system. Despite the presence of multiple studies that repeatedly have proven this assumption to be false and a world literature replete with reports of the success of directly observed therapy, these centers contend that there is no firm evidence demonstrating that directly observed therapy is both effective and essential in the treatment of tuberculosis.

It is time for physician organizations from all parts of the international community to reject such folly and firmly endorse directly observed therapy as the professional standard of care. And as a corollary standard, as soon as a patient is identified as not adhering to treatment appointments and cannot be induced to cooperate with directly observed therapy (even when provided with a range of social supports), public health officials should immediately direct that patient into a specialized tuberculosis treatment center. If we fully and appropriately treat all patients during their first encounter with tuberculosis, including the use of specialized facilities where necessary, the risk and the fear of MDR tuberculosis can fade into history.

The alternative is to stand by and watch as the tidepools described by Iseman slowly enlarge and perhaps return as a flood tide.

John A. Sbarbaro, MD, MPH, FCCP
Denver, CO

Dr. Sbarbaro is Professor of Medicine and Preventive Medicine, University of Colorado Health Sciences Center, Denver, CO. Correspondence to: John A. Sbarbaro, MD, MPH, FCCP, Professor of Medicine and Preventive Medicine, 4200 E Ninth Ave, Denver, CO 80262

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1 Iseman M. ASTER Challenge Lecture. Paper presented at: IUATLD meeting; November 1992; Paris, France

much attention has recently been paid to the problem of smear-negative pulmonary tuberculosis. Quite appropriately, the discussion has focused on low-income countries, home to the vast majority of individuals with tuberculosis and HIV and where the ability to culture diagnostic specimens may be lacking. Yet, there remain legitimate questions concerning this group of patients in industrialized countries. In this issue of CHEST (see page 349), Kanaya et al address one of those questions. Is it possible to predict, among patients with suspected active, smear-negative pulmonary tuberculosis, those patients whose culture specimens will ultimately prove to be positive? The object would be to avoid the adverse consequences that might result from withholding treatment in patients with the disease (remaining ill for excessively long periods of time, and possibly infecting others in the community) or introducing treatment in patients without the disease (their actual illness goes untreated, and they are exposed unnecessarily to possible drug toxicity).

The problem of smear-negative pulmonary tuberculosis is not trivial. In acute-care settings, as many as 8 to 10 patients are suspected to have tuberculosis for every one confirmed case. In our provincial jurisdiction, respiratory specimens from 125 persons are submitted, on average, for every one culture-confirmed case of tuberculosis.

Presently the most important criteria for establishing a presumptive diagnosis of tuberculosis are the acid-fast bacilli (AFB) smear (performed on clinical specimens that are adequate in both quantity and quality) and a case definition, which may be based on radiographic signs, clinical findings, risk factors, or a combination of these factors. The sensitivity of the AFB smear result is known to be poor, varying between 30% and 70% depending on a number of factors relating to how the test is implemented. The sensitivity is improved by concentration of sputum specimens and use of fluorescent microscopy but reduced in patients with HIV disease. The specificity and positive predictive value of the smear results may be reduced in settings of high HIV prevalence or low (high nontuberculous mycobacterial [NTM]) tuberculosis prevalence. Yet, the sputum smear should always be performed because it is quick and easy to activate, provides preliminary confirmation of the diagnosis, and gives a quantitative estimate of the number of bacilli being excreted and therefore the infectivity of the patient (≥ 5,000 bacilli per milliliter of sputum must usually be
A replacement for culture that is equally sensitive and specific, but more rapid, is clearly needed if patients with early-stage disease, low burden infection, and minimal symptoms are to be detected. Technologies that allow for the amplification of specific target sequences of nucleic acids that can then be detected through the use of a nucleic acid probe currently offer the greatest promise of direct detection and identification of \textit{M tuberculosis} in clinical specimens. To paraphrase the recent American Thoracic Society (ATS) statement on Diagnostic Standards and Classification of Tuberculosis in Adults and Children\cite{16}, NAA methods can be applied to clinical specimens within hours. In respiratory specimens that are AFB smear positive, their sensitivity is approximately 95\% with a specificity of 98\%. In specimens that contain fewer organisms and are AFB smear-negative, results are positive in 48 to 53\% of patients with culture-positive tuberculosis and the specificity remains approximately 95\%. An “enhanced” NAA test has been approved by the Food and Drug Administration advisory panel for use on both smear-positive and smear-negative respiratory specimens from patients who are clinically suspected of having tuberculosis. This recommendation is based on a clinical trial in which the “suspicion” of tuberculosis was quantified. In patients (AFB smear-positive and smear-negative) where the clinician had an intermediate or high suspicion of tuberculosis disease, the sensitivity of the enhanced test was 75 to 88\% and the specificity was 100\%. The clinical use of NAA tests in this setting has to be confirmed, and efforts to clarify appropriate uses are underway.\cite{16,18}

