The diagnosis and misdiagnosis of tuberculosis

P. D. O. Davies,* M. Pai†

* Tuberculosis Research Unit, Cardiothoracic Centre, Liverpool, UK; † Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

There are two worlds when it comes to the diagnosis of tuberculosis (TB). One world has only smear microscopy at its disposal. There may also be some radiological facilities, usually at the patients’ expense. The other world has all modern techniques available, including culture, nucleic acid amplification, molecular diagnostics and sophisticated radiological techniques such as computed tomography and positron emission tomography scanning. The ability to diagnose or misdiagnose TB will vary across these two worlds. In this review, we provide an overview of clinical, radiological, molecular and immunological diagnosis of TB and highlight the common difficulties and pitfalls in TB diagnosis.

CLINICAL DIAGNOSIS OF TB

Case definitions for TB

Case definitions of what constitutes a case of TB vary according to the resources available. In general, cases can only be confirmed by culture, i.e., the growth of Mycobacterium tuberculosis complex from a specimen taken from a patient.

The US Centers for Disease Control and Prevention (CDC) classify the clinical case definition as satisfying the following criteria: 1) a positive tuberculin skin test (TST); 2) other signs and symptoms compatible with TB (e.g., abnormal, unstable [i.e., worsening or improving] chest radiographs [CXRs] or clinical evidence of current disease); 3) treatment with two or more anti-tuberculosis medications. The laboratory definition of a case is defined as: 1) isolation of M. tuberculosis from a clinical specimen; or 2) demonstration of M. tuberculosis from a clinical specimen by NAA test; or 3) demonstration of acid-fast bacilli (AFB) in a clinical specimen when a culture has not been or cannot be obtained.1 It is this last definition that satisfies the only criteria available in a resource-poor setting where only microscopy is available.

In the UK, all that is required for a patient to be notified as a TB case is for the attending doctor to ‘believe that the patient is suffering from TB’. This usually means that there is sufficient evidence to start the patient on treatment for TB, whether or not the case has been confirmed by a positive culture result. In practice, only 60% of cases notified in the UK are culture-confirmed: 68% of respiratory cases and 49% of extra-pulmonary cases.2 Data from the most recent report show that the trend remains virtually unchanged, with 62% culture-confirmed in 2006.3 This may suggest either that TB is being over diagnosed, that not enough effort is being made to obtain samples for bacteriology or that even culture results are often too insensitive to confirm the presence of TB.

Risk factors for TB

The recently published National Institute for Health and Clinical Excellence (NICE) guidelines from the UK are very helpful in understanding how the diagnosis of TB is made.4 Epidemiological factors are important in assessing the probability of TB. For example, in the UK, rates among African-born immigrants are over 100 times higher and among Indian-born 70 times higher than in the white UK-born population.5 Local knowledge of the incidence of TB in different groups is therefore important to the clinician faced with a possible case of TB.

Other known risk factors should also be taken into account when assessing a patient, particularly human immunodeficiency virus (HIV) seropositivity, which increases the chance of infection developing into disease by over 100-fold. A list of common medical risk factors is shown in Table 1.6 Lifestyle factors are also important in considering a diagnosis of TB. Smoking, poor diet and factors associated with poverty need to be considered as increasing the likelihood of TB.7-9

A history of contact with a person likely to have infectious TB is one of the most important risks of having TB, especially if the patient is a child. Overall,
Diagnosis and misdiagnosis of TB

Clinicians should consider the context in which they practice, and pay careful attention to known risk factors for TB. The presence of risk factors makes a diagnosis of TB more likely, but care should be exercised: TB may occur even in an individual with absolutely no risk factors.

### Signs and symptoms of respiratory TB

The symptoms of TB may be absent if a patient is detected by contact screening before the disease has had a chance to progress very far. Primary respiratory TB is often asymptomatic, but it can present as a mild respiratory tract infection. Evidence of infection may be obtained by the TST or T-cell based interferon-gamma release assay (IGRA) (see below). Initial infection may be accompanied by erythema nodosum (painful reddish colour swellings usually on the shins and extensor surface of the legs and rarely arms) or phlyctenular conjunctivitis (redness and soreness of the conjunctiva).

