fibroblasts may lead us nearer to the origins of asthma. In addition, these studies could firmly establish the airway epithelium as a major orchestrator of asthma.

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Schedule or Dosage?

The Need to Perfect Intermittent Regimens for Tuberculosis

Sixty years after the introduction of effective chemotherapy, the World Health Organization (WHO) estimates, based on surveillance and survey data, that the number of new tuberculosis (TB) cases has reached 8.9 million in 2004, with an annual rate increase of 0.6% (1). Nine percent of new adult TB cases are attributable to HIV coinfection globally, and that rate is more than 30% in Africa. Importantly, in some industrialized countries, such as the United States, HIV prevalence in young-adult new TB cases is thought to exceed 20% (2).

In addition to the HIV epidemic, homelessness, poverty, immigration, lack of an effective public health infrastructure, and limited access to medical care continue to contribute to the increase in TB worldwide. Not unexpectedly, the spread of TB is accompanied by increased drug resistance. When, in 1990, New York City reported a 132% increase of reported cases as compared with 1980, the increased incidence was accompanied by a greater proportion of patients with multidrug-resistant TB (MDR-TB) (3). On a larger scale, the resurgence of TB in eastern Europe during the 1990s has been associated with high rates of MDR-TB among both new and previously treated patients (1), and MDR-TB outbreaks have been reported among at-risk population groups in Europe (4). The WHO estimates that 321,000–689,000 incident new and retreatment cases have occurred worldwide in 2003, and prevalent cases could be two or three times higher than the number of incident cases (5).

Current standard chemotherapy protocols date back to the 1970s when, with the introduction of rifampin into combination regimens including isoniazid, pyrazinamide and ethambutol, and streptomycin, a short course of 6 months was proven effective (6). However, although shorter than the classic 12- to 18-month treatments, the 6-month course still requires well-structured management plans for the ambulatory care of TB. In many countries, including industrialized countries where patients with TB are often socially disadvantaged, inpatient care is still customary for the more severe TB cases at a great cost for public hospitals that often care for such patients (7). As intermittent regimens are essential for ambulatory programs, they have been widely explored over the past 30 years. Isoniazid, rifampicin, pyrazinamide, and streptomycin are all deemed efficacious when given intermittently (two or three times per week), as when given daily, and ethambutol is usually only given intermittently when also given with rifampin (8). A number of studies have assessed the efficacy of intermittent short-course chemotherapy by testing the intermittent use of rifampin, or rifapentine, in combination with streptomycin, isoniazide, pyrazinamide, and ethambutol in individual formulation or fixed-dose combination (9). However, more effective intermittent regimens are still needed, and formal randomized trials comparing the two modalities, continuous versus intermittent, have been few. A Cochrane collaboration study reanalyzing one of the seminal Hong Kong/British Medical Research Council chemotherapy trials (10)

found that, although bacteriologic responses at the end of the continuous or intermittent therapy courses were superimposable, there was a prevalence of relapses in the intermittent arms of the trial (10), thereby suggesting that more formal randomized trials would have been needed.

Chang and coworkers report in this issue of the *Journal* (pp. 1153–1158) the systematic review of 20 trials of rifampin containing short-course chemotherapy regimens for non-MDR, non-HIV TB (11). Of the 32 cohorts comprised in the trials examined, 12 received daily chemotherapy regimens, six had a daily induction phase and thrice-weekly intermittent continuation phase, three had a daily induction and twice-weekly continuation phase, seven received thrice-weekly and one received twice-weekly regimens throughout, one received a daily induction phase with rifampin and continuation phase with once-weekly rifapentine, and two used intermittent rifampin and rifapentine. Strikingly, the comparison of the number of relapses in these treatment cohorts shows that the relapse rate is directly related to the total dosage of drugs, indicating that intermittent short-course regimens may be less effective than the daily ones.

In the context of the knowledge that the TB and HIV epidemics fuel one another in coinfected people and the observation that the efficacy of current anti-TB drug regimens appears to be reduced in patients with AIDS (12), Chang and coworkers' analysis calls for careful consideration that some intermittent chemotherapy regimens may be associated with more frequent failures or relapses (13, 14). Pharmacokinetics might help explain such failures (15). In a recent study, Tappero and coworkers found that significant proportions of their patients had low isoniazid, rifampin, and ethambutol, but not pyrazinamide, serum concentrations and that low serum concentrations of both isoniazid and rifampin occurred in 23 (26%) of 90 HIV-coinfected patients with TB (16).

The higher relapse rate of the intermittent compared with the continuous regimens for TB may reflect insufficient dosage due to malabsorption or mismatched pharmacokinetics. The observations of Chang and coworkers highlight the need to expand the area of TB drug pharmacokinetics to reassess current protocols. It is foreseeable that 2- to 4-month intermittent regimens might eventually be designed to implement the highly effective directly observed therapy (DOT) strategies. Such therapeutic approaches could simplify in-hospital TB treatment in industrialized countries and significantly reduce TB morbidity and mortality in high-burden areas over the next 20 years.

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