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Review Article

Mycobacterium marches back

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Abstract

The resurgence of tuberculosis world-wide and its association with HIV infection means a greater likelihood of otolaryngologists encountering the disease in one form or another. In this review the features of primary and secondary tuberculosis in various head and neck sites are described, and recent advances in diagnosis are discussed. For the otolaryngologists other important aspects such as infections with atypical mycobacteria, the differential diagnosis of cervical lymphadenopathy in HIV-infected patients, recently recognized problems in drug treatment, and the role of surgery in head and neck tuberculosis are also discussed.

Key words: Tuberculosis; Mycobacterium; Lymphadenopathy; Acquired immunodeficiency syndrome (AIDS)

Introduction

Last year the World Health Organization (WHO) declared tuberculosis (TB) a global emergency (Nakajima, 1993). Tuberculosis now affects more than a third of the world population (Sudre *et al.*, 1992). The rising incidence is due to a number of factors. Prior to the advent of the HIV epidemic, immunization and disease control programmes had waned. The emergence of mycobacterial strains with multiple drug resistance and the rising population of young adults (who form a large group infected by TB) have also fuelled the epidemic such that tuberculosis is now the world's leading cause of death from a single infective agent (Godlee, 1993). HIV-positive patients are prone to mycobacterial infection (Stoneburner, 1988) but the rising incidence of tuberculosis in the UK does not appear to be directly related to the rising incidence of HIV infection (Nisar *et al.*, 1992), whereas its association with poverty remains beyond doubt (Spence *et al.*, 1993). In other parts of the world the association of TB and HIV infection is stronger with 60 per cent of tuberculosis patients being infected with HIV in Zambia (Elliot *et al.*, 1990).

The rising incidence of tuberculosis is not confined to third world countries, with a 12 per cent increase noted in the USA between 1986 and 1991, and over a 30 per cent increase noted in Switzerland over the same period. Since 1987, after a declining incidence for decades in England and Wales, the number of cases of tuberculosis has shown a steady increase. The mean annual rate of tuberculosis during the period 1985–1990 was about 12.7 cases per 100 000 population, with 17 per cent of cases being non-pulmonary. The reported incidence is higher among ethnic minorities at 47.9 per 100 000 and over 40 per cent of these have nonpulmonary tuberculosis (Spence *et al.*, 1993). Many trainees and consultants in otolaryngology in the western world will have limited experience of tuberculosis of the upper aerodigestive tract. The purpose of this review of tuberculosis of the head and neck region is to represent past experience, to aid diagnosis and raise awareness of the growing problem.

Diagnosis of mycobacterial infection

The diagnosis of mycobacterial infection may be suspected from the history, physical examination and histopathological findings, but it is still essential that a definitive diagnosis is achieved by observation of acid-fast bacilli or culture of the causative organism before anti-mycobacterial therapy is started. The diagnosis of mycobacterial infection requires fluid, (e.g. sputum, gastric washings, early morning urine) or tissue samples from the patient. These may be submitted fresh to the microbiology laboratory, or (if the diagnosis is not suspected) fixed in formalin and sent to the histopathology laboratory. Fresh tissue submitted to the microbiology laboratory is examined directly by staining for acid-fast bacilli by Ziehl-Neelsen, Wade-Fite or auramine-rhodamine (fluorescent) techniques. Cultures on classical Lowenstein-Jensen slopes may take as long as six to eight weeks, but can be accelerated through the use of new technology such as the BACTEC H60 to three to seven days (Evans *et al.*, 1992).

Culture is a necessary pre-requisite for drug sensitivity

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testing of mycobacteria which is becoming more important as multidrug-resistant strains are being increasingly isolated. These organisms are extremely dangerous, as once established, there is little treatment that can be offered and immunocompromised patients die rapidly. Atypical mycobacterial infections, such as the *Mycobacterium avium–intracellulare–scrofulaceum* (MAIS) complex and *M. malmoense* are relatively common among the immunosuppressed and may be associated with HIV infection. In recent years, species-specific mycobacterial DNA probes have been developed which allow more rapid identification of species. Organisms are harvested from BACTEC cultures, DNA extracted, run onto gels and hybridized with labelled species-specific DNA probes (Peterson *et al.*, 1989). First generation probes were radiolabelled with, for example, P^{53} but the second generation of commercially available probes used non-isotopic detection methods, for example, acridinium-ester or digoxygenin labelling (Lebrun *et al.*, 1992).

