9

The Management of Extrapulmonary Tuberculosis

L.P. Ormerod

1. Introduction

Although not as frequent numerically as pulmonary and intrathoracic tuberculosis (TB), extrapulmonary forms of TB make up an important proportion of all forms of TB. Indeed, there is some evidence in developing countries that the level of extrapulmonary TB has stayed fairly constant, in the presence of falling levels of respiratory TB, thereby causing the proportion of TB at extrapulmonary sites to rise relative to respiratory TB (1).

In England and Wales, in the most recently published national survey of TB notifications in 1988 (2), 32% of previously untreated patients had extrapulmonary disease. There were important ethnic differences, with 57% of all nonrespiratory disease coming from the 3% of the population of Indian subcontinent (ISC) ethnic origin. Even within nonpulmonary sites, there were ethnic differences. In both white and ISC ethnic groups, lymph node disease was the commonest, with 37% and 52% of cases, respectively, but abdominal TB in the white ethnic group (6%) was under half that of the ISC ethnic group (14%), whereas, conversely, genitourinary TB was much commoner in the white ethnic group (28%) than in the ISC ethnic group (4%) (Table 9.1).

An earlier Medical Research Council (MRC) study in England and Wales in 1983 gave a more detailed breakdown of extrapulmonary sites and incidence (3) and showed that although the overall rate of TB in the ISC population was 25 times that of the white ethnic group, the rate was 51 times higher for extrapulmonary disease. Once again, there were considerable differences between extrapulmonary sites, with the difference in rates between the main ethnic groups

P. R. J. Gangadharam et al. (eds.), *Mycobacteria*

Table 9.1. Extrapulmonary disease in England and Wales in 1988

	Total		White		ISC[a]		Other	
Site	No.	%	No.	%	No.	%	No.	%
Lymph node	329	44	86	37	205	52	38	54
Bone and joint	87	12	31	13	51	13	5	7
Genitourinary	84	11	65	28	16	4	3	4
Abdominal	84	11	14	6	57	14	13	19
CNS	36	5	10	4	21	5	5	7
Miliary	51	7	19	8	27	7	5	7
Abscess	27	4	10	4	14	4	3	4
Other	54	7	18	8	32	8	4	6
Total sites	752		253		423		76	
Total patients[b]	698		233		395		70	

[a]Indian sub-continent (ISC).

[b]Some patients had disease at more than one site.

Source: Ref. 2.

"With permission from Thorax and from Dr. Janet Darbyshire of the MRC Cardiothoracic Epidemiology Group"

ranging from 72 times higher for lymph node disease but only 10 times higher for genitourinary disease.

A rise in the proportion of TB at extrapulmonary sites has not only been seen in the United Kingdom (1) but also in other developed countries. In the United States in 1964, 8% of reported TB was extrapulmonary, which increased to 15% in 1981 and 17.5% in 1986 (4,5). A rise in extrapulmonary TB has also been reported in Hong Kong (6) from 1.2% in 1967 to 6.6% in 1990.

One other factor which plays a part in the increasing proportion of extrapulmonary TB in some situations is HIV coinfection. Not only are such persons more likely to develop TB but also particularly extrapulmonary forms, which occur in over 50% of all such TB/HIV coinfected cases (7). There is also evidence that disease at some extrapulmonary sites such as the central nervous system or lymph nodes are more commonly affected in HIV-coinfected persons than in those without such coinfection (8).

The increase in the proportion of extrapulmonary TB in developed countries such as the United States and the United Kingdom is largely due to the effects of immigration from Third World countries. This trend together with HIV coinfection in the United States and HIV alone in Africa, Asia, and South America will make the diagnosis and management of extrapulmonary tuberculosis most important (9–13). The recognition of extrapulmonary TB has not been helped by the generally falling prevalence of TB, until recently, and hence declining clinical experience. The reduced physician experience, coupled with presentations that

may be of gradual onset or atypical, may mean that TB is not considered in the differential diagnosis for some time during which further morbidity, or even death, can occur. In the less developed world, the problems of diagnosis are compounded by a lack of diagnostic resources, with few forms of extrapulmonary TB being positive on microscopy. Empirical treatment, or trials of treatment, will therefore more likely be given on clinical grounds only, without pathological and/or bacteriological support or confirmation.

2. Lymph Node Tuberculosis

Over 80% of lymph node TB is in cervical lymph nodes, with a small number of cases involving axillary, inguinal, and chest wall nodes (14). In England and Wales, it is most often seen in ISC immigrants in whom it accounts for over 50% of extrapulmonary disease (2). Lymph node disease accounts for 45% of extrapulmonary forms in Hong Kong (6) and 30% in the United States (15).

Mycobacterium bovis, which in the past accounted for a significant proportion of lymph node disease, is now less common, *M. tuberculosis* being the most frequent isolate (16). In young children in developed countries, particularly aged under 5, lymph node disease caused by *M. avium-intracellulare* can simulate TB histologically. If such atypical organisms are isolated, showing a nontuberculous mycobacterial lymphadenopathy, treatment is by surgical excision, not by drug treatment.

The source of infection in lymph node disease is usually by reactivation of disease originally disseminated during the initial primary airborne infection in the lung. Such reactivation occurs, as at other sites, when body defense mechanisms weaken, allowing local reactivation at previously contained sites. Primary lymph node infection and lymphatic spread from adjacent sites also occur. In the United Kingdom, 10% of cervical lymph node disease in ISC patients have associated mediastinal lymphadenopathy (2,3), suggesting retrograde spread from mediastinal to cervical nodes. A prospective study of the source of cervical lymph node TB infection (17), while showing one-third had evidence of current or previous lung TB suggesting earlier dissemination from a pulmonary source, also showed 6% had nasopharyngeal TB and that cervical nodes were part of the primary local infection.

In developed countries, the peak incidence of lymph node disease is between 20 and 40 years of age (18), but in high-prevalence countries, it is highest in childhood. In the ISC ethnic group, there is a female preponderance of this form of disease (19), for which deficiency of vitamin D has been invoked as an explanation.

3. Clinical Features

The lymph node enlargement in TB is usually gradual and painless, but it can occasionally be more rapid and painful. The individual nodes are firm and discrete (Fig. 9.1) but may later become matted together and fluctuate. There is seldom any accompanying erythema or warmth, the so-called "cold abscess." Unless treatment is begun at this stage, the nodes may proceed to discharge with resultant sinuses, superficial abscesses, and scarring. In immunosuppressed patients, the

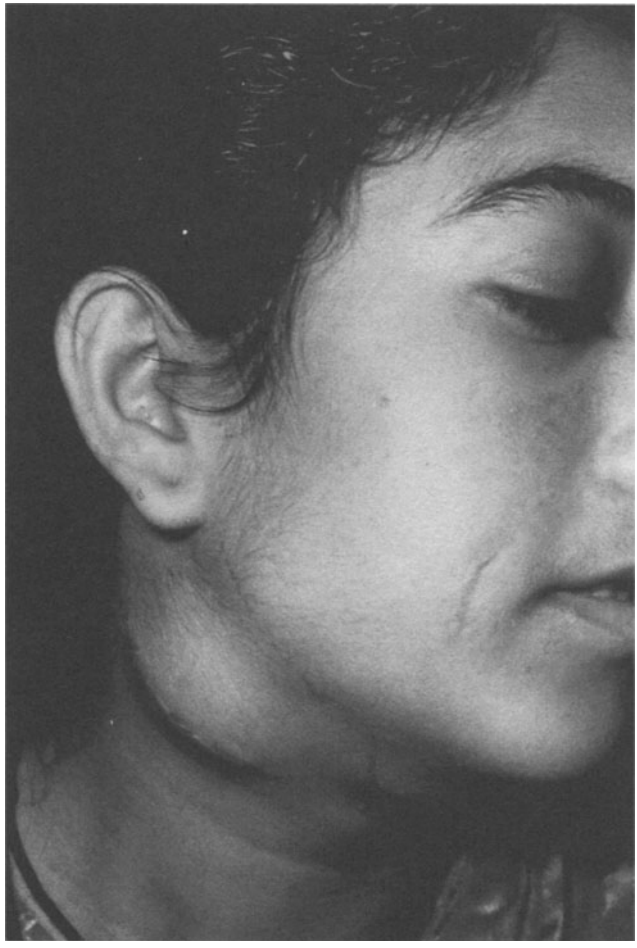

Figure 9.1. Cervical lymphadenopathy in an Asian female; caseating granulomata on biopsy, positive culture for *M. tuberculosis.*

presentation may mimic acute pyogenic infection with marked local pain, swelling, and erythema.

Constitutional features such as fever, weight loss, night sweats, and malaise are seen in a minority of patients, but they are usually absent. There may be clinical or x-ray evidence of tuberculosis elsewhere, usually with either pulmonary parenchymal or mediastinal lymph node involvement (2,3), the latter commonly in ISC or African ethnic patients.

4. Diagnosis

In many developing parts of the world, lymph node tuberculosis is diagnosed clinically from the typical features, sometimes supported by a strongly positive tuberculin skin test. Strictly, the diagnosis depends on the demonstration of *M. tuberculosis* or *M. bovis* in pus or aspirates from nodes. Acid-fast bacilli, however, are only seldom seen on direct smear from such samples, because the actual number of bacilli in infected nodes is small. The majority of the clinical features are not due to the bacterial infection per se but to the marked immunological response to mycobacterial antigens, mainly tuberculoproteins. Acid-fast bacilli are more often seen on smears from biopsy samples from lymph nodes (20), but the positive culture rate only reaches 50–70% (14,18,20,21).

Biopsy of glands shows a spectrum of histology from mild reactive hyperplasia and granulomas through extensive necrosis and caseation. Lymph node biopsy is sometimes carried out because TB is not suspected, but as a diagnostic procedure because of the clinical suspicion of lymphoma or secondary carcinoma. It has been shown that excision biopsy does not speed up healing or enable shorter treatment to be given (14,18). It should be borne in mind that granulomatous histology, particularly if the granulomas are noncaseating, can be caused by fungal infections, brucellosis and sarcoidosis, and, typically, "tuberculous histology" with acid-fast bacilli on microscopy by nontuberculous mycobacteria. Fine-needle aspiration cytology (FNAC) has been shown to have a high specificity (22), and showing granulomatous changes in between 71 and 83% (22–25) in combination with a positive tuberculin skin test (24) is an acceptable alternative to surgical biopsy.

5. Treatment

Several controlled prospective studies over the last 15 years have established the role of chemotherapy as the main treatment for lymph node tuberculosis. A study in the 1970s showed that 18 months' treatment with either isoniazid/rifampicin or isoniazid/ethambutol supplemented by 2 months of initial streptomycin gave good clinical results (26). This was followed by a British Thoracic Society

study which compared 18-month and 9-month regimens of isoniazid/rifampicin, each supplemented by initial ethambutol for 2 months. The 9-month regimen performed just as well during treatment (27) and during 5 years of follow-up (28) when there were no clinical or microbiological relapses; good cosmetic results were obtained with both regimens.

On theoretical grounds, pyrazinamide should be superior to ethambutol in the initial phase of treatment (29), as it acts at intracellular pH, is bactericidal rather than bacteriostatic, and can reach bacteria sequestered inside macrophages or lymphocytes. A retrospective study which compared speed of radiological improvement in mediastinal lymph node tuberculosis with 12 months of isoniazid/rifampicin, supplemented by either ethambutol or pyrazinamide for the initial 2 months (30), showed that the pyrazinamide group responded more rapidly at 2, 5, and 7 months. Following this study, the British Thoracic Society Research Committee carried out a further controlled prospective study of short-course chemotherapy in lymph node tuberculosis. This third study (31) compared two 9-month regimens of isoniazid/rifampicin supplemented by either ethambutol or pyrazinamide for the initial 2 months, with a 6-month regimen of isoniazid/rifampicin supplemented by 2 months' initial pyrazinamide. During treatment, there were no differences among the three regimens in terms of resolution of lymph nodes, or the proportion with residual lymph nodes (31). However, repeat aspiration after commencement of treatment was more common in the ethambutol-treated patients ($p = .005$). Follow-up for 30 months from commencement of treatment (32) showed no differences in enlargement of glands, development of new glands or sinuses, or in the proportions with residual lymph nodes. In the follow-up period, there were nine cases where the clinician felt relapse had occurred, but no bacteriological confirmation was obtained in the five cases where material was cultured.

The most recent short-course regimen trial (32) gave prospective confirmation to the retrospective clinical series of McCarthy and Rudd (33) that a regimen of isoniazid/rifampicin supplemented by 2 months of pyrazinamide is satisfactory for lymph node tuberculosis with sensitive organisms. This regimen is now recommended as standard treatment in the United Kingdom (34). Short-course treatment, but with a different regimen, has also been shown to give a 97% success rate in children in India (35). The regimen used in this trial (34) was thrice-weekly supervised isoniazid/rifampicin/pyrazinamide/streptomycin followed by twice-weekly outpatient isoniazid/streptomycin for 4 months.

In all three of the British trials on lymph node tuberculosis, enlargement of existing nodes and development of new nodes were reported (27,31,36), as was the development of new glands after cessation of treatment or enlargement of persistent nodes which were residual at the end of treatment (26,28,32). The persistence of lymphadenopathy at the end of treatment, and particularly the development of lymph node enlargement or new lymphadenopathy during or after

treatment, causes concern to physicians who are not experienced with treating lymph node disease. This might lead to unnecessary extension of treatment or the reintroduction of treatment on the basis of "relapse." Such events occur in a significant minority of treated patients and do not of themselves mean that progress is adverse. In the 1985 (27) and 1992 (31) studies 12% and 16–22%, respectively, developed new lymph nodes during treatment. After cessation of treatment, similar rates of persistent lymphadenopathy at the end of treatment and development of new nodes of 9% and 11% (28) and 15% and 5% (32) were reported. These nodes, if biopsied, are usually negative on culture (32), and although clinical "relapse" may be diagnosed, they are bacteriologically sterile. It is more than likely that such phenomena are immunologically mediated, being due to hypersensitivity to tuberculoprotein perhaps from disrupted macrophages (27) and may not indicate an unfavorable outcome.

