fast bacilli negative (Table 11). Failure of these parameters to return to normal was invariably associated with persistent excretion of acid-fast bacilli. Although rifampicin, INH and streptomycin may cause thrombocytopenia [50] the fact that the platelet count remained elevated in those whose sputa were positive for acid-fast bacilli excludes the drug as a cause for the decreased platelet count. None of the other drugs used are known to cause the haematological changes found.[50]

Nearly half the patients had hyponatraemia, a well recognised feature of pulmonary TB and attributed to inappropriate secretion of antidiuretic hormone. [51] Another frequently observed biochemical abnormality was a low serum albumin, present in 72% of patients, a reflection of either malnutrition, or more likely, severity of disease. Elevation of the alkaline phosphatase, ASPT and LDH present in approximately one-third of cases, may indicate hepatic disease.

This survey has revealed that haematological and

biochemical abnormalities are relatively common in severe pulmonary TB without clinical features of systemic dissemination. The haematological findings contrast with previous reports [33-37] [43] [52] in terms of severity and frequency, and perhaps are more in keeping with those of disseminated or 'non-reactive' disease, although there are also some differences. [52] [43] All of our patients were reactive in that they had cavitating disease, and the high prevalence of abnormal liver enzymes suggests a strong possibility of hepatic disease as well. The common denominator for haematological and biochemical abnormalities may not be reactivity or non-reactivity as suggested by O'Brien, [53] but dissemination. This may be of relevance in the geriatric population and in those patients with AIDS where cell-mediated responses may be reduced in the former and absent in the latter. Furthermore, as a result of the findings it is suggested that the classification of blood changes in reactive TB suggested by Cameron [35] is inappropriate to the present population sample since these results are in total conflict with his proposals. He has proposed a classification characterised by 6 blood abnormalities in reactive tuberculosis, namely (a) "hypochromic, non-sideropaenic anaemia, (b) iron deficiency anaemia, (c) relative folate deficiency (with or without anaemia), (d) polymorphonuclear leucocytosis, (e) neutropenia" and states that "anaemia is uncommon". Of

these only leucocytosis was found in this study.

The present study suggests that body weight, platelet count, white cell count, haemoglobin level and ESR are useful indices of severity of disease. Return of these indices to normal is a good indication of disease control in that they correlate with sputum conversion to acid-fast bacilli negative and as such can be used (and are by us) in decisions regarding discharge from hospital. Our data suggests that haematinics are almost never required, and in the population we have studied, iron supplements are contraindicated.

3.4 THE RADIOGRAPHY, HAEMATOLOGY AND BIOCHEMISTRY OF PULMONARY TUBERCULOSIS IN THE AGED.

There is controversy about the radiological appearances of pulmonary tuberculosis in the elderly. There are well described radiographic appearances in tuberculosis including atypical findings. [20-25] None of these reports however specifically address the appearances in the elderly although Khan et al [22] records 7 out of 13 subjects over 60 had "unusual" features. There are two reports suggesting that the picture in young adults and elderly is similar [26 27] and one which contradicts these findings.[28] Van de Brande and Pelemans [26] compared 55 patients over 60 years with 59 younger subjects all with bacteriologically proven disease and found no statistically significant differences in the radiological appearances. However in their definition of atypicality they excluded all cases if they "occurred with tomographically demonstrable apico-posterior lesions even minor and inactive. Patients with apico-posterior lesions were classified as typical even if atypical features were present". This makes it difficult to know how many atypical presentations were excluded because of apico-posterior scarring from previous disease. In the report by Alvarez et al [27] no radiological differences were noted between 29 men below 55 years and 35 men over 65 years with pulmonary tuberculosis. However their description of the

abnormalities comprised only "upper lung infiltrates", "diffuse bilateral infiltrates" and "cavitation" leaving doubt about where the cavities or bilateral infiltrates were situated. No mention is made regarding mediastinal or pleural changes in contrast to most other studies. In their study, Katz et al [28] compared the radiographic findings in 27 patients over 60 years and 52 under 60 years. They report (rather cryptically) a "more frequent occurrence of right lower lobe pneumonia in those patients 60 years or older (33% vs 9.6%; $p<0,02$) and of cavitary lesions in the younger patients (48% vs 17%; $p<0,02$). Disease affecting both the pleura and lower lobe was distinctly unusual in patients under 60 years of age (1.9% vs 22%; $p<0,05$)".

In all the studies on elderly tuberculotics quoted above the patient numbers are small. In order to clarify the situation a prospective study was undertaken to clarify radiographic appearances in elderly tuberculosis and to document the haematological and biochemical abnormalities associated with the disease in the elderly. The results of the latter findings are compared to those found in the younger adult population reported in the previous chapter, and to an ancillary investigation appended to this thesis (Appendix E) where the control group was 40 elderly patients with non-tuberculotic chronic destructive lung disease.

Methods

All patients over 60 years who were admitted to the Department of Medicine, Frere Hospital, South Africa from January 1987 to June 1988 with the diagnosis of pulmonary tuberculosis according to the criteria proposed by Escreet and Cowie for the diagnosis in adults [32] were included in this study. The criteria for admission were, generally, (a) pulmonary tuberculosis suspected on either clinical or radiological grounds in unselected patients presenting themselves, or (b) referred by general practitioners or outlying clinics to the Frere Hospital out-patients section. They were all admitted for further investigation and confirmation of the diagnosis, as has been the procedure followed in this Department for some years. Apart from suspicion of pulmonary tuberculosis, no other admission criteria were involved. (c) Also included were patients who during the same time period were residents in old people's homes and whose disease was discovered as a result of active case finding. For details of the method used for the latter please refer to page 116. Thus all known cases of pulmonary tuberculosis occurring in the area in patients over sixty years during the 18 month period were entered. All patients were questioned by myself or a medical officer (as part of the history taking) about cough, weight loss and haemoptysis. The temperature reading was extracted from the

inpatient records. Cough was a complaint of 80% of patients, weight loss in 70% and haemoptysis in 8%. Fever was present in 55% of cases.

Radiographic examination

Chest radiography was performed on all patients. The radiographs were read by two radiologists who were blinded in respect of sputum status. They were asked to describe their findings from the PA and lateral films taken by the standard high KV method in the Department of Radiology, Frere Hospital. The radiologists' opinion was recorded by myself on a standard form (see appendix A). Where the reports differed, I then questioned both radiologists, and recorded any additional comments. Radiographs were analysed for presence and site of fibrosis, pleural reaction (either fluid or thickening), cavitation and opacification consistent with an inflammatory reaction. The apical, mid and lower zones refers to the upper, middle and lower third of the lung field as seen on the posterior-anterior radiograph.

Haematological examination

Full blood and platelet counts were performed on a Coulter plus II counter. A differential count on a May-Grunewald-

Giemsa stained smear counting 100 cells and the Westergren erythrocyte sedimentation rate (ESR) were performed on all cases. "Normal values" were those used by the hospital laboratory.

Biochemical examination

Biochemical profiles were performed on a SMACII analyser, and the range of normal values were those of the hospital laboratory.

Bacteriological examination

Sputum was collected on admission, smeared and stained by the Ziehl-Neelsen method and examined for acid-fast bacilli. Sputums negative for acid-fast bacilli were cultured on Lowenstein Jensen slopes for up to six weeks. Three colonies or more were regarded as positive.

Statistical analysis

The haematological and biochemical variables were classified as either normal or abnormal according to the laboratories normal values and the categories compared using Chi^2 analysis. The significance of differences between means was tested by the Student t-test.

RESULTS

There were 93 patients. Average age was 70 years (range 60-96); there were 46 males and 47 females; 80 were black and 13 white.

Radiological examination

The radiographic appearances were divided into mild (one lobe affected) and severe (two or more lobes affected). In only one case was there disagreement between the radiologists and that concerned the presence of or absence of a pleural reaction in a kyphotic lady. This particular point was excluded from the overall analysis. The radiographic findings were also correlated with the haematological, biochemical changes and clinical features, and to the presence or absence of acid-fast bacilli on smear.

A total of 93 chest radiographs were examined; 60% of these had mild "changes" (one lobe) and 40% severe (more than one lobe affected) of these apical fibrosis compatible with previous disease was present in 40%. 46% had a basal pleural reaction (either fluid or thickening). All patients had opacification compatible with inflammation: apical 7%,

the mid or basal zones.

All patients with cavities on radiography had acid-fast bacilli present on direct smear. Where no cavities were seen 78% were smear positive but in 22% sputum cultures were necessary to detect the bacilli.

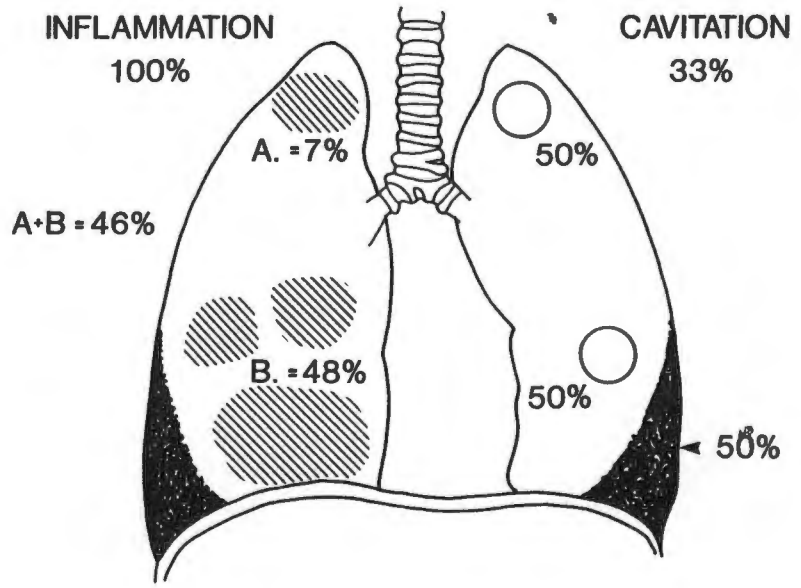


Fig. 13

Summarises the frequency of radiological appearances of pulmonary tuberculosis in the elderly. Opacification consistent with inflammation is depicted by the cross-hatched area, cavitation sites by the open circles and pleural reaction by the black areas in the bases.

Haematological examination

The results are shown in Table 13. The important values falling outside the normal ranges were levels of haemoglobin, neutrophils, and platelets and ESR.

	Haemoglobin		Red cell distribution width	Leucocytes ($x10^9/l$)	Neutrophils ($x10^9/l$)	Lymphocytes ($x10^9/l$)	Monocytes ($x10^9/l$)	Platelets ($x10^9/l$)	ESR (mm/hr)
	Male (g/dl)	Female (g/dl)							
Normal values	13-16	11-14	15	4-11	2-6.5	0.95-3.38	0.50-0.80	150-400	30
Mean	12.1	11.3	15.9	10.7	7.7	1.6	0.6	342	71
Median	11.7	11.0	15.6	9.7	6.9	1.4	0.5	343	80
SD	2.32	2.84	1.96	4.6	3.6	0.9	0.4	137	36
Percentage above upper limit	-	-	66	55	69	-	28	33	90
Percentage below	70	63	0	3	-	22	37	5	-

Table 13 Haematological values in patients with pulmonary tuberculosis.

The comparison of the haematological variables between radiologically mild and severe cases showed no significant differences, although there was a tendency for the severe cases to be more anaemic (11.5g/dl) compared to mild cases (12.6g/dl).

Biochemical examination

The results are shown in Table 14., The important values falling outside the normal range were levels of serum sodium, potassium, albumin and the liver enzymes. It is noteworthy that biochemical analysis was performed before anti-tuberculous therapy was commenced, ruling out enzyme induction as the cause of abnormal liver enzyme levels.

	Sodium (mmol/l)	Potassium (mmol/l)	Urea (mmol/l)	Creatinine (mol/l)	Total protein (g/l)	Albumin (g/l)	Inorganic phosphorus (mmol/l)	Uric Acid (mol/l)	Bilirubin (mol/l)	Alkaline phosphatase) (/l)	ASPT (u/l)	LDH (u/l)
Normal	135-145	3.5-5.0	2.5-6.7	44-106	60-80	35-50	0.94-1.45	120-450	0-20	30-115	7-40	100-225
Mean	134	3.9	5.2	80	69	29	1.23	330	8.5	124	46	277
Median	135	3.9	4.4	76	70	28	1.2	292	6.0	107	30	256
S.D.	4.77	0.78	2.8	21	11.3	6.7	0.24	150	7.7	58	51	122
Percentage below range	60	42	17	-	5	83	-	-	-	-	-	-
Percentage above range	-	-	30	16	37	-	21	30	20	62	77	74

Table 14 Results of biochemical tests for patients with pulmonary tuberculosis.

Comparison of the biochemical variables between radiologically mild and severe cases showed that hypoalbuminaemia was more profound in the severe group compared to the mild group (26g/l vs. 31 g/l $p<0,05$) and affected 90% of patients in the severe group v. 60% in the mild group ($p<0.05$). There were no other significant biochemical differences between the two groups.

Comparison of haematological and biochemical indices with those found in younger adults.

Fig.14

The differences between under 60 and over 60 year old cases of pulmonary tuberculosis with respect to haemoglobin (Hb), White cell count (WBC), platelets, sodium (Na^+), albumin (alb), bilirubin, alkaline phosphatase (Alk Phos), aspartic transaminase (ASPT) and lactic dehydrogenase (LDH). Note that with the exception of the platelet count all the variations from normal are more pronounced in the elderly. Statistical significance was not achieved because of the high variances apart from the bilirubin, alkaline phosphatase and ASPT values ($p<0,05$).

Comparison of haematological and biochemical indices with those found in younger adults.

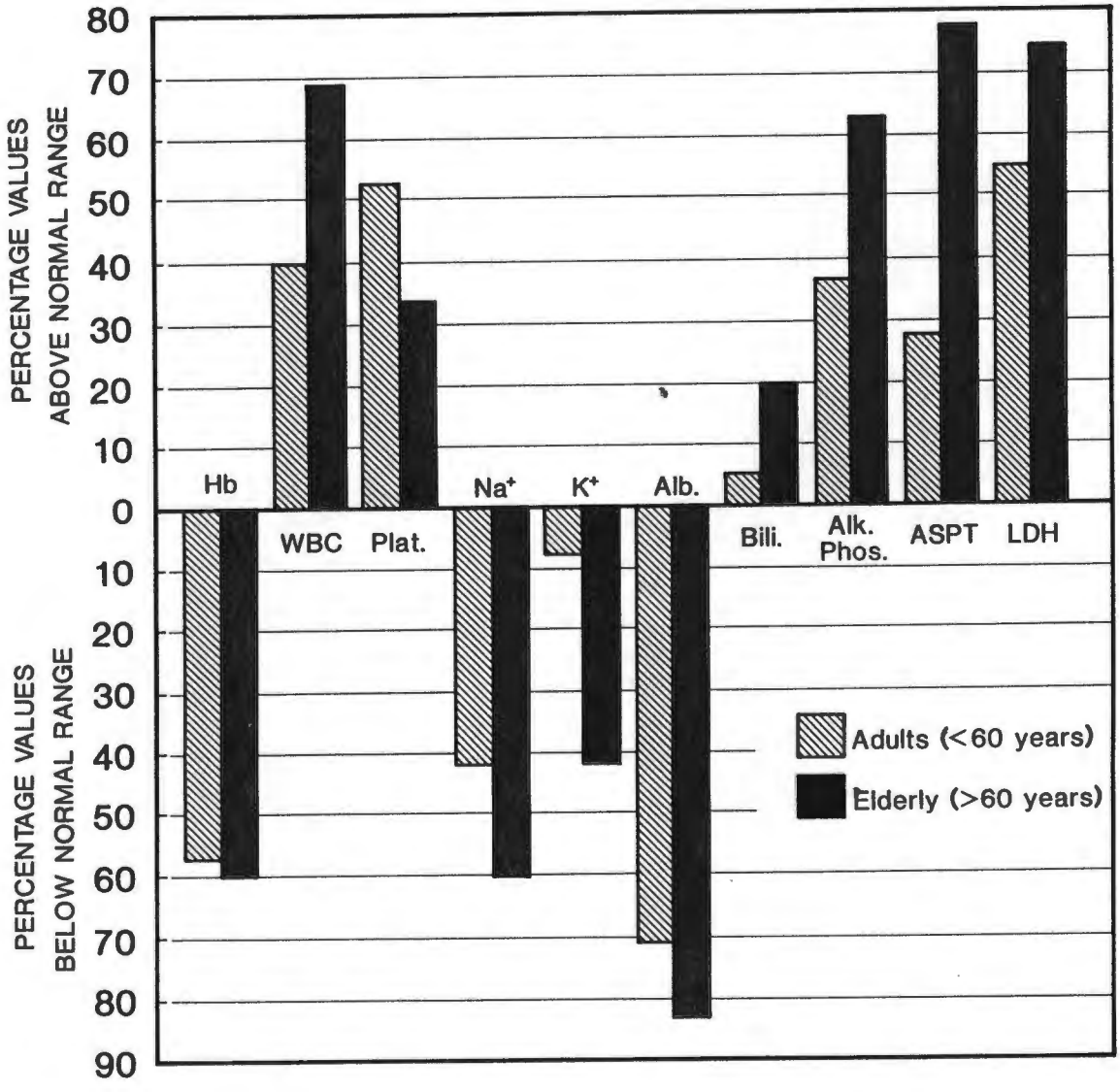


Fig.14

The differences between under 60 and over 60 year old cases of pulmonary tuberculosis with respect to haemoglobin (Hb), White cell count (WBC), platelets, sodium (Na^+), albumin (alb), bilirubin, alkaline phosphatase (Alk Phos), aspartic transaminase (ASPT) and lactic dehydrogenase (LDH). Note that with the exception of the platelet count all the variations from normal are more pronounced in the elderly. Statistical significance was not achieved because of the high variances apart from the bilirubin, alkaline phosphatase and ASPT values ($p<0,5$).

