Non-Respiratory Tuberculosis

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Between the years 1963 and 1979 annual notifications of respiratory tuberculosis in England and Wales fell by half, from 16,000 to 8,000. During the same period, notifications of non-respiratory tuberculosis remained almost constant at 2,500 cases per annum (Fig. 1).

![Figure 1. Annual notifications of respiratory and non-respiratory tuberculosis in England and Wales from 1963 to 1979.](image)

Analysis of these figures by ethnic group reveals that the decline in non-respiratory notifications in the white population has been considerably slower than the decline in respiratory disease. At the same time, the number of notifications of non-respiratory tuberculosis among the immigrant population, particularly those from the Indian sub-continent, has risen considerably. A recent survey of tuberculosis notifications in England and Wales showed that the incidence of non-respiratory tuberculosis is about 80 times higher in immigrants from India, Pakistan and Bangladesh than in the white population and confirmed that disease in non-respiratory sites makes up a greater proportion of cases in these immigrants (Table 1)[1].

### Pathogenesis

There are six pathogenetic mechanisms whereby tuberculous disease may arise at non-respiratory sites.

**Non-pulmonary Primary Infection**

Non-pulmonary primary tuberculosis is now seldom seen in the UK but was formerly of considerable importance as a cause of abdominal tuberculosis following the consumption of milk contaminated with *Mycobacterium bovis*. Primary infection of the skin and mucous membranes may arise from direct inoculation of organisms expectorated by patients with pulmonary disease and may be favoured by local trauma. The risk of spread of infection from tuberculous patients without pulmonary disease can generally be ignored, but occasionally venereal spread from men with tuberculous epididymitis may cause primary infection of the vulva[2].

**Lymphatic Spread from a Pulmonary Primary Complex**

In primary pulmonary infection, mycobacteria spread by the lymphatics from the Ghon focus to the regional lymph nodes at the hilum of the lung. In a proportion of cases the organism passes on to the mediastinal nodes and from there to the posterior triangle of the neck. The clinical expression of disease at these sites and, in the case of the intrathoracic elements, their radiographic visibility, are very variable. In an individual patient, foci of disease may be detectable in the lung or in hilar, mediastinal or cervical lymph nodes or in any combination of these sites. Infection in the lymph nodes of the neck arising from this source or as a result of primary infection of the face, mouth or tonsil may remain quiescent for years before reactivation leads to clinical presentation with post-primary cervical adenitis.

**Haematogenous Spread from a Primary Complex**

The most dramatic result of haematogenous spread from a primary complex is acute miliary disease. This usually occurs within a year of primary infection and is most
common in the youngest patients. Miliary tuberculosis is reported to complicate 15 to 20 per cent of cases of untreated primary infection in children below the age of one year[3]. The most specific clinical sign of miliary tuberculosis is the presence of choroidal tubercules, though these lesions may also be seen in some patients with tuberculous meningitis without radiographic evidence of miliary spread. It is important to remember that miliary and meningeal tuberculosis frequently co-exist. Lumbar puncture should be performed in any patient with miliary disease in whom the least suspicion of meningeal involvement arises.

Haematogenous dissemination of infection from a primary complex may fall short of producing acute miliary disease but be sufficient to establish metastatic foci of infection at distant sites. Occasionally, these produce clinically apparent disease at an early stage (usually in bone) but more commonly the lesions remain quiescent for long periods before reactivation leads to presentation with post-primary non-respiratory tuberculosis. The most frequent sites of such manifestations are the skeletal and the genito-urinary systems but almost any organ may be involved.

The most common site of bony tuberculosis is the spine. Classically the lesion starts at one of the anterior angles of the vertebral body, causing progressive destruction of the body, loss of the disc space and involvement of the contiguous vertebra. Anterior collapse may follow, with angulation of the spine. Radiological examination often shows a paravertebral abscess and this may be present before any obvious bony abnormality appears.