Surgical excision or biopsy plays no part in the treatment of lymph node disease; patients without surgical intervention did just as well as those with such intervention (27,28). Surgical biopsy, however, may be carried out as a diagnostic procedure to obtain both material for histology and culture if aspiration or fine-needle aspiration cytology (22–25) is not used. Surgical biopsy may, however, have a role in obtaining adequate material for culture, and surgical excision is the treatment of choice for nontuberculous mycobacterial lymphadenopathy (37,38).

The success of short-course therapy (28,32) has been shown for fully sensitive organisms but may not apply to isolates with significant drug resistance (e.g., to isoniazid). In the U.K. studies, there was an increasing incidence of isoniazid resistance over time with 0/32 in 1977 (36), 0/29 in 1985 (27) but 13/108 (12%) in 1992 (31). The 6-month regimen (32) is therefore only applicable to fully sensitive organisms and may have to be modified for isoniazid-resistant organisms to a longer period of therapy with rifampicin/ethambutol (34).

6. Bone and Joint Tuberculosis

Bone and joint tuberculosis presents several years after the initial respiratory infection (39), tubercle bacilli becoming hematogenously spread at that time, with a predilection for the spine and the growing ends of long bones lying dormant until clinical disease occurs. In developed countries, orthopedic tuberculosis makes up some 15–20% of extrapulmonary sites, but with a substantially higher incidence in immigrant groups (3). This study (3) showed rates of 0.2/100,000 and 16/100,000 in white and ISC ethnic groups, respectively.

7. Spine

The spine is the commonest site of orthopedic tuberculosis (40,41). The usual presenting symptom is back pain which can have been present for months and

occasionally longer. More unusual presentations with radicular pain mimicking abdominal conditions (42) or with referred neurological symptoms involving legs and sphincters due to spinal cord compression also occur. Local tenderness or slight kyphosis may be found, with progression to grosser kyphosis in advanced disease. Paraspinal abscesses not uncommonly accompany spinal tuberculosis; these can progress to psoas abscess which appears or discharges in the groin, being the presenting feature in some cases, with associated psoas spasm causing hip flexion.

7.1. Diagnosis

This can be delayed in low-prevalence groups because the condition is now very uncommon (41,43). Spinal infection usually commences in the intravertebral disk, and this discitis then spreads by means of the longitudinal and anterior spinal ligaments to involve the vertebral bodies above and below the disk. Thus, x-rays show erosion of the superior and inferior borders of the adjacent vertebrae and loss of disk space. The disease progresses with increasing destruction of the vertebrae, and loss of height and development of kyphosis at that level (Fig. 9.2). The lumbar and thoracic spine are the usual sites of involvement, with the cervical spine being less commonly involved. The disease usually involves a single intravertebral space, but multiple levels can be involved, in some cases with normal vertebrae between involved areas.

Developments in imaging have helped in the diagnosis and assessment of spinal tuberculosis. Computerized tomography (CT) may show involvement before the changes are apparent on plain x-ray (44) and can be better at defining the extent of involvement (44–46). Associated paravertebral and psoas abscesses are well demonstrated (Fig. 9.3). Nuclear magnetic resonance (NMR) imaging is also useful (47,48), with T_2-weighted images demonstrating epidural inflammation (48). The ability of NMR images to be reconstituted in both vertical and horizontal planes can enable full assessment of the extent of disease to be made (49).

Only a minority of cases have evidence of associated pulmonary tuberculosis, but when occurring together with classical spinal x-ray appearances, clinical diagnosis can be made without biopsy. Needle or open biopsy may be needed to make a diagnosis in isolated spinal disease. Unless tuberculosis is considered in the differential diagnosis, appropriate cultures may not be taken for both mycobacterial and pyogenic infections, and the appropriate treatment delayed (43). The main differential diagnosis is between acute pyogenic infection and metastatic spinal disease. With the latter, the radiological features usually are different, with erosion of the pedicles and vertebral body, but with preservation of the disk space, unlike either pyogenic or tuberculous infection. Pyogenic infection (e.g., with Staphylococci) mimic tuberculosis radiologically, but the onset is usually much

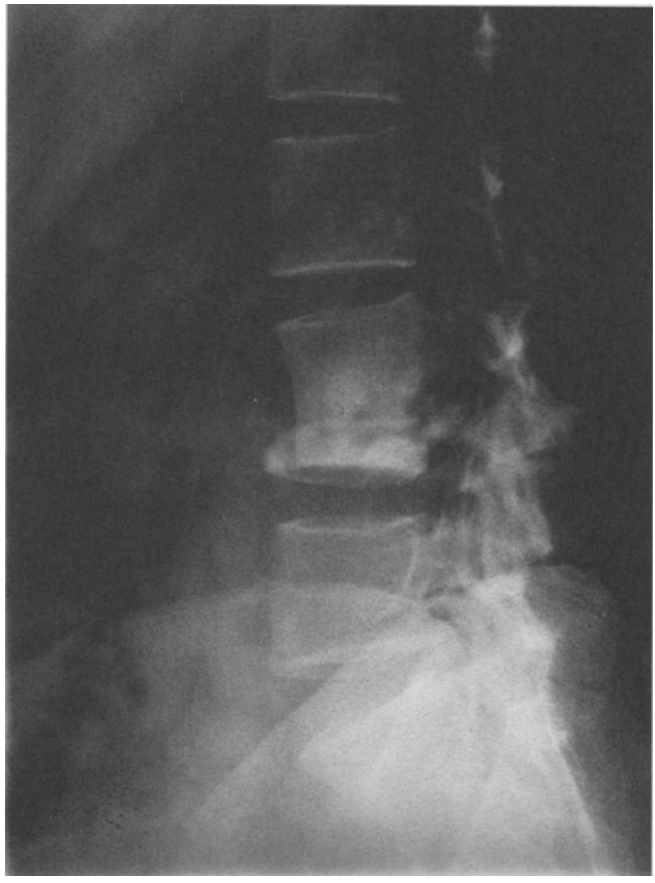

Figure 9.2. Tuberculosis of lumbar spine; L3/4 disk space lost with erosion of adjacent vertebral margins, and substantial destruction of the body of L4.

more acute, the pain can be severe, and there may be accompanying systemic features.

7.2. Treatment

The British Medical Research Council carried out a number of studies over an extended period which helped to define the relative roles of chemotherapy and surgery in the treatment of spinal tuberculosis.

Studies in Korea (50,51), Hong Kong (52), and Rhodesia (53) using isoniazid/para-aminosalicylic acid (PAS) for 18 months gave good results, with over 80%

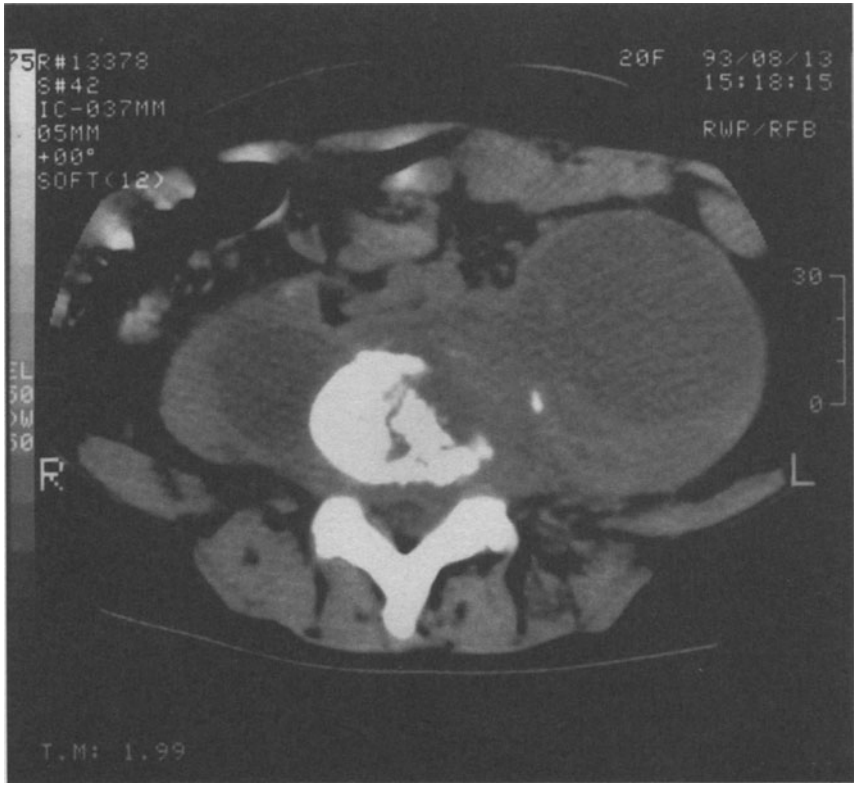

Figure 9.3. CT scan of 19-year-old Asian girl with left inguinal swelling. Erosion of lumbar vertebra with bilateral psoas abscesses (L>R).

of patients achieving favorable status at 3 years. They also showed no additional benefits from the addition of streptomycin for the initial 3 months of therapy, plaster jackets, bed rest for the initial 6 months of therapy, or debridement operations (50–53).

In Hong Kong (54), the so-called "Hong Kong operation," which involved excision of the spinal focus and bone grafting with anterior fusion, in combination with chemotherapy produced less residual deformity and more rapid bone fusion. A later comparison of those patients treated by the "Hong Kong operation" and those by chemotherapy alone showed no additional benefit accrued from surgery (55). These comparisons (56) also showed that 6 or 9 months of treatment with isoniazid/rifampicin supplemented by twice-weekly streptomycin was highly effective. Because pyrazinamide is more bactericidal than streptomycin, has good tissue penetration, but is only required for the initial 2 months of treatment, a

regimen of isoniazid/rifampicin for 6 months with 2 months initial pyrazinamide can be recommended (34).

7.3. Other Bone/Joint Sites

Although the spine accounts for up to 50% of orthopedic disease, any bone or joint can be involved. Clinical series in ISC ethnic patients have shown a wide

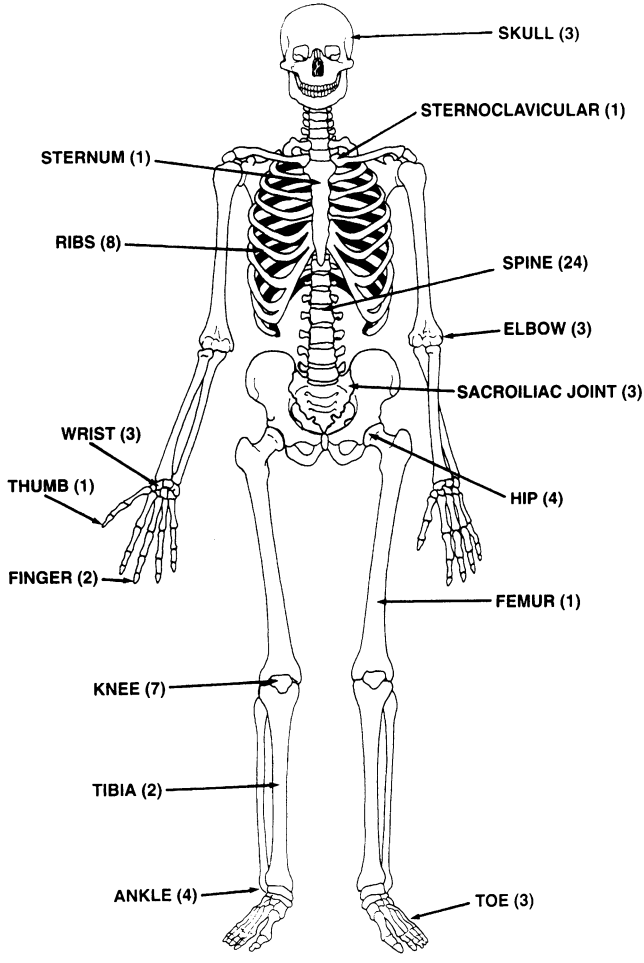

Figure 9.4. Distribution of sites of bone/joint tuberculosis seen in Asian patients updated from Ref. 41.

variety of sites (41) (Fig. 9.4). Tuberculosis should be included in the differential diagnosis of unusual joint lesions, particularly in a monoarthritis in an immigrant group, or there can be substantial delay in achieving a diagnosis (41). Both single (57) and multiple (58) joint presentations are described. There are occasional reports of cases with so many sites and of a cystic type that metastatic bone disease is simulated (59).

These nonspinal sites do not usually require surgical treatment, but surgery by either open biopsy or arthroscopy in the case of certain joints (e.g., knee or elbow) to obtain material for histology and culture is often required to make an initial diagnosis. The 6-month regimen of isoniazid/rifampicin with initial pyrazinamide is recommended (34). Occasionally, surgery is required after the completion of therapy if late presentation or extensive disease has caused major joint disease or instability. Arthrodesis of unstable joints may be necessary, and replacement of hip and knee joints, sometimes under antituberculosis drug cover, has been performed. Combined management of orthopedic tuberculosis, of whatever site, with a physician supervising the antituberculosis drug treatment (34) and the orthopedic surgeon managing the mechanical aspects of the disease is strongly recommended (41).