Bacteriological study

Sputum samples of 76 of the 93 cases (82%) were positive for acid-fast bacilli on direct smear and 17 (18%) were negative on smear but positive on culture.

DISCUSSION

Two previous reports of atypical radiographic features in patients with pulmonary tuberculosis stressed opacification consistent with inflammation of the mid and basal zones, peripheral lesions and pleural reactions.[21 22] However, no differentiation on an age basis was made in either study. One study has reported the similarity of radiographic features of pulmonary tuberculosis in elderly compared to younger males. [26] In another study by Katz [28] comparing the radiographic features between 52 young and 27 elderly males significant differences existed between the two groups. Pleural and lower lobe disease were more common in the elderly and cavitation less frequent. These findings are in keeping with those in the present study where the "atypical" presentations were the norm rather than the exception.
Hilar adenopathy was not detected in any of the cases presumably because these glands had been previously infected and were incapable of enlarging because of fibrosis or calcification. In 40% there was fibrosis of upper lobe or

calcification suggesting previous tuberculosis. In general the radiological changes in this age group associated with active pulmonary tuberculosis were basal and peripheral rather than apical, and these features were similar to those that are usually found in primary tubercular infection.

Consideration of pathologic changes at a cellular level may be important in understanding why the radiographic findings are different. The intra-tissue bacilli are surrounded by macrophages, lymphocytes, fibroblasts, and neutrophils and this results in the formation of granulomata (which are generated by a competent immune system). The granulomata may proceed to fibrosis and possible calcification, or liquefy (caseation). Cavities are produced by discharging the caseous material, usually into the bronchi. The price paid by the host for control of the bacillus is initially tissue inflammation, and if there is an active cell-mediated response, tissue destruction. The radiographic picture therefore is primarily that of an inflammatory infiltrate, which progresses to granuloma formation (micronodular) and a confluent picture of intratissue extension. This may then result in healing by fibrosis, or if caseation has occurred, discharge of material into a bronchus with cavity formation.

A diminished cell-mediated reaction has been reported in the aged. [54] Experiments in mice have shown that the capacity to mount acquired immunity decreases with age, and

that there is an inability to recall any anamnestic response to the re-emerging tubercular infection. [55] With reduced tissue reaction there is reduced granuloma formation and less tissue destruction. The author and others [28] have noted that haemoptysis is less frequent in the elderly and the author postulates that reduced tissue destruction may be the explanation. A further consequence of diminished tissue destruction would be decreased cavitation. Cavitation was present in 1/3 of cases in this study. The frequency of cavitation in younger adults is variable and reports vary from approximately 30% [27] to 75% [23]. Comparison of these historical findings with those found in our population of elderly can only be superficial for the disease is locally common, diagnosis is frequently late and most importantly the selection of cases will be different. A case control study in our population comparing the frequency of cavitation in young and old subjects with tuberculosis would be essential before any conclusions could be reached as to whether cavitation is less frequently present in elderly tuberculosis.

It is interesting to compare the pulmonary radiographic changes in patients with acquired immune deficiency syndrome (AIDS) who have non-specific changes [56 57 58] similar to those found in the mild cases in this study. This is taken as support for the view that reduced cell-mediated reaction plays an important role in determining the "atypical"

radiographic appearances in the aged. Where cavitation does occur it may be in an atypical site because the inflammatory response occurs most commonly in the mid and basal zones, similar to a primary infection.

The radiographic features compatible with the diagnosis of pulmonary tuberculosis in the elderly are apical inflammatory changes with or without cavitation or fibrosis, mid or basal zone inflammatory changes, which may be minimal, are frequently peripheral, and cavitation may or may not be present, and pleural reaction accompanying either of the above. Because the non-specific inflammatory changes in mid and basal zones occur in over half of the cases, it is not possible to over emphasize the importance of any one of these changes in suggesting the diagnosis of M. tuberculosis. Any one of the above or a combination is compatible with, and should raise the suspicion of, tubercular disease. This contrasts with the situation in younger adults where for example, upper lobe cavitation has far more diagnostic significance than lower lobe inflammatory infiltration.[32]

Ideally, an investigation in to the high frequency of a pleural reaction (in half the cases) should have been pursued. For reasons of expense and practical logistical problems, follow up lateral decubitus radiographs to differentiate between pleural thickening or fluid was not done. Ultrasound examination was unavailable at the time of

the study. It was not considered ethical or practical to aspirate fluid for further investigations. Thus the mechanism and significance of this finding remains unclear.

40% of the patients described (page 75) had apical fibrosis compatible with previous disease although only 16% of these had obvious apical cavitation. However one would not expect to see small cavities on chest radiographs. Furthermore, breakdown of an endogenous lesion may disseminate via the blood stream thereby involving many organs including the lungs. With an effective host cell mediated immune response this dissemination results in granulomata and produces a miliary picture. However in an areactive host the disease is diffuse and not easily detectable. "Cryptic Tuberculosis" occurs predominantly in persons over the age of 60, usually with a normal chest x-ray, pyrexia of unknown origin, and a negative tuberculin test. It is notoriously difficult to diagnose.[59]

The means of acquiring the disease may also be different in the elderly, as not all post-primary disease in the elderly is due to reactivation. When clusters of cases occur, as in homes for the aged, an index case has caused either an exogenous initial primary infection or, importantly, reinfection.[81] In the latter case it must be presumed that the previously acquired immunity state has waned, thus making that individual vulnerable to reinfection and disease. Secondly it is possible that endogenous

acquired infection may play a role. Today's elderly person not only contracted the disease at a time when tuberculosis was more prevalent, but effective therapy was non-existent. Most people born in the early 20th century became infected [60] and are therefore liable to reactivate. It is postulated that with decreasing immunity, breakdown of a dormant (apical) lesion containing viable bacilli plus or minus cavitation results in the release of organisms into the airways, endogenously infecting the rest of the lungs by bronchial spread.

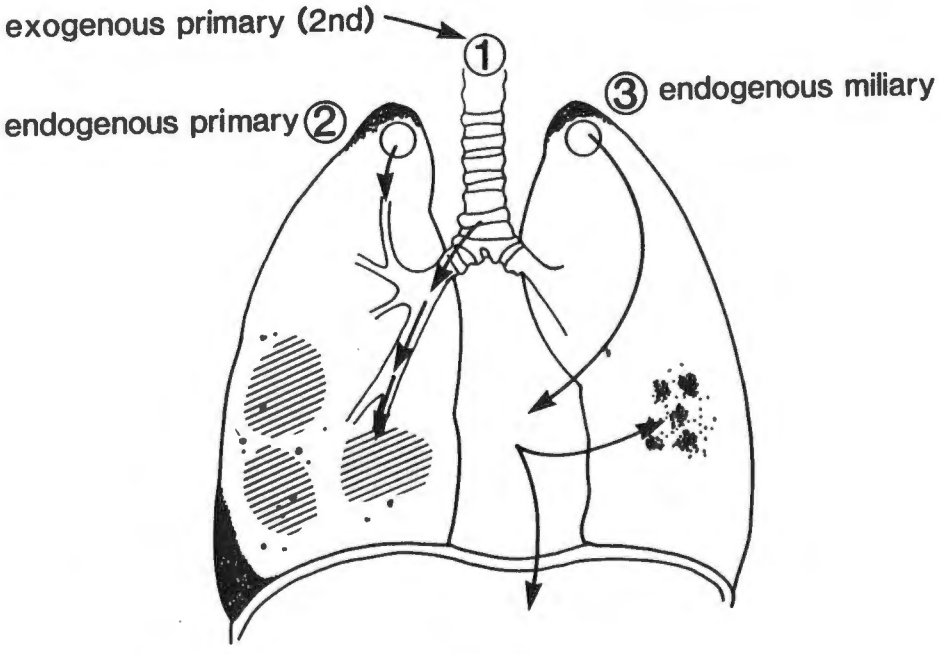


Fig 15

Summarises the three main mechanisms of acquiring the disease in the elderly

1. Indicates inhalation (often the source of a second infection) of exogenous bacilli from an index case, with subsequent involvement of the mid and lower zones (see Fig.8, page 25).

2. A similar result is seen when an endogenous (usually apical) lesion breaks down releasing viable bacilli into the airways.

3. The breakdown of a previously controlled lesion may also gain access to the venous system and hence disseminate via the blood stream causing miliary or cryptic disease (page 91).

It is of great importance from a clinical and diagnostic view point to appreciate that there may be differences between primary and post-primary pulmonary tuberculosis as it presents in childhood and young adults, and the way that it manifests in the elderly. Whether the differences are sufficiently great to permit separate entity deserving a separate classification (rather than an extreme end of the spectrum of the disease) is a matter that can be debated.

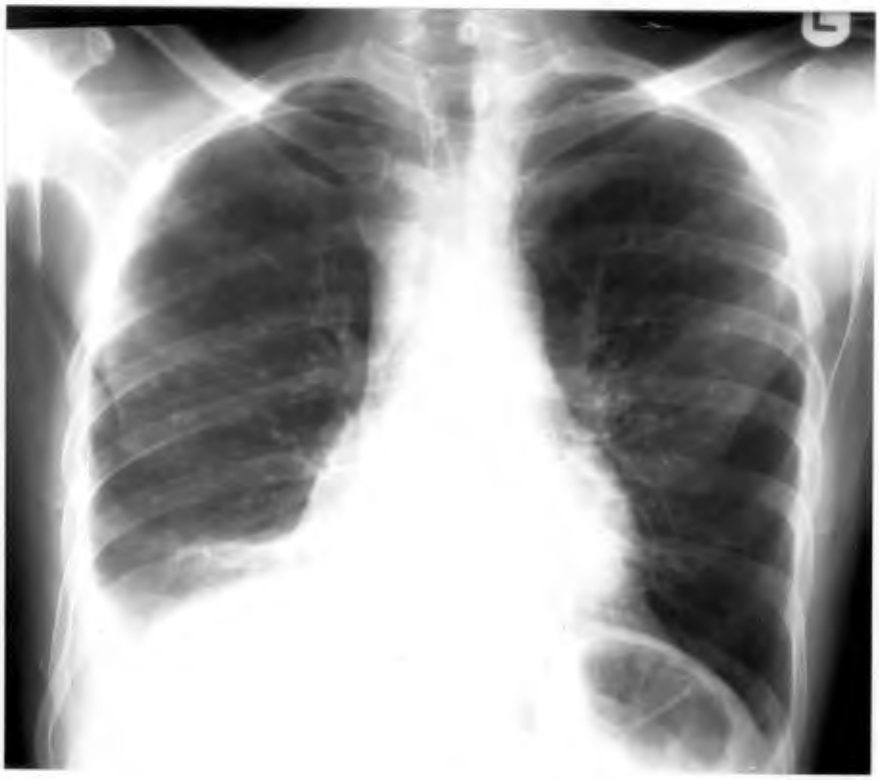
CLASSIFICATION	CHEST RADIOGRAPHS
1. ATYPICAL	
"Pulmonary TB in the elderly"	Lower zone opacities with basal pleural effusions or thickening and few cavities found equally in apex or lower zones.
2. CLASSICAL	
"Post primary" or "reactivated"	Apical interstitial fibrosis and pleural thickening, cavitation and opacities.
3. DISSEMINATED	
Miliary (reactive)	Miliary nodularity
Cryptic (areactive)	Normal

Table 15

The range of radiographic appearances of pulmonary tuberculosis in the elderly (and immunocompromised). The "Atypical" form is common, the "Classical" unusual and the "Disseminated" rare.

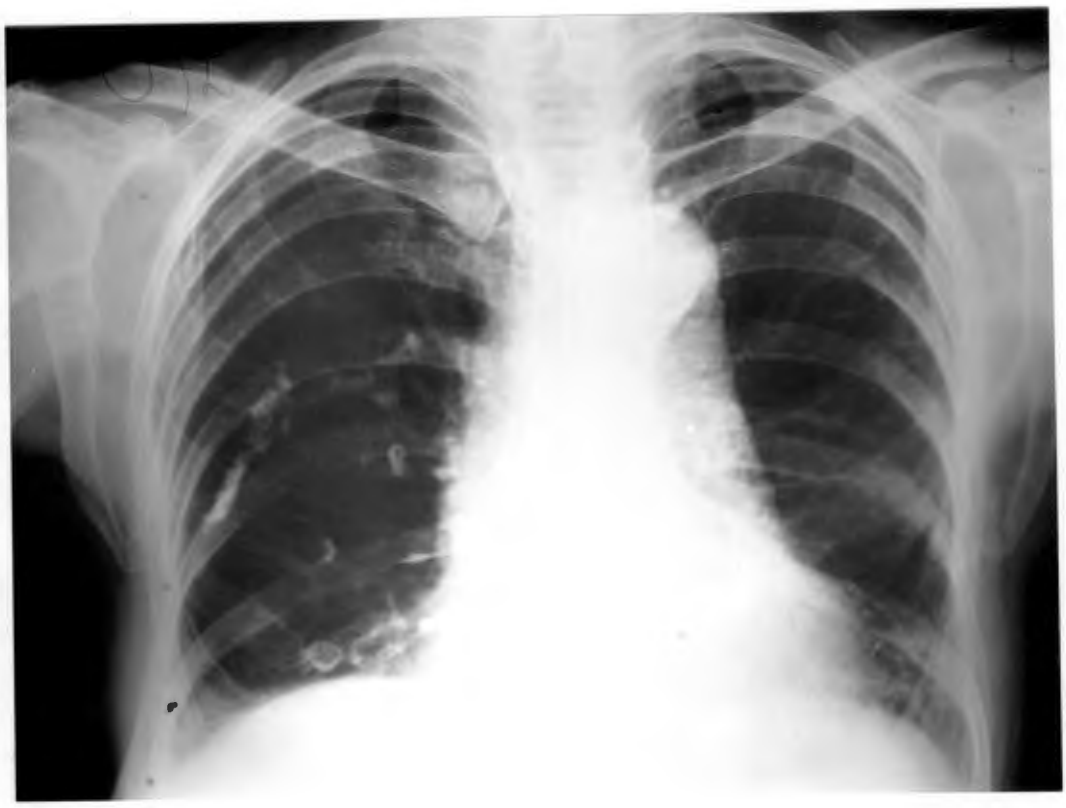
In favour of a new classification is that it would reinforce the differences between this atypical form and the classical disease pattern seen in younger patients, and would emphasise the difficulties in diagnosis. This is of particular importance in developed countries, where because the incidence of the disease is low in the general population, any variation from the text book classical description of the disease further reduces the chance of diagnosis.

