Toward Shorter-Course Antituberculosis Chemotherapy

Fox and Mitchison\(^1\) identified five major landmarks in the development of the chemotherapy of tuberculosis: (1) the discovery of streptomycin; (2) the finding that combining p-aminosalicylic acid with streptomycin prevented the emergence of strains resistant to either of the drugs; (3) the addition of isoniazid, which led to uniformly successful primary chemotherapy; (4) the demonstration that ambulatory out-patient management of bacteriologically positive pulmonary tuberculosis was effective for the patients, as well as being safe for their contacts; and (5) the introduction of supervised intermittent chemotherapy, with its consequent control over drug ingestion. Fox and Mitchison\(^1\) suggest that short-course chemotherapy is the sixth landmark.

When streptomycin was first introduced, patients were treated with a single drug for six weeks to three months.\(^2\) Many patients suffered relapse or developed resistant organisms. The duration of therapy became much longer, generally 18 to 24 months, after multiple-drug regimens were shown to prevent the development of relapses and resistant organisms.

The advantages of a shorter course of chemotherapy include a decreased risk of drug toxicity by reducing the time of exposure, a reduction in costs, and an increased percentage of patients who complete an adequate course of chemotherapy. The British Medical Research Council has performed studies that have found a number of short-course chemotherapeutic regimens to be effective. In the first British Medical Research Council/East African Study,\(^3\) those patients given isoniazid, streptomycin, and rifampin had the same relapse rate at 30 months (3 percent) as the group given a standard regimen. In the second British Medical Research Council/East African Study, a six-month daily two-drug regimen of isoniazid and rifampin was compared to a six-month triple-drug regimen of isoniazid, rifampin, and streptomycin; the results at 30 months have recently been published,\(^4\) and they document that both regimens are highly effective, with the two-drug regimen only marginally inferior to the three drugs. It was concluded that the efficacy of short-course regimens depends far more on the bactericidal activity of the drugs in the early phase of treatment than on their effects in later months. Furthermore, nearly all relapses occurred in the first few months after discontinuing chemotherapy, and most relapses occurred with susceptible organisms; the response to conventional chemotherapy by patients who had relapses was excellent.

In this issue of *Chest* (see page 583), Pilheu has further advanced the cause for short-course chemotherapy. He reports 136 patients from the Tuberculosis Clinic of Buenos Aires, 99 of whom received isoniazid, rifampin, and ethambutol for six months and 37 of whom received the same three drugs for six months followed by seven months of intermittent therapy with isoniazid. No patient was hospitalized for chemotherapy. All patients had bacteriologically negative findings at six months, and there was but one relapse (with sensitive organisms), which occurred four months after stopping chemotherapy. No drugs had to be discontinued because of apparent toxicity. Not only was there only very slight disruption to the lives of these ambulatory patients, but the few patients with primary drug resistance also did uniformly well.

With the conclusion of our bicentennial year, one wonders why there are only foreign studies and where is the US research on short-course chemotherapy. Funding for tuberculosis research recently has had a low priority; however, Public Health Service therapy trial 20 ("Short-Course Chemotherapy of Pulmonary Tuberculosis") is operational and is designed to compare a fairly standard regimen of six months of isoniazid and rifampin followed by nine months of isoniazid and ethambutol with a short-course regimen of six months of isoniazid and rifampin. The results of trial 20 will be available in several years and should help in clarifying the role of short-course chemotherapy, the sixth landmark in the treatment of tuberculosis.

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**REFERENCES**