Earlier definitive diagnosis of the smear-negative case will impact clinical (treatment) and public health (isolation and contact investigation) decision making. Currently, these decisions must be made in the absence of a definitive diagnosis. They require a sophisticated analysis of all available information and an estimate of relative risk. Prediction rules may help in this regard, but they must be understood to reflect the population under study, both patients and physicians. Factors likely to affect physicians’ estimates of relative risk include the customary prevalence of disease in the practice setting, the clinical spectrum of disease, the specialty or experience of the physician, and the quality of the medical history.\cite{19} Prediction rules are also subject to bias, as a more determined effort to seek the diagnosis, and therefore recover the organism, usually attends a higher level of suspicion. At its workshop on rapid diagnostic tests,\cite{16} the ATS developed an algorithm in which the decision to treat, isolate, or commence contact investigation was based on an integration of the following variables: high or low clinical suspicion of

Table 1—Causes of a False-Negative Sputum Smear Finding*  

<table>
<thead>
<tr>
<th>Stages</th>
<th>Cause</th>
</tr>
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<tbody>
<tr>
<td>Sputum collection</td>
<td>Inadequate sputum sample</td>
</tr>
<tr>
<td></td>
<td>Inappropriate sputum container</td>
</tr>
<tr>
<td></td>
<td>Sputum stored too long before microscopic examination</td>
</tr>
<tr>
<td>Sputum processing</td>
<td>Faulty sampling for smear</td>
</tr>
<tr>
<td></td>
<td>Faulty smear preparation and staining</td>
</tr>
<tr>
<td>Smear examination</td>
<td>Inadequate time spent examining smear</td>
</tr>
<tr>
<td></td>
<td>Inadequate attention to smear</td>
</tr>
<tr>
<td>Administration</td>
<td>Misidentification of patient</td>
</tr>
<tr>
<td></td>
<td>Incorrect labeling of sample</td>
</tr>
<tr>
<td></td>
<td>Mistakes in documentation</td>
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</tbody>
</table>

*Adapted from Toman.\cite{16}
tuberculosis, AFB smear-positive or smear-negative results, and positive or negative NAA test results. Actions were compared with or without knowledge of the NAA test. The algorithm was not intended to represent an official recommendation from either the Centers for Disease Control and Prevention or the ATS. In a cogent companion editorial, Peter Barnes\textsuperscript{20} presented guidelines to assist clinicians in using NAA tests and interpreting their results. To the extent that NAA test results lead to deferral of further diagnostic evaluation, they may reduce the yield in culture and the benefits that accrue from recovery of the organism. Ultimately, phage replication systems that can be used for both detection and drug susceptibility testing of live mycobacteria may have greater utility.\textsuperscript{21–23}

A decision to treat a patient with smear-negative finding may influence diagnosis (evidence for or against a therapeutic response) and infectivity (a patient with a smear-negative and ultimately culture-positive finding may be considered noninfectious after 2 weeks of effective treatment\textsuperscript{24}). A decision to treat may or may not intimate a public health action and vice versa.\textsuperscript{7,25–28}

In deciding whether or not to introduce treatment, we have found it helpful to classify patients with smear-negative, culture-positive findings into one of three groups: (1) patients with primary pulmonary tuberculosis who are not HIV coinfected (group 1); (2) patients with primary or postprimary pulmonary tuberculosis who are HIV coinfected (group 2); and (3) patients with postprimary tuberculosis who are not HIV coinfected (group 3).