8. Genitourinary Tuberculosis

In developed countries, genitourinary tuberculosis is one of the commoner sites in white patients (2), with 28% of extrapulmonary cases in the white ethnic group, but only 4% in the ISC ethnic group being genitourinary. An earlier detailed analysis of sites of disease (3) showed rates of genitourinary tuberculosis of 0.4/100,000 and 4.0/100,000 in the white and ISC ethnic groups, respectively. The ratio of ISC : white rates at 10 times greater was the lowest of extrapulmonary sites, and this together with the numerical preponderance of white cases has led to discussions as to why genitourinary tuberculosis is relatively underrepresented in ISC patients (60). This may be an age-related phenomenon, most white patients being considerably older than the ISC ethnic patients, which would fit in with the likely natural history of genitourinary tuberculosis (*vide infra*). The same survey (3) also showed that in white patients, renal tract lesions predominated, but female genital disease predominated in the ISC ethnic group.

Although *M. tuberculosis* can sometimes be detected in the urine within a few months of the primary respiratory infection (39), proving hematogenous dissemination at this early stage, clinical disease usually presents many years after the initial infection (39), having lain dormant, often in the renal parenchyma, for that length of time. In areas where *M. bovis* has been eradicated from cattle for many years, the finding of *M. bovis* in genitourinary isolates (61,62) also supports the proposed natural history. Further support also comes from reactivation tubercu-

losis in transplanted kidneys, from presumed microscopic dormant foci, following immunosuppression (63).

9. Clinical

Renal tuberculosis is a relatively silent disease and can progress to unilateral renal destruction insidiously. Systemic symptoms of fever, weight loss, and nocturnal sweats are not common. As disease progresses, hematuria, dysuria, nocturia, and pain either in the loin or more anteriorly may occur. Loin or abdominal pain seem to be described more commonly in patients who present under the age of 25 years (64).

Renal tuberculosis may be found coincidentally during investigation of hypertension (65) but rarely presents as renal failure due to the destruction of renal parenchyma, or obstructive hydronephrosis from ureteric involvement (66). Renal tuberculosis can also present as a diffuse interstitial nephritis (67), an important diagnosis to be made, as corticosteroids in addition to antituberculosis drugs can significantly increase renal function and hence avoid progression to dialysis (68). Diffuse interstitial nehpritis has also been reported in transplanted kidneys (69).

Disease in the kidneys can progress to the ureter and then to the bladder by seeding of tubercle bacilli into the urine and implantation distally. Ureteric involvement can lead to irregular stenosis with consequent obstructive hydronephrosis and, occasionaly, to complete obstruction leading to a tuberculous pyonephrosis. Bladder involvement can lead initially to cystitis symptoms of dysuria and frequency. As bladder wall inflammation and associated fibrosis worsen, bladder capacity decreases and can become greatly diminished, leading to marked polyuria and nocturia. The urine usually shows hematuria and proteinuria on testing due to the cystitis, but a pyuria on microscopy which is negative on culture for standard bacterial pathogens. Such a sterile pyuria should routinely lead to the sending of early morning urine samples for mycobacterial culture.

9.2. Genital

The commonest genital sites are the prostate and epididymis with the testicle being less frequently involved (69). Although direct spread from adjacent foci in the genital tract or hematogenous spread can occur, antegrade infection from kidney or bladder are much commoner. Local symptoms of discharge or dysuria can mimic bacterial or chlamydial infections and tumors.

Female genital tuberculosis is commoner in the ISC ethnic group (3) and is spread either hematogenously or directly from tuberculous peritonitis. The fallopian tubes are almost invariably infected, with the endometrium in 90%, but ovarian involvement is reported only in 20%, and rarely in the cervix, vagina, and

vulva (70). The commonest presentation is with infertility without associated features but pelvic pain or menorrhagia are reported in 20–25% with much smaller percentages having amenorrhea or postmenopausal bleeding (70).

9.3. Diagnosis

The diagnosis of urinary tract tuberculosis is still based on the intravenous urogram (IVU) and early morning urine cultures. There is a high percentage of abnormality of the IVU in renal disease. In the initial stages, there are just calyceal irregularities or clubbing, and there can be pelviureteric junction narrowing with associated pelvis dilatation. The latter can progress to pelvic obliteration and then to a small or nonfunctioning kidney. Calcification in renal tuberculosis is quite common and is an important pointer to the diagnosis (71) (Fig. 9.5). CT scanning

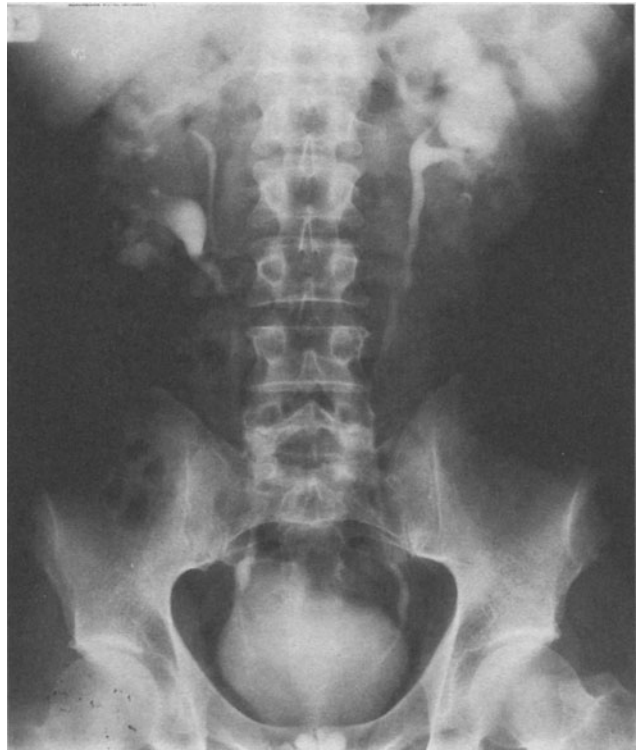

Figure 9.5. IVP showing clubbed and distorted calyces in the right kidney, with calcification in the right kidney and dense prostatic calcification. Early morning urine (EMU) positive for *M. tuberculosis.*

can also be useful with parenchymal retraction and calcification, low parenchymal density, and calycectasis being found in two-thirds of 20 reported cases (72). Pelvic contraction and ureteropelvic fibrosis or obstruction can also be well demonstrated on CT scanning (73). Perinephric abscesses can occur and may point in the groin as with a psoas abscess or in the loin.

Isotope renograms are sometimes of use in assessing differential renal function and may be the first definite indication of ureteric obstruction because of delay in excretion. If there is significant ureteric stenosis, serial renograms will show whether there is improvement in response to treatment.

The diagnosis may be made by biopsy done because of the clinical suspicion of tumor (e.g., renal or testicular), with tuberculosis not being considered until histology is received. Cultures of urine and tissue, if possible, should be done, particularly if an abscess is found in association with the kidney or epididymis.

Urine culture, best done by early morning urine on three consecutive mornings, should be carried out in all patients with urological tuberculosis. The positive yield on microscopy is small, the main positive results being on culture. The finding of a positive microscopy for acid-fast bacilli, which is unusual in genitourinary TB, should raise the question as to whether this is a false-positive one. Such false-positive microscopy can arise due to either contamination of laboratory reagents with environmental mycobacteria or from *Mycobacterium smegmatis,* a saprophytic mycobacteria which can occur in genital secretions. Because of the natural history of genitourinary tuberculosis (39), pulmonary tuberculosis is unusual in association with it. If there is a suspicious chest x-ray lesion present, sputum for acid-fast bacilli should be collected.

10. Management

10.1. Medical

All patients require medical treatment, even if all apparent disease has been removed surgically, because of the likelihood of residual bacilli leading to recurrence and the possibility of other foci elsewhere. Although there is not the support of prospective controlled trials, short-course 6-month regimens are recommended for genitourinary disease. The regimen of rifampicin/isoniazid/pryazinamide for 2 months followed by rifampicin/isoniazid for a further 4 months is recommended in the United Kingdom (34). As with other short-course regimens, it is the inclusion of pyrazinamide that allows the 6-months' treatment duration. If pyrazinamide is omitted or cannot be tolerated, 9 months total treatment should be given. Rifampicin is a particularly good drug for urological tuberculosis because urinary excretion of a significant proportion of the drug means urinary concentrations can reach 100 times that of the serum, and comfortably exceed the minimum inhibitory concentration for *M. tuberculosis.*

It is conventional to use corticosteroids to prevent progression of ureteric strictures. This is advocated by authors in some series (74) but has not been subjected to controlled trial. The addition of corticosteroids, however, has been shown to significantly improve renal function in tuberculous interstitial nephritis (75).

10.2. Surgery

Surgery may initially be to obtain a diagnostic biopsy but has significant roles in genitourinary disease together with effective drug treatment. Sometimes, surgery is excisional because of suspected tumor (e.g., testis) but may also be because of major organ damage, with removal being necessary to prevent possible complications of, for example, a destroyed nonfunctioning kidney. In Gow's major series of 1117 patients (74), 80 (7%) underwent partial nephrectomy because of tuberculous lesions in one pole causing persistent problems such as recurrent infections. In the same series (74), 30% had nephrectomies, 17% epididymectomies, and 4% orchidectomy.

Surgery may also be needed to overcome the mechanical problems of pelviureteric obstruction, ureteric stricture, or reduced bladder capacity of chronic cystitis. In Gow's series (74), reimplantation of the ureter was performed in 6%, 5% had reconstructive bladder surgery, and 2% ureterocolonic transplantation.

Renal function can be monitored both quantitatively and qualitatively by isotope renograms to assess the significance of ureteric stenosis but may have to be repeated serially, and progression can sometimes be rapid (76). Ureteric strictures can be managed by endoscopic dilatation if at the lower end, or by stenting if in the upper ureter, with ureteric reimplantation or diversion reserved for cases where the lesser measures are not possible or fail (77). For the few patients with severe bladder volume reduction as a consequence of chronic tuberculous cystitis, procedures to increase the volume are needed but are best reserved until drug treatment has been completed. Augmentation with a ileal loop attached to the dome of the bladder can add 300–400 ml to bladder capacity.

11. Gastrointestinal Tuberculosis

In developed countries, this form of tuberculosis is uncommon in indigenous populations, being much commoner in immigrant groups. In the United Kingdom in 1983, the rate in the ISC ethnic group was 50 times that of the white ethnic group (3). In the Third World however, gastrointestinal tuberculosis is commonly reported in both HIV-negative and HIV-positive patients. In the pre-HIV era, one-quarter of all ascites was tuberculous in etiology (78), the proportion being over 40% in Lesotho by 1986 (79). In HIV-positive patients, both pulmonary and abdominal tuberculosis have recently been shown to make significant contribu-

tions to the wasting in "slim disease" seen in Africa (80). In such patients, intraabdominal lymphadenopathy is a predominant feature in abdominal disease.

11.1. Clinical Features and Presentation

The gastrointestinal tract can be involved anywhere throughout its length, with infection being due to either ingestion, hematogenous spread, or by local extension to peritoneum from nodes and gut. However, involvement of the upper gastrointestinal tract or perianal disease are uncommon, the former accounting for under 3% of a 500-patient series of surgically treated patients (81). Gastric (82) and duodenal tuberculous ulcers are described, which are not distinguishable from peptic ulcers other than on histology or by a positive culture of *M. tuberculosis* from the stomach or gastric washings. Esophageal disease is described, usually causing dysphagia, which could be caused by aspiration of bacilli or spread from contiguous glands in the mediastinum. At esophagoscopy, ulcerating tumor can be mimicked (83,84).

In a series of 109 patients (82), about one-third had an acute presentation, with the other two-thirds having a more gradual onset. Of the cases with an acute presentation, approximately half had acute right iliac fossa pain simulating appendicitis, and the other half had acute intestinal obstruction (82,85,86).

The commonest symptoms are abdominal pain, fever, malaise, and weight loss (82), being described in 60%, 72%, and 58%, respectively, in another series (87). Abdominal swelling, mainly due to ascites, is described in variable proportions from 10% (82) to 65% (88). Coexisting respiratory disease is found in approximately one-third of cases, 36% in one series (87), and 29% in another (82), of which 23% were active with positive cultures.

There are no diagnostic signs of abdominal tuberculosis (89) and the so-called classical "doughy" abdomen is not reported in large series (82). There may be tenderness in the right iliac fossa simulating appendicitis, or a right iliac fossa mass simulating carcinoma or appendix abscess. The ileocecal region is the commonest site of disease, with frequencies of between 24% and 80% in reported series (82,88,90,91). Here, the presentation may be with acute or subacute small-bowel obstruction with a distended abdomen and vomiting, with or without an abdominal mass (82,86). The colon (other than cecum) is involved in up to 10% (82) and may present with bleeding (92). Anal disease and tuberculous ischiorectal abscess (82) are occasionally described.

11.2. Diagnosis

Because of the nonspecific presentation in most cases, and the fact that two-thirds have normal chest x-rays, the diagnosis is not suspected in up to two-thirds

of cases (86), other diseases such as carcinoma or inflammatory bowel disease being thought likelier.

Normochromic or hypochromic anemia, raised erythrocyte sedimentation rate (ESR), and reduced serum albumin (< 35 g/L) are commonly found but are nonspecific (82). The white blood count is usually normal (91). The tuberculin test is positive in most cases (82) but can be negative in undernourished, immunosupressed, or HIV-positive individuals and in advanced disease.