Complications of primary disease include lobar collapse, pleural effusion, miliary and disseminated disease. Extra-pulmonary disease is usually a long-term effect of dissemination occurring at the time of initial infection but developing perhaps many years later (Figure). Half of all children with primary TB are asymptomatic.

Post-primary TB may be asymptomatic in its early stages. Symptoms, when they develop, in decreasing order of frequency, are cough, sometimes with haemoptysis, fever, weight loss, night sweats, dyspnoea, which may develop late as a considerable part of the lung is destroyed and, unusually, chest pain. A study comparing patients with culture-proven TB with those who had chest infection from another cause showed that only weight loss and night sweats were statistically significantly more common in the TB than other patients.

### Table 1 Common medical risk factors for tuberculosis*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Absolute/1000 person-years</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection &gt; 7 years previously</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Infection &lt; 1 year previously</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Fibrotic lesion</td>
<td>2.0–13.6</td>
<td></td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive treatment</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>10–15</td>
<td></td>
</tr>
<tr>
<td>Gastrctomy</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Jejunileal bypass</td>
<td>27–39</td>
<td></td>
</tr>
<tr>
<td>Carcinoma of head or neck</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.0–3.6</td>
<td></td>
</tr>
</tbody>
</table>

*Reproduced from Rieder et al.*

HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome.

### Figure

Pathophysiology of tuberculosis. Reproduced from Clinical Tuberculosis with the kind permission of Hodder Arnold.

GI = gastrointestinal; Pt = primary tuberculosis; CNS = central nervous system; GU = genitourinary.
the non-TB group.\textsuperscript{10} TB is thus difficult to diagnose on the basis of signs and symptoms alone. Bearing all these presentations in mind, there is virtually no type of respiratory problem that TB cannot mimic.

**Signs and symptoms of non-respiratory TB**

TB can affect virtually any organ of the body. Non-respiratory TB can occur in isolation or in combination with other sites, both respiratory and non-respiratory. In a large study of cases in England and Wales in which a CXR was included in the analysis, disease was classified as respiratory only in 2630 (70\%) of the 3732 patients, non-respiratory only in 848 (23\%) and both in 254 (7\%). Thus, of patients with a non-respiratory site, less than a quarter also had a respiratory lesion.\textsuperscript{11} A CXR may be of some help in diagnosing TB at a non-respiratory site, if it shows evidence of disease, particularly primary TB or a Ghon focus, but a normal CXR cannot be taken to indicate the absence of disease elsewhere.

TB at an exposed site such as a lymph node or limb joint is usually accompanied by pain and swelling but is not necessarily warm to the touch, the so-called cold abscess. Systemic symptoms such as fever, malaise and weight loss are more likely at 'hidden sites' such as disseminated, gastrointestinal or genitourinary disease. TB should always be considered as a cause of unexplained fever, especially in those from high-risk groups.

**Tuberculous meningitis**

Although TB of the central nervous system accounts for only 2\% of all cases in the UK\textsuperscript{3} and probably similar proportions elsewhere in HIV-negative patients, it is of disproportionate importance because of the significant morbidity and mortality associated with it. Early symptoms are non-specific and include anorexia, malaise, headache, vomiting and altered behaviour. In children, the symptoms may include poor feeding, irritability, drowsiness and seizures. Such symptoms are non-specific, and tuberculous meningitis (TBM) may not be considered until late in the disease process. These symptoms are categorised as Stage I in the Medical Research Council (MRC) classification. Stage II may include any of the symptoms of Stage I, and also altered conscious level and/or cranial nerve palsies, of which the most common are 3rd and 6th nerve palsies causing double vision as the eye muscles are affected.

A low index of suspicion is required, and a lumbar puncture is mandatory. Results may mimic viral meningitis with relative low cell counts, usually a few to 500/ml. Protein levels are usually raised and glucose depressed. Microscopy is positive in only about a third of cases and culture in 40–80\%, but serial tests may increase yield. Polymerase chain reaction (PCR) sensitivity results are variable, but are no better than 60\% in highly probable cases.\textsuperscript{12} Clinical suspicion and a lumbar puncture result consistent with TBM should be enough to commence treatment and to continue treatment unless an alternative diagnosis presents, even in the presence of negative culture results.

