

The Realized and Unrealized Benefits From Chemotherapy for Tuberculosis

THOMAS MOULDING, M.D.

TEN EFFECTIVE chemotherapeutic agents for tuberculosis have been introduced during the past two decades, and the ways to use them have been carefully studied and improved. The result is a set of effective tools for treating tuberculosis with a minimum of discomfort and inconvenience to the patient and with nearly 100 percent success. These agents have improved the control of tuberculosis in this country immensely, but many problems still remain because the drugs are not always used properly.

Regimens for the Previously Untreated

A major limitation on use of these chemotherapeutic agents is the potential development of drug resistance. To avoid drug resistance and insure successful treatment, many controlled trials have been made to determine the optimal therapeutic regimens for the patient with no previous drug therapy. These trials have shown conclusively that two or more drugs should be used together in treating active tuberculosis. The exact components of the optimal regimen are still not completely agreed upon because of discrepant results from different trials and

varying value judgments as to which is more serious—failure of chemotherapy or drug toxicity. Several regimens, however, have reportedly been able to achieve close to 100 percent success when chemotherapy is maintained for an adequate period—usually a minimum of 2 years (1-4). Unfortunately, these optimal regimens are not universally used in the United States, and many treatment failures result.

Community Benefits From Chemotherapy

Results show that the chemotherapeutic drugs are of obvious benefit to the tuberculous patient. But do they help the community at large by preventing transmission of the disease? To study this question, some measurement of the recent transmission of tuberculosis is needed. The best measurements are tuberculin surveys of young children. The most illuminating study using this parameter comes from the Yukon-Kuskokwim Delta area of Alaska (5). Results of tuberculin surveys from 1949 to 1951 among Eskimo children of this area in the age group 0-3 years showed an average annual infection rate of 24.6 percent. During the next 10 years, an extensive program of treating all adults and children with active tuberculosis was pursued. In 1960, a similar survey among children in the same age group gave results that showed an average annual infection rate of 1.1 percent—a 95 percent decrease. Social and economic factors probably contributed to this great reduction;

Dr. Moulding is coordinator of the tuberculosis training program of the National Jewish Hospital at Denver, Colo. The paper on which this article is based was presented at the 94th annual meeting of the American Public Health Association, San Francisco, Calif., November 3, 1966.

nevertheless, removal of sources of infection—by hospitalization and successful treatment of the patients with active disease—was apparently the major reason for this marked decrease in the transmission of infection.

Management of Treatment Failures

So much for the successes. What about patients who are considered “treatment failures”? How dismal is their future in an otherwise rosy picture? They usually excrete isoniazid-resistant tubercle bacilli. Animal experimentation has shown that tubercle bacilli resistant to isoniazid are less pathogenic than organisms which are fully sensitive to isoniazid. This lessened pathogenicity is especially characteristic of the organism which is resistant to high concentrations of isoniazid (6).

As a clinical corollary, in those regarded as treatment failures who have isoniazid-resistant organisms, the course of the disease rarely runs downhill as rapidly as it does in patients with isoniazid-sensitive organisms. Although the mortality risk for the patients with isoniazid-resistant organisms is considerably increased over persons free of tuberculosis, a large number of these patients will live for many years despite their chronic lung disease. They will remain persistently sputum-positive but will be well enough to engage in most normal activities until progressive lung destruction leads to severe respiratory crippling. This picture is not too dismal except for the patients' infectiousness.

Can these persons excreting isoniazid-resistant organisms with a low degree of pathogenicity transmit their disease to others? The answer is Yes. There are specific documented cases of persons who had never had any anti-tuberculosis drugs who, upon exposure to tuberculous patients excreting isoniazid-resistant organisms, subsequently developed tuberculosis associated with such resistant organisms (7,8). This drug resistance in a patient who has never had the drugs in question is called “primary drug resistance.” Fortunately, the incidence of primary drug resistance in the United States is low and is apparently not increasing (8-12), except among children in a slum area in New York (13). Thus, it seems that patients excreting drug-resistant organisms probably can

transmit the disease, though not very frequently.

This kind of incomplete information poses terrible practical problems for the health officer. What is he to do with the chronically sputum-positive patient? Confine him to a hospital for life or let him loose on the community despite a small but definite chance that he will transmit tuberculosis? Fortunately, there is an answer to this dilemma in most cases, namely retreatment.

