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From Magic Mountains to Modern Times

A View From the Community Hospital

A fter a patient’s initial evaluation, the physician has to select tests to confirm or exclude diagnostic options. Each must be weighed for sensitivity, specificity, positive and negative predictive value, risk and benefit, invasiveness, speed, price, and convenience, with a level of priority being assigned to each consideration. How important is, for instance, speed? What if the diagnosis is made later? Is empiric treatment needed in the meantime; and what are the risks if it is later found to be incorrect?

In Europe over 20 years ago, when I was first learning about TB, the diagnosis was much easier, not only because it was seldom in doubt, but also because time did not matter. Therapeutic options were few, primary drug resistance uncommon; most patients were treated in the hospital with two drugs, based mainly on radiography, and the timing of bacteriologic confirmation was unimportant.

Alas, those simple times are gone. Some 50 years have passed from the timeless world of the TB sanatorium, as known from Thomas Mann’s immortal, The Magic Mountain,1 which should be required reading for pulmonary physicians, to the conveyor-belt medicine of managed care, reminiscent in spirit of Chaplin’s “Modern Times.” Because tuberculosis became less common, and other diseases more common, our CT scanners may be less helpful than the ceiling-mounted fluoroscope, simple x-ray machine, and tomograph had been. We may have high-tech methods to “fingerprint” individual bacterial strains, but to determine if the patient has TB or another disease, we still use essentially the same tools, smear and culture, as Robert Koch did a century ago. But now we face a range of immunocompromised populations; a migrating, multinational crowd; the escaping genie of multidrug resistance; and unprecedented financial pressure to account for every test, every hospital day, every dollar spent. How useful are those old tools, smear and culture of expectorated sputum, in this juggling act? How can we shorten the diagnostic process and hospital stay, yet avoid missed diagnoses as well as side effects and cost of unneeded empiric treatment, particularly in the sick AIDS patient? How do we balance the need to minimize tying up scarce isolation rooms, thereby causing mental anguish in the patient and family, with protecting society from contagious disease? Clearly, the time-tested methods are no longer fast enough in current American daily practice.

Despite a number of emerging new “high-tech” methods, still experimental at this time,2 sputum microscopy remains the first step once the diagnosis of pulmonary tuberculosis is entertained.3 While this test is neither sensitive (a positive result requires a minimum bacterial concentration of approximately 10⁴/mL) nor specific (dead bacilli, atypical mycobacteria, and occasionally other acid-fast organisms may be seen), it is noninvasive and a valuable predictor of infectivity as the number of visible organisms is proportional to bacterial load, hence smear-negative patients are less conta-
gious. On the other hand, it says nothing about the specimen, which may be little more than saliva, and even if sputum, it may come from the wrong lung unit. It is this problem that has led to the widespread practice of obtaining three samples expectorated on consecutive days.

Cultures, even with radiometric methods, still require weeks, thus negative smears often prompt sputum induction or bronchoscopy. While sputum induction is promising, its value is still unknown. Bronchoscopy requires special expertise and equipment, inconvenience, and some minimal risk to the patient, increased cost to the insurer, and infection control problems to personnel. On the other hand, specimen origin is certain and the yield is superior to that of spontaneous sputum microscopy. Most authors agree that, in suspected smear-negative tuberculosis, bronchoscopy is indicated if an alternative diagnosis is likely or if the patient’s condition requires a quick answer. These criteria are frequently met nowadays, especially in AIDS patients. Bronchoscopy may also be particularly useful in the elderly and perhaps others in whom sputum collection is difficult. If so, how long should we wait for noninvasive verification before resorting to invasive specimen collection methods?

In this issue of CHEST (see page 1174), Finch and Beaty present work that, despite its simplicity, may help to answer this question. They looked for the minimum number of sputum smears needed to reach maximum diagnostic results in HIV-infected patients, but their data are also useful in the HIV-negative population. It appears from their paper that two smears are nearly as good as three to detect active pulmonary TB. If this can be verified in prospective studies, the omission of a single smear may mean substantial financial savings and faster diagnosis. The gain is not just the expense of a smear (approximately $1.15 at our institution, a network of four urban community hospitals) multiplied by the number of patients tested (about 300 a year), but also the calculable savings associated with shorter hospital stays and the uncalculable benefits gained from an earlier certain diagnosis, particularly in AIDS patients. In addition, hospitals benefit from potential shortening of isolation stays when TB is excluded, as isolation rooms are always too few and far too expensive. A difference of a single day often translates to significant acceleration of the diagnostic process in the real world, considering technical delays, weekends, and scheduling conflicts.

