The changing pattern of tuberculosis

D. GERAINT JAMES
M.A., M.D., F.R.C.P.

B. B. MISHRA
M.D., M.R.C.P.

Royal Northern Hospital, London N7

Introduction

Robert Koch (1843-1910) discovered the tubercle bacillus in 1882, and his centenary was commemorated by stamps (Fig. 1), conferences and exhibitions around the world (Sakula, 1979).

In the Annual Report (Department of Health and

FIG. 1. A centenary stamp issued to commemorate Robert Koch (1843-1910) who discovered the tubercle bacillus.

Social Security, 1977) of the Chief Medical Officer of the Department of Health for the year 1976, it was clear that there had been a steady decline in the incidence of tuberculosis in Britain from 80,000 notifications in 1914 to 8,000 in 1974. In 1974, it was

Based on a lecture to the Carmarthen Medical Society to commemorate the centenary of Koch's identification of the tubercle bacillus.

estimated that 1935 hospital beds, just over 1% of the total available, were in daily use for the treatment of tuberculosis. By 1979, the annual rate in England per 100,000 was 18.3 for all ethnic groups, 10.7 for white persons, 382 for those from the Indian subcontinents and 31 for West Indians (MRC, 1982).

It is timely to draw attention to the missed diagnosis of tuberculosis rather than the readily recognised manifestations of this disease. In these days of highly effective antituberculous chemotherapy, missing the diagnosis amounts to a costly tragedy to the patient. The fact that tuberculosis is multisystem cannot be overemphasized to clinicians of all disciplines (Fig. 2). The clinician evaluating switched clues may find himself in unfamiliar territory as when the neurologist follows clues in the chest and vice versa, or the gynaecologist is fumbling with backache due to tuberculous joint disease.

Tuberculosis in children

The Medical Research Council Tuberculosis and Chest Diseases Unit (1982b) has also analysed notifications of childhood disease in England and Wales. For a 6-month period during 1978-79 there were 353 children with newly notified untreated disease; 50% were white and 38% were from India, Pakistan or Bangladesh. The estimated overall notification rate was seven per 100,000 population, with a rate of 130 for those from Pakistan-Bangladesh, 90 in the Indian and 3.6 in the white population. Interestingly, meningitis occurred in 24% of the white children with non-respiratory disease but in only 2% of the Indian subcontinent children.

Tuberculosis in Ireland

The modern profile of tuberculosis differs from traditional descriptions in Ireland, a fact which is emphasised by a recent study of 121 consecutive patients with bacteriologically proven tuberculosis in St Vincent's Hospital, Dublin, during 1974-79. The ratio of pulmonary to extrapulmonary disease was 2:1 compared with unity 5 years earlier, and about

FIG. 2. Clinical examination of a patient with suspected tuberculosis.

one-eighth are multisystem (Buitelir and Fitzgerald, 1982).

Masquerades

Myocardial disease

Tuberculous myocarditis should be considered in the differential diagnosis when cardiac arrhythmias occur in otherwise healthy young immigrants. In an interesting report from Burnley (Behr, Palin and Temperley, 1977), a Pakistani youth and a young adult Indian died from direct spread of tuberculosis from mediastinal lymph nodes to the myocardium. The lungs were normal at autopsy in both.

Peritonitis

Smith (1977) reports a dramatic example of abdominal tuberculosis presenting in the puerperium in a young Asian with jaundice, fever, hepatomegaly and anaemia, followed by electrolyte imbalance and confusion. In all, just over 100 pathology and radiology reports were filed before the diagnosis was made, partly because the chest radiograph remained

normal until the 46th day after delivery, and partly because a Heaf test was only doubtfully positive. A trail of false clues suggested diagnoses which included repeated melaena, appendix abscess and peritonitis due to bacteroides infection, but he felt that the true diagnosis of abdominal tuberculosis could have been made earlier by peritoneal biopsy or salpingectomy. Peritoneal biopsy is most helpful either during laparotomy or by making a small incision in the right iliac fossa under local anaesthesia (Shukla *et al.*, 1982).

