Molecular Biology Applied to Tuberculosis

The Third Landmark

Tuberculosis is the oldest documented infectious disease. It has been affecting mankind for at least 5,000 years, and molecular studies suggest that Mycobacterium tuberculosis could be 15,000 years old. However, the disease course has remained essentially unchanged for thousands of years until a few decades ago.

Today, we are confronting the so-called “third epidemic” or multidrug-resistant tuberculosis. Similarly, I believe that there have been 3 landmarks in the last 100 years, each separated by approximately half a century: the first was the discovery of the tubercle bacillus by Robert Koch; the second was the introduction of effective chemotherapy for the treatment of the disease; and the third was the development of molecular techniques for the study of M. tuberculosis.

Polymerase chain reaction has proved to be a useful tool for the diagnosis of tuberculosis. Several commercial assays are available for the detection in clinical samples of the insertion element IS6110, a DNA sequence highly specific for the M. tuberculosis complex. These procedures allow a diagnosis of tuberculosis with an accuracy at least comparable with the classical culture methods in respiratory samples, and higher than cultures in typically paucibacillary specimens such as cerebrospinal fluid and pleural fluid. But its greatest advantage resides in its celerity, with results that can be available in a few hours as opposed to several weeks with the traditional culture methods.

On the other hand, molecular biology constitutes a powerful tool for the study of the epidemiology of tuberculosis. Fingerprinting by means of restriction-fragment-length polymorphism is an invaluable procedure for the detection of clusters of tuberculosis caused by the same strain, and has also improved our understanding of the transmission of this infection.

Finally, in the last few years molecular biology has entered into a new, unexplored and promising field: the genetic detection of resistance to the major antituberculosis drugs. Undoubtedly, the emergence and spreading of multidrug-resistant tuberculosis and the shortage in first-line antituberculosis drugs have contributed to a growing interest by the investigators on this subject. In 1992 Zhang et al characterized the catalase-peroxidase gene, katG, involved in the resistance to isoniazid; in 1993 Telenti et al reported the mutations associated with the rpoB gene, the gene that encodes for the β-subunit of the RNA polymerase, the target of rifampicin; and in 1994 Banerjee et al described a missense mutation within the inhA gene that confers resistance to both isoniazid and ethionamide.

What benefits should clinicians expect from these techniques? It is not unrealistic to suppose that in a not-too-distant future a diagnosis of tuberculosis and a reliable study of the susceptibility to drugs could be obtained in a very short period of time. Additionally, molecular techniques could be applied to the study of contacts of patients with tuberculosis. Several problems should be solved, however, before the generalized use of these procedures can be a reality. First, a further improvement in the sensitivity and specificity of the test and a full characterization of the genetic mechanisms involved in resistance to the major antituberculosis drugs should be accomplished. Second, all these time-consuming procedures should be highly automated in order to allow the processing of a large number of samples. Third, the costs should be lowered if these procedures are to be generalized, as they are too expensive to be used as a screening method for the diagnosis of tuberculosis and susceptibility to drugs.

A feasible and cost-effective measure could be the establishing of fully equipped reference laboratories on a regional or national basis, depending on the local prevalence of tuberculosis, and the implementation of measures for the rapid transport of the samples from the health facilities where they are collected. Thus, it should be expected to have the results in a period of
time as short as 2 or 3 days maximum. Undoubtedly, such a rapid diagnosis would have a positive impact in decreasing the transmission of tuberculosis in health-care settings.

Fortunately, an unprecedented interest in the knowledge of the biology of the bacillus has emerged at the end of the century. In the near future, several challenges should be overcome in the management of this disease, such as the introduction of new drugs active against the bacillus, the delineation of the role of immunomodulation particularly in multidrug-resistant tuberculosis, the development of more immunogenic vaccines, and the evaluation of immunotherapy as an adjunct to antituberculosis drugs. In addition to these measures, a quicker diagnosis and the implementation of control programs directed to trace the contacts of the patients and to ensure an adequate therapy should desirably lead us to the next, fourth, half-a-century landmark in the fight against one of the oldest infectious diseases. This landmark should be the eradication of tuberculosis.

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References


Evidence-Based Asthma Guidelines

There have been many statements on asthma management published in recent years. In parallel with their publication has been the development of the concept of guidelines and of evidence-based medicine. Guidelines, considered by some to be controversial, are playing an increasing role in medical practice. Although the balance between the art of medicine and the science of medicine are paramount in these discussions, it is clear that guidelines will play an increasing role in the practice of respiratory medicine.

Guidelines appear to impact clinical practice, although convincing evidence of their impact on changing patient outcomes remains to be clearly established. Guidelines with maximum impact appear to be those that are generated locally, with a broad representation of caregivers and ideally include patient representatives. Because of criticisms of previously published asthma guidelines based on methodologic flaws, and also because of a lack of a broad representation, the Asthma Committee of the Canadian Thoracic Society decided to convene a consensus meeting in March 1995 on asthma management and to develop a statement. The working group had broad representation most notably including a number of family physicians. The recommendations developed were categorized according to specific levels of evidence: level I where there was a randomized controlled trial; level II where there was a case control or cohort study, and finally level III where there was only supporting evidence from the consensus group.

The approach adopted was refreshing to participate in, as working groups had prepared detailed briefing statements (which will be published separately) ahead of time, which focused participants discussion. Discussion of various key recommendations were crystallized if an objection could not be supported by a higher level of evidence. The summary document has also been helpful because use of this method allows attention to be drawn to the many areas of asthma management which are not supported by randomized controlled trials.

The key therapeutic recommendation of the state-