The ascitic fluid in abdominal tuberculosis, in common with other serous membrane tuberculosis, is a lymphocyte-rich exudate (protein > 35 g/L) and usually straw colored. Ziehl–Neelsen staining of the fluid is usually negative (93,94) and the percentage with a positive culture is not high. Acid-fast bacilli may be seen in gastric washings, particularly in children; sputum smear and culture should be done if there is a chest x-ray lesion.

Plain abdominal x-rays give no specific help but may show ascites or distended bowel loops, confirming bowel obstruction on an erect film. Barium meal is not helpful, but small-bowel studies and barium enema are. Small-bowel studies may show stricturing (Fig. 9.6), mucosal abnormalities, and even skip lesions and fistulas. These features, however, cannot differentiate tuberculosis from other inflammatory bowel disease on radiological appearance alone (82). Contrast from small-bowel studies often demonstrate ileocecal disease well, but this can also be shown by barium enema, with features of shortening of the ascending colon and vertical passage of the ileum into the colon being highly suggestive (85). In the colon, carcinoma can be mimicked with shouldering and annular lesions (82).

The noninvasive methods of ultrasound and CT give suggestive but not diagnostic features in both ascites and bowel involvement. The CT features are better described. The ascitic element is usually of high (15–30 Hounsfield units) density; the mesentery may be thickened and have a stellate appearance. Lymph node disease may be seen in the retroperitoneum or mesentery. Irregular soft tissue densities in the omentum or lymph nodes with a central, well-demarcated area of low density thought to represent caseation are very suggestive (95). This feature can be enhanced further, with intravenous contrast, the inflammatory rim becoming more predominant (96), but is described in other pathologies including lymphoma and carcinoma. Thickened bowel with nodularity of the wall may also be seen (96,98), and all the above features can be seen in combination within a poorly defined mass including bowel loops (98).

To make a definitive diagnosis requires either positive cultures and/or classical histological features from samples from the gastrointestinal tract or ascites. Laparotomy will give a definitive diagnosis in virtually all cases if adequate samples for histology and culture are collected. To avoid laparotomy, a number of less invasive techniques have been used. Levine (99) described the use of blind, percutaneous, peritoneal needle biopsy with a high yield and few complications. This level of positive results, however, was not reproduced by other series (100), and

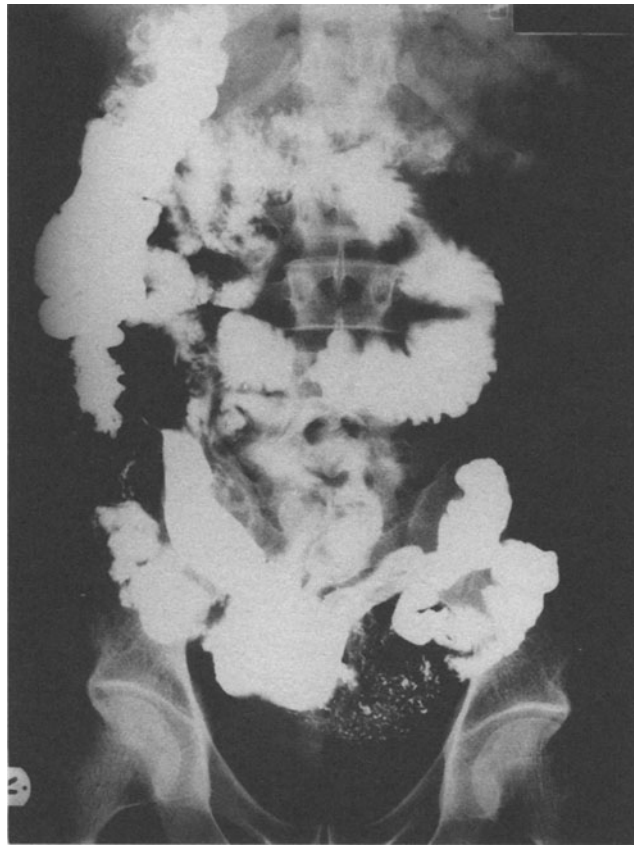

Figure 9.6. Small-bowel barium study showing retracted cecum and markedly narrowed terminal ileum due to tuberculosis. Two further strictures in jejunum and ileum were also present (not seen on this view). Patient required right hemicolectomy and two end-to-end small bowel resections due to intestinal obstruction.

open biopsy of the peritoneum is suggested by some (101) as a preferable alternative, with a lower risk of bowel perforation because the biopsy is taken under direct vision.

Laparoscopy is now the initial procedure of choice and has been shown to be safe, and to give a very high positive rate and few complications (91,94,102,103). Laparoscopy is safe, the risk of bowel perforation being lowest when ascites are present. The only time when open peritoneal biopsy is to be preferred is when there is intense plastic peritonitis present or when CT or ultrasound shows bowel loops adherent to the anterior abdominal wall, thereby increasing the risk of bowel

perforation. Colonic lesions or even the ileocaecal valve area are accessible to the colonoscope, but adequate specimens are essential (104). Fine-needle aspiration in conjunction with colonoscopy has given reasonable preliminary results (105).

If positive cultures are not obtained, there may be histological difficulties in differentiating tuberculosis from Crohns disease. In the former, granulomas are more evident in the lymph nodes associated with the bowel than in the bowel wall itself, whereas in Crohn's disease, the pattern is reversed (106).

11.3. Treatment

In the prechemotherapy days, abdominal tuberculosis carried a high mortality (107,108). The results of published series with modern chemotherapy give a mortality of 5–7% (82,109), although some of the mortality was prior to the diagnosis being made. As with some other forms of nonpulmonary tuberculosis, there are no controlled prospective trials of short-course chemotherapy. Such treatment with a 6-month regimen, as for lymph node and bone disease, is recommended in the United Kingdom (34). Corticosteroids, although theoretically being useful in ascites, are not usually needed and are not recommended for routine clinical practice (82). Resection is only required if there is mechanical obstruction (82), and if resection is carried out, this should be by end-to-end anastomosis instead of by ileo-transverse anastomosis (82,85,110). Modern drug therapy has given good results on follow-up; of 103 patients followed up for 15 months, there was no recurrence of gastrointestinal problems (82), but 10% of female patients of childbearing age had either primary or secondary infertility after the treatment of their abdominal tuberculosis.

12. Miliary Tuberculosis

Miliary tuberculosis occurs when tubercle bacilli are spread acutely through the bloodstream. In high-prevalence areas, the majority of cases follow shortly after initial infection, but in low-prevalence areas, the majority of cases are in the elderly, representing reactivation. The lung is always involved, other organs variably so. Microscopically, the miliary lesions consist of Langerhans giant cells, epithelioid cells, and lymphocytes and contain acid-fast bacilli, sometimes with central caseation. In elderly or immunosuppressed patients, nonreactive pathological appearances are described with necrotic lesions containing no specific tuberculous features but teeming with acid-fast bacilli. In such cases, the diagnosis is usually made at postmortem (111). The symptoms are insidious of onset (112) and include anorexia, malaise, fever, and weight loss and occur in both the "acute" and cryptic forms. Miliary tuberculosis accounts for up to 5% of cases of extrapulmonary tuberculosis in the United Kingdom (3).

12.1. Acute Miliary Tuberculosis

In addition to the general symptoms, headache from coexistent tuberculous meningitis occurs frequently and should alert the clinician to perform a lumbar puncture. Cough, dyspnea, and hemoptysis are less common symptoms. Physical signs are few; the chest almost invariably sounds clear on auscultation. Enlargement of the liver, spleen, or lymph nodes may be found in a small number of cases (113). Involvement of the serosal surfaces can lead to the development of small pericardial or pleural effusions or slight ascites. Fundal examination should be carried out to detect choroidal tubercles which are more commonly seen in children. Skin lesions may also occur in the form of papules, macules, and purpuric lesions. These probably represent local vasculitic lesions caused by reaction to mycobacterial antigen.

The typical x-ray shows an even distribution of uniform-sized lesions 1–2 mm throughout all zones of the lung. Small bilateral pleural effusions may also be seen. An unusual variation with reticular shadowing due to lymphatic involvement had been described (114).

12.2. Cryptic Miliary Tuberculosis

As tuberculosis declines in incidence in developed countries, a form of miliary tuberculosis without typical x-ray shadowing, so-called "cryptic" miliary tuberculosis has been seen more frequently. This is usually seen in patients aged over 60 (115) but may be seen in young patients in some immigrant groups. The symptoms are usually insidious with weight loss, lethargy, and intermittent fever (116). Meningitis and choroidal tubercles are rarely found; mild hepatosplenomegaly may be found but physical signs are usually absent. Because of this, a high index of suspicion is required to reach a diagnosis, and commonly the diagnosis is not made until postmortem (117). The main differential diagnosis is with disseminated carcinoma. Table 9.2 contrasts the features of the classical and cryptic forms of miliary disease.

12.3. Diagnosis

The classical form of miliary disease is usually easy to diagnose because of the typical x-ray appearances which are only absent in the early stages. The tuberculin test is usually positive, and bacteriological confirmation may be obtained from sputum, urine, and cerebrospinal fluid (CSF). The diagnosis of the cryptic form rests initially in having clinical suspicion of the diagnosis, and then carrying out specific tests or monitoring response to a trial of antituberculosis drugs. Blood dyscrasias are not uncommonly seen in the cryptic form, pancytopenia (118,119) leukemoid reactions (120,121), and other granulocyte abnormal-

Table 9.2. Comparison of classical and cryptic forms of miliary TB

Feature	Cryptic	Classical
Age	Majority over 60 years	Majority under 40 years
TB history or contact	Up to 25%	Up to 33%
Malaise/weight loss	75%	75%
Fever	90%	75%
Choroidal tubercles	Absent	Up to 20%
Meningitis	Rare unless terminal	Up to 20%
Lymphadenopathy	Absent	Up to 20%
Miliary shadowing on x-ray	Rare	Usual except in early stages
Tuberculin test	Usually negative	Usually positive
Pancytopenia/leukemoid reaction	Common	Rare
Bacteriological confirmation	Urine; sputum; bone marrow	Sputum: CSF
Biopsy evidence	Liver up to 75%; bone marrow; lymph node	Seldom required

ities (122) have all been reported. Bone marrow aspiration may yield both granulomata on biopsy and acid-fast bacilli on culture, and should be considered if a blood dyscrasia is present. Liver biopsy has the highest diagnostic yield of granulomata which have been reported in up to 75% of biopsies. In cases where the patient is unwilling or where facilities for them do not exist, a clinical trial of antituberculosis drugs should be given. The fever usually responds within 7–10 days, followed by clinical improvement in 4–6 weeks.

12.4. Complications

Tuberculous meningitis may complicate miliary tuberculosis and is a manifestation of acute hematogenous spread. It occurs overtly in up to 20% of cases. Lumbar puncture should be performed if there any symptoms of meningism or headache. A positive microscopy for acid-fast bacilli from the CSF may be the most rapid way of confirming the clinical diagnosis of miliary tuberculosis. Adult respiratory distress syndrome (ARDS) can, rarely, be the presentation of miliary TB (123). In such cases, the breathlessness due to the ARDS can be dominant and the classical x-ray appearances obscured by diffuse confluent or ground-glass shadowing (124,125).

13. Central Nervous System (CNS) Tuberculosis

Although central nervous system (CNS) tuberculosis only makes up some 5% of notified cases in developed countries (3), its importance because of the dispro-

portionate morbidity and mortality associated with this form of tuberculosis cannot be underestimated. In the developing world where difficulties in making a diagnosis and reduced care and treatment availability contribute, it is a major source of death or disability from TB. This is now compounded by an increased risk in HIV-infected individuals with rates for CNS tuberculosis of up to 2/100 in one series (8).

The great majority of cases are of tuberculous meningitis, but intracranial tuberculomata are seen not infrequently in association, and occasionally on their own. Occasional extradural abscesses are reported in association with skull vault bony lesions (41). Tuberculous infection of the meninges is almost always from a focus elsewhere. The method of spread is hematogenous, with up to 20% having overt miliary tuberculosis (Table 9.2). The bacilli usually gain access to the CSF not directly from the bloodstream but from small subpial tuberculomata (126). Symptoms and signs are sometimes as much caused by the intense inflammatory reaction which accompanies the infection as by the infection itself. The meninges look to be covered with gray, thickened exudate, which can be intense and occlude foramina, particularly in the posterior fossa. These meningeal changes lead to endarteritis obliterans which is a more frequent source of focal neurological changes than tuberculomata. The meningeal exudate can extend down the spinal cord onto spinal roots (127).

13.1. Clinical Findings

The initial symptoms are nonspecific, with malaise, anorexia, headache, and vomiting; in children, irritability, poor feeding, drowsiness, or altered behavior may be the dominant features. Unless there is evidence of tuberculosis elsewhere or in low-prevalence countries, the nonspecific nature of the symptoms means that diagnosis may be delayed during the prodromal phase, which can be anything from 2 weeks to 2 months.

The clinical staging developed by the British Medical Research Council based on status at time of diagnosis is helpful (128). In early (Stage I) disease, there is no disturbance of consciousness or focal neurological signs. In medium severity (Stage II), consciousness is disturbed but without coma or delirium; focal neurological signs and cranial nerve palsies may be present. In advanced (Stage III) disease, patients are comatose or stuperose, with or without focal neurological signs.