Crohn's disease

There are many similarities between Crohn's disease and abdominal tuberculosis. '... mistakes will be made least often if the physician at least thinks of tuberculosis in every case of apparent Crohn's disease before starting treatment with steroids. Likewise the surgeon should think of the condition at laparotomy when bowel changes suggest Crohn's disease or carcinoma and when peritoneal nodules suggest carcinoma or starch granuloma...' (Editorial, 1977).

Points in favour of tuberculosis are fever, vomiting, constipation, menstrual upsets, ascites and positive tuberculin skin test. Pointers to Crohn's disease would be the troublesome diarrhoea, the presence of perianal and genital ulceration and fistula formation. Endoscopy with biopsies are usually definitive. The clinician's responsibility to distinguish between gastrointestinal tuberculosis and Crohn's disease cannot be overstated (Findlay, 1982).

Breast cancer

Twenty-one patients were seen at Groote Schuur Hospital, Cape Town, with breast tuberculosis presenting with fixed subcutaneous nodules, large fixed central masses with oedema and ulceration (Dent and Weber, 1977). The initial diagnosis was either breast abscess or advanced carcinoma. When it had the features of cancer it was always considered to be inoperable because of its size, fixity to the chest wall or other tissues, and oedema or ulceration. The tendency of mammary tuberculosis to mimic breast cancer re-emphasises the necessity of histological confirmation before treatment for breast cancer (Guillet *et al.*, 1982). Breast tuberculosis should be especially suspect when a lump is found in patients particularly at risk of tuberculosis (Modai *et al.*, 1984).

Sarcoidosis

Confusion between tuberculosis and sarcoidosis continues because there are superficial similarities but also several significant differences. There are several clinical features which point towards tuberculosis and away from sarcoidosis; they include fever, loss of weight, symptoms and appearance of ill-health, involvement of serous surfaces and ulceration. These pointers are then reinforced by a positive tuberculin skin test, normal serum angiotensin-converting enzyme, negative Kveim test, caseation, and eventual isolation of acid-fast bacilli.

Unlike tuberculosis, sarcoidosis may be associated with uveitis, erythema nodosum, skin plaques, enlarged parotids and lacrimal glands, bone cysts, lack of involvement of serous surfaces, abnormal calcium

metabolism, a negative tuberculin skin test, positive Kveim-Siltzbach skin test, raised serum angiotensin-converting enzyme and lack of response to antituberculous chemotherapy.

The dermatologist and ophthalmologist rarely find difficulty in differentiating the two conditions, whereas the chest physician may find it impossible to do so. If there is any doubt, it is safer in the first instance to treat as though it is tuberculosis with antituberculous drugs rather than assume that it is sarcoidosis and give corticosteroids.

Liver granulomas

When hepatic granulomas are identified by aspiration liver biopsy, it is extremely difficult or impossible to indicate by microscopy whether these are due to tuberculosis or sarcoidosis. The histologist must shift the onus of differential diagnosis back to the clinician, who endeavours to differentiate these two causes by clinical findings, radiography, tuberculin skin test and serum angiotensin-converting enzyme. All biopsy material should, of course, be cultured for tubercle bacilli, but such small samples are rarely positive.

We have analysed a personal series of 138 patients with liver granulomas and compared it with Klatzkin's (1976) large Yale series and also more recently with the Glasgow series (Cunningham *et al.*, 1982) (Table 1). The commonest cause of hepatic granulomas in these centres is sarcoidosis, which is three or four times more frequent than tuberculosis. The second commonest cause is hepatobiliary disease, predominantly primary biliary cirrhosis.