Of course, real life is too complex for simple prescriptions like “bronchoscopy after two negative smears.” Not only is the Seattle investigators’ study limited by its size, its retrospective design, and the uniqueness of their patient group (such as excessive male predominance), but differences between laboratories may also lead to different conclusions elsewhere. More importantly, patient subgroups may be different: Besides radiography, HIV status and other immunologic variables, nutrition, endocrine-metabolic disease, and myriad other circumstances may influence the decision how long to wait for sputum smears and when to switch to invasive means.

Several new tools are close to becoming part of daily clinical usage, including polymerase chain reaction techniques as the most promising example. These may eventually accelerate the diagnosis of TB to the time scale of other infections. It may, however, take considerable time until their role and limitations are sufficiently clarified for the good old acid-fast smear to become obsolete. Meanwhile, we need more simple information like that provided by Finch and Beaty.

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Respiratory Drug Delivery

“A vague idea of the benefit of inhalation in the treatment of diseases of the air passages is present in nearly all physicians; but it rarely assumes any tangible form, because of the dearth of information in the text books.”

John M. Scudder, MD, 1895

The science of aerosolized drug delivery has advanced greatly since the late 19th century, when the use of “medicated inhalations” was viewed by many as quackery (and much of it was). As information has accumulated, it has become clear that the delivery of aerosolized drugs to the lungs is a complex science, and that many variables influence the amount of drug that is deposited on the airway surface. Much of the impetus for research in this area stems from exciting new applications, such as the delivery of aerosol drugs for systemic use, or for the delivery of genetic material to treat diseases such as cystic fibrosis. In spite of a growing body of literature, too little attention is given to those variables affecting aerosolized drug delivery in both research studies and routine clinical use.

In this issue of CHEST (see page 1200), McPeck and colleagues compared drug delivery from a large-volume continuous nebulizer system with that from small-volume nebulizers. To simulate aerosol delivery to the patient, radiolabeled aerosol particles were nebulized and collected on filters at the mouth of a face model during ventilator-generated breathing. The amount of drug captured on the filter, measured as radioactivity, was defined as the “inhaled mass.” The study showed that the inhaled mass was similar for continuous nebulization and for intermittently filled small-volume nebulizers. The results are interesting in that they point out that only a fraction of the drug in a nebulizer is delivered to the patient, that there can be great variability in drug delivery among devices, and that breathing pattern can substantially affect the inhaled mass of a drug. While these are not new findings in aerosol science, they may not be common knowledge for those clinicians and respiratory-care practitioners who are administering inhaled drugs every day.

Bench measurements of nebulizer mass output and particle size characteristics can be helpful for quality control, but these measurements should not be used for predictions of lung dose or efficacy of a nebulized drug. The most accurate predictions of aerosolized drug delivery are those that use conditions most closely approximating the clinical setting, with a patient or patient surrogate breathing on a nebulizer. This can be done with a filter and ventilator set-up, as in the current study, or can be taken a step further, by quantitating lung deposition using gamma scintigraphy in subjects who have inhaled a radioactive aerosol. In experiments using a labeled aerosol, radioactive or otherwise, it is important to confirm that the label behaves similarly to the drug of interest.

The study by McPeck and coworkers points out the difference that breathing pattern can make in determining the inhaled mass of a drug, with implications that are especially pertinent in the pediatric population. For both the large-volume and small-volume nebulizer, the inhaled mass of the pediatric breathing pattern, compared with the adult breathing pattern, was reduced. Theoretical models of respiratory tract deposition have always indicated that breathing pattern will affect quantitative deposition, and experimental studies have corroborated this finding.2-4 Other factors that must be taken into consideration in predictions of respiratory drug delivery include the inherent interdevice variability of nebulizers of the same brand,5 particle size, and the possible changes in particle size and solute concentration that occur during nebulization.6 Although the variables may differ, similar considerations must also be made in examining drug delivery by metered-dose inhaler.

Even with close attention to all the variables and conditions mentioned previously, does an in vitro measurement accurately predict the in vivo lung deposition of drugs in a patient with lung disease? An additional layer of complexity is added when one considers the changes in lung architecture that can occur with disease. We know that the presence of obstructive lung disease alters the behavior of inhaled particles, affecting both the amount and location of deposition. Gamma camera lung scans in patients with asthma,7,8 COPD,9,10 and cystic fibrosis11,12 show increased particle deposition in the central airways and decreased particle penetration to the peripheral airways. These hot spots of increased...