Group 1 patients usually have noncavitary, relatively paucibacillary tuberculosis. Not uncommonly, their specimens are culture-negative.\textsuperscript{9} Their diagnosis is dependent on a good history of tuberculosis contact, a positive tuberculin skin test (TST) result or possibly a TST conversion, and a compatible clinical and radiographic picture. Group 1 patients are often children, and they should be treated promptly, as there is a risk of progression to more sinister forms of disease (neurotuberculosis or disseminated disease). Likewise, treatment with antituberculosis drugs should be initiated promptly in group 2 patients, as both tuberculosis disease and HIV replication may accelerate in their absence.\textsuperscript{29,30} Unfortunately, making a presumptive diagnosis of tuberculosis in patients with advanced HIV disease is not a simple task. Their chest radiographs may be atypical, their histopathologic findings misleading, and their TST results falsely negative. The differential diagnosis may be broad.\textsuperscript{20} The overall characteristics of NAA tests may be uniquely well suited to this population.\textsuperscript{17,30}

From a bacteriologic point of view, patients in group 3 appear to be different from HIV-uninfected patients with smear-positive, culture-positive postprimary pulmonary tuberculosis.\textsuperscript{10,31–33} First, they have been demonstrated to be discharging small numbers of bacilli intermittently.\textsuperscript{10} Second, their infectivity is very much lower than that of patients with smear-positive findings.\textsuperscript{34} Third, the minimal extent of their disease does not, as one might expect, automatically imply that they are in an early stage of what will become smear-positive cavitary disease.\textsuperscript{10,31} And fourth, their prognosis is often very good even without treatment.\textsuperscript{10} Thus, their natural history is usually more benign than that of patients with smear-positive sputum findings. That much is lost by not initiating treatment in some of these patients at the point of suspicion is not at all a given. On the contrary, it may be more appropriate to investigate these patients until a diagnosis is established rather than treating empirically. Certainly if a life-threatening form of nonrespiratory tuberculosis is suspected of being coexistent, then treatment must be instituted promptly. Among group 3 smear-negative, culture-positive patients, it is not established that transmission is greater from those who begin treatment at the point when culture results are found to be positive than those who begin treatment at the point of suspicion. Prudence would dictate that each of these cases be considered individually, with the relative importance of a broad range of determinants, only some of which may be at hand, weighted (Table 2).

Because prediction rules combine in a single score items that would have vastly different levels of

<table>
<thead>
<tr>
<th>Table 2—Factors Influencing the Decision to Place a Sputum Smear-Negative, HIV-Seronegative Patient With Suspect Active (ie, as yet Unconfirmed by Culture) Postprimary Pulmonary Tuberculosis on Antituberculosis Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of tuberculosis contact</td>
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<tr>
<td>History of tuberculosis and the adequacy/inadequacy of its treatment</td>
</tr>
<tr>
<td>Presence of a medical condition that may increase the likelihood of progression from infection to disease</td>
</tr>
<tr>
<td>Presence of compatible symptoms</td>
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<tr>
<td>Presence of a progressive abnormality on serial chest radiographs, particularly if the abnormality involves one or both upper lung zones</td>
</tr>
<tr>
<td>Presence of a CT thorax demonstrating endobronchial disease</td>
</tr>
<tr>
<td>Presence of a transbronchial or surgical biopsy or fine-needle aspirate demonstrating granulomata, particularly if the granulomata are caseating and associated with a positive smear finding on special stain</td>
</tr>
<tr>
<td>Presence of a positive TST result</td>
</tr>
<tr>
<td>Absence of another explanation for the illness</td>
</tr>
<tr>
<td>Likelihood of toxicity from the antituberculosis drugs</td>
</tr>
<tr>
<td>Transmission risk</td>
</tr>
<tr>
<td>Reliability of follow-up</td>
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</tbody>
</table>
importance in different clinical contexts, we remain skeptical that they add much to the decision-making process. Their validation in prospective studies is important.

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Richard Long, MD, FCCP
Edmonton, Alberta, Canada

Dr. Long is a professor in the Pulmonary Division, Department of Medicine, University of Alberta.