Opportunistic mycobacterial disease

Mycobacteria other than the human tubercle bacillus cause diseases similar to tuberculosis in the lungs, skin, lymph nodes, kidneys, liver, spleen, bone and joint. These organisms are identifiable because they may be catalase-positive, niacin-negative and isoniazid-resistant. The prerequisite to development of pulmonary mycobacteriosis is chance simultaneous occurrence both of colonies of organisms and

TABLE 1. A comparison of hepatic granulomas investigated in three centres

	Yale*	London†	Glasgow‡	Total
<i>n</i>	565	138	77	780
Major causes				
—Sarcoidosis	217	75	8	300 (40)§
—Tuberculosis	70	3	8	81 (10)
—Hepatobiliary	174	41	18	233 (30)
—Schistosomiasis	19	1	0	20 (3)
Undiagnosed	37	14	24	75 (10)
Positive Kveim test	389 (69)	100 (72)	—	489 (70)

*Klatzkin, 1976; †Neville, E. *et al.*, 1975; ‡Cunningham, *et al.*, 1982; §Number in parentheses = %.

of impairment of local immunological mechanisms, which may be acute or chronic (Chapman, 1977). This would explain its prevalence in miners and other individuals whose lungs have already sustained damage, its increased frequency in males and in the middle-aged; and its occurrence in the compromised host who has been subjected to corticosteroid and other forms of immunosuppression.

Meningitis

Although it is now rare, tuberculous meningitis (TBM) must not be overlooked. In a series of seven children, the diagnosis was delayed by a misleading negative tuberculin test, and also because of finding Gram-positive organisms in the spinal fluid of one child (Naughten *et al.*, 1981). A Mantoux 1:1000 skin test should be done whenever the diagnosis is considered. A bromide partition test is an additional useful, safe, and easy test; it demonstrates the integrity of the blood-brain barrier which is damaged in tuberculous but not in viral meningitis. When the barrier is damaged the relative concentration of bromide in blood: cerebro-spinal fluid (CSF) approaches 1:1 compared with a normal ratio of 3:1 (Taylor, Smith and Hunter, 1954). A high CSF protein and an abnormal CSF glucose: blood glucose ratio should raise the likelihood of TBM. A CT scan may disclose exudates, tuberculoma, hydrocephalus and infarcts (Rovira *et al.*, 1980).

Renal

Chronic renal failure may be due to tuberculosis, and should be considered in immigrant patients even with normal excretion urography (Mallinson *et al.*, 1981). The predominant histological feature in this reported series was a severe interstitial nephritis related to small tuberculous granulomas. The failure of improvement with effective chemotherapy would suggest that the renal failure was due to an acute inflammatory interstitial lesion, which healed with considerable destructive fibrosis. Therefore, adjuvant therapy with steroids may be helpful by lessening the initial inflammation and subsequent fibrosis.

If excretion urography and bacteriological examination of the urine are unhelpful, renal biopsy may become necessary to clinch the diagnosis in migrants (Mallinson *et al.*, 1981). Tuberculosis may become evident in maintenance haemodialysis patients. In one Indian series it was found with an incidence 13 times more frequently than in the general population (Malhotra *et al.*, 1981).

Skin

Tuberculosis of the skin has become rare, so it may be overlooked. It needs to be distinguished from sarcoidosis and also from other cutaneous mycobacterioses, including leprosy, by histology and by accurate bacteriology.

Pyrexia of unknown origin

Innes (1981) observed tuberculosis presenting as pyrexia of unknown origin in 21 Asian patients in the course of 2 years. There were 13 males and the mean age of the whole series was 37 years. Apart from a constitutional disturbance, fever was the only discernible abnormality. The chest X-ray was always normal, and the tuberculin test was positive in all but one patient. Aspiration liver biopsy revealed granulomas in 12 of 17 patients. Of the patients with abnormal liver biopsies, 11 also had marginally abnormal liver function tests. Eventually, after several weeks, tuberculosis declared itself in lymph nodes in seven patients, was overtly miliary in two, involved meninges, pericardium or pleura once each, and became evident as a psoas abscess in another.

Blood disease

Marrow involvement produces interesting haematological syndromes including leukaemoid reactions, thrombocytopenia, purpura, refractory anaemia or leucoerythroblastic anaemia. The diagnosis remains obscure because the chest radiograph may appear normal and the tuberculin test negative (Twomey and Leavell, 1965; Medd and Hayoe, 1955).