Since the introduction of the familiar drugs—isoniazid, PAS (para-aminosalicylic acid), and streptomycin—seven other antituberculosis agents have appeared—kanamycin, viomycin, capreomycin, pyrazinamide, ethionamide, cycloserine, and ethambutol. These seven drugs are effective, but toxic. Because they are toxic, they are often used timidly, one at a time, with poor results. Recently, however, several centers in the United States and Europe have treated the patient excreting drug-resistant organisms by introducing concomitantly—in the maximum tolerated dosage—two or more drugs that he has never had before and to which the tubercle bacilli in his body are demonstrably sensitive (14-17). Toxic reactions have occurred but, by careful monitoring, the drugs nearly always can be withdrawn before they cause any permanent disability. With this type of aggressive retreatment, conversion rates in the range of 80-90 percent have been obtained. This aggressive approach is used in only a few centers in the United States and needs far wider application.

Optimal Length of Hospitalization

The final question that needs to be discussed is the relation of home treatment for tuberculosis to hospital treatment. In the prechemotherapy era, sanatoriums were needed to provide bed rest for the patient and to isolate him from the community. There are now at least five studies in the literature which indicate that when appropriate chemotherapy is chosen, enforced bed rest is not needed at all (18-22). In one of these studies, a group of patients treated at home was compared with a similar group treated in the hospital (21). In addition to demonstrating that home treatment was as effective as hospital treatment, this study showed

no increase in the transmission of tuberculosis to contacts of patients treated at home (23). Studies in this country, in which guinea pigs were used to monitor the infectiousness of air exhausted from the rooms of tuberculous patients, have shown that as soon as chemotherapy was initiated, the infectiousness of the patient declined markedly, though not down to zero (24). These two pieces of evidence strongly suggest that chemotherapy very rapidly diminishes the danger of transmission of infection by the patient. Certainly by the time the patient's sputum cultures are negative, he is non-infectious, and probably before then. Most patients become culture negative within 3 months. An important question thus arises. How long should the patient be hospitalized?

For the person being retreated with toxic, potentially dangerous drugs, a good case can be made for a year of hospitalization. Even here, however, shorter hospitalization is possible for the very reliable patient who can be followed as an outpatient by an equally reliable and knowledgeable physician. The major controversy over duration of hospitalization centers on the person undergoing original treatment, during which severe toxic reactions are considerably fewer than in retreatment. The crucial issue here is: How do we deal with human failure? Unfortunately, after patients leave the hospital a large number of them—perhaps 20 to 40 percent—take their medication irregularly or discontinue it altogether (25). Consistently successful treatment of tuberculosis requires a minimum of 2 years of chemotherapy, and premature interruption of medication leads to a high risk of relapse. If patients are kept in the hospital, the staff can make certain that they take their medication. But how many of us would like to be kept in the hospital 6 to 9 months solely for that purpose? Not many tuberculous patients like it either.

Furthermore, long hospitalizations are expensive. If the patient who is having his first treatment is kept in the hospital past the point of reversal of infectiousness simply to insure regular drug ingestion, we find ourselves spending about \$20 per day for the sole purpose of getting the patient to take about 20 cents worth of medication. The money involved is considerable, since the estimated annual expenditure for

hospitalization for tuberculosis in the United States is a third of a billion dollars (26). There must be a more economical way of assuring that patients take their medication—and there is.

Dose by Dose Supervision of Outpatients

Most chemotherapeutic agents for tuberculosis can be given once a day, and there is evidence to suggest that this schedule is the optimal method of drug administration (27, 28). Thus, if necessary, it should be possible to send a public health nurse to the patient's home every day to give him medication. In most communities, the cost of this visit would be less than one-third the cost of a day's hospitalization—an obvious saving. There are a few patients who are so completely unreliable that precisely this measure would be required in order to treat them as outpatients. Moreover, since this method is cheaper, more humane, and just as good as hospitalization, why not use it? However radical this approach may sound, I am convinced that we should be prepared to go to the extreme of supervising each dose of medication whenever it is necessary.

To simplify matters, evidence from Madras, India, indicates that if isoniazid and streptomycin are both given twice a week in higher than conventional doses, they can be as effective as isoniazid and para-aminosalicylic acid given daily (29). Thus we have an obvious opportunity for tight control with further economy.