Spinal tuberculosis in Asian immigrants may not conform to the above description but often presents with involvement of the posterior angles of the vertebral body, elements of the neural arch or the transverse process[4]. Although clinical evidence of bony tuberculosis is generally confined to one site, multiple lesions are often present and may be detected by radiographic survey or by isotope bone scanning.

Tuberculous infection of the kidney generally produces little constitutional disturbance but gives rise to local urinary symptoms which by their persistence lead to investigation by pyelography and culture of the urine for M. tuberculosis. Direct microscopic examination of the urinary sediment for acid-fast bacilli should not normally be undertaken, as it cannot distinguish between pathogenic mycobacteria and others that may contaminate specimens of urine. It is often said that there is no point in culturing urine for mycobacteria if pus cells are not present. While this may be true in the investigation of patients with urinary symptoms, it is not necessarily the case in other forms of tuberculosis. Positive urine cultures for M. tuberculosis are frequently obtained in otherwise normal specimens from patients with acute miliary tuberculosis, and from a smaller proportion of patients with 'uncomplicated' primary infection or post-primary infection at non-urinary sites (Table 2).

Tuberculous meningitis presents some of the most difficult problems of diagnosis and management. It may occur on its own or in association with acute miliary disease. In either case the clinical features are generally...
Table 2. Positive urine cultures for *Mycobacterium tuberculosis* in 88 cases of 'non-urinary' non-respiratory TB.

| Conventionally recognised site       | Urine microscopy | Number |
|-------------------------------------|------------------|--------|
| Acute miliary                       | Neg              | 2      |
| Subacute disseminated               | Neg              | 2      |
| Cervical adenitis                   | Neg              | 1      |
| Uterus                              | Neg              | 1      |
| Carpal bones                        | Pyuria           | 1      |
| Total                               |                  | 7      |

Those of a feverish illness starting with apathy, malaise and anorexia followed by general symptoms of meningitis and, subsequently, by focal neurological signs and disturbance of consciousness. These features usually develop over a period of one to two weeks. Correct diagnosis is a matter of great urgency, as delay in treatment of only a few days may greatly reduce the prospects of complete recovery. The diagnosis depends on CSF examination. Although the characteristic abnormality is of lymphocytosis with elevation of protein and depression of glucose levels, cases are described in which the CSF was initially normal or showed a preponderance of polymorphs. Difficulty may also arise where the CSF contains an excess of lymphocytes but the abnormality in protein or glucose is minimal. In such cases, if the suspicion of tuberculous infection is raised by the clinical features but no definite neurological abnormality is present, it is reasonable to observe the patient for twenty-four hours, performing a chest X-ray to detect miliary disease and repeating the lumbar puncture. If after this time there has been no improvement it is best to start anti-tuberculosis treatment. Under these circumstances the evolution of the illness and of the abnormality of the CSF over the following two or three weeks is likely to be of help in deciding on the correct diagnosis.

**Haematogenous Spread from a Post-primary Lesion**

Blood-borne spread of tubercle bacilli from an active post-primary lesion can cause acute miliary disease. With the decline in the incidence of infantile primary tuberculosis in the UK, this pathogenic mechanism has assumed greater importance as a cause of acute disseminated forms of the disease. It is particularly likely to happen in the elderly and in those with immuno-deficiency. In such patients there may be no abnormality of the chest X-ray and histologically the cellular reaction may be irregular and non-specific. Conversely, Ziehl-Neelsen staining of biopsy material may show many organisms to be present. Such cases are often referred to as 'cryptic' or 'areactive' miliary tuberculosis. The diagnosis may be very difficult to confirm, and treatment often has to be started speculatively. The rising age incidence of disseminated tuberculosis over the past 60 years in the UK is shown in Table 3.