Some examples of radiographic features of pulmonary tuberculosis in the elderly.



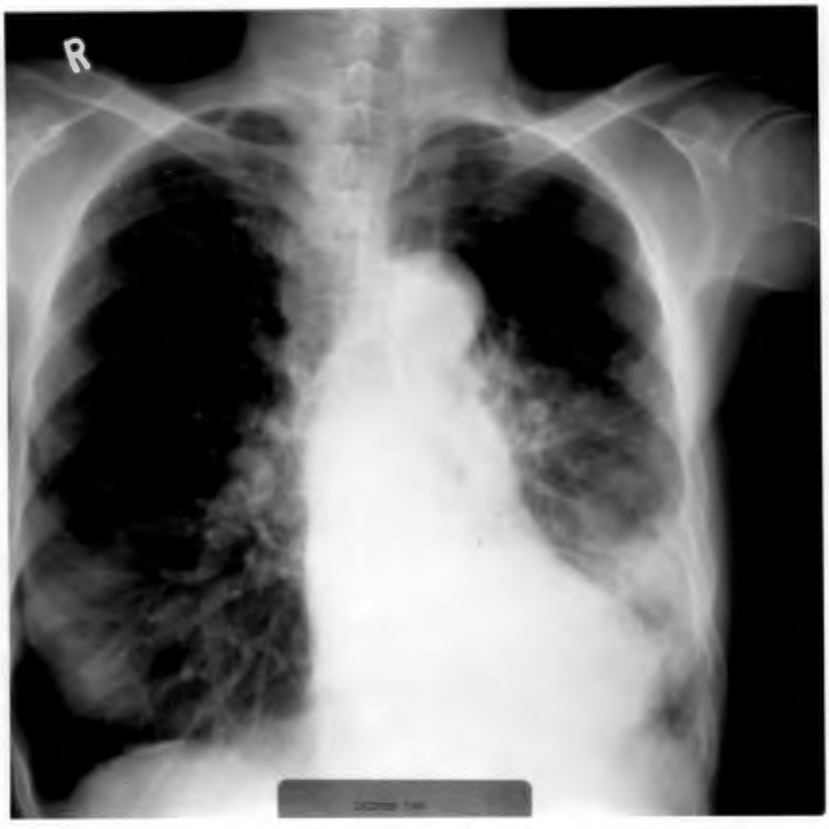
Radiograph 11

A 60 year old male with an opacity in the right lower lobe. The effusion was a transudate, and the pleural histology showed granulomata. Acid fast bacilli were cultured from the sputum.



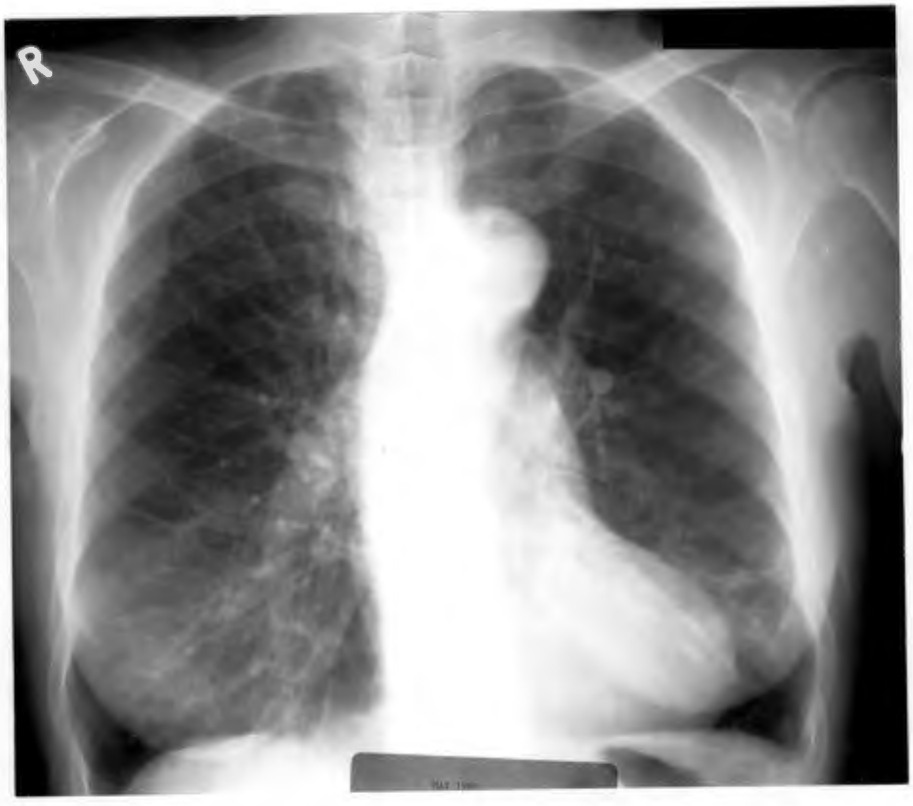
Radiograph 12

An 86 year old female with bilateral opacification and a right basal pleural reaction. AFB's were cultured in the sputum.



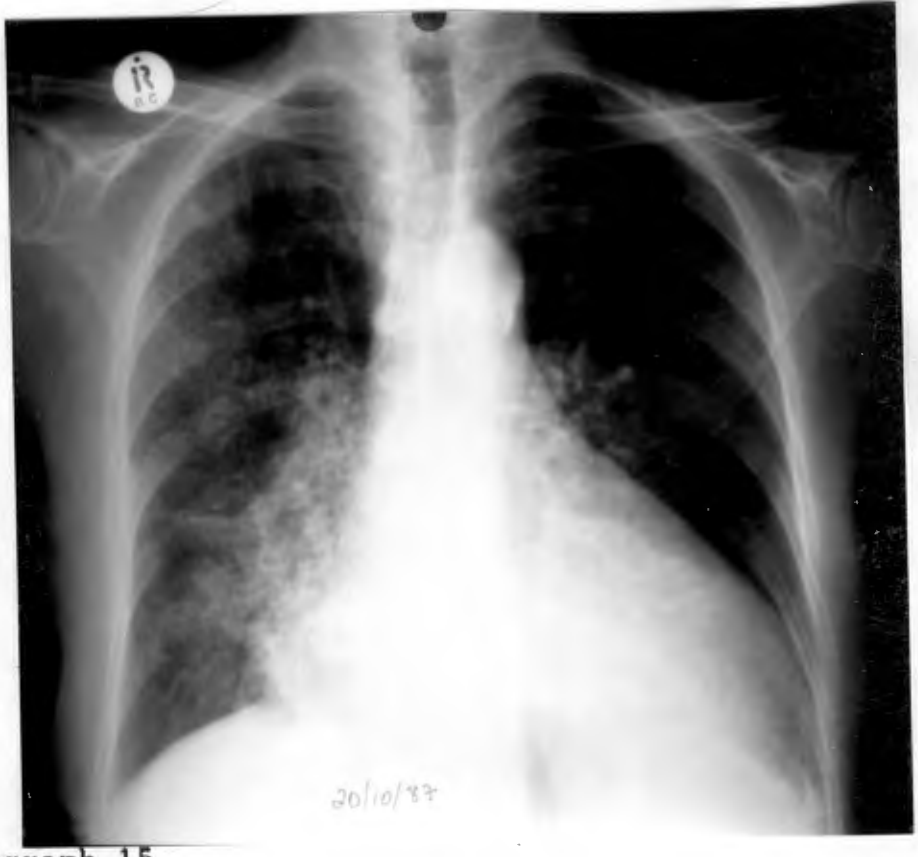
Radiograph 13

A 66 year old female with a persistent productive cough in whom AFB's were found on smear. There is a non specific opacification in the left lower zone.



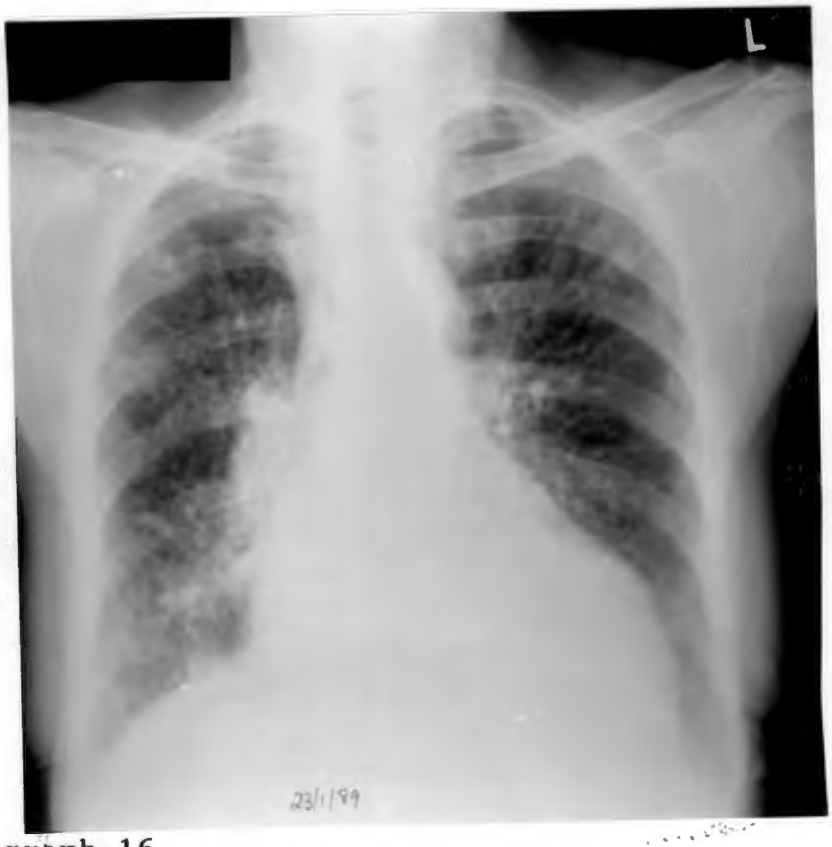
Radiograph 14

The same patient as in 13, who eight months previously had presented with the same symptoms. In retrospect the left lower zone opacities (better seen on the original radiographs) were probably due to tuberculosis.



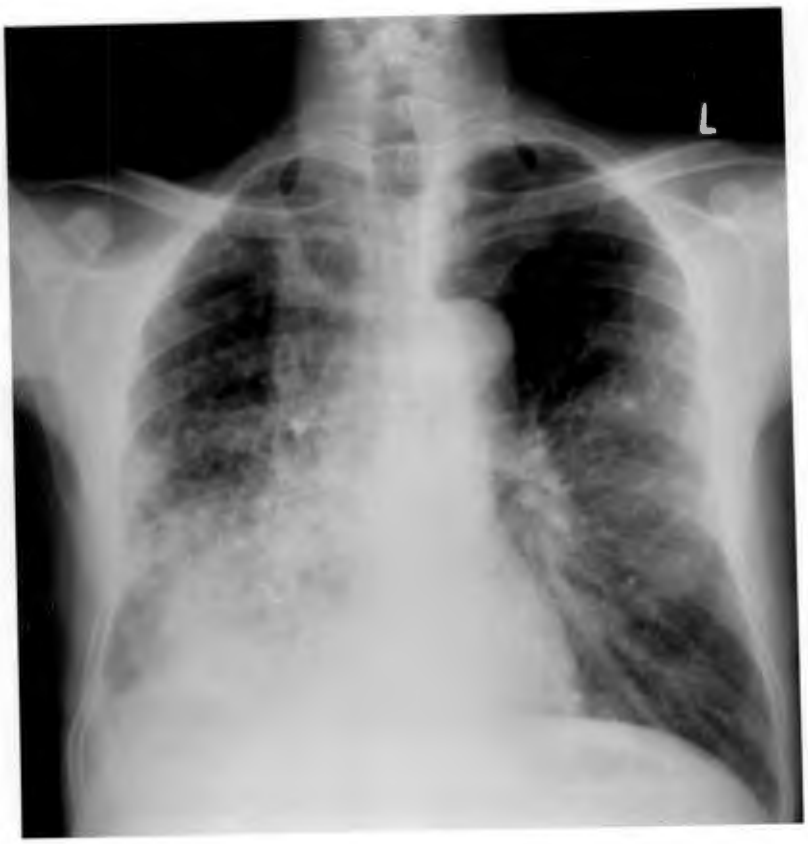
Radiograph 15

An 86 year old female with coincident ischaemic cardiac failure. Her complaint was a persistent cough, and she had been frequently diagnosed as recurrent right lower lobe bronchopneumonia. She was seen by the author in January 1989 with the radiographic appearances seen below.



Radiograph 16

Diffuse nodular changes with bilateral pleural reactions and basal opacifications. AFB's were found on smear. The changes in 15 are also those of pulmonary TB in the elderly.



Radiograph 17

This is an advanced "classical" case of pulmonary tuberculosis in the elderly. Bilateral basal opacification is seen with a right basal effusion. There is some nodularity in the right mid/upper zones. Usually, the changes are not as marked as this and it is presented to illustrate the range of changes on chest radiography between chest radiograph 11 and this one.

It can be appreciated that the radiographic appearances do not have the same diagnostic value as in younger adults and that mild and non-specific changes are compatible with the diagnosis of pulmonary disease.

The incidence of anaemia in older males (70%) and females (63%) is similar to the findings in younger adults with tuberculosis (males 72% and females 45%). (page 61) In 95% of cases anaemia is a normochromic normocytic type associated with chronic disorders. In younger adults the anaemia is associated with increased levels of B12 and ferritin with normal folate levels. (page 57) Although these indices were not specifically measured in this study of the aged there is no reason to suspect that the situation is any different.

The elevated white cell count in 55% of the subjects, thrombocytosis in 33%, and elevated ESR in 90% are findings similar to those reported in the younger adult population. We have shown that these haematological features return to normal with sputum conversion and may therefore be valuable clinical markers of disease control (page 61).

Hyponatraemia and hypokalaemia were more common in the geriatric group than in younger adults (Table 14). The hyponatraemia is considered to be due to an inappropriate secretion of ADH, [51] but the reason for the large percentage of patients presenting with hypokalaemia is not known. None of these patients was on diuretics, or had alkalosis. The total protein levels were elevated reflecting an increase in gammaglobulins and there was hypoalbuminaemia in the majority of cases (Table 14, page 80). Whether hypoalbuminaemia is a reflection of active disease or a

marker of pre-existing malnutrition predisposing towards the disease is not known. Because of the high variance, none of these values differed significantly from those found in the younger tuberculotics. The findings of elevated alkaline phosphatase, ASPT, and LDH levels before treatment in approximately two-thirds of patients differ significantly ($p<0,05$) from these values in younger adults where approximately a third of patients had elevated levels. They are also significantly higher than those found in an age matched control group of non-tubercular chronic destructive lung disease/bronchiectasis (see Appendix E). Here significant elevations of liver function tests were found in the tuberculin group compared with a group who had destructive lung disease but no tuberculosis. The predictive value of this finding is low ranging between 21% for bilirubin to 74% for LDH and therefore the increased numbers falling outside the range of normal cannot be regarded as anything more than an indicator, and in a high prevalence setting viewed with suspicion for the presence of tuberculosis. This may be a reflection of unsuspected extrapulmonary disease as these values approximate to the findings in disseminated [43] and hepatic tuberculosis.[61]

The most important factor in making the diagnosis of pulmonary tuberculosis is the demonstration of acid-fast bacilli on smear or culture. In this study where cavities were radiographically obvious, sputa were all smear positive

for acid-fast bacilli. In 62 patients with non-cavitating disease 78% were smear positive and cultures were required to make the diagnosis in 22%.