Recently, identification of *M. tuberculosis* has been made in sputum and other fresh samples by extraction of DNA and specific amplification of *M. tuberculosis* DNA using the polymerase chain reaction (PCR). Short nucleotide sequences (oligonucleotide sequences) have been selected in different studies from the 65 Kd (heat shock protein) gene (Pierre *et al.*, 1991), the gene for 38 Kd *M. tuberculosis* specific peptide (Sjobring *et al.*, 1990) and the IS986 insertion element of the *M. tuberculosis* genome (Kolk *et al.*, 1992). These studies on clinical material performed prospectively on concurrently cultured material have shown excellent sensitivity (98 per cent). A single mycobacterium contains 5 femtograms of DNA and the PCR technique using the IS986 insertion primers can detect as little as 1 femtogram of *M. tuberculosis* complex DNA in a single PCR vial. These techniques are reliable when used on fluids or fresh biopsy material, but have not yet been evaluated for use in formalin-fixed or paraffin-embedded material.

Currently, if no fresh material has been submitted for analysis or culture, the diagnosis rests on finding acid-fast bacilli histologically which may be difficult, time-consuming and often unrewarding. Successful application of molecular techniques would allow definitive diagnosis on histologically suggestive material in which no organisms could be seen by inspection. It is important to emphasize that these molecular biological techniques for the detection of *M.tuberculosis* would also pick up dead, non-viable and so non-culturable organisms in sputum after effective chemotherapy allowing retrospective diagnosis. Using DNA fingerprinting to identify a particular isolate of *M. tuberculosis* it is now possible to investigate transmission of an organism from one individual to another which may be useful epidemiologically or medicolegally (Godfrey-Faussett *et al.*, 1992). Because of their sensitivity, PCR techniques are prone to false-positive results from environmental contamination and great care is required with technique and appropriate controls (Kitchen *et al.*, 1990).

These techniques are being evaluated currently and are not yet widely available on a routine basis. The recently published trials suggest that non-isotopic reliable PCR based diagnosis of mycobacterial infection and species identification is applicable to routine practice providing that the cost per test is not prohibitive (Brisson-Noel *et al.*, 1991).

Otolaryngological manifestations of tuberculosis

Patients may present to the otolaryngologist with primary tubercular infection somewhere in the head and neck, most commonly as cervical lymphadenopathy (up to five per cent of all TB patients) but also more unusually with manifestations in the larynx, ear, nose, pharynx, and cervical spine. Other sites such as the salivary glands are only rarely infected.

Otolaryngological manifestations may be secondary to established pulmonary tuberculosis. For example, 90 per cent of cases of laryngeal tuberculosis are associated with pulmonary TB. In other sites the association is less strong (aural 50 per cent, pharynx 20 per cent, cervical nodes 5 per cent). Consequently all patients who have TB of the head and neck region must have further investigation (chest X-ray, sputum culture and possibly culture of early morning urine and gastric washings) to exclude pulmonary or systemic TB.

Otolaryngologists may also have to manage problems that arise as a result of the treatment of tuberculosis, in particular the consequences of ototoxicity.

Cervical nodes

Approximately five per cent of all patients with tuberculosis develop tuberculous cervical lymphadenitis (Shikhani *et al.*, 1989). About 70 per cent of patients with tuberculous lymphadenitis have cervical node involvement alone, about seven per cent have inguinal node involvement, seven per cent have axillary node involvement, and the remaining 16 per cent have multiple sites of lymph node involvement (Dandapat *et al.*, 1990). In the cervical region the commonest affected nodes are those in the posterior triangle (Kheiry and Ahmed, 1992). Affected lymph nodes may be discretely enlarged but in about 75 per cent of cases are matted together and clinically indistinguishable from lymphoma (Dandapat *et al.*, 1986). A third of patients have bilateral disease (Lee *et al.*, 1992) and about one in five patients present with a discharging sinus or abscess formation. Ultrasound will delineate the lymphadenopathy and although typical features of tuberculous lymphadenitis have been described this investigation cannot reliably differentiate between tuberculosis and other causes of lymphadenopathy (Winkelbauer *et al.*, 1993).

Associated acute active pulmonary tuberculosis affects five per cent of patients with cervical lymph node disease (Dandapat *et al.*, 1990), whereas 10–15 per cent of patients have radiological evidence consistent with previous pulmonary tuberculosis (Cantrell *et al.*, 1975; Lee *et al.*, 1992).