The meningeal process is accompanied by a low-grade fever, with some neck stiffness in adults, and irritability or drowsiness in children with neck retraction, and in infants, tense fontanelles. Papilloedema is not uncommon and may not be accompanied by raised intracranial pressure and is usually without reduced visual acuity. Choroidal tubercles may occasionally be seen. Cranial nerve palsies occur in a significant proportion of patients. Third- and sixth-nerve palsies are com-

moner than seventh- or eight-nerve palsies. Less common but of more serious import are lateral gaze palsies or internuclear ophthalmoplegias, which carry a poorer prognosis because of involvement of vital structures in the brain stem (129). A variety of other neurological signs can develop, including cerebellar signs and extrapyramidal movements including choreoathetosis, monparesis, and hemiparesis. Involvement of the spinal meninges can lead to reduced or absent deep tendon reflexes; occasionally this is a dominant feature (129), with a paraplegia with urinary and anal sphincter involvement. Epilepsy can occur at any stage (I–III) but is commoner in children.

13.2. Diagnosis

Diagnosis depends substantially on CSF examination, blood tests giving nonspecific abnormalities, and the tuberculin test being maybe negative. If there is associated miliary tuberculosis (Table 9.2), or changes of pulmonary tuberculosis, which in some series (130) is present in up to 50% cases, the diagnosis is much more easily suggested and made. The CSF pressure is usually raised, but lumbar puncture is safe in this form of chronic meningitis and can be carried out even if papilloedema is present. The leukocyte count is raised but seldom above 500/mm^3 (131). In the early stages, the leukocytosis is of polymorph predominance (131) but changes to a lymphocyte-predominant pattern as the disease proceeds. The CSF is usually clear, but the CSF protein is almost invariably raised (131); the CSF glucose is usually reduced (132) but may be within the normal range. A completely normal CSF result in protein, cell count, and glucose effectively excludes tuberculous meningitis. In the early stages, particularly if a polymorph leukocytosis is present, the differential diagnosis includes a partially treated bacterial meningitis if antibiotics have been given. It may be necessary to perform serial lumbar punctures to establish a diagnosis if no acid-fast bacilli are seen on microscopy. The CSF changes of a partially treated bacterial meningitis improve over weeks, whereas those of TB meningitis do not. The identification of acid-fast bacilli on microscopy or on culture clinches the diagnosis. A thorough search should be made on microscopy, with success being greater if a larger (up to 10 ml) volume of CSF is analyzed. The first sample taken is most likely to give a positive result (133), but all samples taken should be sent for culture, the majority being negative on microscopy. If the clinical diagnosis is felt to be tuberculous meningitis, consideration should be given to sending sputum, urine, or gastric washings for culture, but the initiation of treatment should not be delayed. Because culture can take several weeks to give a positive result, early confirmation of diagnosis by detecting the presence of mycobacterial constituents (e.g., tuberculostearic acid or mycobacterial DNA) would be most useful. Of the techniques tried, the polymerase chain reaction (PCR) (134) is the most promising, but the technical resources and expense may largely limit its use to developed countries.

13.3. Medical Treatment

Antituberculosis drug treatment should be commenced as soon as possible, which may well be before the diagnosis is proven, unless the CSF is microscopy positive for acid-fast bacilli when the diagnosis is suspected. The penetration of antituberculosis drugs into the CSF depends partly on their serum protein binding and on whether the blood-brain barrier is intact.

Isoniazid penetrates very well (135,136), reaching many times the required minimal inhibitory concentration (MIC), even when the blood-brain barrier is intact. Streptomycin penetrates adequately only when the blood-brain barrier is defective (135). Rifampicin penetrates poorly (137–139) and its penetration may be related partly to inflammation (140). Pyrazinamide penetrates well (141,142) and reaches the MIC required (143,144) independent of stage or activity of disease.

The recommendations for the treatment of tuberculous meningitis are based on clinical experience and series, not on prospective clinical trials. In countries with low rates of isoniazid resistance, treatment with rifampicin and isoniazid for 12 months supplemented by 2 months of pyrazinamide is recommended (34). In areas where there is a higher rate of isoniazid resistance, a fourth drug should be used initially. In Hong Kong, streptomycin is used for the initial 2 months when CSF penetration is better. Alternative fourth drugs for the initial phase of treatment are ethambutol and ethionamide. Ethambutol penetrates the CSF poorly except when there is inflammation (145–147). Ethionamide has good CSF penetration not dependent on inflammation (148,149), and in South Africa, it is preferred to streptomycin (150).

Streptomycin should be given intramuscularly, intrathecal use is not required, but should be avoided in pregnancy. Ethionamide should also be avoided in pregnancy as it maybe teratogenic. In comatose patients, drugs should be administered on an empty stomach via a nasogastric tube (34).

The optimum duration of treatment is unknown. Twelve months' treatment is probably adequate, although some authors give up to 18 months for Stage III disease and between 18 and 24 months for tuberculomata (151). Satisfactory results, however, have been obtained from 6 months' (152,153) and 9 months' treatment (154). When to use corticosteroids in tuberculous meningitis can be controversial. Their use in meningitis was investigated (155) and shown to improve survival in Stage II and III disease and is supported by earlier literature reviews (156). Their use is also definitely indicated for tuberculous encephalopathy (157). Their use in spinal arachnoiditis is more controversial but are usually given although no definite evidence that outcome is altered is available. Their use in Stage II and III disease is, therefore, recommended (34,151).

13.4. CT Scanning and Surgery

Computer tomographic scanning in CNS tuberculosis is useful (158–161) and should be performed if available at diagnosis and if there is any clinical deterio-

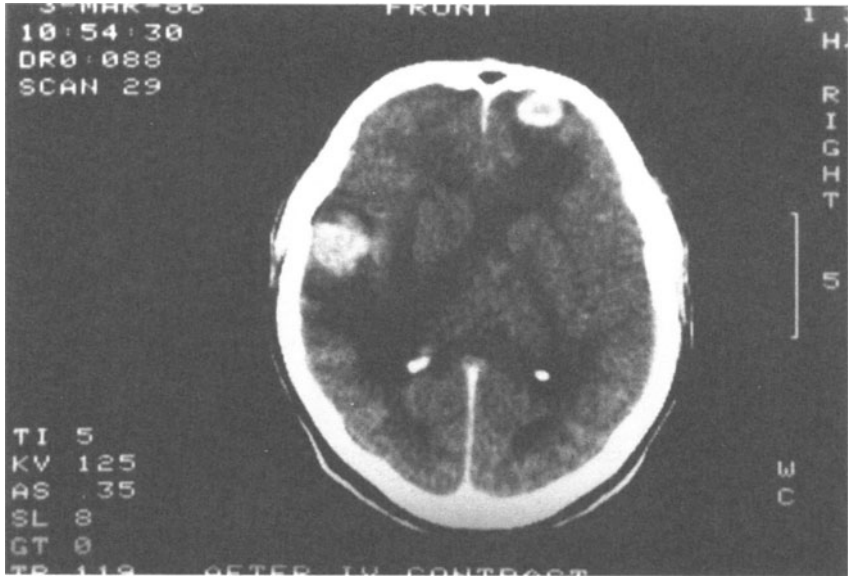

Figure 9.7. CT scan of 40-year-old taken 6 weeks after commencement of treatment of Stage I meningitis when initial CT scan normal. Multiple tuberculomas present. Resolved with continuation of drug therapy and additional corticosteroids.

ration thereafter (Fig. 9.7). The main values are in detecting tuberculomata, giving evidence of associated infarction, and detecting hydrocephalus. The demonstration of the development of tuberculomata on treatment is now well demonstrated (162,163), and paradoxical expansion of those present at diagnosis on treatment is also recorded (164). Surgery is rarely needed for tuberculomata, being required in only 6% (165), but may be necessary if a vital structure (e.g., optic chiasm) is compromised (166).

Computer tomography may show hydrocephalus that ventricular shunting is required. Early drainage of hydrocephalus is required (159,167,168), those drained doing better than those not drained (169). If an intracranial tuberculous abscess forms, neurosurgical drainage may be needed (170).

13.5. Prognosis

The main determinants of outcome with more modern treatment are patient age and stage of disease at presentation (171), with children under 3 years having a worse outcome, independent of stage. A study in Chinese children (131) again showed age and stage at presentation as the only significant factors on multivariate

analysis, demonstrating the importance of early diagnosis and prompt treatment. This same study (131) showed recovery in 96%, 78%, and 21% respectively with Stage I, II, and III disease. These results are clearly better than those achieved at the beginning of chemotherapy with streptomycin alone, when mortalities of 46%, 66%, and 81% were recorded for Stages I, II, and III, respectively. Mortality has also been shown to be related to the severity of the hydrocephalus (168,172). HIV coinfection does not appear to alter presentation, symptoms, or prognosis, except in patients with CD4 counts of under 200 μL, when survival is reduced (8).

14. Tuberculous Pericarditis

Pericardial tuberculosis is uncommon in developed countries, making up approximately 1% of cases in the United Kingdom (3) and between 1% and 2% in the United States (173). Conversely, in developed countries, tuberculosis accounts for between 4% and 7% of cases of acute pericarditis, tamponade, or constrictive pericarditis (174,175). In developing countries, it is more important, and in some areas (e.g., southern Africa), it is an important cause of congestive heart failure (176).

The infection usually reaches the pericardium by direct extension from adjacent mediastinal glands, but occasional hematogenous spread can occur with pericardial involvement in miliary disease. An acute pericarditis can be seen, which is thought to represent an allergic response to tuberculoprotein. In chronic pericardial effusion and pericardial constriction, the pathology is granulomatous, which can proceed to fibrosis and calcification at a later date. Although the pericardium is the major site of cardiac involvement, postmortem studies (177) show lesser degrees of involvement of the myocardium and endocardium in some cases.

14.1. Clinical

The onset, as with some other forms of tuberculosis, is insidious with fever, malaise, sweats, weight loss, cough, retrosternal discomfort, and tachycardia. The peak occurrence is in the third to fifth decades (178). If the effusion is sufficient to cause tamponade, dyspnea may be the major symptom. With an effusion, the major signs are low blood pressure, narrow pulse pressure, pulsus paradoxus, edema, and raised venous pressure, with the latter two being more pronounced if tamponade is present. The electrocardiogram is usually of low voltage and shows widespread T-wave changes. The chest x-ray shows an enlarged cardiac outline in over 80% of cases (175), with associated pleural effusions in over 50%.

Pericarditis can progress to constriction any time from a few weeks to several years after the onset of pericarditis. Tuberculosis is the commonest cause of con-

strictive pericarditis in Africa and Asia, responsible for over 60% of cases in one Indian series (179). The symptoms of constriction are dyspnea, abdominal distension, and edema. The heart sounds are quiet, with pulsus paradoxus, and a raised venous pressure which rises in inspiration (Kussmauhls sign). Constrictive pericarditis causes apparent cardiac enlargement in over 50% of cases (179).

14.2. Diagnosis

The diagnosis should be suspected in patients with a combination of fever and pericardial effusion or signs of tamponade, particularly if from a high incidence ethnic group. The chest x-ray, in addition to an enlarged heart shadow, may show pericardial calcification in constrictive pericarditis and associated active pulmonary tuberculosis in up to 30% (180,181). Sputum smear and culture should be performed if the chest x-ray shows any evidence of pulmonary tuberculosis. In common with other serous membrane tuberculosis, the tuberculin test is positive

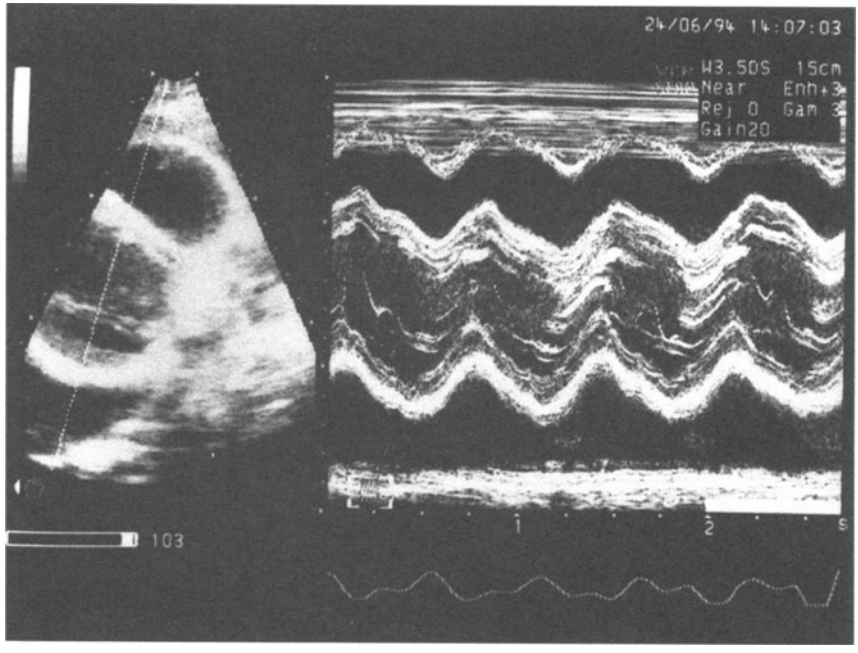

Figure 9.8. Echocardiogram of 24-year-old Asian man with large pericardial effusion showing substantial pericardial fluid and debris. Fluid lymphocyte-rich exudate with positive culture for *M. tuberculosis.* Rapid response to corticosteroids and drug therapy.

in between 80% and 100% of cases (175). Echocardiography is the best way of confirming effusion (Fig. 9.8). In addition to fluid, this may also show pericardial thickening or amorphous material within the pericardial space. Computerized tomography and nuclear magnetic resonance have also been used successfully to confirm pericardial effusion and/or thickening (182). Pericardiocentesis, done either from the subxiphisternal approach or the apical approach, preferably under echocardiographic guidance particularly with the latter approach, gives fluid which is an exudate (protein $>$ 35 g/L) and usually lymphocyte predominant on cytology. The cell count can be of polymorph preponderance in the initial stages. The definitive diagnosis depends on the isolation of acid-fast bacilli from the fluid or obtaining histological confirmation. The fluid can be positive on microscopy for acid-fast bacilli with rates of up to 40% described. Positive culture rates of 59% and positive histology rates of 70% were found in the Transkei study (180). Pericardial biopsy usually requires thoracotomy, but a nonsurgical biopsy technique under x-ray control has been described (183) with encouraging initial results.