**Cryptic miliary disease**

One of the most difficult diagnoses to make is that of cryptic miliary TB. The picture is usually of a patient slowly losing weight with malaise and non-specific symptoms. Intermittent pyrexia is usual, but not invariable. Plain CXR and blood tests are usually normal. If disease is suspected, a bone marrow or liver biopsy for histology and culture are the tests most likely to prove positive. In the absence of a positive test and in the face of deteriorating clinical condition, a trial of therapy may be indicated. This should be of all four first-line anti-tuberculosis drugs: because of the increased incidence of drug resistance, a trial of therapy with a limited number of drugs can no longer be justified.

**HIV positivity**

HIV infection results in an increased incidence of extra-pulmonary disease. Manifestation depends on the length of time over which HIV infection has been present, and the decline in CD4 cell count. At the early stage of infection, when CD4 counts are near normal, presentation is usually pulmonary, even with cavitation. As infection progresses and CD4 count declines, extra-pulmonary disease occurs with increasing frequency. Disseminated, miliary or meningeal disease is most often evident with lowest CD4 counts.\textsuperscript{13} Lack of Type IV cellular immunity, which occurs with HIV infection, makes non-cavitatory disease the rule rather than the exception, with a decreased likelihood of sputum smear positivity. In poor-resource settings where only sputum smear results are available for diagnosis, confirmation of disease is therefore more problematic.

**RADIOLOGICAL DIAGNOSIS OF TB**

When a physician develops a clinical suspicion, based on patient history, that TB is a possible diagnosis, CXR is usually the next step in the diagnostic algorithm, although this modality is not universally available. Radiographic findings in TB have been well described.\textsuperscript{14} However, given the increasing prevalence of HIV co-infection in TB patients around the world, it is critical to recognise radiographic presentations of TB that are more common in immunocompromised hosts, such as mediastinal or hilar adenopathy without lung parenchymal abnormalities.\textsuperscript{15}

There is a tendency to overuse the CXR as a diagnostic tool in TB at the expense of sputum smear result. It should be borne in mind that radiography is a non-specific investigation for TB. Only the identification of *M. tuberculosis* from a specimen can confirm the disease. For this reason, the World Health Organization (WHO) has proposed that smear-negative cases should not exceed 50\% of the total of cases from any diagnostic centre. The International Standards...
for TB Care recommend that all persons with CXR findings suggestive of TB should have sputum specimens submitted for microbiological examination.

**BACTERIOLOGICAL DIAGNOSIS OF TB**

**Sputum smear microscopy**

Sputum smear examination is the mainstay of the diagnosis of pulmonary TB (PTB); however, its sensitivity is modest. The technique used to obtain the respiratory sample strongly influences the ability to detect PTB. Expectorated sputum is generally the starting point. Three samples are collected on three separate days and stained for AFB. Although the utility of collecting three samples has been questioned, the overall yield for smear and culture is superior to that of collection of fewer specimens. The WHO recommends that the number of specimens to be examined for screening of TB cases can be reduced from three to two in places where a well-functioning external quality assurance (EQA) system exists, where the workload is very high and human resources are limited. Samples are generally sent simultaneously for smear and culture, as culture is essential to confirm the diagnosis. However, in resource-poor countries, the cost of culture is often too great, resulting in reliance solely on AFB smears.

The sensitivity of sputum AFB smears for detecting PTB is limited by the threshold of detection, which is 5000–10,000 bacilli per ml of specimen. The sensitivity of expectorated sputum ranges from 34–80%, and is highest in patients with cavitary disease, and lowest in those with weak cough or less advanced disease. Recent systematic reviews suggest that the sensitivity of microscopy can be increased by using fluorescence microscopy and sputum concentration methods. A negative sputum smear does not eliminate the diagnosis of active TB, particularly if the clinical suspicion is high, especially in HIV-infected persons. Instituting treatment in such cases is often warranted while awaiting culture results. If a patient with suspected PTB is smear-negative on expectorated sputum or is unable to produce sputum (30% of patients in one series), further diagnostic evaluation may be considered, including sputum induction, fiberoptic bronchoscopy and perhaps gastric washings.