**Contiguous Spread from Organ to Organ**

When suppuration occurs at sites of tuberculous infection it is common to find that the resultant pus spreads to
involve the surrounding tissues and often makes its way to the surface of the body. The most frequent clinical examples of this mechanism are externally discharging infections in superficial lymph nodes and in bone. By the same mechanism, infection may spread to the serous membranes from hilar, mediastinal or mesenteric lymph nodes. Characteristically, pleural, pericardial and peritoneal tuberculosis present with a combination of local and systemic symptoms and signs. As the bacterial population of the associated effusion is generally too small to allow them to be identified by direct microscopy, biopsy of the involved membrane is the only way to obtain immediate confirmation of the diagnosis. If this cannot be done, treatment will have to be given on the basis of clinical suspicion and the exclusion, as far as possible, of alternative causes of the illness. These patients generally show a high degree of tuberculin sensitivity, and a negative tuberculin test casts serious doubt on the diagnosis of serous membrane tuberculosis.

**Epithelial Implantation**

Tubercle bacilli shed from a site of active infection may become implanted in healthy epithelial surfaces over which they pass as they are discharged from the body. The best example of this method of spread is infection of the larynx, which was formerly a common development in patients dying of extensive pulmonary disease and whose sputum contained large numbers of bacilli. Infected sputum may also cause ulceration in the alimentary canal down which it passes after being swallowed. In both these cases the local clinical features are usually overshadowed by symptoms and signs of the associated pulmonary disease.

Epithelial implantation also explains the frequent involvement of the ureter in cases of renal tuberculosis. Ureretic lesions are important because they may lead to stricture formation which often does not appear until after the start of treatment. For this reason, all patients with renal tuberculosis should have the patency of the ureters checked by pyelography or isotope renography six weeks after starting treatment.

**Tuberculosis Presenting as Pyrexia of Uncertain Origin**

Most patients with tuberculosis present with local signs or symptoms that may be accompanied by constitutional disturbance; a small proportion present with constitutional disturbance only, and no clinical focus of infection.

**Table 3.** Age incidence of disseminated tuberculosis. (Courtesy British Journal of Hospital Medicine.)

| Author | Peak age incidence (years) | Over 60 years (%)
|--------|---------------------------|-----------------|
| Hartwich, 1922 | 10 | 13 |
| Chapman and Whorton, 1946 | 20-30 | 30 |
| Biehl, 1958 | 60-70 | 41 |
| Proudfoot et al., 1969 | 70-80 | 57 |

patients and 12 showed granulomas. Of the patients with abnormal liver biopsies, 11 also had marginally abnormal liver function tests. Although all of these patients ultimately made good recoveries, their progress on treatment was marked by a variable speed of remission of fever, ranging from 2 to 28 days, and by the frequency with which focal tuberculous infection became evident during the first six weeks of treatment (Table 5). Because of the unpredictable early course of these patients’ illnesses, the use of a combination of two narrow spectrum antituberculosis drugs, such as isoniazid and ethambutol, to perform a diagnostic trial of therapy is inadvisable, as it is difficult to identify a satisfactory end-point. Furthermore, the appearance of active disease at new sites during treatment may raise doubts about the initial choice of drugs and provoke inappropriate alterations in treatment. If there are sufficient grounds for starting anti-tuberculosis treatment, it should be started with three drugs and be continued to its conclusion, unless a positive alternative diagnosis can be made to explain the patient’s illness.

**Table 4.** Tuberculosis presenting as pyrexia of uncertain origin in Asian adults, Department of Communicable and Tropical Diseases, East Birmingham Hospital, 1978–1980.

| No. of patients: | 21 |
| Sex: | 13 male, 8 female |
| Mean age: | 37 years (range 18-65) |
| Symptoms and signs: | Constitutional disturbance, Pyrexia, Otherwise well, No clinical focus of infection |
| Mean duration of illness: | 9 weeks (range 1-52) |
| Chest X-ray: | Normal |
| Tuberculin test: | Positive in 20/21 ( >5 mm induration to 10 TU) |

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**Table 5.** Tuberculosis presenting as pyrexia of uncertain origin in Asian adults; frequency and site of late focal disease in 21 patients.