Between 74 per cent (Dandapat *et al.*, 1990) and 96 per cent (Lee *et al.*, 1992) of patients with tuberculous cervical lymphadenitis are Mantoux positive. A positive test does not necessarily mean that the cause of the lymphadenopathy is tuberculosis. A negative result, especially with a high dose PPD (purified protein derivative) of 100 or 250 tuberculin units, rules out tuberculosis as the cause providing the patients is HIV-negative or not immunocompromised in any other way.

An increasingly popular approach to diagnosis is fine needle aspiration cytology (FNAC) which, in the diagnosis of tuberculous cervical lymphadenitis, has a reported specificity (the chance of a negative FNAC when

the lymphadenopathy is not due to tuberculosis) of 93 per cent and a sensitivity (the chance of a positive FNAC when the lymphadenopathy is tuberculous) of 77 per cent (Lau *et al.*, 1990). Confirmation that FNAC can correctly diagnose tuberculous lymphadenitis in up to 83 per cent of cases establishes FNAC as a useful investigation (Dandapat *et al.*, 1990; Hsu *et al.*, 1990; Lee *et al.*, 1992). In approximately a quarter of cases where cytology shows no evidence of tuberculosis the culture will be positive (Lee *et al.*, 1992) (see Table I).

Because cultures take four to six weeks to grow adequately (unless BACTEC is available) a negative FNAC should be followed by excision biopsy of a cervical node to confirm the diagnosis histologically. An open biopsy of a lymph node rarely causes difficulty on histology but in approximately 20 per cent of cases culture will be positive when histopathology was inconclusive.

In children, most mycobacterial lymphadenitis in developed countries is caused by nontuberculous mycobacteria (so called atypical mycobacteria) such as the *M. avium–intracellulare–scrofulaceum* (MAIS) complex and *M. malmoense*. There are histological features in an excised cervical lymph node such as ill-defined nonpalisading granulomas, irregular or serpiginous granulomas, lack of caseation, and sarcoid-like features that may suggest an atypical mycobacterial infection (Pinder and Colville, 1993).

An important differential diagnosis is that of Hodgkin's disease which can present with cervical lymphadenopathy and so-called 'B' symptoms similar to those of TB. Histology occasionally shows non-caseating tuberculoid granulomatous centres which may obscure the features of Hodgkin's disease and may raise the possibility of mycobacterial disease, but of course culture will be negative. Granulomas have also been reported in uninvolved lymph nodes and other organs in the presence of Hodgkin's disease elsewhere (Kadin *et al.*, 1970).

Treatment of cervical mycobacterial infection

In atypical infections, excision of the node before it ruptures is the only treatment required. In more widespread infection chemotherapy on the basis of drug sensitivity is required. Many of the atypical mycobacteria are resistant to commonly used agents and may require treatment with second line agents such as cycloserine (Mandell and Sane, 1990).

Tuberculous infection of lymph nodes in children can be successfully treated using a six-month course of combination chemotherapy. Using streptomycin, rifampicin, isoniazid and pyrazinamide three times a week for two months followed by streptomycin and isoniazid twice a week for four months only three per cent of children needed further treatment over a three-year follow-up (Jawahar *et al.*, 1990). Adults may require a nine-month course of chemotherapy (Dandapat *et al.*, 1990). Despite successful treatment lymphadenopathy exceeding 10 mm may persist and rebiopsy is mandatory to exclude residual infection. About 10 per cent of these will require further treatment (Jawahar *et al.*, 1990). In up to a quarter of patients the nodes enlarge when treatment is commenced, a feature thought to be due to a hypersensitivity reaction to the tuberculin released from killed bacilli. One should consider poor compliance as a cause of failure, and possibly admit patients for a period of supervised treatment.

TABLE I

Typical features of TB on FNAC
Multinucleated giant cells
Acid-fast bacilli on Ziehl-Neelsen stain
Epithelioid cells
Caseous necrosis

Laryngeal tuberculosis

At the turn of the century tuberculosis was the commonest condition to affect the larynx. Sir St. Clair Thompson estimated in 1919 that a quarter of the 400 000 people thought to have pulmonary tuberculosis in the UK at that time had laryngeal involvement (Thompson, 1919). Before the introduction of effective chemotherapeutic agents there was an associated morbidity of 70 per cent with laryngeal disease (Ormerod, 1951), and Morell Mackenzie in 1880 stated that 'the prognosis of laryngeal phthisis is always extremely unfavourable, and it is not certain that any cases ever recover' (Thompson, 1919).