**Culture**

Because cultures of mycobacteria require only 10–100 organisms to detect *M. tuberculosis*, the sensitivity of culture is excellent, ranging from 80% to 93%. Moreover, the specificity is 98%. Cultures increase the sensitivity for diagnosis of TB, allow speciation and drug susceptibility testing, and, if needed, genotyping for epidemiological purposes. All specimens should therefore be cultured if facilities are available.

There are three types of culture media: solid media, including egg-based (Löwenstein-Jensen [LJ]), agar-based (Middlebrook 7H10 and 7H11) and liquid media (Middlebrook 7H12 and other broths). Solid media—for a long time the standard for culturing mycobacteria—yield *M. tuberculosis* more slowly than liquid media, which are now widely employed alongside solid media to increase sensitivity and reduce recovery time. LJ, 7H10 and 7H11 media may detect mycobacteria in <4 weeks, but they require incubation for 6–8 weeks before they can be classified as negative. In contrast, broth media combined with DNA probes for rapid species identification typically provide results in <2 weeks with smear-positive samples and longer with smear-negative samples. Microscopic observation drug-susceptibility (MODS) assay is another culture approach that has shown promise, especially in resource-limited settings.

**MOLECULAR DIAGNOSIS OF TB**

NAA assays amplify *M. tuberculosis*-specific nucleic acid sequences with a nucleic acid probe, enabling direct detection of *M. tuberculosis* in clinical specimens. Such assays complement (but do not replace) the conventional laboratory approach to the diagnosis of active disease. Whereas AFB smears are rapid and specific, but lack sensitivity, and culture is both sensitive and very specific but may take from 2 to 8 weeks to produce results, NAA assays allow for rapid detection of *M. tuberculosis* that is fairly sensitive and highly specific. The sensitivity of commercially available NAA assays is at least 80% in most studies with respiratory specimens, and as few as 10 bacilli in a sample yield a positive result under research conditions. Although the sensitivity of these assays is lower in AFB smear-negative (and non-respiratory) samples than in smear-positive ones, newer assays are considerably more sensitive than earlier versions in smear-negative specimens, increasing overall sensitivity. NAA assays are also highly specific (98–99%) for *M. tuberculosis*. Immune-based tests for TB fall under two categories: tests that measure the cellular immune response to detect latent TB infection (LTBI) and tests that detect serological antibodies for diagnosing active TB.

**IGRA for diagnosing LTBI**

In recent times, blood tests known as IGRA have emerged as alternatives to TST. These assays detect LTBI by measuring interferon-gamma (IFN-γ) released from T cells after stimulation with specific TB antigens. Two commercial kits are now available—the QuantiFERON-TB Gold [QFT-G] (Cellestis, VIC, Australia, approved by the US Food and Drug Administration [FDA] in 2005), the QuantiFERON-TB Gold In-Tube [QFT-GIT], a simplified variant of the QFT-G test (FDA-approved in 2007), and the T-Spot.TB test (Oxford Immunotec, Abingdon, UK, currently awaiting FDA approval). Both QFT-G and T-Spot.TB are CE marked for use in Europe.
As reviewed elsewhere, IGRAs have excellent specificity (90–100%), and are unaffected by previous bacille Calmette-Guérin (BCG) vaccination. In patients with confirmed active TB, IGRAs are on average about 80% sensitive. QFT-G has a lower average sensitivity (75–80%) than for T-SPOT.TB assay (90–95%). In low-incidence settings, the results of IGRAs correlate well with surrogate markers of exposure. In addition, IGRAs have several potential advantages over the TST: testing requires only one patient visit, and these assays are ex vivo tests, which reduce the risk for adverse effects and eliminate potential boosting when testing is repeated. IGRAs are therefore promising tools for LTBI screening.