This study has shown that the systemic effects of pulmonary tuberculosis in the elderly are common and may be markers of the disease. In particular the presence of unexplained normochromic normocytic anaemia, leucocytosis, thrombocytosis, elevated ESR, hypoalbuminaemia, hypokalaemia, and hyponatraemia, should be viewed with suspicion and elevated alkaline phosphatase, bilirubin, LDH and ASPT are important features which are associated with tuberculous disease. Although there was a trend for both haematological and biochemical abnormalities to be more frequent in the severe and cavitating disease, the failure to show significant differences may be due to the relatively small numbers of patients in each group. The classic radiographic appearances of apical lesions in reactivated disease is the exception and peripheral and basal opacification with or without cavitation and/or pleural reaction is the rule. This presents the clinician with the problem of having to consider a much wider differential diagnosis than is the case in the typical apical lesion of PTB. The radiographic changes may be minimal and are not as valuable in diagnosis of disease as they are in younger adults. Demonstration of acid-fast bacilli is the prime diagnostic feature but sputum examined by the smear method

may be negative particularly in radiologically non-cavitating disease and sputum culture is mandatory.

3.5 SPUTUM EXAMINATION IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN THE ELDERLY.

Pulmonary tuberculosis in the elderly has been shown to be common and in institutions and residences for the old may reach epidemic proportions,[1] (pages 117 and 130). It has also been shown that the disease presents differently from young adults (Chapter 3.4), and its diagnosis may be difficult. [62] [63] [64] The criteria, taken in combination, to make the diagnosis are the radiographic features, reaction to tuberculin, histology, and detection of acid fast bacilli by smear (or culture). [32] Pulmonary tuberculosis is not usually difficult to diagnose in younger adults when there is commonly cavitating disease, and hence large numbers of bacilli in the sputum (usually easily seen on smear) (page 94); the tuberculin reaction is usually positive and the radiographs are usually typical. In the elderly however, the diagnosis can be difficult particularly with non cavitating disease (hence few bacilli), less specific "atypical" radiographic changes (Chapter 3.4), and the Mantoux reaction may be a falsely negative due to anergy; thus finding acid fast bacilli in the sputum is even more crucial in making the diagnosis. However because 66% of cases in the aged had non-cavitating disease, (and hence few bacilli which are easily missed on smear) sputum cultures are required to exclude the diagnosis, (Chapter 3.4). [65]

There is no study in the elderly which has investigated the pattern of excretion of bacilli in the sputum in paucibacillary disease or which determines the minimum number of negative cultures required before the disease can be reasonably excluded. This study investigates these aspects.

Methods

1. The diagnostic value of sputum examination

The study was a surveillance study over 26 months (from June 1987 to September 1989) and the cohort comprised all the permanent residents in 12 homes for the elderly (whites and those of mixed race). The sole entry criterion for the study was a productive cough for 3 weeks or more in any resident, irrespective of any known or presumed cause of cough e.g. smoking, obstructive airways disease, bronchitis, carcinoma. All the residents were informed of the study and those who complained of persistent cough or who were identified by staff or other residents were interviewed by the nursing staff. Other subjects (usually frail or demented) were identified by the nursing staff of the residence. Subjects were asked to volunteer to provide 3 or more early morning sputum specimens. The specimens were sent daily to the laboratory and processed within 24 hours

of collection. There were 4 subjects who were known to have persistent cough from whom it was not possible to collect sputum; they were not subjected to nasogastric tube aspiration.

Smears were stained by the Ziehl-Neelsen method and were examined by an experienced technologist. The sputum was cultured on Lowenstein-Jensen slopes for at least 6 weeks and considered to be positive if 3 or more colonies appeared. Those who were sputum positive had chest radiographs and Mantoux tests performed by a Nursing Sister (trained by the Tuberculosis Research Institute and experienced). The antigen, (0,1 ml of 5 TU Japan freeze dried PPD) was injected intracutaneously on the volar surface of the forearm and the transverse diameter of induration read at 72 hours. The reaction was regarded as positive if the induration measured by caliper was 10 mm or more. The diagnosis of pulmonary tuberculosis was made according to established criteria.(32) Briefly, the diagnosis requires either positive cultures on 2 separate sputum samples, or 3 positive smears, or a single positive sputum associated with the other diagnostic criteria (radiological and/or tuberculin reaction).

Results

The total number of possible residents at any one time was 1275 although this was temporarily reduced at times due to death or discharge. 205 subjects satisfied the entry criteria and were investigated. There were 56 males, 149 females. The age ranged from 61 to 99 with a mean of 77 years. 170 of the subjects were white, and 35 of mixed race. The number of specimens examined for each subject were: one specimen in 24% of subjects, two specimens in 16% and 3 or more in 60% of subjects.

Of the 446 smears examined 7 were positive for acid fast bacilli and of the 433 cultures 32 were positive for M. tuberculosis. These identified 19 patients with pulmonary tuberculosis, 18 of whom had non-cavitating disease on chest radiograph.

Two patients may have yielded false positive results; one had a single positive culture and the second a positive smear, whereas neither had any other evidence of disease, including normal chest radiographs (Table 16).

The pattern of distribution of positive and negative cultures and smears in successive specimens is shown in Table 16.

	Culture 1 2 3 4 5 6 7	Smear 1 2 3 4 5 6 7	Mantoux	Radiographic findings
1	- - + - -	- - - - -	+	Basal opacification
2	- - - + + + -	- - - - - - -	+	"
3	+ + + +	- - - -	+	Basal opacification and pleural reaction
4	- - + +	- - - -	-	Basal opacification
5	- - +	- - -	+	"
6	+ + +	+ + +	+	Cavitating disease
7	- - + + - -	- - - - - -	-	Basal opacification and apical fibrosis
8	- +	- - - - -	+	Basal opacification
9	- + -	- - - - - - -	+	"
10	+ -	- - - -	+	Basal opacification and pleural reaction
11	- - +	- - - - -	+	Basal opacification
12	+ +	- -	-	"
13	+ - -	- - -	+	"
14*	- - - -	+ - - -	-	Basal opacification and pleural reaction
15	+ - - - +	- - - - -	+	Normal
16*	- - - - -	+ - + - +	-	Basal opacification
17	+ - - +	- - - -	-	"
18	+ +	- -	+	"
19	+ + - -	- - - -	-	Basal opacification and pleural reaction
20	- - - -	+ - - -	-	Normal
21	+ - -	- - -	-	Normal

* No good explanation for the discrepancy between positive smear but negative culture can be offered.

TABLE 16

Comparisons between smears and cultures showing their relative value in elderly patients with a productive cough and non-cavitating disease.

Discussion

It is important to realise that the diagnosis of pulmonary tuberculosis is made on a number of variables. The criteria used in these studies were strict and are well accepted for young adults.[32] In the elderly the diagnostic values pertaining to the Mantoux reaction and acid fast bacilli found on smear and culture are probably the same as for young adults. However the chest radiographic appearances differ markedly from those in younger adults. The atypicalality of presentation may be seriously misleading. (Chapter 3.4)

The reaction to tuberculin (Mantoux) is an indicator of hypersensitivity to tuberculin resulting from infection or immunization. A negative reaction does not exclude infection (or disease) and taken in isolation, is of little diagnostic value. The difficulties with these diagnostic tests make the demonstration of tubercle bacilli in sputum the most important diagnostic criterion. However, a single positive smear or culture, unless found in conjunction with compatible radiographic changes or a positive tuberculin reaction, does not confirm the diagnosis of pulmonary tuberculosis. It is as important not to miss the disease as it is not to over diagnose it. In one case (Case 20) a single smear was positive and another (Case 21) a single culture, but there was no radiographic evidence of disease;

the Mantoux tests were negative, and careful follow up for two years showed that no disease had developed. The reasons for these false positives may be due to mycobacteria in the water, air, or laboratory contamination. They may also be due to recently inhaled bacilli which are harboured in bronchial secretions and as such are not yet pathogenic.

In a population at high risk for pulmonary tuberculosis (e.g. elderly individuals in high density accommodation) who have a chronic productive cough, sputum culture as a screening procedure results in a high yield of tubercle bacilli. 19/205 subjects were diagnosed as having pulmonary tuberculosis giving a case rate in those who had a productive cough of 9268/100 000. Thus apart from being a diagnostic essential it is a useful screening procedure in this context. For reasons described chest radiography is a very poor method of screening (page 125) and the role of the Mantoux test, in this age group has not been totally clarified. (page 132). The high yield of positive sputum in this population of people who had a productive cough (for any reason) makes it advisable to exclude the disease.

Although these recommendations are derived from studies in a population where tuberculosis is common in the general population, and therefore may be considered irrelevant where there is a low incidence, the issue is not the role of macro environment but the prevalence of disease in the micro environment of old people in residences. In the U.S.A. a

low prevalence country, the incidence of tuberculosis in residences for the elderly (695/100 000) approximates to the 1080/100 000 found in South Africa. (page 140) Therefore there is no room for complacency in first world countries, and surveillance of the elderly in homes seems advisable, irrespective of a low national incidence. Where tuberculosis is common there is a greater chance of exposing a susceptible population (in a residence for the elderly) to an external infective case. Once the disease is introduced into that environment, it spreads extensively with clusters of cases occurring in individual residences.[81]

In 17 cases sputa were repeatedly smear negative, but culture was positive. In only 2 out of 19 cases did smear positivity (these were inexplicably culture negative) contribute to the diagnosis (Table I). This confirms that AFB smears are not sufficiently sensitive to diagnose non-cavitating pulmonary tuberculosis, and that sputum must be cultured in elderly patients who may be ill despite a low bacillary excretion rate.

In sequential cultures in non-cavitating paucibacillary disease the pattern of distribution of positive or negative results is often haphazard (Table 15). In only 10/19 cases eventually diagnosed as tuberculous disease, were the first specimens positive. 7 of these required a second positive to confirm the diagnosis and in 2 collateral evidence was available. In 7 cases sufficient diagnostic criteria were

met with the second culture but in 4 cases only with the fourth specimens. Combining all the diagnostic criteria (radiography, tuberculin reaction and sputum results) 18/19 cases were diagnosed on one or more of the first 3 cultures (the exception being Case 2 where a positive sputum appeared for the first time on the 4th culture). Thus when pulmonary TB is suspected in the elderly a minimum of 4 sputum cultures may be required before the diagnosis can be confirmed or safely excluded.

Despite the intention to obtain at least 3 sputum specimens from each subject, 40% of the 205 cases were under-investigated in that they had only one or two cultures done. This was a defect of the study and it is possible that some cases of tuberculosis were missed. The usual reasons for not getting adequate numbers of specimens in the elderly is inability to produce sputum due to illness or weakness, lack of patent co-operation, and a negative attitude from nursing personnel. Both patients and staff need to be fully informed and sufficiently motivated to obtain adequate material.

Co-morbidity of the cohort was not recorded, and while this may be regarded as a defect of the study it would not have been logistically possible to confirm other possible diseases for the purposes of this survey. In those who were positive for tuberculosis no clinical, radiological, haematological or biochemical evidence for any disease other

than tuberculosis was found.

In the elderly, the diagnosis of non-cavitatory pulmonary tuberculosis hinges on positive sputum culture. This study has demonstrated that bacillary excretion is scanty and haphazard and at least 4 negative cultures are probably required to reasonably exclude the diagnosis.

3.6 THE VIABILITY AND PERIOD OF EXCRETION OF BACILLI IN PATIENTS ON TREATMENT FOR CAVITATING DISEASE.

As shown in the previous chapter, the excretion of bacilli in non cavitating disease is haphazard, and the number of bacilli are few. For these reasons an investigation into the pattern of excretion in non cavitating disease, and period of viability on treatment would not be meaningful. For the same reasons these patients probably do not represent a hazard to others. However, as was recorded in Chapter 3.2, the patients with cavitating disease pose a public health hazard since they cough up large numbers of bacilli. This section describes an investigation which was performed to determine the duration of excretion of viable bacilli in elderly patients on treatment. Once the diagnosis is made and treatment started, it has been generally accepted that although tubercle bacilli continue to be excreted, these are probably non-viable and thus non-infective. There are however contrary opinions.[66] Because there is diminished immunity in the aged [54] [55] and increased risk of the elderly contracting the disease in closed environments,[1] we need to know whether elderly patients on treatment excrete viable bacilli and if so for how long.

Method

The subjects were 10 consecutive hospital in-patients aged 65 years or more on daily supervised treatment for radiological cavitating tuberculous disease. They were all smear positive, and all patients had weekly sputum specimens examined (Ziehl-Neelson smear and Lowenstein-Jensen culture) commencing 1 week after the first day of treatment until at least 3 smears or two cultures were negative. There were 6 males and 4 females and all of the subjects were black. The treatment given was rifampicin, pyrazinamide, ethambutol and INH.

Results

The correlation between culture and smear positivity, and the time taken to convert is shown in Table 17.

	Conversion time (weeks)		
Case	AFB culture	AFB smear	Difference
1	4	4	0
2	4	4	0
3	5	5	0
4	6	6	0
5	8	8	0
6	3	6	3
7	6	10	4
8	9	13	4
9	6	12	6
10	6	14	8
Mean	5.7(weeks)	8.2(weeks)	

Table 17

The time taken for cases with cavitating disease to convert to acid fast bacilli (AFB) sputum negative. Cases are ranked according to the difference in time (weeks) between culture and smear conversion.

Discussion

The background as to the means of acquiring the infection and disease (in a population who were probably all infected in childhood), and some of the pitfalls in making the diagnosis has recently been outlined. It has also been emphasised that the presentation of pulmonary tuberculosis in the aged may be very different to that found in younger adults. (Chapter 3.4)

These diagnostic difficulties make it imperative that we do not unnecessarily expose the growing cohort of elderly subjects to a disease which should have been eradicated, but has become an increasing threat to society.

In half the cases conversion of both smear and culture coincided, but neither occurred less than 4 weeks after commencing treatment. In the remainder, culture negativity preceded smear negativity by periods varying between 3 and 8 weeks. This confirms that non-viable bacilli (i.e. culture negative) may continue to be excreted and be detected by smear. Thus smear negativity is a delayed but reliable indicator of disease control. Patients in this study had cavitating disease which is usually associated with much greater numbers of tubercle bacilli, the time taken to sputum conversion on treatment may have been longer than in milder non-cavitating cases where there are comparatively few bacilli. However, the excretion of bacilli from

patients with non-cavitating disease is so scanty and haphazard (Chapter 3.5) that it is not possible to compare these two groups.

The fact that the cultures took an average of 5.7 weeks and up to 9 weeks to convert to negative is of concern. It could be argued that culturing the bacilli *in vitro* does not necessarily imply that they would be infective. Although guinea pig inoculation was not done in this study, it has been performed previously in a similar study and showed good correlation between the *in vitro* and *in vivo* culture.[66] For these reasons it is fair to assume that positive *in vitro* culture does equate with the potential for infection. Whether it is valid to extrapolate the potential for infection in guinea pigs to humans is a moot question. However, as an alternative experimental animal model has not been used, one must regard positive guinea pig inoculation as an acceptable indicator that humans could also be infected by the same bacilli. Therefore it is prudent to suggest that elderly people (and others who may be immunocompromised) who are at high risk, should probably not have sustained contact with patients on treatment for radiologically cavitating tuberculous disease until the latter have converted to smear (or culture) negative. This may take up to 10 weeks. This applies particularly to those who are living in residences for the elderly, or other high density accommodation.

PART II

4.1 PREVALENCE OF PULMONARY TUBERCULOSIS IN GERIATRIC HOMES

The foregoing discussion and investigations form a prelude to the second main objective of this thesis namely to test the hypothesis that the high background incidence of tuberculosis in the black and coloured population in East London, renders the population of white and coloured elderly residents in homes for the aged susceptible to a significantly higher incidence of the disease than that of the general population. In order to put the epidemiological aspects of this part of the study in perspective, the national and local incidence rates have been provided (page 11-23). These were further subdivided into provincial incidence rates to show the pattern in the Eastern Cape, and the National age and sex specific rates for 1986 are given as are the number of cases reported since 1985 in East London. Unfortunately the age specific rates for the latter cannot be given as ages are not recorded by the local authorities.

Methods

Twelve old-age homes in East London (11 for whites and 1 for coloured people of mixed race) with a total population of

1000, were surveyed for the prevalence of the disease in a cross sectional study. (Some of these homes were the same ones visited for the subsequent incidence study). The investigation took place February - June 1987. The residents were informed that a tuberculosis survey was being undertaken, that participation was entirely voluntary, and that the investigations would comprise skin and blood tests, a chest radiograph, and sputum culture were possible.