14.3. Treatment

MEDICAL

Studies from the Transkei (180,185) have shown that rifampicin/isoniazid for 6 months supplemented by pyrazinamide and streptomycin for the initial 3 months is effective in both effusion and constriction. These studies also assessed the usefulness of prednisolone. When given to patients with constriction, for 11 weeks tapering from an initial dose of 30–60 mg/day, the active group improved more rapidly, needed pericardectomy less, and had a lower death rate (4% versus 11%). In patients with effusion, the need for open drainage and repeated pericardiocentesis was lessened, and the death rate was also lessened (4% versus 14%). Corticosteroids should, therefore, be given in tapering dose over the first 2–3 months of treatment (34).

SURGERY

There are conflicting views on when this is necessary. An active policy of pericardial window procedure with pericardectomy if thickening is present has been advocated (185). A conservative approach is suggested by others (186), who found no constrictive pericarditis in 14 patients treated medically on follow-up. Since the evidence from the Transkei (180,185) of the beneficial effects of steroids, it is probably best if surgical intervention is reserved for those who present

late with constriction and calcification, or who fail to respond to the initial 6–8 weeks of medical treatment and still have a raised venous pressure, or those with life-threatening tamponade at any stage (175,176).

15. Tuberculosis of the Skin

Skin involvement is uncommon but can occur in a number of ways. There are forms of skin disease, which involve infection of the skin with direct inoculation or by blood-borne spread, and the tuberculides, which are thought to be cutaneous immunological reactions to tuberculous infections elsewhere in the body.

Primary infection of the skin can be seen particularly in children where inoculation occurs due to minor skin trauma, often from a sputum smear-positive family member. A primary infection develops at the site of inoculation, usually a limb which may ulcerate and proceed to regional lymphadenopathy. This type of infection has also been recently described in needle-stick injury from a HIV-positive patient (187). Other forms of cutaneous tuberculosis are verrucosa cutis, a warty form, and verruca necrogenita, which is more painful and acute. Post-mortem workers, and those who may come into contact with *M. bovis* (e.g., veterinary surgeons, abattoir workers, and butchers) are at risk.

Skin involvement in acute hematogenous tuberculosis, miliary disease, is described with multiple, usually extensive, small papular lesions from which acid-fast bacilli can sometimes be cultured. This form may be becoming more common with the advent of HIV disease, being described in such patients (188) and with coinfection with *M. avium-intracellulare* (189).

The commonest form of skin tuberculosis is lupus vulgaris. This slowly progressive form, usually in older patients, can progress insidiously for months or even years. The extremeties, head, and face are the usual sites, with dull reddish or violaceous lesions, sometimes with a plaquelike psoriaform edge of active disease and residual scarring of a tissue paper type where past infection has occurred. A mutilating form can involve deeper tissue (e.g., cartilage) in ears and nose leading to deformity, and occasionally squamous carcinoma can complicate lupus vulgaris.

Of the forms of tuberculosis without direct skin involvement, the tuberculides, a number of patterns are described. Erythema nodosum associated with tuberculosis is seen usually 3–8 weeks after initial infection and is associated with tuberculin conversion so the skin test is strongly positive (39). Erythema induratum (Bazin's disease), papular and papulonecrotic tuberculides, and other forms of panniculitis with perivascular inflammation of arterioles and venules but also of fat and subcutaneous tissues are also described. The tuberculin test is strongly positive, there may be evidence of tuberculosis elsewhere, and the lesions respond to antituberculosis drug treatment.

16. Miscellaneous

16.1. Adrenal

Tuberculosis is now an uncommon cause of hypoadrenalism; in developing countries autoimmune adrenalitis is more common. Adrenal tuberculosis is seldom an isolated occurrence and is usually part of disseminated tuberculosis (190). Rifampicin, which is included in all short-course regimens, can unmask subclinical adrenal involvement, with adrenal crisis 2–4 weeks after the commencement of treatment being described (191). Being a potent inducer of hepatic microsomal drug metabolism, rifampicin significantly reduces the plasma half-life of corticosteroids (192) and may, thus, precipitate adrenal crisis in those whose adrenals are just producing enough cortisol under maximum stress to maintain minimum serum levels. This phenomenon has been postulated as a factor in the unexplained deaths soon after the commencement of antituberculosis drug therapy (193).

16.2. Liver

The liver is usually involved by hematogenous spread, particularly in miliary disease (Table 9.2), with a diffuse infiltration (194) which is usually diagnosed on needle liver biopsy. A nodular form of hepatic tuberculosis is also described which can mimic carcinoma or cirrhosis (195). This form can present with bleeding gastric varices (196) or portal hypertension (197). The miliary involvement of liver can produce a "bright" liver on ultrasound (198), which is nonspecific. Diagnosis depends on finding granulomas and acid-fast bacilli on biopsy, so liver tissue should routinely be cultured if tuberculosis is suspected. Localized abscesses can develop (82) that cannot be distinguished from amoebic or pyogenic abscesses on ultrasound or CT scan appearances (199,200). Occasionally, multiple microabscesses occur or pseudotumor masses (201).

Conclusion

Nonpulmonary forms of tuberculosis are challenging to clinicians because of the wide diversity of types and presentations. Clinical awareness needs to be maintained so that the diagnosis is suspected, the appropriate investigations are performed, ensuring there is no undue delay in reaching a diagnosis. The management of the drug treatment of nonpulmonary forms should be by physicians experienced in tuberculosis treatment (34), with any surgical aspect dealt with in conjunction with surgical colleagues in a team approach. Because of the often paucibacillary nature of samples of fluid (e.g., ascites, pus or tissue in extrapulmonary forms), the development of reliable molecular biological methods of rapid

diagnosis has considerable potential over the next few years in the earlier confirmation of the diagnosis.

References

1. Innes JA (1981) Non-respiratory tuberculosis. J Roy Coll Phys (Lond) 15:227–231.
2. Medical Research Council Cardiothoracic Epidemiology Group (1992) National survey of notifications of tuberculosis in England and Wales in 1988. Thorax 47:770–775.
3. Medical Research Council Tuberculosis and Chest Diseases Unit (1987) National survey of tuberculosis notifications in England and Wales in 1983: characteristics of disease. Tubercle 68:19–32.
4. Weir MR, Thornton GF (1985) Extrapulmonary tuberculosis. Am J Med 79:467–478.
5. Pitchenik AE, Fertel D, Bloch AB (1988) Pulmonary effects of AIDS; mycobacterial disease—epidemiology, diagnosis, treatment and prevention. Clin Chest Med 9:425–441.
6. Chest Service, Medical and Health Department (1990) Annual report. 1990. Hong Kong Government: Hong Kong.
7. Pitchenik AE, Cole C, Russell BW, Fischl MA, Spira JJ, Snider DE (1984) Tuberculosis, atypical mycobacteriosis and acquired immunodeficiency syndrome among Haitian and non-Haitian patients in South Florida. Ann Intern Med 101:641–645.
8. Berenguer J, Santiago M, Laguna F, Morena S, Vincente T, Adrados M, Ortega A et al. (1992) Tuberculous meningitis in patients infected with the human immunodeficiency virus. N Engl Med J 326:668–672.
9. Coleblunders RL, Ryder RV, Nzilambi N, Dikulu K, Willame J-C, Kaboto M et al. (1989) HIV infection in patients with tuberculosis in Kinshasa: Zaire. Am Rev Respir Dis 139:1082–1085.
10. Elliot AM, Luo N, Tembo G (1990) Impact of HIV on tuberculosis in Zambia: a cross-sectional study. Br Med J 301:412–415.
11. Harries AD (1990) Tuberculosis and HIV infection in developing countries. Lancet 335:387–390.
12. Modilevsky T, Sattler FR, Barnes PF (1989) Mycobacterial disease in patients with HIV infection. Arch Intern Med 149:2201–2205.
13. Soriano E, Mallolas J, Gatell JM, Lattore X, Miro JM, Pecchiar M et al. (1988) Characteristics of tuberculosis in HIV-infected patients: a case control study. AIDS 2:429–432.
14. Campbell IA, Dyson AJ (1977) Lymph node tuberculosis: a comparison of various methods of treatment. Tubercle 58:171–179.

15. Mehta JB, Dutt A, Harvill L, Matthews KM (1991) Epidemiology of extrapulmonary tuberculosis. Chest 99:1134–1138.
16. Alvarez S, McCabe WR (1984) Extrapulmonary tuberculosis revisited: a review of experience at Boston City and other hospitals. Medicine 63:25–53.
17. Lau SK, Kwan S, Lee J, Wei WI (1991) Source of tubercle bacilli in cervical lymph nodes: a prospective study. J Laryngol Otol 105:558–561.
18. British Thoracic Society Research Committee (1985) Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. Br Med J 290:1106–1108.
19. Finch PJ, Millard FJC, Maxwell JD (1991) Risk of tuberculosis in immigrant Asians: culturally acquired immunodeficiency? Thorax 46:1–5.
20. Huhti E, Brander E, Ploheimo S, Sutinen S (1975) Tuberculosis of cervical lymph nodes; a clinical, pathological and bacteriological study. Tubercle 56:27–36.
21. British Thoracic Society Research Committee (1992) Six-months versus nine-months chemotherapy for tuberculosis of lymph nodes: preliminary results. Respir Med 86:15–19.
22. Lau SK, Wei WI, Hau C, Engzell UC (1990) Efficacy of fine needle aspiration cytology in the diagnosis of tuberculosis cervical lymphadenopathy. J. Laryngol Otol, Jan 104(1):24–7.
23. Lau SK, Wei WI, Kwan S, Engzell UC (1988) Fine needle aspiration biopsy of tuberculous cervical lymphadenopathy. Aust NZ J Surg 58:947–950.
24. Lau SK, Wei WI, Kwan S, Yew WW (1991) Combined use of fine-needle aspiration cytologic examination and tuberculin skin test in the diagnosis of cervical tuberculous lymphadenitis: a prospective study. Arch Otolaryngol Head Neck Surg 117:87–90.
25. Shaha A, Webber C, Marti J (1986) Fine needle aspiration in the diagnosis of cervical lymphadenopathy. Am J Surg 152:420–423.
26. Campbell IA, Dyson AJ (1977) Lymph node tuberculosis: a comparison of various methods of treatment. Tubercle 58:171–179.
27. British Thoracic Society Research Committee (1985) Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. Br Med J 290:1106–1108.
28. British Thoracic Society Research Committee (1988) Short course chemotherapy for lymph node tuberculosis: final report at 5 years. Br J Dis Chest 82:282–284.
29. Jindani A, Aber VR, Edwards EA, Mitchison DA (1980) The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 121:139–148.
30. Ormerod LP (1988) A retrospective comparison of two drug regimens RHZ2/RH10 and RHE2/RH10 in the treatment of tuberculous mediastinal lymphadenopathy. Br J Dis Chest 82:274–278.
31. British Thoracic Society Research Committee (1992) Six-months versus nine-months chemotherapy for tuberculosis of lymph nodes: preliminary results. Respir Med 83:15–19.
32. British Thoracic Society Research Committee (1993) Six-months versus nine-months chemotherapy for tuberculosis of lymph nodes: final results. Respir Med 87:621–623.

33. McCarthy OR, Rudd RM (1989) Six-months chemotherapy for lymph node tuberculosis. Respir Med 89:425–427.
34. Ormerod LP for the Joint Tuberculosis Committee (1990) Chemotherapy and management of tuberculosis in the United Kingdom; recommendations of the Joint Tuberculosis Committee of the British Thoracic Society. Thorax 45:403–408.
35. Jawahar MS, Sivasubramanian S, Vijayan VK, Ramakrishnan CV, Paramasivan CN, Selvakumar et al. (1990) Short course chemotherapy for tuberculous lymphadenitis in children. Br Med J 301:359–361.
36. Campbell IA, Dyson AJ (1979) Lymph node tuberculosis; a comparison of treatments 18 months after completion of chemotherapy. Tubercle 60:95–98.
37. Prissick FH, Masson AM (1956) Cervical lymphadenitis in children caused by chromogenic mycobacteria. Can Med Assoc J 75:798–803.
38. McKellar A (1976) Diagnosis and management of atypical mycobacterial lymphadenitis in children. J Paediatr Surg 11:85–89.
39. Wallgren A (1948) The timetable of tuberculosis. Tubercle 29:245–251.
40. Davies PDO, Humphries MJ, Byfield SP, Nunn AJ, Darbyshire JH, Citron KM et al. (1984) Bone and joint tuberculosis in a national survey of notifications in England and Wales in 1978/9. J Bone Joint Surg 66B:326–330.
41. Hodgson SP, Ormerod LP (1990) Ten-year experience of bone and joint tuberculosis in Blackburn 1978–87. J Roy Coll Surg (Edin) 35:259–262.
42. Humpries MJ, Sister Gabriel M, Lee YK (1986) Spinal tuberculosis presenting as abdominal symptoms—a report of two cases. Tubercle 67:303–307.
43. Walker GF (1968) Failure of early recognition of skeletal tuberculosis. Br Med J i:682.
44. Gorse GJ, Pais JM, Kurske JA, Cesario TC, Ip M, Chen NK, So SY, Chiu SW, Lam WK (1983) Tuberculous spondylitis: a report of six cases and a review of the literature. Medicine 62:178–193.
45. Ip M, Chen NK, So SY, et al. (1989) Unusual rib destruction in pleuropulmonary tuberculosis. Chest 95:242–244.
46. Lin-Greenberg A, Cholankeril J (1990) Vertebral arch destruction in tuberculosis: CT features. J Comput Assist Tomogr 14(2):300–302.
47. Bell GR, Stearns KL, Bonutti PM, Boumphrey FR (1990) MRI diagnosis of tuberculous vertebral osteomyelitis. Spine 15(6):462–465.
48. Smith DF, Smith FW, Douglas JG (1989) Tuberculous radiculopathy: the value of magnetic resonance imaging of the neck. Tubercle 70:213–216.
49. Angtuaco EGC, McConnell JR, Chadock WM, Flannigan S (1987) Magnetic resonance imaging of spinal epidural sepsis. Am J Roentgen 42:1249–1253.
50. Medical Research Council Working Party on Tuberculosis of the Spine (1973) A controlled trial of ambulant outpatient treatment and inpatient rest in bed in the management of tuberculosis of the spine in young Korean patients on standard chemotherapy. A study in Masan, Korea. J Bone Joint Surg 55B:678–697.

