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## Rapid Detection of Tuberculosis and Drug-Resistant Tuberculosis

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Tuberculosis remains one of the major unresolved global health problems, and the situation is worsening in many parts of the world, primarily because of the association between tuberculosis and the epidemic of human immunodeficiency virus (HIV) infection and AIDS and the growing prevalence of drug resistance. The highest prevalence of both tuberculosis and drug resistance is found in countries with limited resources, which cannot afford to implement modern methods of epidemic control of tuberculosis. The detection of new cases of tuberculosis in these areas is based on provisional diagnosis by means of direct acid-fast bacilli testing of sputum smears, a diagnostic tool that can provide positive results in less than 50% of patients with newly diagnosed pulmonary tuberculosis confirmed on culture. Furthermore, the sputum-smear test does not address detection of persons with drug-resistant strains of *Mycobacterium tuberculosis*.

The most common method of detecting drug-resistant strains of tuberculosis in many countries (even those with a moderate economic level) is often limited to use in patients with no response to the initial standard treatment regimen. Therefore, detection of drug resistance is attempted only when there is a clinical suspicion of drug resistance. The loss of 9 to 12 (or more) months of the provision of appropriate tuberculosis therapy has several potentially critical consequences: patients with multidrug-resistant tuberculosis may have progressive disease or may die while receiving ineffectual treatment; the presence of amplified drug resistance, including the loss of pyrazinamide and ethambutol, may create the next level of an extensively drug-resistant tuberculosis

pathogen; and, most important, ongoing transmission is likely to occur.

A more efficient and cost-effective alternative to that expensive so-called strategy would be the implementation of culture isolation for more complete detection of new cases of tuberculosis and the testing of all initial culture isolates for susceptibility to isoniazid and rifampin. Such an alternative would be feasible and effective under two conditions: the method should be inexpensive and easy to implement and the turnaround time of laboratory testing should be short enough that providers could make timely adjustments to the treatment regimens when drug resistance is detected. For many years, the implementation of testing for drug susceptibility has been one of the most neglected aspects of health care, despite the large number of bacteriologic and molecular methods developed for testing.<sup>1</sup> The situation today demands further development in this area, with a focus on methods that can be implemented in countries with limited resources.

In this issue of the *Journal*, Moore and colleagues<sup>2</sup> attempt to address these problems. They have evaluated a method called the microscopic-observation drug-susceptibility (MODS) assay, which is considered an inexpensive tool for the bacteriologic diagnosis of tuberculosis and the detection of drug resistance. This method, originally described in 2000,<sup>3</sup> with additional data reported in 2004,<sup>4</sup> is based on direct inoculation of the selective 7H9 liquid culture medium in 24-well plates with a sputum specimen subjected to the digestion–decontamination procedure with the use of a mixture of two reagents, *N*-acetyl-L-cysteine and sodium hydroxide, for two pur-

poses.<sup>5</sup> The first purpose is digestion, or liquefaction, accomplished with *N*-acetyl-L-cysteine and is required for the subsequent concentration of the mycobacteria by centrifugation. The second purpose is decontamination, which is performed with sodium hydroxide and is required to kill microbes that otherwise would interfere with the isolation of a pure mycobacterial culture. Concentration by centrifugation is presumed to be the final step of the procedure. Detection of the typical cord formation (“microcolonies”) of *M. tuberculosis* in the wells on microscopical examination (under an inverted light microscope at a magnification of  $\times 40$ ) constitutes the basis of diagnosis. Growth (or the lack thereof) in drug-containing wells, as compared with growth in drug-free wells, is the basis for reporting the results as “susceptible” or “resistant” to medication. The reported<sup>2</sup> sensitivity of this method in the recovery of mycobacteria from sputum specimens was higher than the sensitivity of either the MB/BacT automated mycobacterial system or traditional culture on Löwenstein–Jensen medium.

The results of Moore et al. complement two previous publications from a group in Peru,<sup>3,4</sup> in one of which<sup>3</sup> the sensitivity of the MODS assay appears to be equal to that of the mycobacteria growth-indicator tube system and showed higher sensitivity than culture on agar plates. Results of testing for drug susceptibility with four drugs (isoniazid, rifampin, ethambutol, and streptomycin) agreed well with those obtained with the use of the MB/BacT system.<sup>2</sup> The most impressive data reported by Moore et al. are on the turnaround time of the assay: the median time was 7 days for the detection of growth on culture and testing direct-drug susceptibility, whereas the MB/BacT system required 13 and 22 days, respectively, and culture on Löwenstein–Jensen medium required 26 and 68 days, respectively.

This report by Moore et al. as well as the two previous reports provide support for an affordable, rapid method of culture-based diagnosis and detection of drug resistance in countries with limited resources. We believe that, in its current form, the MODS assay will require further improvement and standardization before it can be recommended for broad application in such countries.