Postmortem studies a century ago showed that 48 per cent of patients dying of tuberculosis had laryngeal involvement (Habersohn, 1905; Thompson, 1924). Today laryngeal tuberculosis accounts for less than one per cent of all cases of tuberculosis (Galietti *et al.*, 1989). Previously the mode of infection was direct spread along the airway, but currently about six per cent of cases have no evidence of pulmonary disease (Bailey and Windle-Taylor, 1981), and 30 per cent have positive early morning urine culture indicating haematogenous dissemination of disease (Hunter *et al.*, 1981).

Nevertheless, the reports on tuberculous laryngitis state that the majority, if not all, of the patients have a previous history of tuberculosis or evidence of active pulmonary disease (Bull, 1966; Bailey and Windle-Taylor, 1981; Hunter *et al.*, 1981; Gertler and Ramages, 1985; Galietti *et al.*, 1989; Rupa and Bhanu, 1989; Soda *et al.*, 1989; Ramadan *et al.*, 1993). The commonest chest X-ray changes are of bilateral, poorly defined, nodular shadows involving predominantly the upper and middle zones and occasionally the lower zones. Cavitation is seen in about half the patients (Hunter *et al.*, 1981). It is likely but by no means certain therefore that the clinician will be alerted to the possibility of tuberculosis.

Early descriptions of laryngeal tuberculosis identified the posterior part of the larynx as being the part most frequently affected (Thompson, 1924). This may have been due to its association with gross pulmonary disease in patients who were bed bound and in whom infected sputum accumulated over the interarytenoid region. This is no longer the case. The vocal folds are the most common site affected (50–70 per cent of cases) closely followed by the ventricular bands (40–50 per cent of cases) (Bailey and Windle-Taylor, 1981; Soda *et al.*, 1989). The other sites affected in approximately 10–15 per cent of cases are the epiglottis, aryepiglottic fold, arytenoid, posterior commissure and subglottis. Contrary to the older descriptions the anterior half of the larynx is affected twice as often as the posterior half (Bailey and Windle-Taylor, 1981).

The symptoms of laryngeal tuberculosis are those of any chronic laryngeal affliction, namely hoarseness, dysphagia, odonophagia, referred otalgia, cough and stridor.

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Painful dysphagia may be the prominent symptom (Hunter *et al.*, 1981) and may appear to be much worse than expected from the degree of laryngeal pathology visible on laryngoscopy.

On laryngoscopy tuberculosis laryngitis is indistinguishable from carcinoma or chronic laryngitis (Bull, 1966). Early descriptions are unsurpassed (Thompson, 1919). Because of the varied appearance of tuberculous laryngitis a description of the typical appearance of the larynx is not possible. Early descriptions made a distinction between a low grade chronic infection known as 'lupus' characterized by discrete nodules with no associated oedema and a more aggressive acute form of infection known as tuberculous laryngitis characterized by oedema and painful ulceration affecting the laryngeal cartilages (Thompson, 1919). Patients with the lupus form of infection tended to be generally well with many healing spontaneously with residual scarring and cicatrization. True oedema is said to be infrequent and when seen usually accompanies late stages of tuberculosis. Infiltration of the lax mucosa around the arytenoids produces a pale, fleshy swelling that may appear tense and shiny as if full of fluid, but is in fact solid. This has been referred to in the past as pseudo-oedema (Thompson, 1919). Stridor is usually secondary to granulations occluding the glottis. These typically ulcerate with spontaneous improvement in stridor but may be severe enough to necessitate tracheostomy (Gertler and Ramages, 1985). Alternatively stridor may be due to vocal fold paralysis secondary to mediastinal disease (Shah and Ramakantan, 1990), or due to stenosis and fibrosis of the larynx. Permanent laryngeal deformity and fibrosis may cause laryngeal incompetence or stenosis which can only be resolved with surgery – either tracheostomy or laryngectomy (Gertler and Ramages, 1985).

Because the appearance of tuberculosis can easily be mistaken for other conditions the diagnosis may only become apparent when a biopsy has been performed for what was suspected to be a carcinoma. Many patients will have had a chest X-ray prior to direct laryngoscopy and laryngeal tuberculosis may be suspected on identification of pulmonary disease which accompanies over 90 per cent of cases. However, chest X-ray changes may only reflect previous inactive lung disease and cannot be relied on to make a diagnosis of active disease.