Where to seek out tuberculosis

Defective cell-mediated immunity

Poor cell-mediated immunity occurs in patients with reticuloses, cancer, hepatic cirrhosis, uraemia and in the elderly. Where there is satisfactory cell-mediated immunity, the tuberculin skin test and leucocyte migration inhibition are both positive, the histology shows epithelioid cell granulomas, and the response to antituberculous chemotherapy is excellent. When cell-mediated immunity is poor, there are negative skin test and leucocyte migration inhibition, disseminated lesions and a poor response to antituberculous chemotherapy (Table 2). Poor cellular immunity leads to disseminated disease and a poor outcome.

Genetically determined defective immune responses may account for differences in susceptibility to tuberculosis (Seth, 1981). Differences in cell-mediated immune-response to various mycobacteria have been demonstrated in high-resistance and low-resistance mice (Adu, Curtis and Turk, 1981). Monocyte chemotaxis and macrophage killing are defective in tuberculosis. This could be a factor contributing to the chronicity of the disease (Collins, 1982).

TABLE 2. A spectrum of human tuberculosis, suggested by Lenzini, Rottoli and Rottoli (1977)

Feature	Reactive	Intermediate	Unreactive
Distribution Clinicoradiographic	Localized Micronodular localized	Intermediary Nodular with cavitation and lymphadenopathy fistulas	Disseminated Acute miliary
T cells B cells Histology	Strong Weak Localized lesions with lymphocytes and epithelioid cells	$\pm$ $\pm$ Cavitation with surrounding fibrosis	Weak Exuberant Rapid diffusion of lesions throughout body. Polymorphs and macrophages containing mycobacteria
Tuberculin	Strong induration persisting 72-96 hr	Biphasic reaction erythema/oedema from 3-48 hr (early and late phases)	Negative
Serum anti-tuberculin antibodies	Negative	$\pm$	Positive
Bacilli in sputum tissues	o o	$\pm$ +	+ ++
Leucocyte migration inhibition	+	$\pm$	—
Lymph node germinal centre paracortical	$\pm$ ++	+ +	$\pm$ —
Response to antituberculous chemotherapy	Good	Fairly good	Poor

The elderly

There is evidence of poor cell-mediated immunity in the elderly (James, 1977). If elderly normal subjects have a negative skin test to 100 international units of tuberculin, they will almost certainly also have negative responses to *Candida*, *Aspergillus*, streptokinase-streptodornase and dinitrochlorobenzene. Skin test anergy is associated with a low percentage of peripheral blood T cells and a poor capacity to respond to mitogens such as phytohaemagglutinin. This anergic non-reactive state is associated with latent tuberculosis, which eventually disseminates widely in acute miliary fashion, and often, at this late stage, with a poor response to chemotherapy.

In the United States, new active case rates amount to about 14 per 100,000 population rising to 45.1 in the non-white population and rising still further to 154.7 in non-white males over 65 years old. Three-fifths of new cases occur in those aged over 45 years (United States DHEW, 1976). In a recent Dublin survey, one-third of those with pulmonary tuberculosis were over 65 years of age (Buittleir and Fitzgerald, 1982). Other prominent risk factors were a family history of tuberculosis (in 20.9%), immunosup-

pressive therapy (9.2%), and previous gastrectomy (7.6%).

Migrants

There can be no doubt of the predisposition to tuberculosis in our migrant community from India, Pakistan and Bangladesh. The overall rate of tuberculosis for all ethnic groups is 18.3 per 100,000 population; the rate for the white ethnic group being 10.7, the Indian subcontinent group 38.2 and the West Indian group 31.2 (MRC, 1982a).

Drug addicts

This unfortunate group is prone to a variety of infections, some self-inflicted. Because of their innate lack of resistance and also because of close bodily contact with similar individuals, it is important to keep tuberculosis in mind at all times.

