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The Acid-Fast Bacilli Smear: Hail and Farewell

When Robert Koch reported his discovery of the tubercle bacillus in 1882 in a lecture and in the scientific paper he published just a few weeks later in *Berliner Medicinische Wochenschrift*, he described the staining techniques that allowed him to see the rod-shaped bacteria that he had successfully isolated and grown in pure culture (1). Paul Erlich had attended Koch's lecture and quickly refined the staining technique, making it easier and quicker. Shortly thereafter, Ziehl and Neelsen further modified the technique and developed the method basically still used today. By 1883, Koch recognized that the development of a relatively simple and rapid staining method had important implications for patient care. He wrote, "It was soon found that with Ehrlich's method of staining, the recognition of tubercle bacilli could readily be made use of in diagnosis. We owe it to this circumstance alone that it has become a general custom to search for the bacilli in the sputum" (2).

The acid-fast bacilli (AFB) smear remains the main mode of diagnosis of tuberculosis in most of the places in the world where tuberculosis is common. If tuberculosis were something like beer brewing, or cheesemaking, this kind of artisanal approach to diagnosis might seem authentic and appealing. But tuberculosis is not beer brewing or cheesemaking, and the persistence of a 19th-century technique for diagnosing the world's leading cause of death resulting from a single infectious agent in the 21st century is a disgrace. By now, it is well-appreciated that smears detect only about half of all cases of culture-positive tuberculosis, and quality control is notoriously difficult, especially in places where it is relied on most heavily (3, 4). The article in this issue of the *Journal* by Lee and colleagues (pp. 784–794) provides further evidence that it is time for the AFB smear to find its place in medical museums and history books, rather than in modern diagnostic labs (5).

Sputum samples were collected from each of nearly 3,000 consecutive patients being evaluated for possible tuberculosis. One aliquot was analyzed using semiquantitative nucleic acid amplification with GeneXpert MTB/RIF, and one was analyzed by conventional AFB smear microscopy and culture. Culture results were considered the gold standard for a diagnosis of tuberculosis.

The results were clear and convincing. Overall, 8.9% of patients provided samples that were culture positive for *Mycobacterium tuberculosis.* Of those, 102 had AFB smear-positive sputum and 161 were smear negative. In addition, another 9% (265) of patients were culture positive for nontuberculous mycobacteria, and 82 of those patients were AFB smear positive. Overall, then, the sensitivity of AFB smear was 38.8%, and the specificity was 96.7%. This compares with a sensitivity of 74.1% and a specificity of 97.5% for Xpert. Notably, AFB smear sensitivity varied by time of collection (morning samples had greater yield than spot samples), but this was not true for Xpert. Results from Xpert were reported back to clinicians on average about 16 hours faster than results from AFB smears. Thus, Xpert results overall were more accurate, available more quickly, and less affected by several operational issues than were AFB smears.

This article amplifies results of many earlier, smaller, or laboratory-based studies that showed the promise of nucleic acid amplification-based tuberculosis diagnostics (6–9). Indeed, uptake of Xpert has been advancing around the world in both resource-rich and resource-limited settings and in countries with both high and low burdens of tuberculosis (10). Technological advances that will make it easier to use this test at the point of care will likely accelerate this trend. Still, there has been reluctance and even opposition to making this test the standard initial means of diagnosis for suspected pulmonary tuberculosis (11). Objections have been raised that the test is too costly, requires too much maintenance, does not provide information regarding infectiousness, and does not allow a clinician to assess response to therapy in the way that a decreasing AFB smear grade does. In addition, an early paper noted that introduction of Xpert in South Africa had not resulted in a decrease in TB mortality in the communities in which it was being used, although there was realization that this was mostly a systems issue (12).

These concerns are real, but we should also not overestimate the performance of AFB smears, especially in many high-burden countries, where quality control is chronically terrible. Cost is a serious issue, and national tuberculosis control programs, ministries of health, advocacy groups, and others should work hard to negotiate reasonable prices. Still, we should accept the fact that newer tools (diagnostics, drugs, and vaccines) are likely to have some additional costs associated with them under any circumstances. This is the cost of progress, and improving the lives of patients by allowing them access to the best diagnostics and drugs should be a priority that competes with other budgetary demands. In addition,

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the costs of delayed diagnosis (and the prolonged infectious period that accompanies it) and of incorrect diagnosis are also considerable, both in real dollars and in the under- and overtreatment of individual patients that result. As the paper by Lee demonstrates, Xpert is semiquantitative enough to allow it to probably replace AFB smear grading for use in determining infectiousness and response to treatment (5). In addition, in a world in which multidrug-resistant tuberculosis is a still unchecked threat, and in which, by the best estimate of the World Health Organization, only a small minority of patients are even diagnosed, Xpert provides nearly immediate information about whether a strain of *M. tuberculosis* is susceptible to rifampin or not. An AFB smear cannot do this.

The concern that introduction of Xpert in many regions has not led to decreases in tuberculosis mortality is both serious and a bit misleading. Ultimately, the goal of introducing new diagnostics, drugs, and vaccines is of course to reduce TB incidence and mortality. But this is often as much of a systems issue as it is an issue of the tools themselves. It behooves TB control programs to work diligently to adopt these new tools in a way that takes advantage of their potential (12, 13). The operational and economic considerations are not trivial. However, it would not have made sense to tell the Wright brothers not to bother inventing airplanes because there were no airports at which to land them. A recent letter proposed that clinicians say the following to any patient who is offered only an AFB smear for diagnosis of possible tuberculosis: "I apologize for only being able to offer you a century-old test that will miss the diagnosis half the time and may cause you to take toxic medications that won't work because the test can't detect resistance. We have not been successful in bringing modern diagnostic tests into use" (14). Precisely. ■

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Neil W. Schluger, M.D.*
Columbia University
New York, New York

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