Sputum

Specimens were collected from all persons who had a productive cough. These were submitted for smearing and staining for AFB as well as for culture on Lowenstein-Jensen medium. Cultures were run for 6 weeks before being declared negative. A culture was considered positive if 3 or more colonies grew. Subjects whose Mantoux test and ELISA were positive and who could not produce sputum were subjected to nebulised 5% saline inhalations in an attempt to collect a specimen.

Radiographs

Mass miniature 100 mm chest radiographs were taken. These were read by two experienced observers. When there were any suspicious findings repeat radiographs with full-sized

plates were taken, screened by the author and checked by a radiologist.

Enzyme-linked immunosorbent assay (ELISA)

Blood specimens were taken from all 138 residents in two homes (A and C) where clusters of cases were found (Table 17). An ELISA on serum for antibodies against adsorbed mycobacterial sonicated antigen was done. The test has been fully reported.[31]

Mantoux testing

This was performed and read by a Nursing Sister who was trained by the Tuberculosis Research Institute. Japan freeze-dried tuberculin purified protein derivative (PPD) 0,10 ml (5TU), manufactured by Japan BCG Laboratory, was injected intracutaneously on the volar surface of the forearm. The degree of induration was measured in the transverse plane after 72 hours.

Results

Of the total population of 1000 residents, 809 were present and willing to participate in the first investigation (the Mantoux test). The average age was 79 years, there were 185

males and 624 females, and 58 were coloured and 751 white.

Sputum

An attempt was made to obtain sputum specimens from all the residents. However, only 93 were able to produce any sputum and a total of 240 specimens from these residents was obtained for direct smear and culture; 8 cultures were positive in duplicate and 2 in triplicate. In 2 cases a single positive culture was obtained, one growing 10 - 99 colonies and the other 100 - 200 colonies. In none of the culture-positive cases were AFB seen on smear.

Case	Cultures 1	2	3	ELISA	Mantoux test (mm)	Radiographic appearance	Age (yrs)	Sex	Race	Residence
1	+	+		-	0	Old apical and left mid-zone fibrotic changes.	77	M	C	A
2	+	+	+	-	18	Bronchopneumonia spread and consolidation.	72	M	C	A
3	+	+		+	0	Old tuberculosis with left apical reactivation. Nodular changes and confluent shadows with cavitation.	76	M	C	A
4	+	+	+	+	15	Old fibrotic changes left lung.	71	M	C	A
5	+			-	20	Fibrotic change both mid-zones and right base.	75	M	C	A
6	+	+		-	0	Normal chest	80	F	C	A
7	++	+		-	20	Left basal patchy consolidation. Old pleural thickening right base.	86	F	W	B
8	+			-	18	Persistent left lower lobe inflammatory infiltrate.	81	M	W	C
9	+	++		-	0	Right basal consolidation and minimal pleural reaction.	87	M	W	C
10	+	+		+	20	Left basal fibrosis and bronchiectasis.	71	F	W	C
11	++	+		-	0	Persistent posterior basal inflammation.	79	M	W	C
12	+	+		-	20	Persistent bilateral basal inflammatory infiltrates with patchy consolidation.	85	F	W	C

Table 18 Details of 12 cases of tuberculosis in old-age homes. *

* Note clustering of cases in residences A and C. All cases were smear negative for acid-fast bacilli. M=Male; F=Female; W=White; C=Coloured.

Radiographs

A total of 533 residents had 100 mm films taken. In 226 of these cases radiographs with full-sized plates were taken, either for technical reasons or because suspicious lesions were present. In 1 positive case apical confluent densities with cavitation suggesting re-activation of pulmonary tuberculosis was present, in 10 there were basal infiltrates or patchy fibrotic changes (in 1 a small pleural effusion was present) and 1 patient had a normal chest radiograph (Table 18). Two hundred and seventy-six residents did not have radiographs taken because they refused, were too frail to stand, or were bed-ridden.

ELISA

One hundred and thirty-eight tests were performed on all the residents of the two homes (A and C, Table 18) where the cases were clustered. Of the results 3 were true positive, 9 false negative, 20 false positive and 106 true negative. The sensitivity was 25%, specificity 84%, positive predictive value 13%, and negative predictive value 84%.

Mantoux tests

Eight hundred and nine Mantoux tests were done, of which 25% were positive (>= 10 mm). There were 7 true positives.

Positive diagnoses

The diagnosis of tuberculosis was made according to the criteria of Escreet and Cowie. [32] There were 12 subjects who met the criteria for a positive diagnosis - 6 came from a home for coloureds with a total of 58 residents (the point prevalence for that residence was therefore 10 344/100 000)(95% CI 7958,12730) while 5 were from a home for whites with 73 residents (point prevalence 6849/100 000)(95% CI 5386,8312). One other white subject with a positive diagnosis was in a separate home, giving a combined point prevalence for whites in old-age homes of 798/100 000 (95% CI 743,854) and an overall case rate of 1 483/100 000 (95% CI 1382,1583) for residents of old-age homes in East London.

Sex differences

There was a significant predominance of male subjects, positive results being obtained in 8 of 185 males (4.3%) and 4 out of 624 females (0.6%) (Fisher's exact test; $P < 0,002$).

Discussion

The overall case rate of 1 483/100,000 supports the findings of Stead et al[1] that elderly people living in old-age homes are at particular risk of developing active tuberculous disease. The estimation of prevalence as opposed to incidence would usually be an overestimate of incidence for chronic diseases. Whites, who are regarded as a low-risk group, had a national incidence rate in 1986 of 16/100,000 and for those over 65 in the Eastern Cape 83/100,000. Overall we found the prevalence in white residents of old-age homes to be 798/100,000, a 50-fold increase over the National incidence and 10 fold increase over the Eastern Cape age specific rates. The figures are worse for the coloured old-age home, where 10,3% of residents had detectable disease at the time of the survey. These findings were subsequently supported by a survey conducted in Port Elizabeth (also in the Eastern Cape) where similar figures were obtained.[67]

Diagnosing tuberculosis in the geriatric population is not easy, and various problems were encountered during the survey. One was that a few patients who had the initial Mantoux tests refused to undergo further tests at some point. We realised that surveys among the elderly are not benign procedures. Our presence alone caused some people to fear that they had already contracted tuberculosis. In one home a degree of suspicion was engendered by residents against anyone who had the slightest cough. Furthermore, misunderstandings about modern-day treatment led many people to think that they would be removed to an institution and lose their rooms if they had the disease. These fears were allayed by personal discussions, but the problem of misperception remained difficult to dispel. These problems gave rise to a further difficulty with this study in that amongst other possibly relevant criteria the ages, physical state of health, cognitive function, social and nutritional status were not recorded for the population. Therefore there was no way of determining whether those subjects who refused to participate initially or during the course of this study would have skewed the outcome. Thus it is possible that cases of tuberculosis were missed, and the sample might not have been representative of the population. It should be emphasised however that none of the subjects presented with symptoms or signs of pulmonary tuberculosis and the diagnosis was made only because it was being

actively pursued. It is therefore unlikely that a bias in favour of tuberculotic patients was present.

Another problem experienced was in obtaining radiographs. There were many frail people who could not stand still or co-operate by holding their breath, or who were markedly kyphotic, so that the costophrenic angles were frequently obscured. Mass miniature radiography is not a practical proposition in this age group. The reasons were inability to climb into the frame; unsteadiness and fear of falling off the frame; fear of being exposed to the outside elements; and poor definition of the picture. As over half the subjects had to have the radiographs repeated, it was also not a cost effective exercise. Although there were 276 residents who did not have chest radiographs taken and this must be regarded as a shortcoming of the study, we were dealing with a frail group of people in many of whom it is logistically impossible to obtain radiographs.

An attempt was made to obtain sputum specimens from all the residents. The fact that we were successful in only 93 cases may be a criticism of the study, but from a practical point of view, people who do not cough usually cannot produce sputum. Although we attempted to obtain sputum with hypertonic saline inhalations, the procedure was poorly tolerated. Furthermore, it is time-consuming and because we did not wish to antagonise the residents and possibly jeopardise further follow-up, we did not persist.

Of the total population 191 subjects did not enter the study. Some were not physically present and others refused to participate. Because of the sensitivity of residents it was not possible to categorise this population further in an attempt to determine whether their absence could in any way have influenced the outcome. In that we do not know whether the sampled group, was any different to the non-sampled group, we cannot be sure that there is no bias, and this is a defect in the study.

The forearm skin may be very thin in elderly people, and considerable skill is required to ensure intracutaneous delivery of PPD for the Mantoux test. As we were surveying for disease we did not repeat the test in negative reactors as would be done in a survey of infection, as was subsequently done (see page 134). The Mantoux reaction is intended to diagnose infection and not disease. It was positive in 25% of the population, a prevalence similar to that in other surveys.[1 22 28 30] However, the test was positive in 7 of our patients with active disease (58%).

The essential element of diagnosis of tuberculosis in this population is a positive sputum culture. 13% of subjects who produced sputum were culture-positive. The high false-negative rate for AFB smears excludes it as a reliable test in this population.

We have shown that the ELISA we used is disappointing in that its predictive value was only 13% and there were too

many false-positive results. The problems with this diagnostic tool have recently been described in a "state of the art" review.[68]

The radiographic aspect of the survey contributed the important information that 11 patients had minimal changes (Table 17), confirming the findings reported in Chapter 3.4. Although previous reports have indicated that this may be expected in this age group, the fact that there was only one "typical"picture of apical cavitating pulmonary tuberculosis reinforces the contention that "atypical" or normal chest radiographs do not exclude the diagnosis of pulmonary tuberculosis in the elderly. [21] [22] There are a few possible explanations for the paucity of radiographic changes in this group in whom the diagnosis was only made because it was being actively looked for. Firstly, the disease may be endobronchial, either from rupture of a caseous node into a bronchus or as direct extension from tuberculous pneumonia. Secondly, there may be failure of cellular response to the presence of active tubercle bacilli. The presence of virulent organisms cultured from normal lung tissue with no histological evidence of granulomas was demonstrated over 50 years ago.[69] [70] The typical nodular pattern seen in tuberculosis on chest radiographs is due to granuloma formation. Patients with acquired immunodeficiency syndrome where no or few granulomas are formed have radiographic findings similar to those observed by us.[71] While the

diagnostic criteria of Escreet and Cowie (page 46) are accepted for diagnosing post-primary infections in adults, the values given by them to radiographic changes may not be valid for elderly people in whom primary reinfection or abnormal cellular response seems to play an important role. Hence these values may need to be modified in the elderly, with greater emphasis on basal and mid-zone infiltration, and pleural reactions. These non specific radiological findings emphasises the role of mycobacterial culture of sputum as a fundamental component of the diagnostic process.

The question of using BCG immunisation in Mantoux negative elderly subjects needs to be addressed. There is no information available as to its safety in this group. It must be remembered that many of these patients are immunocompromised to a varying degree, and there is concern that the vaccine may cause septicaemia. There is no indication either as to how effective it might be in this age group. This subject should be further studied.

PART III

INCIDENCE OF PULMONARY TUBERCULOSIS IN OLD AGE HOMES AND THE VALUE OF THE MANTOUX IN ITS DETECTION.

The diagnosis of pulmonary tuberculosis in the elderly is well recognised as being very difficult, and the disease is frequently diagnosed only at post mortem. [72] [73] [74] The prevalence study (Chapter 4 page 117) has confirmed that the disease is probably far commoner in institutions for the elderly than in the general population. With a much higher background incidence of the disease in the general population (approximately 200/100,000) (page 12) it has been shown that the overall point prevalence in old age homes for whites was 798/100,000 and in a single home for coloureds, 10.3% (page 123). It is known that the elderly have a decreased immunity to infections. Susceptibility to infection is a function not only of decreasing immunity but also to the numbers of organisms to which the individual is exposed, (page 28) which would be more in a high density residence such as an old age home. It is important therefore that the incidence of disease in this setting should be determined by means of a prospective, longitudinal study in order to confirm the conclusions of the cross-sectional study described in Part II.

With regard to the diagnosis of the disease in this age group it has been shown that chest radiographs may be

atypical compared to the picture in younger adults and are poor detectors of the disease (page 121). The changes are frequently atypical and are usually non specific and do not carry the same diagnostic importance as the classical features of re-activated disease in younger adults. Furthermore the use of mass miniature radiography is impractical in this age group for reasons already discussed (page 125). Sputum examination is a valuable means of identifying the disease but collection is often difficult (page 126). Nevertheless despite the difficult logistics of obtaining adequate sputum specimens the yield of bacilli is high in people who have a persistent productive cough (page 94). Other markers for the disease such as weight loss, cough, fever and haemoptysis are helpful, but non-specific, as are the haematological changes (page 78) and biochemical changes (page 81) which are known to occur in tuberculosis sufferers in this age group viz. normochromic normocytic anaemia, leucocytosis and thrombocytosis, an elevated ESR, hyponatremia, hypoalbuminaemia, hypokalaemia, and elevated liver function tests. If otherwise unexplained, abnormalities in these should alert the clinician to the possibility of tuberculosis but are not diagnostic markers (page 100).

In view of these difficulties with making the diagnosis, there is a need for a practical, quick and cheap method of screening. The Mantoux reaction has long been

used as an indicator of infection. In children under the age of 2 years a positive reaction signifies a recently acquired infection and approximately 10% chance of developing the disease. In young adults, particularly those who live in a high incidence environment a positive reaction signifies infection which may be of long standing and hence has a low positive predictive value for disease. In the elderly where it is assumed in both 1st and 3rd world countries that most if not all have had a previous tuberculous infection there is an age related decrease in the prevalence of positive reactions. [75] [76] [77] It has been stated that the tuberculin skin test is of little value in economically advanced countries as a screening test in residences for the old. [75] Because of this, conclusions about reactions in people under 60 years old may not be applicable to those in their 80's and 90's.[75] However the author postulates that because of waning immunity, strongly positive (i.e. => 20 mm) Mantoux reactions may be of greater significance in the elderly than in younger subjects, particularly where there is a high incidence of disease. We test this hypothesis in this study. It has been shown that conversion from negative to positive, or an increase in size of 12 mm or more in successive tests,[78] may reflect recently acquired infection in the elderly and prophylactic INH has been advocated for these positive reactors.[79] The potential for developing the disease in infected subjects (as judged

by Mantoux conversion) is given as 7.5% for females and 11,7% for males.[78]

In the elderly the Mantoux test is often difficult to perform for technical reasons in that the skin of the forearm may be extremely thin and delivery of the required amount (0,1 ml of 5 T.U. PPD) can be inaccurate. In addition there is the problem of anergy. Some subjects (particularly the elderly) may show no reaction to the first test dose. However when retested with the same dose of antigen within a short period (7-14 days) 6-10% show a significant reaction (=> 5 mm). This is the "booster" or recall phenomenon.[80] It is important in a screening exercise to exclude anergy immediately to prevent false positive conversions at a later stage. There is no evidence that repeated PPD administration will by itself produce a positive skin test, and it is assumed that those who convert with subsequent testing have been newly infected.

This section of the study therefore sets out to establish the incidence of the disease in old age homes, and to determine the value of the Mantoux reaction in monitoring the rate of infection and testing its ability to identify a susceptible group of people for further investigation (i.e. radiography and sputum examination).

METHODS

A longitudinal prospective study was undertaken in all the registered old age homes in East London. In the previous study (page 124) a problem of misperception amongst residents had arisen about the purposes of the study and in an attempt to overcome this each resident was sent a letter of information and encouragement to continue to participate in the survey (attached appendix B). Participation was entirely voluntary.

A date mutually acceptable to the home, and to the investigators was decided upon and all residents who were present and willing to participate on that day were given a Mantoux test as has already been described. The PPD used was RT23 (Denmark) 0.1 ml (5TU) was injected intracutaneously by a nursing sister specifically trained by the Tuberculosis Research Institute in the technique. A questionnaire (Appendix C) was completed. The Mantoux was read at 72 hours (by the same observer throughout the study), measured by caliper in the transverse diameter and if it was negative (less than 5 mm) it was repeated within 10 days of that visit in order to assess the booster phenomenon.