Do IGRAs have a role in the diagnosis of active TB? As noted previously, the diagnosis of active TB rests on microbiological detection of M. tuberculosis. T-cell-based IGRAs do not directly detect M. tuberculosis—they merely indicate a cellular immune response to recent or remote sensitisation with M. tuberculosis. So, why have several studies assessed the sensitivity of IGRAs in patients with active TB?

There are two reasons for evaluating IGRAs among patients with active TB: 1) to use active TB as a surrogate reference standard for LTBI (most published studies have used this approach); and 2) to determine if IGRAs will be helpful in diagnosing active TB. There are issues with both approaches. The first approach is based on the rationale that a person with active TB must necessarily have TB infection. Because LTBI has no gold standard, it makes sense to use active TB as the surrogate gold standard. However, from an immunological perspective, active TB occurs because the host immune response has failed to contain the infection. Active TB may therefore not be the perfect model for LTBI. It is also well known that diminished immune response occurs in patients with active TB at the time of diagnosis, particularly with more advanced disease, malnutrition, older age and co-infection with HIV. It is thus possible that the sensitivity of IGRAs in active disease may not reflect their sensitivity in LTBI (which is unknown).

The second approach is based on the assumption that evidence of TB infection (i.e., a positive IGRA result) is useful to diagnose active disease. While this is indeed helpful in the evaluation of childhood TB (where microbiological diagnosis is very difficult), it is problematic in adults, because IGRAs, like the TST, are incapable of distinguishing between LTBI and active disease. Also, most cases of TB disease occur in populations with a high background prevalence of LTBI. Thus, in high-incidence countries, a positive IGRA test in an adult will have low specificity for TB disease and will not necessarily indicate active disease—in most instances, it will reflect pre-existing LTBI. It is for this same reason that the TST is not used to diagnose active TB among adults in high-burden settings. It is also worth emphasising that IGRAs provide no qualitative or quantitative information on the severity or clinical activity of TB disease, nor do they provide data on drug susceptibility. Clinicians who manage patients with suspected TB disease in high-burden countries should therefore align their practice with the International Standards for TB Care, and use sputum smear microscopy and culture to investigate patients with suspected active TB.

However, IGRAs may have some potential to assist in the diagnosis of active TB in low-incidence settings, among selected populations such as young children, immunocompromised persons and individuals with smear-negative and extra-pulmonary disease. In these populations, microbiological diagnosis is often hard to establish, and IGRAs, especially the more sensitive T-SPOT.TB test, may offer supporting evidence that may be helpful in establishing a diagnosis of TB. However, because IGRAs are only about 80% sensitive in active TB, a negative IGRA (or TST, for that matter) cannot be used alone to exclude the diagnosis of active TB. While they may be used as supplementary tests, they cannot and should not be the primary investigations for patients with suspected active TB. Some investigators have attempted to use IGRAs on specimens such as bronchoalveolar lavage and pleural fluid, with the intention of detecting more specific local immune responses at the site of disease. These approaches are promising but will need validation. Lastly, it should be kept in mind that IGRAs were designed to detect M. tuberculosis infection, not active TB. They definitely should not be considered as replacements for sputum smear microscopy.

Serological antibody assays for diagnosing active TB
Serological (i.e., humoral, antibody-mediated) tests have been in use for many years, although no guideline recommends their use for the diagnosis of TB. In many low-income countries, test manufacturers market dozens of different commercial serological tests. In theory, serological tests would seem to offer the potential to improve TB diagnosis because of their rapidity (some tests are point-of-care) and potential simplicity compared with microscopy and culture, particularly for detecting smear-negative and extra-pulmonary disease.

Have serological tests lived up to this promise? Two recent systematic reviews have synthesised the available evidence on serological tests for TB (Table 2). The evidence suggests that, at this point in time, published data on commercial serological tests for both PTB and extra-pulmonary TB (EPTB) produce inconsistent estimates of sensitivity and specificity. For PTB, there were insufficient data to determine the accuracy of most commercial tests in smear microscopy-negative patients, and none of the assays performed well enough to replace microscopy. For EPTB, there were no studies of commercial tests of sufficient quality to enable their evaluation in patients with HIV infection or in children, as it is in these groups that the tests could be most helpful. Thus, at the present time,
serological tests have little or no role to play in the diagnosis of TB.46–48

Work is underway to develop improved versions of point-of-care serological tests.49 Although it is unclear if such tests will succeed, a better understanding of TB immunology and the application of new approaches such as genomics and proteomics may facilitate the development of the ideal rapid serodiagnostic test that has eluded us for decades.