This type of high-dosage intermittent regimen has been used in this country recently (30). It was used for 25 difficult, unreliable, and usually alcoholic patients from skid row, after an initial period of treatment with isoniazid, para-aminosalicylic acid, and streptomycin in the hospital. In most instances, the patients came to the clinic twice a week for an injection of streptomycin and ingestion of isoniazid. In a few instances, however, the public health nurses made regular twice-weekly home visits. If the patients missed a single dose of medication, they were immediately sought.

Over a period averaging 12 months for each patient, only one was lost to health department supervision, and he was picked up in another State. The remaining 24 patients missed only 1.5 percent of their scheduled doses of medication. The total cost was less than 8 percent of

the cost of giving comparable treatment in the hospital. While at the time of reporting, the long-term results were not yet known, there had been no relapses. Further studies in this area are badly needed.

Identifying the Unreliable Patient

Since the majority of patients are reliable enough to take their medication by themselves at home, it would be foolish to place all patients on a program requiring supervised administration of each dose. But how do you sort out the patients who will not take their drugs? Often the method of differentiation is obvious. A patient who misses appointments frequently, disappears from supervision, or frankly admits he is not taking his medication can easily be identified. Rebellious or psychologically disturbed patients are suspect. In addition, various checks on patients have been developed, such as urine tests for the presence of medication, counts of the amount of medication dispensed and of the amount remaining in the patient's possession, and even a simple medication dispenser in which radioactive material and photographic film record the times when pills are removed (31,32). By intelligent use of all these measures, we should be able to identify nearly all patients who need to have medication directly administered to them dose by dose.

Keeping Patients on Treatment

Supervision must also be concerned with seeing that contact is maintained with patients who move or go visiting. If contact is lost, medication is often interrupted. The patient must, therefore, be sought promptly and brought back to therapy if he misses even one appointment. As clues to places to look for lost patients, a list of relatives, friends, and other persons likely to know the patient's whereabouts in the future needs to be established for all patients during their first few weeks of hospitalization. In addition, whenever the patient moves or contemplates doing so, meticulous attention must be paid to insuring communication between health agencies.

Although tight supervision is essential to make certain that all patients, including the difficult ones, complete a full course of chemotherapy, it should not be forgotten that the ma-

majority will cooperate fully. To maintain and foster this cooperation, clinic service must be convenient, personal, and courteous. Equally important, if not more so, is the need for carefully and repeatedly educating the patient to see the absolute importance of taking medication for the full period of therapy.

It would seem reasonable to begin this education of the patient in the hospital. Evidence suggests, however, that this desirable practice is not always followed. For instance, in a recent survey (33), 87 tuberculous patients in 10 different areas of the country, who had either been recently discharged from the hospital or were ready for discharge, were asked one simple question: "What is the most important thing for you to do in the next year to make sure that you will never again have tuberculosis?"

We all would agree, I believe, that the answer to that question should be: "Take my medication." The answers that the patients gave included: "Get lots of rest." "Eat good food." "Don't work too hard." "Wash my hands." Only 27 percent even mentioned the taking of medication. Hospitals, at least in these 10 areas, could update their patient-education programs.

Many other significant aspects of the optimal outpatient program for treating tuberculosis have been discussed elsewhere and need to be applied (34). But what is really important is that health departments recognize that interruption of the chemotherapy of tuberculous outpatients is a serious problem, realize that it can be solved, and develop the will and organization to do the job.

Need for Improved Performance

How well are we doing with tuberculosis treatment today? In general, rather poorly. The Tuberculosis Program of the National Communicable Disease Center, Public Health Service, has been collecting data from case registers in those areas supported by special tuberculosis project grants on the percentage of patients with "therapy prescribed." Patients were considered to have had therapy prescribed if drugs had been recommended within the 3 months preceding the cutoff date for data collection, and if there was no record of patient refusal. This criterion is a very rough measurement, but one

by which it should be easy to establish a good record.

According to the reports available from the case registers as of June 30, 1966 (personal communication from A. M. Lowell, chief of the Statistical Services Unit, Tuberculosis Program), therapy had been prescribed for only 61.2 percent of the known active patients living at home—a rather deplorable performance. Some of this deficiency was probably due to a lack of accurate reporting by clinics and physicians of the patients who were actually taking drugs. On the other hand, there must have been many patients who were recorded as having had therapy prescribed who were not taking their medication.