For the purpose of this study any subject whose Mantoux was greater than 20 mm, or one which had converted from negative (<5 mm) to positive (equal to or greater than 10

mm) or had increased by more than 12 mm in a 12 month period, was identified for further investigation. Where possible, successive early morning sputums were collected by the staff of the nursing homes and despatched to the laboratory of the Frere Hospital for direct smear for acid fast bacilli and mycobacterial culture. For logistical reasons, and because at this stage of the study we were uncertain whether it could be justified, we did not obtain gastric specimens or induce sputum by means of saline inhalations or perform bronchoscopies on those who were considered at risk. Hence subjects who did not have a productive cough had no sputum cultures done.

In those subjects where sputum culture was positive, a full blood count, ESR, routine biochemistry, and body weight were recorded. A chest radiograph was taken at the Department of Radiology, Frere Hospital. The diagnosis was made on the basis of the criteria already described (page 47). The testing of subjects commenced in June 1988 and was completed at the end of June 1990.

During the course of the 2 years of the study all new incoming residents were subjected to a Mantoux test within a month of their arrival, and retested in July 1989 and 1990.

The number of deaths were recorded but not the cause of death as this could not be checked and is considered unreliable data. Using an Epi Info 5 programme, the statistical analysis of the results which follows were done

by ourselves and double checked by the Medical Research Council's statistical department. Thus there was duplicate data entry which enabled cross checking for clerical error.

Results

Old Age Home	Maximum no. of residents	1st year (July 1988 - June 1989)	2nd year (July 1989 - June 1990)	Both years	New Residents (1st year)	Died (1st year)	Lost (1st year)
Berea Gardens Valley	156	79	27	20	7	- *	59
Berea Gardens	251	195	90	73	17	- *	122
Manor	98	81	77	63	14	9	9
Red Cross	75	75	56	49	7	0	26
Eldorado	127	102	74	65	9	0	37
D.J. Sobey	59	59	50	42	8	10	7
Lodge	46	47	36	29	7	11	7
Silver Crown	34	35	31	31	0	4	-
Victoria	78	80	71	61	10	14	5
Fairlands	142	173	127	111	16	30	32
Kennersley	97	97	93	67	26	18	12
Stirling Lodge	88	34	29	20	9	3	11
St Pius	24	22	19	17	2	1	4
TOTAL	1275	1079	778	648	130	100	331

Table 19 Shows the details of subjects seen in the first year (July 1988 to June 1989) and second year (July 1989 to June 1990) and those seen in both. Note the poor follow up and absence of deaths in Berea Gardens and Berea Gardens Valley. Reasons for this are discussed in the text. (The figure in column 2 for Fairlands exceed the capacity of that home and represents new cases entered during the year).

* It was not possible to determine who had died from these homes, but the numbers are included in the "Lost" column. The reasons for the rest of patients being "Lost" as not further categorised. They were either too ill or in hospital or refused further participation. Had any of these "Lost" subjects developed tuberculosis, the local authority with whom we were working in close co-operation, had agreed to inform. No cases were notified.

The total number of patients seen in 1988 (1079) and 1989 (778) was 1857. Of these 648 (60%) were seen in both years; there were 123 (19%) males and 525 females (81%). 130 subjects entered the homes during the first year of the study. Of the 1079 subjects first seen in 1988, 100 patients died and 331 (34%) were lost to follow up. (Part of the reason for this low follow up rate is that severe difficulties were experienced in one complex comprising two homes, Berea Gardens and Berea Gardens Valley, where the nursing sister in charge developed a personality clash with the sister who was doing the Mantoux testing, and it was later discovered had actually dissuaded residents from participating further in the study. 181 patients were lost to follow up from these homes. If these are disregarded then the loss to follow up was 23%).

AGE AND SEX

The age and sex distribution were as shown in Fig. 16.

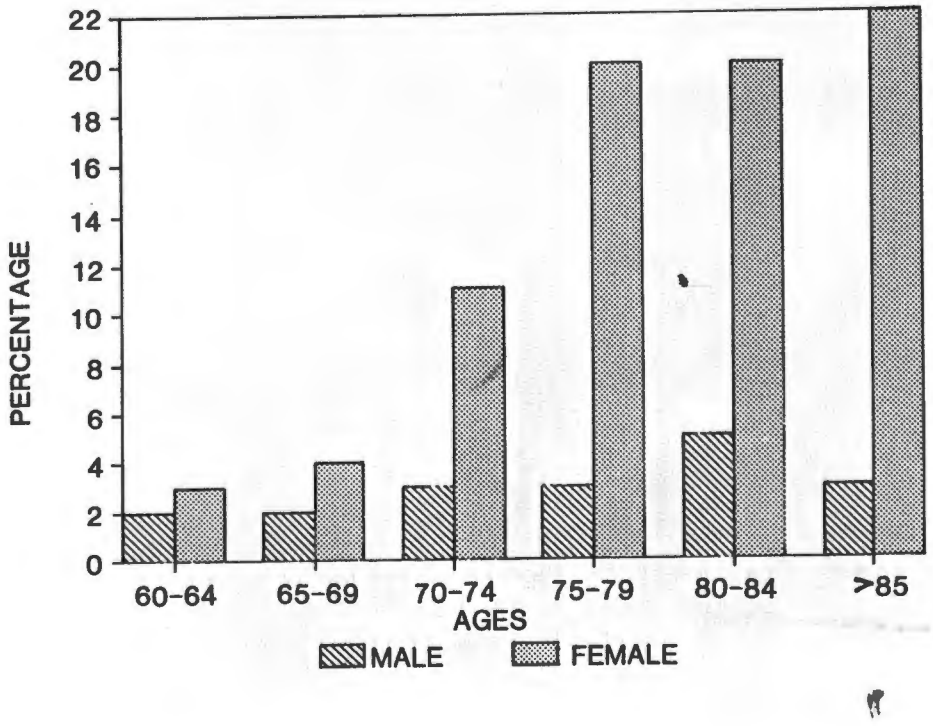


Fig. 16
Age and sex distribution of the population studied. (Total = 648).

INCIDENCE

In order to establish the incidence of disease anyone suffering from the condition prior to the start of the study must be excluded. Thus in the first year all residents were screened and the study population in the second year are all those in whom tuberculosis was not found. Thus only those that developed the disease in the second year give the true incidence.

A total of thirteen subjects were diagnosed during the two years of the study as having pulmonary tuberculosis. 12 of these were found during the prevalence study and the 13th subject was found after the prevalence and before the incidence study. Five were diagnosed during the 1st year (July 1988 - June 1989) thus giving a period prevalence of 5/1079 = 463/100 000 (95% CI 435,490). A further 8/648 were diagnosed between July 1988 and June 1989. 7 of the eight (Table 24) cases had been entered the previous year and one was a newly entered case and as such not part of the assessment of incidence. The incidence therefore was 1080/100 000.

SEX RATIO

There were 4 males and 9 females. The relative male predominance is significant at the 1% level.

MANTOUX

(15 subjects were under the age of 60 and are not included in the analysis of Mantoux reactions).

Age	60-64		65-69		70-74		75-79		80-84		=>85	
Year	88	89	88	89	88	89	88	89	88	89	88	89
Male(mm)	15	17	14	16	12	12	12	15	11	11	14	15
Female(mm)	15	14	14	15	11	14	11	14	12	14	13	14
Total(mm)	15	16	14	15	11	14	12	14	12	13	13	14
% Negative on entry	2.2%		2.0%		7.0%		9.8%		15%		15.5%	
Number(n)	28		38		92		153		161		161	

Table 20

Table 20 shows the age related mean Mantoux diameters in millimeters for those subjects that were Mantoux positive. The ages given are those on entry into this study. It should be noted that there is no obvious decrease in the mean reaction size, although the numbers of negative reactors increases with age. This suggests an all-or-nothing response.

BOOSTER EFFECT

In the first year (1988/89) there were 339 subjects who were Mantoux negative, and 43 of these became positive on boosting (12.3%). 325 were still non reactive on the third test in the second year (i.e. in 1989/90). 39 subjects who were originally negative after boosting had converted to positive the following year. It was significant that the highest proportional rate of conversion in these 39 subjects

occurred in the 3 homes where positive cases of tuberculosis had been identified. 17 out of 151 subjects from these homes converted in the second year, as opposed to 22 out of 518 in the other homes where no tuberculosis had been diagnosed. (Significant $p=0.004$ chi^2 test).

TB POSITIVITY/MANTOUX SIZE

The relationship between TB positivity and the size of the Mantoux reaction is shown in Table 21.

	1988	1989	No. TB positive
No. =<5mm	342	320	0
No. <10mm (=>6 mm)	89	74	0
No. =>10mm and =<19mm	183	188	3
No. =>20mm	19	51	10
No. increased >12mm		23	1*
No. =<5 and =>10 (i.e. negative to positive)		35	2*

Table 21

The number of subjects in each category of Mantoux reaction are shown for 1988 and 1989. These are compared to the number of TB positive cases found in each category. 22% of cases had a positive reaction (=>10 mm) in 1988. Clearly a Mantoux reaction of => 20 mm is an important indicator of disease. (The cases marked * are recounts (see Table 25) of positive cases who were also included in either the => 10mm and =< 19 mm or the => 20 mm category).

Age	60-64		65-69		70-74		75-79		80-84		=>85	
Year	88	89	88	89	88	89	88	89	88	89	88	89
<5mm	57	39	32	29	48	49	47	43	60	55	64	62
5-9	7	14	8	3	22	13	19	12	12	13	9	11
=>10mm	32	32	55	53	28	30	34	44	25	24	24	21
>20mm	4	14	5	16	2	8	3	8	2	7	2	6
Number	28		38		92		153		161		161	

Table 22
Shows the age specific percentage of subjects in each age category for a given Mantoux size, in 1988 and 1989. The only statistically significant differences are for the increase in total numbers with a reaction > 20 mm between 1988 and 1989 ($p<0,01$).

The breakdown for age in terms of a change in the Mantoux reaction size is shown in Table 23.

Age	60-64	65-69	70-74	75-79	80-84	=>85
Number	28	38	92	153	161	161
Decrease up to 5mm	11%	21%	17%	12%	14%	10%
Decrease > 5mm	7%	5%	8%	6%	6%	9%
Increase >5 and <12	21%	16%	11%	17%	10%	9%
Increase >12mm	7%	3%	3%	2%	4%	3%
Pos to Neg	11%	8%	5%	7%	4%	4%

Table 23
Shows the age specific percentage of subjects whose Mantoux reactions changed over the study period. It shows the percentage of subjects who increased or decreased the initial reaction size and the percentage who converted from positive to negative. These figures compare with the data in Table 20, and confirm the remarkable consistency in maintaining the ability to react.

In the three categories showing change in the Mantoux reaction size attempts were made to get sputum for culture. Table 24 shows the Mantoux reaction, and the number of cultures done for each category.

Mantoux	No.not cultured	No.cultured	=>3cultures	TB +ve
>20mm	38	59(61%)	51(86%)	10
Increase >12mm	11	13(54%)	9(70%)	1
<5mm- >10mm Neg to Pos	15	5(33%)	5(100%)	2

Table 24

Of the 13 patients with TB detected the highest number came from the group with Mantoux reactions measuring 20 mm or more. The numbers of subjects unable to produce sputum was also proportionately lower in this group as reflected in the "number not cultured" column. The majority of the subjects had 3 or more sputum cultures performed.

The behaviour of the Mantoux reaction in all patients who were TB positive during this study is shown in Table 25. It should be noted that patients who were shown to be positive in 1987 and described in the prevalence study (see page 117) have been included in this table and another case discovered after the end of the study. Whilst they are not part of this incidence study, it is justifiable to include them to illustrate the pattern of change in the Mantoux reaction. The nursing sister who performed and read the reaction size was the same, and although the PPD used was different, it has been shown to elicit a comparable response to the one used in the incidence study. (Dr P.B. Fourie, personal communication).

Patient	Age	1987	1988	1989
1	74	-	20*	-
2	82	-	20*	15
3	85	-	22*	15
4	76	-	0	13*
5	76	-	13	21*
6	77	-	18	22*
7	79	-	-	23*
8	75	-	0	15*
9	70	0	18*	-
10	85	0*	0	0
11	76	0*	14	24
12	93	0*	-	-
13	77	0*	-	-
14	80	2*	16	-
15	60	2*	7	13
16	77	4*	11	15
17	80	10	21*	14
18	62	10	12	22*
19	70	14	15	25*
20	76	15*	13	17
21	71	15*	-	-
22	69	18	14	22*
23	72	18*	-	-
24	87	20*	0	0
25	89	22*	18	20
26	75	40*	-	37

Table 25

The pattern of the Mantoux reaction in the 26 patients with active disease. The asterisk indicates the year in which the disease was diagnosed, (- indicates that no Mantoux was performed). The cases in 1987 are not consecutive cases but are ranked according to the size of the reaction.

MORTALITY

100 subjects died in 1988 (See Table 19) of whom 54/342 were negative reactors and 46/1079 positive ($p < 0.001$ Chi^2).

LIFE EVENTS (APPENDIX C)

There was no indication that adverse life events (death of a friend or relative, major personal illness or injury, or poor financial status predisposed to the development of the disease. Of the 13 patients with disease, only 2 admitted to adverse life events.

HIGH VS LOW RISK EXPOSURE

"High risk" were identified as either having had treatment for reactivated tuberculous disease within 2 years, or who had had household (includes residential home) contact with a known positive case within 2 years. "Low risk" were those who had no known contact or disease. Of the 13 positive cases 6 were in the "low risk" category.

DISCUSSION

Incidence

The incidence of 1080/100 000 confirms the conclusions of the earlier prevalence study (page 123) that the aged in residences for the elderly are at high risk for contracting pulmonary tuberculosis. In a separate investigation in Port Elizabeth similar prevalence figures were found.[67] Thus the situation amongst white South Africans in old age homes and their susceptibility to develop pulmonary tuberculosis differs only in a degree to the report from the United States.[1]

In the home for coloureds in 1987 there were 6 cases, no cases were discovered in 1988/89, and in 1989/90 a further 4 cases out of 52 residents. The detailed records of this home are appended in appendix D. These results are not entirely unexpected and illustrate the importance of ongoing surveillance in those at risk. It was not possible to determine whether one of the new subjects entering this home acted as an index case, or whether the patients were infected from an outside source. The pattern of disease however suggests that these were not endogenous infections, but rather precipitated by an index case with exogenous infection being responsible. The reason for saying this is that had it been due to a gradual waning of immunity in this

population we would have expected to have found cases in 1988. This is in keeping with other observations, [1 81] where both types of infection were reported.

As in the prevalence study the preponderance of males to females is confirmed and this concurs with other reports.

There was no correlation between the development of the disease and either adverse life events or, surprisingly, high risk exposure. It is expected that with greater numbers of patients this may alter. One hundred patients died during the period of the study. Of these the greatest attrition occurred in the Mantoux negative group confirming two studies [1 82] which showed a similar trend. It is presumed that areactivity indicates a compromised immune system and susceptibility to infections apart from tuberculosis which may have been responsible for death. Unfortunately no autopsies were performed, and there was no mechanism to allow this to be done in any event. From personal knowledge accuracy of locally completed death certificates are inaccurate and therefore it was not felt justifiable to analyse that data.

MANTOUX

The mean diameters of Mantoux reaction shown in Table 20 for the age group between 60 to over 85 show a remarkable consistency. What is apparent however is that with

increasing age the number of negative reactors increases successively. This observation is in keeping with other reports,[83] and suggests that the Mantoux reaction in the elderly is an all or nothing phenomenon. Whether the anergy is due to the presence of suppressor lymphocytes [84] or to factors related to a progressive declining immune response is not yet established. However if the increment in numbers becoming anergic is explained by the latter, then there should be a progressive decrease in size of reaction and not a constant size as shown in this study.