DIFFICULTIES AND COMMON PITFALLS IN TB DIAGNOSIS

The decline in the publication of case histories in many journals, because they are rarely cited and therefore reduce impact factor scores, is to be regretted. The desire for evidence base may be appropriate, but the loss of educational value from the individual case history reduces the ability of the inexperienced doctor to learn clinical skills from publications.

The extraordinary change in clinical presentation of TB in the UK, resulting from immigration from the Indian subcontinent in the 1960s and 1970s, although hinted at by the change in notification data, could only be verified by case studies. One such publication in the Lancet first described in detail the change in the presentation of PTB to the primary form.50 Such publications, virtually impossible to publish in today’s climate, helped alert physicians to a change in clinical presentation.

Sometimes we were slow to appreciate this change. One of the authors (PD) recalls, as a new Senior House Officer (SHO) working in West London, accompanying one of the consultant gastro-enterologists on a ward round. An elderly woman who had recently arrived from India with weight loss and constipation was puzzling them and had been under investigation on the ward for about 2 weeks. Physical examination revealed the classical doughy abdomen of advanced gastrointestinal TB. As an SHO in Chest Medicine, I was probably more aware than most working in other specialties of the unusual presentations then being seen in recent immigrants from the Indian subcontinent. I suggested they start treatment for TB as soon as possible. She died a day or two later and post mortem revealed white nodules through the abdomen. A disseminated cancer was assumed until histological results came through a day later, showing features characteristic of TB.

It is of interest that the most highly cited medical journal in the world, the *New England Journal of Medicine*, is not shy of publishing cases. A recent case outlines in half a page an unusual presentation of a large cerebral tuberculoma.51

The ‘timetable’ of TB

A clinician diagnosing TB should be familiar with the Wallgren outline of the pathophysiology of TB as it infects and affects the human host.52 The hypothesis is shown in simple terms in the Figure. Wallgren divided the development of TB into four stages.

Stage 1  Five to 6 weeks after infection: symptoms caused by primary TB, TST positivity, fever, erythema nodosum and the primary complex.

Stage 2  Following immediately, the malignant forms of TB such as disseminated disease, military and meningitis and lasting about 3 months.

Stage 3  The pleurisy period, arising 3 months after Stage 1 and lasting about 4 months.

Stage 4  Roughly 3 years after the primary infection, manifested by such forms as skeletal TB and post-primary TB.

---

Table 2  Results of recent systematic reviews of commercial serological tests for the diagnosis of pulmonary and extra-pulmonary tuberculosis*  

<table>
<thead>
<tr>
<th>Focus of the systematic review</th>
<th>Number of studies in the review</th>
<th>Serological tests evaluated</th>
<th>Key findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-pulmonary tuberculosis</td>
<td>21</td>
<td>Anda-TB, ICT TB, Pathoyme-Mycobacterium, Pathoyme-TB Complex Plus, SEVA TB</td>
<td>All tests provided highly variable estimates of sensitivity (range 0–100%) and specificity (range 59–100%) for all extra-pulmonary sites combined. For all tests combined, sensitivity estimates for both lymph node (range 23–100%) and pleural TB (range 26–59%) were poor and inconsistent. There were no data to determine the accuracy of the tests in children or in patients with HIV infection.</td>
<td>Steingart et al.46</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>68</td>
<td>Anda-TB, Detect-TB, ICT TB, Kaolin agglutination test, MycoDot, Pathoyme-Mycobacterium, Pathoyme-TB Complex Plus, TB EIA-TB, TB glycolipid assay</td>
<td>Overall, tests varied widely in performance (sensitivity, range 10–90% and specificity, range 47–100%). Sensitivity was higher in smear-positive than smear-negative samples. There were insufficient data to determine the accuracy of most commercial tests in smear-negative patients, as well as their performance in children or persons with HIV infection.</td>
<td>Steingart et al.47</td>
</tr>
</tbody>
</table>