Reports of the identification of *M. tuberculosis* on the basis of the “string-and-tangle appearance”<sup>2</sup> of growth detected on microscopical examination of the wells should be considered

provisional, rather than final. Some strains of *M. tuberculosis* may not produce this serpentine formation. Also, many isolates of *M. kansasii* also may produce cording in broth and have morphologic features and a timing of appearance indistinguishable from those of isolates of *M. tuberculosis*. An additional problem in countries where there is a significant prevalence of bovine tuberculosis is the differentiation between *M. tuberculosis* and *M. bovis*. These problems of identification can be addressed if isolation on a solid medium to obtain a pure culture is implemented along with the MODS assay, and such cultures can be used, if necessary, for subsequent confirmation of the diagnosis.

Critical drug concentrations implemented for the MODS assay were adopted by the authors from those developed for the Bactec system (BACTEC 960, Becton Dickinson). Although the results obtained correlated well with results obtained with the use of two other methods, in general, each technology is known to require special calibration of critical concentrations halfway between the highest minimal inhibitory concentrations for susceptible strains and the lowest minimal inhibitory concentrations for resistant strains.

The major difficulty in the implementation of the MODS assay or any other new cultivation method is that of biosafety, which is not fully addressed by Moore et al. Although it is not stated in their report, we assume that the sputum digestion–decontamination procedure was performed in conjunction with concentration of the specimens, as required by the original description of this technique.<sup>5</sup> Concentration must be performed in aerosol-contained centrifuges. In addition, the manipulation of infected well plates is a potential hazard requiring special caution and should be performed only in biosafety cabinets. Use of these measures, along with other biosafety issues, can be properly addressed only in a well-organized tuberculosis laboratory using mandatory implementation of biosafety level 3 standards.<sup>6</sup> Regardless of how simple and inexpensive the newly introduced technique is, there is the issue of the cost of the materials needed for the test and the total cost of the procedure, including the costs of labor, laboratory equipment (centrifuges, biosafety cabinets, inverted light microscopes, among other types of equipment), and overhead. In other words, implementation of an “inexpensive” test can be successful only if it is incorpo-

rated into the overall algorithm of the laboratory protocol. Thus, the introduction of a new procedure (such as the MODS assay) requires the existence of a basic tuberculosis laboratory.

The establishment of microbiology laboratories in countries with a high prevalence of tuberculosis and growing rates of drug-resistant tuberculosis should become one of the urgent priorities in the global fight against tuberculosis epidemics, especially in countries with limited resources. The MODS technique may well move this process forward.

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## Angiotensin-Converting–Enzyme Inhibitors for Impaired Glucose Tolerance — Is There Still Hope?

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In our increasingly sedentary society, the rates of overnutrition, the metabolic syndrome, and frank diabetes mellitus are rising at an alarming rate.<sup>1</sup> Once diabetes has developed, the risks of cardiovascular and renal disease are markedly increased.<sup>2</sup> Given the immense costs of diabetes — both personal and economic — considerable attention has been focused on identifying effective strategies to prevent or delay its onset in people at high risk.

The benefits of diet and exercise in reducing the risk of diabetes are well accepted. Numerous observational studies have documented that both adiposity and physical inactivity are strong independent risk factors for diabetes. The Diabetes Prevention Program, a randomized trial of lifestyle changes and metformin in people with impaired glucose tolerance, showed a 58% reduction in the progression to diabetes in the group that underwent caloric reduction and regular exercise<sup>3</sup>; the group receiving metformin also had a reduced risk of diabetes (by 31%), but this reduction was significantly less than that resulting from the lifestyle changes. Another multicenter randomized trial, the Finnish Diabetes Prevention Study,<sup>4</sup> reported a reduction in the incidence of diabetes as a result of lifestyle changes that was similar to the reduction in the Diabetes Prevention Pro-

gram. Lifestyle changes are currently the standard recommendation for patients recognized to be at high risk for diabetes, especially obese patients. Yet maintaining adherence to these nonpharmacologic strategies is notoriously challenging. Thus, the possible use of pharmacologic interventions to prevent diabetes in people at high risk remains of keen interest.

The concept that an angiotensin-converting–enzyme (ACE) inhibitor might reduce the risk of diabetes emerged from secondary findings of several trials. The Captopril Prevention Project,<sup>5</sup> designed to assess complications and death from cardiovascular disease among patients with hypertension who were randomly assigned to receive captopril or to receive diuretics or beta-blockers, showed a 14% lower incidence of diabetes in the captopril group. However, it was unclear whether this finding might be attributable to adverse metabolic effects of the non-ACE inhibitor medications. Data from the Heart Outcomes Prevention Evaluation (HOPE) trial, designed primarily to test the hypothesis that an ACE inhibitor (ramipril) or vitamin E would reduce the risk of cardiovascular events among patients at high risk, provided more persuasive support for a possibly beneficial effect of ACE inhibitors on the risk of