With regard to the booster effect, 43 of the subjects (12.3%) became positive on boosting. These figures are similar to those in the United States where the figures vary between 2% and 13%.[85] It has [1] [85] also been suggested that one booster is insufficient and two need to be done. However in this study 328 of the subjects (88%) were still negative on the third challenge and those that had converted were seen to be more prevalent in the homes where positive cases had been identified. These findings imply that conversion after an initial negative and a negative booster reaction must be considered indicative of a new infection and not a reaction to the third dose of PPD as suggested. These cases will need to be carefully observed to see whether their reaction size increases and whether they develop evidence of pulmonary tuberculosis.

The relationship between those cases who were found to

be TB positive and the Mantoux reaction is shown in Table 21. Of the 13 positive cases, 10 were identified in the group with reactions of 20 mm or more, and three were in the 10 to 19 mm category. Two of the latter had converted from negative to positive, and one had increased by more than 12 mm and hence were counted twice (See Table 21). This high yield in the category of 20 mm or more suggests that this is a good cut off point to identify the population at risk for harbouring the disease. It is not possible to calculate positive or negative predictive values for this statement because not all of the subjects who had such a strong reaction were subjected to exhaustive testing in order to exclude the disease. These would include bronchoscopy, saline inhalations, and gastric aspirates in subjects who are unable to produce sputum. It may be seen as a defect of this study that this was not done, but initially it was not appreciated at what Mantoux size it would become a cost effective exercise, and the logistics of performing these tests was beyond the scope of the facilities available at the time of the study. This may be seen as a further defect in the study, but as there is no indication in the literature of what points to accept as cut off levels this information provides the basis for further study. The failure for the category of an "increase of 12 mm or more" to identify the subjects as has been suggested by Stead, [78] may merely be a reflection of the density of positive cases

and their clustering in relatively small homes. The high background incidence of the disease in our population may also be a factor which explains why most of our subjects were in the strongly reacting group.

The age specific percentage of subjects who were Mantoux positive for a given Mantoux size is shown in Table 20. This data confirms Table 20 and 23 where the increase in numbers of negative reactors is an age related phenomenon. Of interest is the increase in the group of 20 mm or more between 1988 and 1989. It is presumed that this reflects an increase in the number of new infections. The possibility of disease in these patients is presumed to be high, and follow up of these cases is continuing.

The regression of Mantoux reaction over the period of study is shown in Table 23. The decreases have been divided into up to 5 mm and beyond 5 mm decrease and there is a remarkable consistency in the attrition rate across the age spectrum. This reversal to negativity seems to be offset by 79 (12%) cases that increased their reaction size by >5 mm and <12 mm.

With regard to the contention that an increase of 12 mm or a conversion from positive to negative is indicative of recent infection it should be noted that the percentages are very small in both of these categories. It would seem in this population however that the absolute reading of 20 mm or more is a more meaningful indicator of recent infection

and disease.

The Mantoux test is a relatively crude biological indicator of infection, and does not make the diagnosis of the disease. It is accepted that the main criteria for diagnosis is demonstration of sputum positivity. Table 24 shows the breakdown of subjects who fell into the three categories of Mantoux reaction that were taken for this study namely 20 mm or more, an increase of 12 mm over the year, or a conversion from negative to positive. The number of subjects with positive sputum culture was greatest in the 20 mm bracket and lowest in the few who converted from negative to positive. This is a reflection of the ability to produce sputum in the main, but as has been mentioned previously may partially be due to unwillingness on the parts of the subjects or the nursing staff to collect sputum. The yield obtained is very similar to that reported from Canada [76] where 60% of patients were able and/or willing to produce a sputum sample. It is perhaps significant that in the "greater than 20 mm group" where the highest number of TB positives were found, was also the group which managed to produce the most sputum. It was recommended (page 99) that at least 4 sputum samples need to be collected to exclude the disease. However that particular portion of the study was completed late in the period of investigation and when the protocol for this (the Mantoux) study was written, a minimum of 3 sputum samples

for TB culture was considered to be adequate. Hence the analysis was done on that basis, and it can be seen that an acceptable percentage of subjects had 3 cultures or more done.

The history of the Mantoux reactions in the 26 patients who were identified during the total course of the studies here reported is shown in Table 25. The numbers are too small to draw any meaningful conclusions, but it is of interest to see the various patterns in the people who were followed for 3 years. Information such as this does not exist in the literature and it will be part of an ongoing project to monitor these people for as long as possible.

CONCLUSION

It would be possible to conclude the outcome of this study with the brief bald statement that pulmonary tuberculosis in the elderly is common, is difficult to diagnose, and presents in a different way from that in younger adults. This would not be entirely new, and indeed in 1689 Richard Morten, writing about tuberculosis, observed

> "The consumption of Young Men, that are in the Flower of their Age, when the heat of the Blood is yet brisk, and therefore more disposed to a Feverish Fermentation, is for the most part Acute. But in Old Men, where the Natural Heat is decayed, it is more Chronical".

Furthermore it would tell only a small part of the story. What has emerged from this study is that the extremely high incidence of pulmonary tuberculosis in homes for the white and coloured ("mixed race") elderly in East London is known, (and there is no reason to expect the situation to be different in the rest of Southern Africa); the diagnostic criteria have been defined and tested and the differences in presentation have been quantitated.

In the prevalence study done in old age homes an overall rate of 1483/100 000. Prevalence and incidence are

not comparable and this promoted an incidence study which showed an overall yearly incidence of 1080/100 000. Thus the disease in this setting is common, and far commoner than was anticipated. Therefore the first hypothesis tested in this thesis, namely that because of the high background incidence of disease in the community, the susceptible aged would have an even higher incidence was correct. It may be asked why this disease pattern has not been previously appreciated, and the answer is that had we not actively looked for these cases it is unlikely that we would have found them.

This raises the question of the difficulty in making the diagnosis. Difficulties in obtaining sputum from the elderly, the controversy about the role of the PPD reaction (in this case the Mantoux), and the debate about the type and frequency of the radiographic appearances all have been equivocal areas. No information existed about systemic markers for the disease either haematological or biochemical. The work reported in Section I has shown that the radiological, haematological and biochemical features of pulmonary tuberculosis in the elderly age group are very different when compared to those in classical post primary disease (page 75).

Although the clinical presentation of pulmonary disease in the aged does not differ significantly from that in younger subjects there are marked differences in the

radiological appearance. There is also greater variation from normal limits in the haematological and biochemical indices, and although these changes are not diagnostic their otherwise unexplained presence, particularily abnormally raised liver function tests should alert clinicians to the possibility of tuberculosis.

It is axiomatic that acid fast bacilli need to be detected in the sputum in order to make the diagnosis. The investigation of the pattern of bacillary excretion in non-cavitating disease revealed the haphazard pattern of excretion and underlined the absolute necessity for sputum culture in order to detect the bacilli. As a result of this it can be recommended that at least 4 negative sputum cultures must be obtained before confidently excluding the diagnosis. In those with cavitating disease the bacillary excretion is usually high and detectable on smear. A prospective study of bacillary viability in patients with cavitating tuberculosis on treatment revealed that they remain infective for periods between 4 and 9 weeks. The question as to whether they should be allowed to return to an environment where other people are at high risk (e.g. old age homes) for developing the disease is raised.

As a result of the experience gained using the diagnostic features already mentioned in the prevalence study, it was recommended that monitoring of this disease in old age homes should be mandatory. The steps outlined were

that an initial baseline chest x-ray should be taken which, in an asymptomatic individual may be of little diagnostic importance, it may be helpful to detect any differences at a later stage. An initial Mantoux should be performed, and if this is negative repeated within a fortnight to exclude a false negative response to the first test. This should then be repeated at yearly intervals. These recommendations are in line with the subsequent guidelines published by the American Geriatric Society.[86 87] The value of the Mantoux was shown in the incidence study where it appears to be a good means of identifying subjects at risk, in particular where the reaction is greater than 20 mm. It is recommended therefore that sputum be actively collected from anybody who has a productive cough for more than 3 weeks and those who have a Mantoux reaction greater than 20 mm.

The collection of sputum may be a problem in about 1/3 of cases. It remains to be seen whether a more aggressive approach such as saline inhalation, gastric aspirates, or bronchoscopy is warranted in this population group. My personal feeling is that saline inhalations or gastric aspirates should be used in those in whom the disease is strongly suspected, not only on the result of a Mantoux reaction, but in conjunction with other clinical, biochemical, haematological, or radiological findings. Should this not be successful then bronchoscopy would be the next step. However, many of these patients are frail, often

senile, and may have co-existent disease which makes aggressive diagnostic procedures inappropriate. Furthermore as we found, to our cost, antagonism to this kind of survey is easily engendered and while it may not be ideal medically, it may be wiser in the long run to confine one's diagnostic efforts to a practical minimum for the greater good. It should be noted that the chest radiograph has a low specificity in this age group and as such plays a less important role in the diagnosis of disease compared to younger adults. It can be said that non-specific findings which are frequently present are compatible with the diagnosis.

Thus, pulmonary tuberculosis in the elderly is common and this thesis has shown how common. It is difficult to diagnose, and we have shown in part a practical way to identify those at high risk and what to do to make the diagnosis. Finally, it does present in a different way from that in younger adults, and the results of this study have shown where and to what extent. Hopefully this will enhance the diagnostic ability in an attempt to contain this epidemic of one of the oldest of diseases, and increasingly, a disease of the old.

SUMMARY OF RECOMMENDATIONS

1. AWARENESS OF PULMONARY TUBERCULOSIS IN RESIDENCES FOR THE ELDERLY.

1.1 South Africa has a high prevalence of tuberculosis.

1.2 The elderly population is more susceptible to developing the disease, and the elderly living in old age homes have a much higher incidence than those living in the community.

For these reasons

a) Public Health authorities should regard this population as a priority in health screening in order to detect unsuspected cases
b) Doctors (family practitioners and district surgeons) who attend patients in these residences should be made aware of the importance and extent of the problem.

2. AWARENESS OF THE ATYPICAL MANIFESTATIONS OF PULMONARY TUBERCULOSIS IN THE ELDERLY.

The medical and nursing community should be informed and regularly reminded of the atypical manifestations of the disease in the old. To some extent the author has embarked on this educating campaign by means of presentations to
a) Congresses
b) Symposia and
c) Publications (* See footnote).

3. SCREENING OF NEW ENTRANTS TO RESIDENCES FOR THE ELDERLY.

It is recommended that all new subjects entering an old age home should have a) a chest radiograph and b) a baseline Mantoux which if negative should be repeated within 2 weeks (to exclude a false negative response).

4. MONITORING OF RESIDENTS IN OLD AGE HOMES

As long as the Republic of South Africa remains a high prevalence country for tuberculosis, regular screening of populations at risk for reactivation or a re-infection by the tubercle bacillus will be cost effective. Furthermore early diagnosis will prevent epidemics occurring in this susceptible population.

In the light of the investigations described in this thesis it is recommended therefore that,

4.1 All residents have an annual Mantoux test as a means of identifying a group at high risk of either recent infection or disease. These people would be identified by the degree of, or change in reaction as follows:

a) conversion from negative (less than 5 mm) to positive (5 mm or more)

b) an increase in diameter of 12 mm or more,

c) a reaction of 20 mm or more.
These subjects should be investigated further by means of sputum examination and possibly chest radiographs.

4.2 All residents with a productive cough of more than 3 weeks duration should be screened for tuberculosis by

a) sputum collection for culture. 4 negative cultures are required to exclude the diagnosis.

b) other investigations, e.g. regular weighing, chest radiographs, Mantoux reaction, haematological and biochemical tests may all serve as markers for the disease.

c) if the sputum remains negative despite a high index of suspicion of the disease, then gastric aspiration or bronchoscopy needs to be considered.

5. INFECTIOUS PRECAUTIONS

Cases who are found to be sputum positive for pulmonary tuberculosis and have cavitating disease, should be regarded as infectious for up to 10 weeks after commencing anti-tuberculosis therapy. A negative smear is a reliable indicator of disease control. In cases with non-cavitating disease the production of bacilli is haphazard and scanty, and these subjects can probably be treated quite safely in their environment.

6. RECOMMENDED FURTHER INVESTIGATIONS

6.1 The role of pharmacological prophylaxis (e.g. INH, or a combination of Rifampicin and Pyrazinamide etc.) in sputum negative, but Mantoux positive elderly subjects.

6.2 The role of BCG vaccination in the elderly Mantoux negative population.

Footnote

* Morris C.D.W., Nell H. Epidemic of pulmonary tuberculosis in geriatric homes. S Afr Med J 1988;74:117-20.

* Morris C.D.W. The radiography, haematology and biochemistry of pulmonary tuberculosis in the aged. Q J Med 1989;71:529-35.

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APPENDIX A

Name: Folder No. X-Ray No.

LEFT

	Cavity	Inflam.	Fibrosis	Reaction
Ant				
Post				
Apical				
Mid				
Basal				
Pleural				

RIGHT

	Cavity	Inflam.	Fibrosis	Reaction
Ant				
Post				
Apical				
Mid				
Basal				
Pleural				

Conventions used:

1. "Inflam." - opacification which is consistent with inflammation.

2. "Fibrosis" - opacification with evidence of distortion of either lung markings, pleura, hilar, bronchi and teachea or mediastinal structures.

3. "Reaction" - this might have been either a basal pleural fluid or thickening; investigations were not done to determine which (Page 86).

4. "Apical", "Mid", and "Basal" - refer respectively to the upper 1/3, middle 1/3 and lower 1/3 of the lung field seen on the PA film.

APPENDIX B

TUBERCULOSIS SURVEY IN EAST LONDON OLD AGE HOMES.

The survey of old age homes which was begun last year has now come to the end of phase II. You are probably aware that as people get older their susceptibility to develop the disease of tuberculosis rises, and this is the prime reason for doing the survey. We have discovered a number of cases of tuberculosis in old age homes in East London and these people have been treated. It is important to remember that TB is curable and it is important for you and those close to you that we discover it and treat it. This circular is to bring you up to date with the results and to inform you of our plans for 1989.

The skin test project in which you very kindly participated, has identified 84 residents from various homes in the City who have acquired an infection during the course of the last year. This does not necessarily mean that they have tuberculosis, but merely that they are at high risk of developing it. In order to determine whether this is so we are going to ask these people to co-operate and have chest x-rays (which we will arrange) and provide us with specimens of sputum for bacteriological examination. These people at risk will be informed personally and if you have not been contacted and asked to produce sputum specimens, it means that you are not at risk. The sputum examination takes 8 - 12 weeks and the results will be made available as soon as possible.

We intend to continue with the skin test survey on all new residents, those who have not been tested before, and to repeat these tests on a yearly basis. It is important from everybody's point of view that we discover and treat all those with the disease. We would like to thank you for your co-operation in this effort to improve the health of all our Senior Citizens.