Sputum microscopy for *Mycobacterium tuberculosis* is positive in 70 per cent (Bailey and Windle-Taylor, 1981) to 80 per cent (Hunter *et al.*, 1981) of patients with laryngeal disease. Laryngeal tuberculosis responds rapidly to treatment. Symptoms resolve within two weeks of instituting chemotherapy (Hunter *et al.*, 1981) and the sputum becomes clear of mycobacteria. The persistence of a suspicious lesion after treatment may be due to non-compliance, a resistant organism, or a concomitant carcinoma which should be excluded by biopsy (Chodosh and Willis, 1970; Hunter *et al.*, 1981).

Aural tuberculosis

In 1915 Logan Turner reported that two per cent of all Scottish children with middle ear suppuration had tuberculous infections of the middle ear, most of which were caused by *M. bovis*: the younger the child the higher the incidence such that over a quarter of two year olds had tuberculous infection and a half of one year olds (Turner and Fraser, 1915). All these babies were bottle fed on unsterilized cow's milk. One in five developed labyrinthine infection, facial palsy occurred in about half the patients, nearly all had associated lymphadenopathy and before the introduction of chemotherapy the condition was universally fatal (Dickie, 1929). Since the inoculation of cattle against bovine tuberculosis and the general reduction in tuberculosis the incidence of aural tuberculosis has fallen. In 1960 Jeanes and Friedmann reported that 0.05 per cent of patients seen over a ten-year period with suppurative otitis media in London had tuberculous infection (Jeanes and Friedmann, 1960).

About 50 per cent of patients have evidence of pulmonary disease on chest X-ray (Windle-Taylor and Bailey, 1980; Ramages and Gertler, 1985). Despite extensive destruction the infection is surprisingly painless. The typical appearance is of pale granulations visible through a central perforation and scanty mucoid discharge. Contrary to popular belief multiple perforations are rare and probably represent an early and transient stage of infection. Bony sequestrum is visible on otoscopy in about 10 per cent and is a common finding on surgical exploration. Facial palsy is a common complication and occurs in about 20 per cent of cases (Windle-Taylor and Bailey, 1980; Ramages and Gertler, 1985). Many patients have swelling over the mastoid and about one in five develop a discharging sinus.

Microscopy of the aural discharge has a sensitivity of about 73 per cent, whereas culture of middle ear mucosa has a sensitivity of 96 per cent (Ramages and Gertler, 1985).

Surgery may be required to obtain histological material and also when complications intervene. Indications for surgery are facial palsy, subperiosteal abscess, fistula formation, labyrinthitis, intracranial complications and progressive disease caused by resistant mycobacteria (Ma *et al.*, 1990).

Oral cavity

As a rule oral infection is secondary to pulmonary disease. Primary infection requires a port of entry and is therefore associated with poor oral hygiene or other causes of mucosal damage including dental extraction. Oral tuberculous infection manifests itself as a painless ulcer with associated regional lymphadenopathy. The ulcer crater classically has an undermined edge and little in the way of induration. The commonest sites affected are the gum, the tongue (Prabhu *et al.*, 1978; Hashimoto and Tanioka, 1989), the palate (Haddad *et al.*, 1987), and the floor of mouth (Rauch and Friedman, 1978). The appearances are indistinguishable from carcinoma and therefore biopsy is mandatory. Histological diagnosis may not be evident at first, the features being of nonspecific chronic inflammation. In this situation failure to respond to conventional antibiotics, and the absence of pain should alert the clinician to the possibility of an unusual pathology (Dimitrakopoulos *et al.*, 1991). The local tissue reaction and the small numbers of tubercle bacilli in oral lesions makes the isolation of tubercle bacilli especially difficult in oral tuberculosis. As a result culture and microscopy may be negative for bacilli and treatment may have to be initiated on the basis of histology and supporting evidence

from a chest X-ray and positive Mantoux. Newer techniques that use DNA polymerase chain reaction should improve the diagnostic yield in oral tuberculosis. In addition to carcinoma other conditions that may mimic tuberculosis and therefore require exclusion prior to starting chemotherapy include, syphilis, sarcoidosis and deep mycotic infections.

Pharynx: nasopharynx, oropharynx, hypopharynx

Prior to the introduction of chemotherapy 1.4 per cent of all adenoids (Crowe *et al.*, 1917) and 6.5 per cent of all tonsils (Thompson, 1919) removed from asymptomatic patients were infected by tubercle. Pharyngeal infection is usually slowly progressive and presents as a chronic nodular irregularity of mucosal surfaces. Older descriptions differentiate between this mitigated form of infection and the acute tuberculous ulceration which was rarely seen. The former was referred to as 'lupus' and the latter as tuberculous pharyngitis (Thompson, 1919). The so-called lupus infection of the pharynx causes small pink nodules with yellow 'apple-jelly' centres. These nodules eventually coalesce forming areas of raised bosselated epithelium covered by a mucinous secretion.