| Site | Number |
|------|--------|
| Lymph node | 7 |
| Overt miliary | 2 |
| Meninges | 1 |
| Pericardium | 1 |
| Pleura | 1 |
| Psoas abscess | 1 |

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**Conclusion**

Non-respiratory tuberculosis in England and Wales is as common now as it was 16 years ago. However, over this period there have been changes in the distribution of patients by ethnic group and in the varieties of clinical presentation.
Most non-respiratory tuberculosis causes local symptoms and signs and the diagnosis can be confirmed by conventional methods of bacteriology, histology and radiology. In the small number of patients who have constitutional disturbance but no evidence of focal infection, the diagnosis may be supported by techniques such as liver biopsy and culture of the urine.

Whatever the variety of tuberculosis, the first step towards early diagnosis is clinical suspicion. The doctor who understands the natural history of the disease and the pathogenesis of its different forms will be in the best position to recognise and investigate the patient with non-respiratory tuberculous infection.

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References
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Cause of Death?

The OPCS Mortality Statistics are not, one imagines, everyone’s favourite bedside reading. If they were, Section XVI would quickly reveal that many patients die from natural causes without it being possible to affix a satisfactory diagnostic label. Rubric 790 (Nervousness and debility) shows that you can in fact still be frightened to death and, during the five years 1974-78, 76 deaths were so attributed. Moreover, Rubric 795 shows that you can die from ‘Observation, without need for further medical care’, and Rubric 791 that ‘Headache’ can still be fatal, but no deaths were recorded from these causes during the last quinquennium for which records have been published. Rubric 795 ‘Sudden death (cause unknown)’ accounted for 1,471 deaths in England and Wales in 1978, nearly all cot deaths, regarding the nature of which we know so little.

In their quest for sensationalism the media flatter the medical profession by trying to convince the public that today any failing organ can be replaced, that the cure for cancer is just around the corner and that ever-lasting life (God forbid) is in sight. In the USA a gullible and avaricious populace is increasingly convinced that medical practice is simple and foolproof and that if a doctor’s results fall short, for comparative purposes, of those achieved by Jack Nicklaus on the golf course, they are entitled to damages sufficient to enable them to live in idleness and luxury for ever. Sadly, these attitudes show signs of crossing the Atlantic and distinguished but unhappy members of our profession find themselves supporting claims that owe their existence and success to Legal Aid and the knowledge that a defence organisation will pay, and that the judge will be generous, despite the fact that he has no medical knowledge to equip him to make a judgement.

While no one would wish to diminish the confidence of the public in their physicians, it would be a very important service to medicine and to the patients it strives to help if its abilities were not exaggerated.

The Medical Services Study Group studied 1,220 medical deaths under the age of 50, in 23 of which it was impossible to say with certainty from what the patient died. The position is typified by a letter from a modest, able and experienced physician, to the general practitioner ‘We were in some difficulty in placing a label on her, and I am afraid the P.M. did not make the situation very much clearer.’ In 15 of the 23 patients an autopsy was carried out and in six this included histology. Though death was clearly due to natural causes in all the patients and everything possible and justifiable in investigation and treatment was done, the certified cause of death was not likely to be correct in all cases. To give just one example, a man of 26 was admitted with a history of dyspnoea and swollen, painful calves for one week. He was confused, restless and cyanosed. His pulse rate was 120, his liver was enlarged and his ECG showed right ventricular strain. All other investigations were negative. He was thought to have thrombo-embolic disease but despite anti-coagulant and supportive therapy he died within 48 hours. Autopsy showed pulmonary oedema (but no emboli), pleural effusions, an enlarged heart with normal coronary arteries, a congested liver and normal leg veins. Histology of the heart and lungs showed only oedema and of the liver centrilobular congestion and fatty change. The death certificate ‘Pulmonary embolus, deep venous thrombosis’ was later amended to ‘Cardiomyopathy’, which is doubtless the most accurate diagnosis that could have been made but which is only marginally better than ‘morbis cordis’.

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