Thus, in my opinion, the uncompleted task of first priority in tuberculosis control for most health departments is not school tuberculin testing programs, not casefinding, not followup of persons with inactive disease, not prophylaxis, but simply adequate treatment of every patient with an active case. The other tasks need to be done, but they are not of first priority. Our crying need is for outpatient facilities capable of supervising chemotherapy for ambulatory patients. Such facilities are easy to justify on the basis of economy alone. More important, they are the key to far more humane treatment, for they allow the period of hospitalization for tuberculosis to be shortened with safety.

Summary

Chemotherapy has greatly improved the control of tuberculosis. By using optimal drug regimens, close to 100 percent therapeutic success can be achieved among previously untreated patients. Even among patients with isoniazid-resistant organisms who are considered treatment failures, 80–90 percent sputum conversion can be attained by aggressive, but careful, use of the relatively toxic retreatment drugs. Such successful treatment protects the public by interrupting the patient's transmission of the disease to other people. Wider application of these optimal drug regimens is needed.

Chemotherapy makes it possible to shorten hospitalization for tuberculosis. Enforced bed rest is no longer needed, and the patient rapidly

becomes noninfectious. The difficulty with such shortened hospitalization, however, is that outpatients frequently interrupt their medication before completing the necessary 2 years of chemotherapy. To obviate such interruptions, exceedingly tight supervision of tuberculous outpatients is required, along with high-quality convenient services and intensive patient education.

Many health departments are deficient in this area of outpatient treatment, which should be their activity of first priority in tuberculosis control. Establishment of better supervised outpatient programs would make it possible to shorten hospitalization safely, producing both marked savings for the taxpayers and far more humane treatment for the tuberculous patient.

REFERENCES

- (1) Crofton, J.: "Sputum conversion" and the metabolism of isoniazid. *Amer Rev Tuberc* 77: 869–871 (1958).
- (2) Russell, W. F., Jr., et al.: Combined drug treatment of tuberculosis. III. Clinical application of the principles of appropriate and adequate chemotherapy to the treatment of pulmonary tuberculosis. *J Clin Invest* 38: 1366–1375 (1959).
- (3) Thomas, H. E., et al.: 100% sputum-conversion in newly diagnosed pulmonary tuberculosis. *Lancet* 2: 1185–1186, Nov. 26, 1960.
- (4) Armstrong, A.: Alternating regimen for far advanced disease. *In* Transactions of the 24th Research Conference in Pulmonary Diseases. Veterans Administration Department of Medicine and Surgery, Washington, D.C., 1965, p. 18.
- (5) Comstock, G. W., and Philip, R. N.: Decline of the tuberculosis epidemic in Alaska. *Public Health Rep* 76: 19–24, January 1961.
- (6) Middlebrook, G., and Cohn, M. L.: Some observations on the pathogenicity of isoniazid-resistant variants of tubercle bacilli. *Science* 118: 297–299 (1953).
- (7) Lepeuple, A., et al.: Identification des sources de contagion dans quelques cas de résistance primaire tuberculeuse. *Rev Tuberc* 27: 53–66 (1963).
- (8) Zitrin, C. M., and Lincoln, E. M.: Initial tuberculous infection due to drug-resistant organisms with a review of the world literature on initial infection due to isoniazid-resistant tubercle bacilli. *J Pediat* 58: 219–225 (1961).
- (9) Chaves, A. D., et al.: The prevalence of drug-resistant strains of mycobacterium tuberculosis isolated from untreated patients in New York City during 1960. *Amer Rev Resp Dis* 84: 647–656 (1961).