Cervical lymphadenopathy accompanies nasopharyngeal tuberculosis in about 70 per cent of cases and is the only feature in 50 per cent of cases (Waldron *et al.*, 1992). Conversely just over a quarter of children and young adults under the age of 20 years with tuberculous cervical lymphadenopathy have evidence of tuberculous infection of the adenoids (Mahindra *et al.*, 1981). After cervical lymphadenopathy, the commonest features of nasopharyngeal tuberculosis are nasal obstruction and nasal discharge. Low grade fever and malaise is uncommon and may be transitory with only about 30 per cent of patients having some sort of systemic upset (Waldron *et al.*, 1992). The affected adenoid tissue has no characteristic appearance other than hypertrophy (Mahindra *et al.*, 1981). Histologically caseation is unusual whereas giant cells are abundant. Tubercle formation occurs deep within the adenoid tissue accounting for the normal external appearance on macroscopic examination. The majority of cases of nasopharyngeal tuberculosis are primary infections. Evidence of lung involvement on chest X-ray is seen in less than 20 per cent of cases although hilar lymphadenopathy has been described in up to 50 per cent of cases (Mahindra *et al.*, 1981). Because of the paucity of accompanying clinical signs, nasopharyngeal tuberculosis can easily be missed or misdiagnosed. Standard chemotherapy treatment should produce rapid improvement such that failure to improve within two weeks should call the diagnosis into question and other granulomatous conditions should be considered (Couldery, 1990).

Tonsillar tuberculosis was demonstrable in over one third of patients with cervical lymphadenitis at the beginning of the century (Mitchell, 1914). The tonsils were usually infected with *M. bovis* by drinking infected cows milk, consequently tonsillar tuberculosis is rarely seen nowadays. The early descriptions stated that tonsils became fibrotic as a result of infection and that most patients presented with cervical lymphadenopathy (Fordyce and Carmichael, 1914).

Nasal cavity

The commonest site to be affected is the cartilagenous septum. Women appear to be affected twice as often as men (Thompson, 1919; Havens, 1931), a trend that appears to be reflected in recent reports which all involve women (Messervy, 1971; Harrison and Knight, 1986; Gentric and Garre, 1992). The typical early appearance is of mucosal pallor with minute 'apple-jelly' nodules which fail to blanch with topical adrenaline which renders them more obvious against the surrounding mucosa. As these nodules coalesce the mucosa becomes granular and the septum may perforate. The bony septum is said never to perforate (Thompson, 1919), a feature that distinguishes tubercle from syphilis. The edge of the perforation is irregular and surrounded by pale mucosa. The disease is painless and causes nasal obstruction and catarrh. Bacilli are difficult to detect and diagnosis usually requires careful examination of biopsy material. As in nasopharyngeal disease nasal disease is often primary with few systemic symptoms. Confirmation of tuberculosis by culture is mandatory because acid-fast bacilli obtained from the nose seen on microscopy may be *Mycobacterium leprae*.

Salivary glands

The largest series of tuberculous salivary gland disease was published in 1961 (Donohue and Bolden, 1961) in which they review the clinical features of 79 cases. The parotid gland is the commonest gland affected, followed by the submandibular gland and then the sublingual gland. Two varieties of tuberculous infection are described, firstly an acute and diffuse inflammatory involvement, and secondly the more chronic, encapsulated variety which is indistinguishable from neoplastic disease (Berman and Fein, 1932; Batsakis, 1974). Recent reports suggest that amongst the UK population Asian immigrants are at higher risk of parotid gland infection than non-immigrants (Kuruvilla *et al.*, 1981; Dilkes *et al.*, 1991), and one study found tuberculosis to be as common as pleomorphic adenoma in this group of patients (Ubhi *et al.*, 1988).

Infection within the parotid most often arises in the intraparotid lymph nodes, and is often the only site affected, the bacilli presumably reaching the gland either via the duct or through lymphatic channels with a focus of entry in the pharynx or tonsil (Batsakis, 1974). Because these patients are often generally well with no evidence of pulmonary involvement tuberculous infection is often indistinguishable from neoplasm, and the diagnosis may not be suspected until histology reveals the nature of the 'tumour'. Facial palsy is rare and pain is a late manifestation. Prior to the introduction of antituberculous chemotherapy surgery was the treatment of choice (Berman and Fein, 1932). If the diagnosis of tuberculosis is suspected, fine needle aspiration may be diagnostic, and conventional antituberculous chemotherapy commenced thus avoiding unnecessary surgery.