* Adapted from Steingart et al.48

TB = tuberculosis; ICT = immunochromatographic test; HIV = human immunodeficiency virus; EIA = enzyme immunoassay.
It should be said that this outline must be subjected to much modification, especially in timing, and that the manifestations of TB seen in Stage 3, such as pleural disease, may precede manifestations in Stage 2, such as meningeal disease, in many patients. Immuno-modification seen in HIV infection or in immigrants from hot to cold climates, perhaps due to vitamin D deficiency, will alter the ‘timetable’. Leitch and others have pointed out that many of the stages occurring in Wallgren’s ‘timetable’ developed in the pre-antibiotic era of Sweden in the 1940s have changed, particularly in low-prevalence areas where the elderly, those aged >65 years, are now the ones most commonly afflicted by TB, and particularly the Stage 2 miliary form. The authors suggest that the ‘timetable’ of TB needs to be extended to include stations further along the line.

Patients are frequently diagnosed as having TB if they have upper lobe cavitation. If good sputum specimens can be obtained from such a patient and they (or bronchial washings) are smear-negative for AFB, then the diagnosis of PTB is unlikely.

In more industrialised countries, indigenous white patients over the age of 40 with positive sputum smear for AFB are more likely to have an infection with an environmental mycobacterium than TB. Rapid diagnostic tests using PCR and nucleic acid probes (e.g., Accuprobe, Gen-Probe Inc, San Diego, CA, USA) are therefore most useful in this category of patient, to avoid the unnecessary expense and concern of contact tracing and the use of antibiotics such as pyrazinamide.

Tuberculous pleuritis may occur a few months after a primary infection. Specimens for diagnosis should be taken from the pleura for histology and culture, as the sputum is only rarely positive. The pleural fluid will regress spontaneously in most cases, but unless treated TB may return in a more aggressive form, sometimes as tuberculous meningitis.

Patients from high-risk groups with a biopsy showing non-caseating granuloma are more likely to have TB than sarcoidosis. It is very difficult to exclude TB in such patients, and it may be wise to treat for the disease, or provide regular follow-up with CXR if high-dose steroids are to be used.

Patients with extensive lung damage may continue to excrete AFB in their sputum long after cultures have turned negative. This is of particular concern in patients with drug-resistant disease, but cultures, if available, and not smear results, should be seen as the indication of cure. Treatment extension is not required with such patients.

The diagnosis of TB in the elderly can be problematic. Symptoms may be masked by generalised debility, and a high index of suspicion is required. Care is often needed in treatment, as adverse effects of drugs are common.

The possible diagnoses other than TB are very wide. In the well-resourced setting where the inci-
dence of TB is low, care should be taken to exclude the many alternative diagnoses in the absence of a clear positive test for TB. A list of the differential diagnoses of TB is given in Table 3.

CONCLUSIONS

TB can be one of the easiest diseases to diagnose, and also one of the most difficult. The patient with clear signs and symptoms of pulmonary disease with a sputum smear-positive result presents no problems to diagnose. Unfortunately, with the advent of HIV, resulting in a decreased likelihood of sputum smear positivity and the increase in non-respiratory disease, the ease of diagnosis is becoming more difficult. Sometimes a trial of therapy may be justified in the absence of clear proof of disease. If this is carried out, clear criteria of what would constitute clinical improvement should be determined beforehand and the use of treatment reconsidered if these are not met within 2 months. Clinical ‘hunch’ and experience still play a major part in determining whether treatment should be given. More sensitive diagnostic tests are desperately needed.

Acknowledgement

The authors would like to thank Dr N Schluger for his assistance with the review.

References

Il y a vraiment deux mondes en ce qui concerne le diagnostic de la tuberculose (TB). Dans le premier, seul l'examen microbioscopique des frottis est disponible ; il peut exister également quelques services radiologiques, mais habituellement à charge du patient. L'autre monde dispose de techniques modernes comme la culture, l'amplification des acides nucléiques, les diagnostics moléculaires et des techniques radiologiques sophisti-