Multiple Drug Resistance in Tuberculosis

To the Editor:

Dr. Sbarbaro’s challenge to practicing physicians, as well as to the leadership of the American College of Chest Physicians (May 1997), deserves to be taken seriously. Since it is unlikely that directly observed therapy will be universally implemented in our lifetime, we must strive to eliminate monotherapy now. Monotherapy, inadvertent or deliberate, is the root cause of all tuberculosis drug resistance and multiple drug resistance. However, Dr. Sbarbaro ignores a critical factor in the generation of drug resistance: use of combination medications that have not been proven bioavailable by an independent laboratory.

The World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) have endorsed fixed combination medications of demonstrated bioavailability. The late Dr. Gianni Acocella demonstrated how the lack of bioavailability can lead to drug resistance. Fixed combinations that meet these criteria are available in the US and around the world, but outside of the US, there are cheap, likely non-bioavailable combinations whose manufacturers often are able to underbid quality-controlled drugs for local contracts.

If we are to adopt Dr. Sbarbaro’s suggestion, then we must first require an ongoing mechanism to assure bioavailability by independent assessors as suggested, but not yet implemented, by IUATLD and WHO. Only then can we assure the correct use of such combination drugs and the eventual elimination of drug resistance.

Lee B. Reichman, MD, MPH, FCCP
Departments of Medicine, Preventive Medicine and Community Health
New Jersey Medical School
National Tuberculosis Center
Newark, New Jersey

REFERENCES
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To the Editor:

Dr. Reichman is correct. In many countries, substandard manufacturing by unregulated pharmaceutical companies has indeed occurred, is still occurring, and no doubt will continue to occur, especially if supported by governmental officials prompted by community pride or perhaps less honorable motives. To make matters worse, for many years the only test method used to insure the therapeutic availability of a pill’s ingredients was a solubility analysis, which simply measured the ability of a pill to dissolve in water.

The problem identified by Dr. Reichman is that excipients (substances added during the manufacturing process to hold the pill together), an unsuspected chemical interaction between the different medications in a combination pill, or even a poor formulation can reduce absorption through the intestinal tract. Unless adequate serum levels are achieved effectively for all ingredients, a combination pill becomes a single drug—the anathema of all effective tuberculosis treatment. In fact, studies have documented inadequate absorption rates, especially for rifampin, from such combination formulations.

Fortunately, the World Health Organization (WHO) and World Bank are fully aware of the problem and are moving aggressively to minimize the problem. At a meeting attended by all major pharmaceutical firms involved in developing combination antituberculosis medications (Geneva, Switzerland; December 1994) which I chaired, there was concurrence that bioavailability studies in humans would be required before a combination product received the endorsement of WHO’s Global Tuberculosis Programme. A WHO endorsement is essential if a product is to become eligible for purchase with WHO or World Bank funds.

Equally important, there was acknowledgment that only independent laboratories, located in countries other than the site of manufacturing, should be used to perform these bioavailability studies. WHO has already identified such laboratories and been in contact with them concerning bioavailability studies. By accepting a leadership role in changing physician practices worldwide, the American College of Chest Physicians should expect that the quality of products prescribed by our members mirror the quality expected of our members. Only those products providing evidence of bioavailability in human studies should be prescribed—the same position we should take with regard to all medications produced by local or national companies—including cardiac and pulmonary drugs.

John A. Sbarbaro, MD, MPH, FCCP
Departments of Medicine and Preventive Medicine
University of Colorado Health Sciences Center
Denver, Colorado