Cervical spine

The commonest vertebra to be infected by *M. tuberculosis* in adults is T_{10} and the cervical spine is affected in less than a fifth of cases of Potts' disease of the spine. Spinal disease is commoner and more variable in position in prepubertal children than in adults.

Pain is the commonest symptom in tuberculosis of the

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cervical spine, and results in neck stiffness. As the disease progresses patients often support the head with their hands, and if the nerve roots are irritated pain may be referred to the shoulders or arms. Abscess formation is initially contained behind the prevertebral fascia and will present as a retropharyngeal abscess or more rarely laterally behind sternomastoid or even as a parotid mass (Dilkes *et al.*, 1991). Spinal infection arises from blood spread, and may be associated with pulmonary disease. Radiological features are not diagnostic for tuberculosis, although CT scanning demonstrates bony destruction and MRI will show loss of central fatty marrow before frank bony destruction (Vidyasagar and Murthy, 1994). Neoplastic lesions can produce similar changes and therefore biopsy is necessary.

Diagnosis can be made by obtaining material through needle aspiration of a retropharyngeal abscess. Surgery is required for large abscesses, when neurological deficit occurs or in the presence of spinal instability secondary to bony erosion (Dilkes *et al.*, 1991). About half of the patients with neurological complications secondary to cervical cord compression have sparing of sensation and useful motor function distal to the spinal injury (classified as group D using the Frankel classification (Frankel *et al.*, 1969), and all of these recover fully with treatment (surgical decompression and chemotherapy). More severe neurological loss (complete neurological deficit – Frankel group A, or sparing of some sensation but no motor function – Frankel group B) may not fully recover despite early treatment with surgery (Vidyasagar and Murthy, 1994).

Mycobacterial disease and HIV

As many as 50 per cent of patients with HIV infection develop mycobacterial infections at some time during their illness. In 1985 the Centre for Disease Control (CDC) of North America modified the surveillance definition of AIDS to include extrapulmonary tuberculosis in patients with confirmed HIV infection, and in 1993 expanded the definition to include pulmonary tuberculosis.

Tuberculosis is extrapulmonary in approximately a half of the HIV-infected patients who develop tuberculosis, some of whom also have pulmonary disease (Llibre *et al.*, 1992). Extrapulmonary tuberculosis is probably indicative of greater immunosuppression than pulmonary disease alone, patients with extrapulmonary disease having a lower $CD4^+$ count. In addition oral and oesophageal candida is frequently and strongly associated with tuberculosis in these patients and often precedes the development of tuberculosis by a few months (Garcia *et al.*, 1992). Eighty-five per cent of patients with extrapulmonary tuberculosis have lymphadenopathy and the majority of these have cervical node disease (Harries, 1990).

TABLE II

Condition	Investigation
Syphilis	VDRL
Brucellosis	Serology
Tuberculosis	FNAC
E-B virus	Paul-Bunnell
Cytomegalovirus	Serology
Toxoplasma	Serology
Lymphoma	Node biopsy
Leukaemia	Node biopsy
Sarcoidosis	Kviem test

Diffuse cervical lymphadenopathy is one of the commonest findings during the early stages of AIDS and may be due to one of numerous different causes including non-infective follicular hyperplasia. Some other causes of cervical lymphadenopathy and the relevant investigation in HIV-positive patients are listed in Table II.

In some cases the lymphadenopathy reflects infection with opportunistic organisms. FNAC is useful in identifying tuberculous infection in AIDS patients. In a recent study over one-third of AIDS patients with cervical lymphadenopathy had evidence of some type of infection including tuberculosis. Significantly, all those with either unilateral lymphadenopathy or nodes larger than 3 cm had some form of specific infection (e.g. tuberculosis, toxoplasmosis, atypical mycobacterium, methicillin-resistant staphylococcal infection) (Shapiro and Pincus, 1991). Fine needle aspiration should be performed on AIDS patients if opportunistic infection is suspected. Specimens should be sent for cytology, bacterial and fungal culture, and acid-fast smear and culture. In the presence of unilateral lymphadenopathy or nodes greater than 3 cm a negative FNA result may require exisional biopsy for diagnosis. The indications for open biopsy are listed in Table III.