Department of Medicine
FRERE HOSPITAL

APPENDIX C

RECORD FORM

TUBERCULOSIS IN RESIDENTS OF EAST LONDON OLD AGE HOMES

SECTION I. BACKGROUND INFORMATION	CODE
FILE IDENTIFICATION	
Index number (e.g. 0001) ---->	___ ___ ___ ___
Date file opened (month and year) (e.g. 0688 for June 1988) ---->	___ ___ ___ ___
Date file closed (month and year) ---->	___ ___ ___ ___
Reason: _____	
PERSONAL DETAILS	
Name: _____	
Sex (M or F) ---->	___
Age (years) ---->	___ ___
Date old age home entered (month & year) ---->	___ ___ ___ ___
TUBERCULOSIS STATUS AT TRIAL ENTRY	
Contact of household TB case (Y/N) ---->	___
If yes: Before or after entering the old age home (B/A) ---->	___
Which year? (e.g. 53 for 1953) ---->	___ ___
Currently on treatment for TB (Y/N) ---->	___
Previously treated for TB (Y/N) ---->	___
If yes: From (month and year) ---->	___ ___ ___ ___
To (") ---->	___ ___ ___ ___
Date X-ray taken (month and year) ---->	___ ___ ___ ___
Pathology compatible with TB (Y/N) ---->	___
If yes: Probably recent (progressive) = 1 Probably old (inactive) = 2	___

SECTION II. INVESTIGATIONS

IDENTIFICATION

Index number _____

Visit number (1, 2, 3 etc) ----> |___|

MANTOUX TEST

NOTE: If first test measures less than 5 mm, then a repeat test after 14 days is required

Date (month and year) ----> |___|___|___|___|

Induration (mm): First test ----> |___|___| , |___|

Repeat test ----> |___|___| , |___|

SPUTUM

Date collected (month and year) ----> |___|___|___|___|

Smear positive or negative (P/N) ----> |___|

Culture " (P/N) ----> |___|

Strain resistant/sensitive (R/S) ----> |___|

MAJOR LIFE EVENTS DURING PAST SIX MONTHS / SINCE LAST VISIT

Death of a close family member (Y/N) ----> |___|

Death of a close friend (Y/N) ----> |___|

Major personal injury or illness (Y/N) ----> |___|

Financial status worse (Y/N) ----> |___|

APPENDIX D

D.J. SOBEY OLD AGE HOME

	SEX	AGE	1987 MANTOUX	1988 MANTOUX	1989 MANTOUX
1	F	80	12	14	23
2	F	68		19	20
3	F	68		0 (6)	
4	F	77	8	10	15
5	M	75	3	9	
6	F	71		0 (9)	28
7	F	66		8	11
8	F	80		13	
9	F	72	0	0 (13)	11
10	M	99	20	17	22
11	F	77	0	16	19
12	F	81		8	
13	M	75		15	
14	F	77	15	24	25
15	M	76	12	11	17
16	F	69	12	14	24
17	M	76	0	0	0
18	M	79		0 (10)	20
19	M	58		12	15
20	F	66		9	
21	M	72		11	10
22	M	62	12	18	18
23	M	76	15 *	13	17
24	F	82		0	0
25	F	47	0	20	48
26	M	77		7	
27	M	68	8	11	11
28	M	61	14	13	15
29	F	55	12	22	28
30	F			12	11
31	F	77	18	16	13
32	M	78	18	19	16
33	M	83		0	
34	F	69	18	14	22 *
35	F	59		13	17
36	F	71	16	16	0
37	F	61	0	18	29
38	F	85	0	0	11
39	F	66	12	14	
40	F	58	0	13	27
41	M	59	24	15	
42	M	76	0 *	14	24
43	M	69		0	
44	F	76	14	25	27
45	F	79	8	13	
46	F	78	14	22	40
47	M	74		9	10
48	F	70	14	15	25 *
49	M	65	12	10	
50	M	62	10	12	22 *
51	F	60	2 *	0 (7)	13
52	M	66		15	19

	SEX	AGE	1987 MANTOUX	1988 MANTOUX	1989 MANTOUX
53	F			8	
54	M	75		11	17
55	M	61	0	8	
56	M	77	20	19	13
57	M	54	24	15	
58	F	70		5	0
59	M	64		12	
60	M	60		9	10
62	F	76		0	13 *
62	M	72			16
63	F	57			0
64	F	88			17
65	F	88			0
66	M	59			11
67	F	82			0
68	F	65			14
69	M	71	15 *		
70	M	72	18 *		
71	M	77	0 *		

* Those who had TB

APPENDIX E

Comparison of biochemistry of elderly tuberculotics and elderly patients with destructive lung disease.

In Chapter 3.4 (page 70) data was shown which suggested that in elderly patients, tuberculosis is associated with abnormal values for haemoglobin, white cell and platelet count, sodium, potassium and albumin. Although the trend for all these tests was towards more pronounced abnormalities in the elderly compared to the younger age group, the differences were not statistically different because of the high variances. There was however a significant increase in the proportion of patients with abnormally high alkaline phosphatase, aspartic transaminase and bilirubin in the elderly, compared to a younger group of tuberculosis patients. In order to confirm that the finding of abnormal liver enzymes was a phenomenon related to TB in the elderly and not merely a manifestation of general debility due to any respiratory disease, the results of the elderly tuberculotics (subjects from the main study) (See page 72) were compared with those of a selected elderly group of subjects who had chronic destructive lung disease in whom active pulmonary tuberculosis had been actively excluded.

Method

From July 1987 to the end of June 1990 the records of all patients admitted to the Department of Medicine, Frere Hospital were summarised on discharge, on the summary form devised by the author. (See Appendix F). On

discharge of the patient all relevant details were personally checked by the author and all patients who had the diagnosis of bronchiectasis, chronic destructive lung disease, or post tubercular lung disease were identified. The hospital notes were scrutinised to ensure that adequate investigations had been performed to exclude active pulmonary tuberculosis (sputum smear and mycobacterial culture negative). The routine haematological and biochemical profiles which are done on admission to hospital were extracted from these patients' records. The reasons for admission of these patients included acute infective exacerbation of chronic bronchitis, cardiac failure, or respiratory failure. The common problem to all was chronic destructive lung disease in whom no active tuberculosis was found. During the total period of both studies the same laboratory was used and they did not change their equipment, methodology, format of reporting or normal ranges.

Statistical evaluation was done by Chi2 analysis of categorical data. The number of results falling outside the normal range in each parameter measured were compared in the two groups. In some subjects items of data were not available usually because of technical reasons in the laboratory. In these cases the denominatior was adjusted to the number of data entries.

Results

A total of 10 350 records were scrutinised. Of these 113 patients fulfilled the criteria. There were 68 males and 45 females. The mean age was 51 years (range 17 to 94). There were 3 whites, 10 coloureds and 100 black subjects. 73 were below the age of 60 years and 40 were 60 years or more.

	Age (years)	Male	Female	Race	Alb (g/l)
<60 years N=73	Mean 40 Range 17-58	73%	37%	Black 89% Coloured 11%	31,5 SD 9,5
>=60 years N=40	Mean 70 Range 60-94	55%	45%	Black 87% Coloured 5% White 8%	29,5 SD10,5

Table I

The age, sex and race distribution of those under 60 years compared to 60 years and over with destructive lung disease (D.L.D.). The Albumin (Alb) levels are shown as an indicator of general illness.

	Age (years)	Male	Female	Race
D.L.D. N = 40	Mean 70 Range 60-94	55%	45%	B = 87% C = 6% W = 7%
T.B. N = 93	Mean 70 Range 60-96	50%	50%	B = 86% W = 14%

Table II

The age, sex and race distribution for those 60 years or over with either tuberculosis (T.B.) or Destructive Lung Disease (D.L.D.). B = Black C = Coloured W = White

The biochemical and haematological results were as follows:

	Haemoglobin (g/dl)		Leucocytes (x 10^9/l)		Platelets (x 10^9/l)	
Normal Range	>12		4 - 11		150 - 400	
	D.L.D.	T.B.	D.L.D.	T.B.	D.L.D.	T.B.
Mean	12.6	12.1	11.9	10.7	368	342
S.D.	2.9	2.3	5.8	4.6	179	137
Percentage above upper limit	-	-	38	55	50	33
Percentage below lower limit	39	70	-	-	-	-

Table III

The haematological parameters comparing patients >= 60 years with Destructive Lung Disease (D.L.D.) and those with tuberculosis (T.B.). There were no significant differences.

There were no significant differences in the biochemical results between the younger below (60 years) and older group (60 years and above) suffering from destructive lung disease (Table IV).

	Sodium (mmol/l)		Potassium (mmol/l)		Albumin (g/l)		Bilirubin (mmol/l)		Alkaline Phosphatase (u/l)		ASPT (u/l)		LDH (u/l)	
ormal Range	135-145		3.5-5.0		35-50		0-20		30-115		7-40		100-225	
	<60	>60	<60	>60	<60	>60	<60	>60	<60	>60	<60	>60	<60	>60
ean	138	134	4.06	3.74	31.4	29.5	8.16	6.47	90.2	57.48	30	26	205	202
.D.	4.99	2.2	1.88	1.08	9.3	10.5	5.0	4.47	45.2	55.17	43	35	93.8	79
ercentage bove range	-	-	-	-	-	-	1	1	18.5	5	20	15	28	35
ercentage elow range	20.5	20	19	42	60	67	-	-	-	-	-	-	-	-

Table IV

The comparison of the biochemical results obtained in the younger (<60 years) and the older (>= 60 years) in patients suffering from non-tuberculous destructive lung disease.

However, when the results of the older group of non-tuberculous lung disease was compared with those suffering from tuberculosis then significant differences in the liver function tests were seen (Table V).

	Sodium (mmol/l)		Potassium (mmol/l)		Bilirubin (mmol/l)		Alkaline Phosphatase (u/l)		ASPT (u/l)		LDH (u/l)	
Normal Range	135-145		3.5-5.0		0-20		30-115		7-40		100-225	
	D.L.D.	T.B.	D.L.D.	T.B.	D.L.D.	T.B.	D.L.D.	T.B.	D.L.D.	T.B.	D.L.D.	T.B.
Mean	134	134	3.74	3.9	6.47	8.5	95	124	26	46	202	277
S.D.	2.2	4.7	1.08	0.78	4.47	7.7	36	58	35	51	79	122
Percentage above range	-	-	-	-	1	20	1	62	15	77	35	74
Percentage below range	20	60	42	42	-	-	-	-	-	-	-	-
P Value (Chi^2)	0.001		N.S.		=0.01		<0.001		< 0.001		<0.01	
Sensitivity					95%		61%		87%		83%	
Specificity					41%		88%		60%		45%	
Positive predictive value					21%		95%		65%		74%	

Table V

Shows the variations from the normal range in non-tuberculous destructive lung disease (D.L.D.) and tuberculosis (T.B.) and their significance as markers for the disease.

Formal evaluation of abnormal liver function tests as a group (i.e. bilirubin, alkaline phosphatase, ASPT and LDH) as being a marker for active tuberculosis (as against D.L.D. complicated by acute non-tuberculous infections, cardiac failure, or respiratory failure) showed: Sensitivity 76%, specificity 48% and positive predictive value 60%.

Discussion

The results obtained in the original study namely that there appeared to be more abnormal results in elderly tuberculosis patients than in younger subjects were unexpected (page 70) and opened the path for further investigation. In view of the practical importance of assessing the diagnostic value of any of the markers for active disease, an extension of the original research protocol was undertaken whereby the haematological and biochemical abnormalities which appear to exist in the elderly patient with tuberculosis were compared to a control group of patients of similar age suffering from non-tuberculous chronic destructive lung disease. The important difference is seen in the liver function tests where there are signifcant statistical differences. The sensitivity, specificity and predictive value of these parameters is insufficient to make them diagnostic on their own, but they may be important indicators of the presence of disease.

The fact that the control group was retrospectively selected and studied may be criticised. It was not possible to match subjects (as in a case control study) for sex, race and severity of disease. Thus selection bias is inherent. Furthermore data is often unavailable for many reasons (lost folders, investigations missing or not recorded, laboratory ommissions), and hence the data base may be non-representative. In this particular study it was not possible to match for severity of disease on the basis of weight, skin thickness, albumin, ferritin etc. which could have been done in a prospective comparative study. This might be a factor which could skew the data.

Despite these difficulties the fact that there are significant increases in the liver function tests particularly the alkaline phosphatase levels is seen as an indication that pulmonary tuberculosis in the elderly may be more widely disseminated than previously realised and that otherwise unexplained abnormal liver function tests should be regarded as a possible marker for tuberculosis. The other possible cause for these abnormal findings could be related to there being more alcohol abuse in the elderly, but this is unlikely to be significantly different between tuberculous and non-tuberculous subjects from similar backgrounds. The influence of anti-tuberculous therapy on the liver function tests was precluded by the fact that blood samples were collected before therapy had been started.

This exercise was prompted by the question whether the earlier findings (page 70) warranted a prospective controlled trial. In view of these results, it is suggested that a prospective survey might be a valuable study.

APPENDIX F

FRERE HOSPITAL F.H. 1907

MEDICAL DEPARTMENT SUMMARY

SURNAME: _____ FIRST NAMES: _____

FOLDER NO.: _____ NEW FOLDER NO.: _____ AGE: _____ SEX: _____ RACE: _____

WARD: _____ ADMITTED: _____ DISCHARGED/DECEASED: _____

REFERRED BY: _____

FIRM: _____ MEDICAL OFFICER: _____

AREA: /RURAL (S.A.) /URBAN (S.A.) /RURAL (CISKEI) /MDANTSANE (CISKEI) /TRANSKEI

CLINICAL FINDINGS:

INVESTIGATIONS: Diagnosis /Confirmed /Results awaited Haemoptysis Please tick /Yes /No

FINAL DIAGNOSIS: I.C.D.

_____ _____

ASSOCIATED DISEASES:

a) _____ _____

b) _____ _____

c) _____ _____

DRUGS

	Which ones	Dosage		Which ones	Dosage
A.	Diuretics		F.	Anti-diabetes	
B.	Anti-hypertensive		G.	Anti-asthma	
C.	Anti-inflammatory		H.	Anti-T.B.	
D.	Anti-failure		I.	Steroids	
E.	Anti-biotics		J.	Other	

FOLLOW UP: _____

INFECTIONS
002 Typhoid parathyroid
006 Amebiasis
038 Septicaemia
070 Viral hepatitis
095 Syphilis
094 Neurosyphilis
123 Cysticercosis

T.B.
011 Active P.T.B.
012 Pleural T.B.
013 T.B.M.
014 Gut, peritoneum
016 Genito urinary
018 Miliary
019 Pericardial T.B.
137 Late effects of T.B.
999 Other

MALIGNANCY (Solid tissue)
150 Oesophagus
155 Liver
162 Bronchus and Lung

MALIGNANCY (Haematological)
204 Lymphoid
205 Myeloid
998 Other

ENDOCRINE
242 Thyrotoxicosis
244 Hypothyroidism
250 Diabetes
997 Other

BLOOD
280 Iron deficiency anaemia (microcytic hypochromic)
281 B12/Folate (macrocytic)
285 Normochromic normocytic
286 Coagulation defects
289 Platelet disorders
996 Other

MENTAL DISORDERS
290 Senile and pre-senile organic psychosis (e.g. multi infarct dementia)
291 Alcoholic psychosis
298 Non organic psychosis
300 Anxiety / 311 Depression
312 Disturbance of conduct
E950 Attempted suicide
E850 Accidental overdose
995 Other

CENTRAL NERVOUS SYSTEM
320 Bacterial meningitis
321 Meningitis due to other organisms
013 T.B. Meningitis
331 Alzheimers
332 Parkinsons
342 Hemiplegia
345 Epilepsy
346 Migraine
430 Subarachnoid
431 Intracerebral bleed
434 Cerebral artery occlusion
435 Transient cerebral ischaemia
349 Trauma
994 Other

CARDIOVASCULAR
394 Rheumatic mitral valve
395 Rheumatic aortic valve
396 Rheumatic mitral and aortic valve
397 Bacterial endocarditis
401 Essential hypertension
402 Hypertensive heart disease
410 Acute myocardial infarct
413 Angina
414 Other ischaemic heart disease
416 Cor pulmonale
420 Pericarditis
019 T.B. Pericarditis
425 Cardiomyopathy
427 Cardiac arrythmias
428 Cardiac failure (state cause)
443 Peripheral vascular disease
453 Deep vein thrombosis
993 Other

LUNG DISEASE
480 Viral pneumonia
482 Bacterial pneumonia
485 Broncho pneumonia, organism unspecified
490 Bronchitis
493 Asthma
494 Bronchiectasis
496 COAD
511 Pleural effusion
513 Lung abscess
518 Pulmonary embolus
135 Sarcoidosis
992 Other

GASTRO-INTESTINAL TRACT
150 Oesophagus carcinoma
531 Peptic ulcer
535 Gastritis
558 Non infective colitis and gastro enteritis
570 Hepatitis
572 Liver abscess
578 Gastrointestinal haemorrhage
609 Cirrhosis, alcoholic
530 Diseases of oesophagus
577 pancreas
575 gall bladder
573 liver
153 colon
537 stomach and duodenum
991 Other

GENITO URINARY TRACT
580 Acute glomerulonephritis
581 Nephrotic syndrome
584 Acute renal failure
585 Chronic renal failure
590 Pyelonephritis
595 Cystitis
600 Prostatomegaly
596 Diseases of Kidney
990 Other

ARTHROPATHY
712 Gout
714 Rheumatoid arthritis
715 Osteo arthritis
989 Other

GENERAL
710 Connective tissue disorder
690 Dermatological disorder