- (10) Prevalence of drug resistance in previously untreated patients. U.S. Public Health Service cooperative investigation. *Amer Rev Resp Dis* 89: 327-336 (1964).
- (11) Hobby, G. L., et al.: A continuing study of primary drug resistance in tuberculosis in a veteran population within the United States. *Amer Rev Resp Dis* 89: 337-349 (1964).
- (12) Hobby, G. L., Lenert, T. F., Maier, J., and O'Malley, P.: Primary drug resistance. II. A continuing study of tubercle bacilli in a veteran population within the United States. *Amer Rev Resp Dis* 91: 30-34 (1965).
- (13) Steiner, M., and Cosio, A.: Primary tuberculosis in children. I. Incidence of primary drug-resistant disease in 332 children observed between the years 1961 and 1964 at the Kings County Medical Center of Brooklyn. *New Eng J Med* 274: 755-759 (1966).
- (14) Fischer, D. A., Kass, I., Dye, W. E., and Lester, W.: Treatment of isoniazid-resistant tuberculosis. In *Antimicrobial agents and chemotherapy* (transactions of 1964 Interscience Conference on Antimicrobial Agents and Chemotherapy), edited by J. C. Sylvester. American Society for Microbiology, Ann Arbor, Mich., 1964, p. 699-707.
- (15) Corpe, R. F., and Blalock, F. A.: Retreatment of drug-resistant tuberculosis at Battey State Hospital. *Dis Chest* 43: 305-310 (1963).
- (16) Zierski, M.: Treatment of patients with cultures resistant to the primary anti-tuberculosis drugs. *Tubercle (London)* 45: 96-100 (1964).
- (17) Jančík, E.: Effets des agents antibacillaires dits secondaires sur la tuberculose pulmonaire. *Advances Tuberc Res* 13: 121-218 (1964).
- (18) Dressler, S. H., et al.: Ambulation of patients with pulmonary tuberculosis under protection of chemotherapy. *Amer Rev Tuberc* 70: 1030-1041 (1954).
- (19) Wier, J. A., Taylor, R. L., and Fraser, R. S.: The ambulatory treatment of patients hospitalized with pulmonary tuberculosis. *Ann Intern Med* 47: 762-773 (1957).
- (20) Tuberculosis Society of Scotland (research committee): The treatment of pulmonary tuberculosis at work: A controlled trial. *Tubercle (London)* 41: 161-170 (1960).
- (21) Tuberculosis Chemotherapy Centre (Madras, India): A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. *Bull WHO* 21: 51-144 (1959).
- (22) Tyrrell, W. F.: Bed rest in the treatment of pulmonary tuberculosis. *Lancet* 1: 821-823, June 2, 1956.
- (23) Ramakrishnan, C. B., et al.: Influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 2-year period in close family contacts in South India. *Bull WHO* 24: 129-148 (1961).
- (24) Riley, R. L., et al.: Infectiousness of air from a tuberculosis ward: ultraviolet irradiation of infected air: comparative infectiousness of different patients. *Amer Rev Resp Dis* 85: 511-525 (1962).
- (25) Fox, W.: Self-administration of medicaments. *Bull Int Un Tuberc* 32: 307-331 (1962).
- (26) The future of tuberculosis control. A report to the Surgeon General of the Public Health Service by a task force on tuberculosis control. PHS Publication No. 1119. U.S. Government Printing Office, Washington, D.C., December 1963.
- (27) Tuberculosis Chemotherapy Centre (Madras, India): A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. *Bull WHO* 23: 535-585 (1960).
- (28) Carr, D. T., and Karlson, A. G.: Optimal regimens of anti-tuberculous drugs. *Amer Rev Resp Dis* 84: 90-92 (1961).
- (29) Tuberculosis Chemotherapy Centre (Madras, India): Intermittent treatment of pulmonary tuberculosis. A concurrent comparison of twice-weekly isoniazid plus streptomycin and daily isoniazid plus p-aminosalicylic acid in domiciliary treatment. *Lancet* 1: 1078-1080, May 18, 1963.
- (30) Sbarbaro, J. A., and Johnson, S.: Twice-weekly directly administered tuberculosis chemotherapy for "recalcitrant" outpatients. Paper presented at the annual meeting of the American Thoracic Society, Pittsburgh, Pa., May 25, 1967.
- (31) Moulding, T., Knight, S. J., and Colson, J. B.: Vertical pill calendar dispenser and medication monitor for improving the self administration of drugs. *Tubercle (London)* 48: 32-37 (1967).
- (32) Moulding, T.: Varied designs for pill calendars and time recording pill dispensers. Unpublished material. Available from author on request.
- (33) Rakich, J. H., and Moulding, T.: Education of patients by tuberculosis hospitals. *Amer Rev Resp Dis* 85: 754-757 (1962).
- (34) Moulding, T.: New responsibilities for health departments and public health nurses in tuberculosis—keeping the outpatient on therapy. *Amer J Public Health* 56: 416-427 (1966).