Correspondence to: Richard Long, MD, FCCP, Department of Medicine, University of Alberta, Room 2E4.21, Walter C. Mackenzie Center, 8440–112 St, Edmonton, Alberta T6G 2B7, Canada; e-mail: richard.long@ualberta.ca

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Pleural Effusion

Adenosine Deaminase in the Diagnosis of Tuberculous Pleural Effusion

In some parts of the United States, pleural tuberculosis accounts for < 5% of all cases of tuberculosis. In some countries, the incidence of pleural tuberculosis is much higher. It is generally linked to the local prevalence of tuberculosis. Pleurisy with effusion as a complication of primary pulmonary tuberculosis has been reported to occur in 2 to 38% of children with pulmonary disease, but it is more likely to occur in adolescents and adults. However, tuberculous pleural effusion in older patients with classic reactivation of tuberculosis also can occur. Tuberculous pleural effusion is thought to result from a delayed hypersensitivity reaction in response to the presence of mycobacterial antigens in the pleural space. These mycobacterial antigens may gain access to the pleural space from the rupture of a small subpleural focus. A significant number of patients (50 to 59%) with primary tuberculosis who develop pleural effusion may have roentgenographically apparent parenchymal tuberculosis. Delayed hypersensitivity reaction causes the stimulation and differentiation of lymphocytes that perform a variety of functions, including the release of certain lymphokines that activate macrophages for enhanced mycobactericidal effect.

The diagnosis of tuberculous pleural effusion can be difficult because of the low sensitivity of the various diagnostic tools. Lymphocytic exudate seen in tuberculous pleural effusion also can occur in other diseases such as malignancy and collagen vascular diseases (ie, rheumatoid arthritis and systemic lupus erythematosus). Cultures for acid-fast bacilli are positive in 20 to 30% of pleural fluid samples and in 50 to 80% of pleural biopsy specimens. The sensitivity of polymerase chain reaction for active disease is 78%. The cutaneous response to purified protein derivative may also be negative in one third of the patients. Thus, despite a comprehensive evaluation, almost 20% of tuberculous pleural fluids will defy a definitive diagnosis.

The determination of ADA level in the suspected pleural fluid appears to be the most promising marker because of the ease, rapidity, and cost-effectiveness of the ADA assay. ADA is found in most cells, but its chief role concerns the proliferation and differentiation of lymphocytes, especially T-lymphocytes. For that reason ADA has been looked on as a marker of cell-mediated immunity, which encompasses the delayed hypersensitivity reaction.

The determination of ADA activity was first proposed as a serologic diagnostic marker for lung cancer in 1970. Later, Piras et al in 1978 reported the usefulness of ADA in diagnosing tuberculous pleurisy. ADA is an enzyme involved in the purine catabolism. It catalyzes the deamination of adenosine to inosine and of deoxyadenosine to deoxyinosine. There are several isoforms of ADA, but the prominent ones are ADA1 and ADA2, which are coded by different gene loci. ADA1 isoenzyme is found in all cells, with the highest concentration found in lymphocytes and monocytes, whereas ADA2 isoenzyme appears to be found only in monocytes. ADA1 is the predominant isozyme in the tuberculous pleural effusion, accounting for 88% (median) of total ADA activity, whereas ADA1 is elevated in empyema, accounting for 70% (median) of total ADA activity. This would suggest that ADA2 is the more efficient marker of tuberculous pleural effusion. However, in clinical practice, the difference in the use of total ADA and isoform ADA2 is not significant. In fact, there is an advantage in the measurement of total ADA because of its low cost and rapid turnover. ADA1 activity is determined by subtracting ADA2 from total ADA. The measurement of ADA2 is almost 10 times more expensive and is not available in the United States except for research purposes. The colorimetric method for the measurement of total ADA described by Guisti and Galanti has an advantage over other methods because of its low cost, simplicity of technique, and rapid turnover. With this technique, the sensitivity and specificity of elevated level of ADA in the tuberculous pleural fluid ranges from 91 to 100% and 81 to 94%, respectively. The positive and negative predictive values range from 84 to 93% and 89 to 100%, respectively. The reported diagnostic cutoff value for ADA varies from 40 to 60 U/L, and choosing a lower value will increase sensitivity at