The symptoms of tuberculosis in HIV-positive patients are similar to those seen in other patients. Pulmonary tuberculosis typically presents with cough, sputum production and dyspnoea. The commonest presentation in the head and neck area is cervical lymphadenopathy. Following the above guidelines, investigation of suspicious lesions should include a chest X-ray which may reveal typical tuberculous changes, examination of sputum, and tuberculin skin testing. Although many patients with HIV infection may be anergic due to low lymphocyte counts, up to 80 per cent without AIDS react to PPD, and 30–50 per cent with AIDS have a >10 mm reaction. Fine needle aspiration of suitable nodes should be performed initially, and nodes only need to be excised if FNA is inconclusive and one or more of the features listed in Table III appertain.

Suspicion of tuberculosis at any other head and neck site should be investigated in the usual manner. Unlike other opportunistic infections tuberculosis is also infectious for healthy individuals and therefore obtaining secretions and biopsy material for examination require care and adherence to infection control procedures. In most cases precautions entail wearing gown, mask and possibly spectacles to protect the eyes. This is especially important when performing laryngoscopy or bronchoscopy.

TABLE III

Indications for node biopsy
Unilateral lymphadenopathy
Nodes >3 cm diameter
Constitutional symptoms – fever, night sweats, weight loss
Painful nodes
Sudden increase in size

Treatment of tuberculosis

It is beyond the scope of this review to discuss the treat-

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ment of mycobacterial infection in detail. However, there are a few topics which are important enough to warrant highlighting. Multiple drugs are used to treat tuberculosis to reduce the probability of the emergence of drug-resistant mutants. When there is monotherapy, irregular taking of drugs, omission of some drugs, suboptimal dosage, poor drug absorption, or an insufficient number of active agents in a drug regimen, resistance may emerge to multiple drugs in a matter of months (Gostin, 1993). In the US the prevalence of drug-resistant organisms among patients with pulmonary TB has increased from two per cent in 1960 to nine per cent currently (Iseman *et al.*, 1993). Some organisms are resistant to the two most effective anti-tuberculous agents (rifampicin and isoniazid) and are termed multidrug resistant.

Prior to 1960 patients were treated in hospitals but after this time most patients were treated as outpatients no longer being regarded as an infectious risk while on treatment. Patients were given several different drugs and expected to take them regularly for six months. Non-compliance is now recognized as an important problem in the development of resistance and also in failure to respond to treatment (CDC-MMWR, 1993) particularly in those who are homeless, drug addicts or coping with a serious concurrent disease (such as AIDS). To increase compliance many centres employ a combination of strategies such as incentives and directly observed therapy (DOT) in which a health worker witnesses the patient taking the medication (Sibbison, 1992; Iseman *et al.*, 1993). Another approach has been to combine isoniazid and rifampicin in a single capsule but there is no direct evidence that this increases compliance (Iseman, 1993). Assays for drugs in the urine are available to check compliance. The best predictor of multidrug resistance is a history of previous treatment for TB. Inadequate therapy is the most common reason for the emergence of multidrug resistance and multidrug resistant strains have been transmitted to contacts. Standard antituberculous drugs are effective in treating tuberculosis in AIDS patients. In Africa, the rate of recurrence which may be due to reinfection or re-emergence of 'persister' organisms has been shown to be 34 times greater in HIV-positive patients than in HIV-negative patients (Hawken *et al.*, 1993).

Otolaryngological complications of treatment

The untoward effects of tuberculous chemotherapy are well recognized and are described in detail elsewhere (Mandell and Sane, 1990). Streptomycin is ototoxic in up to four per cent of patients with tuberculosis, whereas the figure is reportedly higher (up to 20 per cent) in other conditions such as bacterial endocarditis (Wilson *et al.*, 1984). Streptomycin is preferentially toxic to the vestibular system although the cochlea is also affected. Ototoxicity results from damage to the sensory cells of the crista ampullaris (type I cells are more sensitive than type II cells) and the Organ of Corti (outer hair cells are more sensitive than the inner hair cells, and the basal turn is affected first). The effects are irreversible and may be delayed by several weeks.

The predominant symptoms include vertigo, tinnitus and deafness. After the acute vestibular phase chronic dysfunction is characterized by unsteadiness on sudden movements and oscilopsia (loss of vestibulo-ocular reflexes). Isoniazid may cause optic neuritis, dizziness and ataxia, but rarely causes dryness of the mouth and tinnitus. Rifampicin and pyrazinamide are both well tolerated, hepatitis being the most serious complication of both drugs. Headache, dizziness and ataxia have been reported and may occur with either drug. Ethambutol can cause optic neuritis as well as headache and dizziness. The second-line drug ethionamide can cause a metallic taste and olfactory disturbances.

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