Diabetics

The uncontrolled or unrecognised diabetic is peculiarly prone to tuberculosis, which is liable to be fulminant because of this predisposition. Underlying

tuberculosis should be considered when diabetes becomes unstable or difficult to control. The Dublin survey (Buitléir and Fitzgerald, 1982) showed that diabetes occurred in 4.3% of patients with tuberculosis.

AIDS

Tuberculosis has not been a conspicuous feature of the acquired immunodeficiency syndrome, except in Haitians in whom it is already particularly frequent. A recent survey of 20 heterosexual Haitians resident in Miami identifies their frequent opportunistic infections and Kaposi's sarcoma and an inversion of the normal T helper to T suppressor ratio; all these features are strikingly similar to findings in American homosexuals. Tuberculosis was noted in 10 (50%) and eight of these had widely disseminated disease. In seven patients, disseminated tuberculosis preceded other infections by 2–15 months (Pitchenik *et al.*, 1983).

The way ahead

The MRC Tuberculosis and Chest Diseases Unit is undertaking a second survey during 1983, and the Biostatistics Unit is assessing the efficacy of BCG vaccination in preventing tuberculosis among young adults. The preventive efficacy of BCG for British schoolchildren was at a very high level, but it is important to analyse whether this benefit continues. In the age-group 15–24 years, the incidence of tuberculosis is now halving every 5 or 6 years and the benefits of schools' BCG vaccination scheme may also be diminishing to the same extent.