51. Medical Research Council Working Party on Tuberculosis of the Spine (1973) A controlled trial of plaster-of-Paris jackets in the management of ambulant outpatient treatment of tuberculosis of the spine in children on standard chemotherapy: a study in Pusan, Korea. Tubercle 54:261–282.
52. Medical Research Council Working Party of Tuberculosis of the Spine (1974) A controlled trial of anterior spinal fusion and debridement in the surgical management of tuberculosis of the spine in patients on standard chemotherapy: a study in Hong Kong. Br J Surg 61:853–866.
53. Medical Research Council Working Party on Tuberculosis of the Spine (1974) A controlled trial of debridement and ambulatory treatment in the management of tuberculosis of the spine in patients on standard chemotherapy. A study in Bulawayo, Rhodesia. J Trop Med Hyg 77:72–92.
54. Medical Research Council Working Party on Tuberculosis of the Spine (1982) A 10-year assessment of a controlled trial comparing debridement and anterior spinal fusion in the management of tuberculosis of the spine in patients on standard chemotherapy in Hong Kong. J Bone Joint Surg 64B:393–398.
55. Medical Research Council Working Party on Tuberculosis of the Spine (1985) A ten-year assessment of controlled trials of inpatient and outpatient treatment and of plaster-of-Paris jackets for tuberculosis of the spine in children on standard chemotherapy: studies in Masan and Pusan. J Bone Joint Surg 67B:103–110.
56. Medical Research Council Working Party on Tuberculosis of the Spine (1986) A controlled trial of six-month and nine-month regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the Spine in Hong Kong. Tubercle 67:243–259.
57. Parkinson RW, Hodgson SP, Noble J (1990) Tuberculosis of the elbow: a report of 5 cases. J Bone Joint Surg 72B:523–524.
58. Valdazo JP, Perez-Ruiz F, Albarracin A, Sanchez-Nievas G, Perez-Benegas J, Gonzales-Lanza M et al. Tuberculous arthritis: Report of a case with multiple joint involvement and periarticular tuberculous abscesses. J Rheumatol 17(3):399–401.
59. Ormerod LP, Grundy M, Rahman MA (1989) Multiple tuberculous bone lesions simulating metastatic disease. Tubercle 70:305–307.
60. Ormerod LP (1993) Why does genitourinary tuberculosis occur less often than expected in ISC ethnic patients. J Infect 27:27–32.
61. Stoller JK (1985) Late recurrence of *Mycobacterium bovis* genitourinary tuberculosis: case report and review of the literature. J Urol 134:565–566.
62. Yaqoob M, Goldsmith HJ, Ahmad R (1990) Bovine genitourinary tuberculosis revisited. Quart J Med 74:105–109.
63. Lichtenstein IH, MacGregor RR (1983) Mycobacterial infections in renal transplant recipients: report of five cases and a review of the literature. Rev Infect Dis 5(2):216–226.
64. Ferrie BG, Rundle JSH (1985) Genitourinary tuberculosis in patients under twenty five years of age. Urology XXV(6):576–578.

65. Datta SK (1987) Renal tuberculosis presenting as hypertension. J Assoc Physicians India 35(11):798–799.

66. Benn JJ, Scoble JE, Thomas AC, Eastwood JB (1988) Cryptogenic tuberculosis presenting as a preventable cause of end-stage renal failure. Am J Nephrol 8(4):306–308.

67. Morgan SH, Eastwood JB, Baker LRI (1990) Tuberculous interstitial nephritis—the tip of the iceberg? Tubercle 71:5–6.

68. al-Sulaiman MH, Dhar JM, al-Hasani MK, Haleem A, al-Khader A (1990) Tuberculous interstitial nephritis after kidney transplantation. Transplantation 50(1):162–164.

69. Gorse GJ, Belshe RB (1985) Male genital tuberculosis: a review of the literature with instructive case reports. Rev Infect Dis 7:511–524.

70. Sutherland AM (1985) Gynaecological tuberculosis: analysis of a personal series of 710 cases. Aust NZ J Obstet Gynaecol 25:203–207.

71. Dolev E, Bass A, Nossinowitz N (1985) Frequent occurrence of renal calculi in tuberculous kidneys in Israel. Urology 26:544–545.

72. Okazawa N, Sekiya T, Tada S (1985) Computed tomographic features of renal tuberculosis. Radiat Med 3:209–213.

73. Goldman SM, Fishman EK, Hartman DS (1985) Computed tomography of renal tuberculosis and its pathological correlates. J Comput Assist Tomogr 9:771–776.

74. Gow JG, Barbosa S (1984) Genitourinary tuberculosis. A study of 1117 cases over a period of 34 years. Br J Urol 56:449–455.

75. Morgan SH, Eastwood JB, Baker LRI (1990) Tuberculous interstitial nephritis—the tip of the iceberg? Tubercle 71:5–6.

76. Psihramis KE, Donahoe PK (1986) Primary genitourinary tuberculosis: rapid progression and tissue destruction during treatment. J Urol 135:1033–1036.

77. Osborn DE, Rao NJ, Blacklock NJ (1986) Tuberculous stricture of ureter. A new method of intubated ureterotomy. Br J Urol 58:103–104.

78. Nwokolo C (1961) Ascites in Africa. Br Med J 1:33.

79. Menzies RI, Alsen H, Fitzgerald JM, Mohapeola RG (1986) Tuberculous peritonitis in Lesotho. Tubercle 67:47–54.

80. Lucas SB, De Cock KM, Hounnou A, Peacock C, Diomande M, Honde M, et al. (1994) Contribution of tuberculosis in slim disease in Africa. Br Med J 308:1531–1533.

81. Mukerjee P, Singal AK (1979) Intestinal tuberculosis: 500 operated cases. Proc Assoc Surg East Africa 2:70–75.

82. Klimach OE, Ormerod LP (1985) Gastrointestinal tuberculosis: a retrospective review of 109 cases in a district general hospital. Quart J Med 56:569–578.

83. deMas R, Lombeck G, Rieman JF (1986) Tuberculosis of the oesophagus masquerading as an ulcerated tumour. Endoscopy 18:153–155.

84. Gupta SP, Arora A, Bhargava DK (1992) An unusual presentation of oesophageal tuberculosis. Tuberc Lung Dis 73:174–176.
85. Addison NV (1983) Abdominal tuberculosis—a disease revived. Ann Roy Coll Surg Eng 65:105–111.
86. Lambrianides AL, Ackroyd N, Shorey B (1980) Abdominal tuberculosis. Br J Surg 67:887–889.
87. Sherman S, Rohwedder JJ, Ravikrishnan KP, Weg JG (1980) Tuberculous enteritis and peritonitis—report of 36 general hospital cases. Arch Intern Med 140:506–508.
88. Bastani B, Shariatzadeh MR, Dehdashti F (1985) Tuberculous peritonitis—report of 30 cases and a review of the literature. Quart J Med 56:549–557.
89. Shukla HS, Hughes LE (1978) Abdominal tuberculosis in the 1970s: a continuing problem. Br J Surg 65:403–405.
90. Gilinsky NH, Marks IN, Kottler RE (1983) Abdominal tuberculosis. A 10 year review. S Afr Med J 64:849–857.
91. Das Pritam, Shukla HS (1976) Clinical diagnosis of abdominal tuberculosis. Br J Surg 63:941–946.
92. Pozniak AL, Dalton-Clarke HJ (1985) Colonic tuberculosis presenting as massive rectal bleeding. Tubercle 66:295–299.
93. Rodriguez de Lope C, San Miguel Joglar G, Pons Romero F (1982) Laparoscopic diagnosis of tuberculous ascites. Endoscopy 14:178–179.
94. Sochocky S (1967) Tuberculous peritonitis. A review of 100 cases. Am Rev Respir Dis 95:398–401.
95. Hanson RD, Hunter TB (1985) Tuberculous peritonitis: CT appearance. Am J Radiol 144:931–932.
96. Hulnick DH, Megibow AJ, Naidich DP, Hilton S, Cho KC, Balthazar EJ (1985) Abdominal tuberculosis—a CT-evaluation. Radiology 157:199–204.
97. Denath FM (1990) Abdominal tuberculosis in children: CT findings. Gastrointest Radiol 15:303–306.
98. Epstein BM, Mann JH (1982) CT of abdominal tuberculosis. Am J Radiol 139:861–866.
99. Levine H (1967) Needle biopsy of the peritoneum in exudative ascites. Arch Intern Med 120:542–545.
100. Singh MM, Bhargava AN, Jain KP (1969) Tuberculous peritonitis: an evaluation of pathogenic mechanisms, diagnostic procedures and therapeutic measures. N Engl J Med 281:1091–1096.
101. Shukla HS, Naitrani YP, Bhatia S, Das P, Gupta SC (1982) Peritoneal biopsy for diagnosis of abdominal tuberculosis. Postgrad Med J 58:226–228.
102. Jorge AD (1984) Peritoneal tuberculosis. Endoscopy 16:10–12.
103. Manohar A, Simjee AE, Haffejee AA (1990) Symptoms and investigative findings in 145 patients with tuberculous peritonitis diagnosed by peritoneoscopy and biopsy over a five year period. Gut 31:1130–1132.

104. Kalvaria I, Kottler RE, Marks IN (1988) The role of colonoscopy in the diagnosis of tuberculosis. J Clin Gastroenterol 10:516–523.

105. Kochhar RJ, Rajwanshi A, Goenka MK, Nijwahan R, Sood A, Nagi S et al. (1991) Colonoscopic fine needle aspiration cytology in the diagnosis of ileo-caecal tuberculosis. Am J Gastroenterol 86:102–104.

106. Tandon HD, Prakash A (1972) Pathology of intestinal tuberculosis and its distinction from Crohns disease. Gut 13:260–269.

107. Abrams JS, Holden WD (1964) Tuberculosis of the gastrointestinal tract. Arch Surg 89:282–293.

108. Dineen P, Homan WP, Grafe WR (1976) Tuberculous peritonitis: 43 years experience in diagnosis and treatment. Ann Surg 84:717–723.

109. McMillen MA, Arnold SD (1979) Tuberculous peritonitis associated with alcoholic liver disease. NY State J Med 79:922–924.

110. Byrom HB, Mann CV (1969) Clinical features and surgical management of ileocaecal tuberculosis. Proc Roy Soc Med 62:1230–1233.

111. Bobrowitz ID (1982) Active tuberculosis undiagnosed until autopsy. Am J Med 72:650–658.

112. Monie RDH, Hunter AM, Rocchiccioli KMS, White JP, Campbell IA, Kilpatrick GS (1983) Retrospective survey of the management of miliary tuberculosis in South and West Wales 1976–78. Thorax 38:369–373.

113. Sahn SA, Neff TA (1968) Miliary tuberculosis. Am J Med 56:495–505.

114. Price M (1968) Lymphangitis reticularis tuberculosa. Tubercle 49:377–384.

115. Proudfoot AT, Akhtar AJ, Douglas AC, Horne NW (1969) Miliary tuberculosis in adults. Br Med J ii:273–277.

116. Proudfoot AT (1971) Cryptic disseminated tuberculosis. Br J Hosp Med 5:773–780.

117. Grieco MH, Chmel H (1974) Acute disseminated tuberculosis as a diagnostic problem. Am Rev Respir Dis 109:554–560.

118. Medd WE, Hayhoe FGJ (1955) Tuberculous miliary necrosis with pancytopenia. Quart J Med 24:351–364.

119. Cooper W (1959) Pancytopenia associated with disseminated tuberculosis. Ann Intern Med 50:1497–1501.

120. Hughes JT, Johnstone RM, Scott AC, Stewart PD (1959) Leukaemoid reactions in disseminated tuberculosis. J Clin Pathol 12:307–311.

121. Twomey JJ, Leavell BS (1965) Leukaemoid reactions to tuberculosis. Arch Intern Med 116:21–28.

122. Oswald NC (1963) Acute tuberculosis and granulocytic disorders. Br Med J ii:1489–1496.

123. So SY, Yu D (1981) The adult respiratory distress syndrome associated with miliary tuberculosis. Tubercle 62:49–53.

124. Heap MJ, Bion JF, Hunter KR (1989) Miliary tuberculosis and the adult respiratory distress syndrome. Respir Med 83:153–156.