References

- ADU, H.O., CURTIS, J. & TURK, J.L. (1981) Differences in cell-mediated immune responses of 'high-resistance' and 'low-resistance' mice to a nonpathogenic mycobacterium. *Scandinavian Journal of Immunology*, **14**, 467.
- BEHR, G., PALIN, H.C. & E TEMPERLEY, J.M. (1977) Myocardial tuberculosis. *British Medical Journal*, **1**, 951.
- BUTLEIR, M. & FITZGERALD, M.X. (1982) The changing profile of tuberculosis in a general teaching hospital—a five-year review of 121 cases. *Irish Medical Journal*, **75**, 390.
- CHAPMAN, J.S. (1977) *The Atypical Mycobacteria and Human Mycobacteriosis*. Plenum Medical Book Company, London.
- COLLINS, F.M. (1982) The immunology of tuberculosis. *American Review of Respiratory Diseases*, **125**, 42.
- CUNNINGHAM, D., MILLO, P.R., QUIGLEY, M.M., PATRICK, R.S., WATKINSON, G., MACKENZIE, J.F. & RUSSELL, R.I. (1982) Hepatic granulomas: Experience over a 10-year period in the West of Scotland. *Quarterly Journal of Medicine*, **51**, 162.
- DENT, D.M. & WEBBER, B.L. (1977) Tuberculosis of the breast. *South African Medical Journal*, **51**, 611.
- DEPARTMENT OF HEALTH AND SOCIAL SECURITY (1977) *On the state of the Public Health for the year 1976*. Annual Report of the Chief Medical Officer. Her Majesty's Stationery Office, London.
- EDITORIAL (1977) Abdominal tuberculosis in Britain. *British Medical Journal*, **1**, 1557.
- FINDLAY, J.M. (1982) Medical management of gastrointestinal tuberculosis. *Journal of the Royal Society of Medicine*, **75**, 583.
- GUILLET, J.L., SALMON, R.J., DURAND, J.C. & PILLERON, J.P. (1982) Mammary tuberculosis. *Lancet*, **ii**, 166.
- INNES, J.A. (1981) Non respiratory tuberculosis. *Journal of the Royal College of Physicians, London*, **15**, 227.
- JAMES, D.G. (1977) Immune dysfunction when the body's defences give up. *Modern Geriatrics*, **7**, 25.
- KLATSKIN, G. (1976) Hepatic granulomata: problems in interpretation. *Annals of the New York Academy of Sciences*, **278**, 427.
- LENZINI, L., ROTTOLI, P. & ROTTOLI, L. (1977) The spectrum of human tuberculosis. *Clinical and Experimental Immunology*, **27**, 230.
- MALHOTRA, K.K., PARASHAR, M.K., SHARMA, R.K., BHUYAN, U.N., DASH, S.C., KUMAR, R. & RANA, D.S. (1981) Tuberculosis in maintenance haemodialysis patients. Study from an endemic area. *Postgraduate Medical Journal*, **57**, 492.
- MALLINSON, W.J.W., FULLER, R.W., LEVISON, D.A., BAKER, L.R.I. & CATTELL, W.R. (1981) Diffuse interstitial renal tuberculosis—an unusual cause of renal tuberculosis. *Quarterly Journal of Medicine, New Series L*, **198**, 137.
- MEDD, W.E. & HAYHOE, F.G.J. (1955) Tuberculous miliary necrosis with pancytopenia. *Quarterly Journal of Medicine*, **24**, 351.
- MODAI, D., WEISSGARTEN, J., REIFF, R., SIEGAL, B. & GABIZON, D. (1984) Breast mycobacterial infection in a haemodialysis patient. *Postgraduate Medical Journal*, **60**, 164.
- MRC TUBERCULOSIS AND CHEST DISEASES UNIT (1982) The geographical distribution of tuberculosis notifications in a national survey of England and Wales (1978–1979). *Tubercule*, **63**, 75.
- Ibid. (1982b) Tuberculosis in children. *Archives of Disease in Childhood*, **57**, 734.
- NAUGHTEN, E., WEINDLING, A.M., NEWTON, R. & BOWER, B.D. (1981) Tuberculous meningitis in children. Recent experience in two English centres. *Lancet*, **ii**, 973.
- NEVILLE, E., PIYASENA, K.H.G. & JAMES, D.G. (1975) Granulomas of the liver. *Postgraduate Medical Journal*, **51**, 361.
- NIELSEN, H., BENNEDSEN, J., LARSEN, S.O., RHODES, J.M. & VISKUM, K. (1982) Defective monocyte chemotaxis in pulmonary tuberculosis. *European Journal of Respiratory Diseases*, **63**, 122.
- PITCHENIK, A.E., FISCHL, M.A., DICKINSON, G.M., BECKER, D.M., FOURNIER, A.M., O'CONNELL, T., COLTON, R.M. & SPIRA, T.J. (1983) Opportunistic infections and Kaposi's Sarcoma among Haitians: Evidence of a new acquired immunodeficiency state. *Annals of International Medicine*, **98**, 277.
- ROVIRA, M., ROMERO, F., TORRENT, O. & IBARRA, B. (1980) Study of tuberculous meningitis by CT. *Neuroradiology*, **19**, 137.
- SAKULA, A. (1979) Robert Koch (1843–1910). Founder of the Science of Bacteriology and discoverer of the tubercle bacillus. *British Journal of Diseases of the Chest*, **73**, 389.
- SETH, V., MALAVIYA, A.N., SAHAI, V., ARORA, N. & SUNDARAM, K.R. (1981) Cell mediated immune response in childhood tuberculosis. *Indian Journal of Medical Research*, **73**, 68.
- SHUKLA, H.S., BHATIA, S., NAITRANI, Y.P., DAS, P. & GUPTA, S.C. (1982) Peritoneal biopsy for diagnosis of abdominal tuberculosis. *Postgraduate Medical Journal*, **58**, 226.
- SMITH, A.M. (1977) Abdominal tuberculosis in Britain. *British Medical Journal*, **2**, 263.
- TAYLOR, L.M., SMITH, H.V. & HUNTER, G. (1954) The blood C.S.F. barrier to bromide in the diagnosis of tuberculous meningitis. *Lancet*, **226**, 700.
- TWOMEY, J.J. & LEAVELL, B.S. (1965) Leukaemoid reactions to tuberculosis. *Archives of Internal Medicine*, **116**, 21.
- UNITED STATES DEPARTMENT OF HEALTH, EDUCATION AND WELFARE (1976) *Tuberculosis in the United States*. HEW Publication No. (CDC), 76–8322.

(Accepted 24 May 1983)