125. Dyer RA, Chappell WA, Potgeiter PD (1985) Adult respiratory distress syndrome associated with miliary tuberculosis. Crit Care Med 13:12–15.

126. Bishburg E, Sunderam G, Reichman LB, Kapila R (1986) Central nervous system tuberculosis with the acquired immunodeficiancy syndrome and its related complex. Ann Intern Med 105:201–213.

127. Rich AR, McCordock HA (1933) The pathogenesis of tuberculous meningitis. Bull Johns Hopkins Hosp 52:5–37.

128. Medical Research Council Streptomycin in Tuberculosis Trials Committee (1948) Streptomycin treatment of tuberculous meningitis. Lancet i:582–597.

129. Teoh R, Humphries MJ, Chan JCN, Ng HK, O'Mahoney G (1989) Internuclear ophthalmoplegia in tuberculous meningitis. Tubercle 70:61–64.

130. Wadia NH, Dastur DK (1969) Spinal meningitis with radiculomyelopathy. Part 1: clinical and radiological features. J Neurol Sci 8:239–260.

131. Humphries MJ, Teoh R, Lau J, Gabriel M (1990) Factors of prognostic significance in Chinese children with tuberculous meningitis. Tubercle 71:161–168.

132. Jeren T, Beus I (1982) Characteristics of cerebrospinal fluid in tuberculous meningitis. Acta Cytol 26:678–680.

133. Kennedy DH, Fallon RJ (1979) Tuberculous meningitis. J Am Med Assoc 241:264–268.

134. Shankar P, Manjunath N, Mohan KK, Prasad K, Behari M, Shrinivas et al. (1991) Rapid diagnosis of tuberculous meningitis by polymerase chain reaction. Lancet 2:5–7.

135. Ellard GA, Humphries MJ, Allen BW (1993) Penetration of isoniazid, rifampicin and streptomycin into the cerebrospinal fluid and the treatment of tuberculous meningitis. Am Rev Respir Dis 148:650–655.

136. Fletcher AP (1953) CSF isoniazid levels in tuberculous meningitis. Lancet ii:694–697.

137. D'Olivera JJ (1972) Cerebrospinal fluid concentrations of rifampicin in meningeal tuberculosis. Am Rev Respir Dis 106:432–437.

138. Forgan-Smith R, Ellard GA, Newton D, Mitchison DA (1973) Pyrazinamide and other drugs in tuberculous meningitis. Lancet ii:374.

139. Kaojarern S, Supmonchai K, Phuapradit P, Mokkhavesa C, Krittiyanunt S (1991) Effect of steroids on cerebrospinal fluid penetration of antituberculosis drugs in tuberculous meningitis. Clin Pharmacol Therapeut 49:6–12.

140. Woo J, Humphries MJ, Chan K, O'Mahoney G, Teoh R (1987) Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. Curr Therap Res 42:235–242.

141. Ellard GA, Humphries MJ, Gabriel M, Teoh R (1987) The penetration of pyrazinamide into the cerebrospinal fluid in patients with tuberculous meningitis. Br Med J 294:284–285.

142. Donald PR, Seifart H (1988) Cerebrospinal fluid pyrazinamide concentrations in children with tuberculous meningitis. Paediatr Infect Dis J 7:469–471.

143. Stottmeier KD, Beam RE, Kubica GP (1967) Determination of drug suspectibility of mycobacteria to pyrazinamide in 7H10 agar. Am Rev Respir Dis 96:1072–1075.

144. Carlone NA, Acocella G, Cuffini AN, Forno-Pizzoglio M (1985) Killing of macrophage-ingested mycobacteria by rifampicin, pyrazinamide, pyrazinoic acid alone and in combination. Am Rev Respir Dis 132:1274–1277.

145. Gundert-Remy U, Lett M, Weber E (1964) Concentration of ethambutol in cerebrospinal fluid in man as a function of non-protein-bound fraction in serum. J Clin Pharmacol 6:133–136.

146. Borrowitz ID (1972) Ethambutol in tuberculous meningitis. Chest 61:629–632.

147. Place VA, Pyle MM, de la Huerga J (1969) Ethambutol in tuberculous meningitis. Am Rev Respir Dis 99:783–785.

148. Hughes IE, Smith HV, Kane PO (1962) Ethionamide and its passage into the cerebrospinal fluid fluid in man. Lancet i:616–617.

149. Donald PR, Seifart HI (1989) Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. J Pediatr 115:383–386.

150. Donald PR, Schoeman JF, O'Kennedy A (1987) Hepatic toxicity during chemotherapy for severe tuberculous meningitis. Am J Dis Child 141:741–743.

151. Humphries MJ (1992) The management of tuberculous meningitis. Thorax 47:577–581.

152. Phuapradit P, Vejjajiva A (1987) Treatment of tuberculous meningitis: the role of short course chemotherapy. Quart J Med 239:249–258.

153. Jacobs RF, Sunakorn P, Chotitayasunonah T, Pope S, Kelleher K (1992) Intensive short course chemotherapy for tuberculous meningitis. Pediatr Infect Dis 11:194–198.

154. Acharya VN, Kudva BT, Retnam VJ, Mehta PJ (1985) Adult tuberculous meningitis: comparative study of different chemotherapeutic regimens. J Assoc Physicians India 33:583–585.

155. Shaw PP, Wang SM, Tung SG, Niu QW, Lu TS, Yu XC, et al. (1984) Clinical analysis of 445 adult cases of tuberculous meningitis. Chin J Tuberc Respir Dis 3:131–132.

156. Horne NW (1966) A critical evaluation of corticosteroids in tuberculosis. Adv Tuberc Res 15:1–54.

157. Udani PM, Dastur PK (1971) Tuberculous encephalopathy with and without meningitis: clinical features and pathological correlations. J Neurol Sci 14:541–561.

158. Bhargava S, Gupta AK, Tandon PN (1982) Tuberculous meningitis—a CT study. Br J Radiol 55:189–196.

159. Bullock MR, Welchman JM (1982) Diagnostic and prognostic features of tuberculous meningitis on CT scanning. J Neurol Neurosurg Psychol 45:1098–1101.

160. Teoh R, Humphries MJ, Hoare RD, O'Mahoney G (1989) Clinical correlation of CT changes in 64 Chinese patients with tuberculous meningitis. J Neurol 236:48–51.

161. Kingsley DPE, Hendrickse WA, Kendall BE, Swash M, Singh V (1987) Tuberculous

meningitis: role of CT scan in management and prognosis. J Neurol Neurosurg Psychol 50:30–36.

162. Teoh IR, Humphries MJ, O'Mahoney G (1987) Symptomatic intracranial tuberculoma developing during treatment of tuberculosis; a report of 10 cases and review of the literature. Quart J Med 241:449–460.
163. Lees AJ, Macleod AF, Marshall J (1980) Cerebral tuberculomas developing during treatment of tuberculous meningitis. Lancet i:1208–1211.
164. Chambers T, Hendrickse WA, Record C, Rudge P, Smith H (1984) Paradoxical expansion of intracranial tuberculomas during treatment. Lancet ii:181–184.
165. Tandon PN, Bhargava S (1985) Effect of medical treatment on intracranial tuberculoma—a CT study. Tubercle 66:85–97.
166. Teoh R, Poon W, Humphries MJ, O'Mahoney G (1988) Suprasellar tuberculoma developing during treatment of tuberculous meningitis requiring urgent surgical decompression. J Neurol 235:321–322.
167. Roy TK, Sircar PK, Chandar V (1979) Peritoneal-ventricular shunt in the management of tuberculous meningitis. Indian J Paediatr 16:1023–1027.
168. Palur R, Rajshekar V, Chandy MJ, Joseph T, Abraham J (1991) Shunt surgery for hydrocephalus in tuberculous meningitis. A long-term follow-up study. J Neurosurg 74:64–69.
169. Peacock WJ, Deeny JE (1984) Improving the outcome of tuberculous meningitis in childhood. S Afr Med J 66:597–598.
170. Tang ESC, Chau A, Fong D, Humphries MJ (1991) The treatment of multiple intracranial abscesses: a case report. J Neurol 238:183–185.
171. Ogawa SK, Smith MA, Brennessel DJ, Lowy FD (1987) Tuberculous meningitis in an urban medical centre. Medicine 66:317–326.
172. Arens LJ, Deeny JE, Molteno CD, Kibel MA (1977) Tuberculous meningitis in children in the western Cape: neurological sequelae. Paediatr Rev Commun 1:257–275.
173. Larrieu AJ, Tyers GF, Williams EH, Derrick JR (1980) Recent experience with tuberculous pericarditis. Ann Thorac Surg 29:464–468.
174. Lorell BH, Braunwald E (1988) Pericardial disease: tuberculous pericarditis. In: Braunwald E, ed. Heart Disease—A Textbook of Cardiovascular Medicine, 3rd Ed., pp. 1509–1511. Philadelphia: WB Saunders.
175. Fowler NO (1991) Tuberculous pericarditis. J Am Med Assoc 266:99–103.
176. Strang JIG (1984) Tuberculous pericarditis in Transkei. Clin Cardiol 7:667–670.
177. Dave T, Narula JP, Chopra P (1990) Myocardial and endocardial involvement in tuberculous constrictive pericarditis. Int J Cardiol 28:245–251.
178. Rooney JJ, Crocco JA, Lyons HA (1970) Tuberculous pericarditis. Ann Intern Med 72:73–78.
179. Bashi VV, John S, Ravimukar, Rooney JJ, Crocco JA, Lyons HA (1988) Early and

late results of pericardectomy in 118 cases of constrictive pericarditis. Thorax 43:637–641.

180. Sagrosta-Sauleda J, Permanyer-Miralda G, Soler-Soler J (1988) Tuberculous pericarditis: ten year experience with a prospective protocol for diagnosis and treatment. J Am Coll Cardiol 11:724–728.
181. Strang JIG, Kakaza HHS, Gibson DG, Girling DJ, Nunn AJ, Fox W (1988) Controlled trial of complete open drainage and prednisolone in the treatment of tuberculous pericardial effusion in Transkei. Lancet ii:759–763.
182. Pohost GM, O'Rourke RA, eds. (1991) Principles and Practice of Cardiovascular Imaging, p. 457. Boston: Little Brown.
183. Endrys J, Simo M, Shafie MZ, et al. (1988) New non-surgical technique for multiple pericardial biopsies. Cathet Cardivasc Diagn 15:92–94.
184. Strang JIG, Kakaza HHS, Gibson DG, Girling DJ, Nunn AJ, Fox W (1987) Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet ii:1418–1422.
185. Quale JM, Lipshick GY, Heurich AE (1987) Management of tuberculous pericarditis. Ann Thorac Surg 43:653–655.
186. Long R, Younes M, Patton N, Hershfield E (1989) Tuberculous pericarditis: long term outcome in patients who received medical treatment alone. Am Heart J 117:1133–1139.
187. Kramer F, Sasse SA, Simms JC, Leedom JM (1993) Primary cutaneous tuberculosis after a needle stick injury from a patient with AIDS and undiagnosed tuberculosis. Ann Intern Med 119:594–595.
188. Stack RJ, Bickley LK, Coppel IG (1990) Miliary tuberculosis presenting as skin lesions in a patient with the acquired immunodeficiency syndrome. J Am Acad Dermatol 23:1031–1035.
189. Lombardo PC, Weitzman I (1990) Isolation of *Mycobacterium tuberculosis* and *M. avium* complex from the same skin lesions in AIDS. N Engl J Med 323:916–917.
190. Van Kralingen KW, Slee PH (1987) A patient with miliary tuberculosis and acute adrenal failure. Neth J Med 30:235–241.
191. Wilkins EGL, Hnizdo E, Cope A (1989) Addisonian crisis induced by treatment with rifampicin. Tubercle 70:69–73.
192. McAllister WAC, Thompson FJ, Al-Habet S, Rodgers S, Nagai H, Shimizu S, Kawamoto H, Yamanove M, Tsuchiya T, Yamamoto M (1982) Adverse effects of rifampicin on prednisolone deposition. Thorax 37:792.
193. Ellis ME, Webb AK (1983) Cause of death in patients admitted to hospital with pulmonary tuberculosis. Lancet i:665–667.
194. Essop AR, Posen JA, Hodgkinson JH, Segal I (1984) Tuberculous hepatitis: a clinical review of 96 cases. Quart J Med 212:465–477.
195. Nagai H, Shimizu S, Kawamoto H, et al. (1989) A case of solitary tuberculosis of the liver. Japan J Med 28:251–255.

196. Sheen-Chen SM, Chou FF, Tai DI, Eng HL (1990) Hepatic tuberculosis; a rare cause of bleeding gastric varices. Tubercle 71:225–227.

197. Gibson JA (1973) Granulomatous liver disease and portal hypertension. Proc Roy Soc Med 66:502–503.

198. Andrew WK, Thomas RG, Gollach BL (1982) Miliary tuberculosis of the liver—another cause of 'bright liver' on ultrasound examination. S Afr Med J 62:808–809.

199. Spiegel CT, Tuazon CU (1984) Tuberculous liver abscess. Tubercle 65:127–131.

200. Epstein BM, Leibowitz CB (1987) Ultrasonographic and computed tomographic appearance of focal tuberculosis of the liver. A case report. S Afr Med J 71:461–462.

201. Denath FM (1990) Abdominal tuberculosis in children: CT findings. Gastrointest Radiol 15:303–306.