tubercle bacilli in pulmonary lesions resected from humans after longterm chemotherapy, demonstration of viability at times may be difficult to achieve.

In the effective use of antimicrobial agents, one is concerned with populations of organisms, not with individual cells. Complete sterilization may occur only rarely. Yet, in the presence of sufficiently high concentrations of drug, bactericidal effects against a major portion of the cells within any susceptible microbial population generally are demonstrable. The experimental studies summarized in this issue of Chest clearly indicate that such is the situation with rifampin. The drug may be bactericidal, bacteriostatic, or both, depending in part on the microbial population involved, the drug concentration used, and on environmental factors, and depending in part on one's point of reference.

The important questions are: to what extent are those organisms that survive contact with rifampin capable of producing or perpetuating disease? Can the immunologic defenses of the host and/or the concomitant or sequential administration of other drugs eradicate these persisting viable microbial cells?

From the outset it has been apparent that emergence of resistance to rifampin might occur rapidly. It is therefore fortunate indeed that the use of carefully designed drug combinations for the treatment of tuberculosis has in recent years become virtually mandatory, for otherwise the value of this powerful new antimicrobial agent might have been lost early in its development. Of considerable interest in this regard is the fact that in the Veterans Administration-Armed Forces Pilot and Cooperative Studies on Rifampin, emergence of microbial resistance to rifampin was only rarely observed; in the United States Public Health Service Trial of Rifampin none was observed (Am Rev Resp Dis 1972, 105, in press and 1971, 103:461). One or more presumably active antimicrobial agents, however, were administered in conjunction with rifampin in all instances.

Kradolfer and Schnell (Chemother 1970, 15:242) have demonstrated that about one organism among each 10^6 tubercle bacilli spontaneously develops resistance to the rifamycins and that the emergence of resistant bacteria is therefore related to inoculum size. Since there apparently is no cross-resistance with other antimicrobials, combination therapy in tuberculosis presumably can be carried out with any other class of antibiotics. Some, however, may be more effective than others and their respective mechanisms of action on microbial cells perhaps should be considered in selecting drugs for use in combination with rifampin.

In this regard it is of interest that conversion to rifamycin resistance is apparently due to a one-step mutation (Austin and Scaife: J Mol Biol 1970, 49:263) and it seems, therefore, that rifamycin is bound to a specific site of the RNA polymerase. Substitution of single amino acids alters this site so that binding with the antibiotic becomes difficult, if not impossible.

Little information exists at present concerning the effect of intermittent contact with rifampin upon the rate of emergence of drug-resistant cells. Its high cost, however, precludes its widespread daily use over long periods of time and interest centers on its possible efficacy when administered only intermittently. Experimental studies suggest that it should be fully as effective when administered once weekly in appropriate dosage as when given daily, but insufficient information is available to date concerning the pharmacologic and immunologic effects of such intermittent regimens.

Much has been learned about rifampin and the rifamycin series of antimicrobial agents, in a very few years. Much remains to be learned. As biochemists and molecular biologists apply their new knowledge and new technology to elucidation of the action of this group of compounds, one may look forward to increased opportunity for their more effective use as chemotherapeutic agents.

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Rifampin: Its Role in the Treatment of Tuberculosis

By the time rifampin was discovered, exceedingly effective antimicrobial therapy for tuberculosis was already available. What then could be the advantages of a new drug? Four things: easier administration, less toxicity, faster conversion, shorter total duration of therapy.

When the Public Health Service organized a cooperative group study of rifampin (as a controlled trial), it was elected to test rifampin in combination with isoniazid and in combination with isoniazid plus ethambutol, against the optimal regimen then available—isoniazid, streptomycin and ethambutol. This was done by a central office randomly assigning one of the three drug regimens to 632 patients, all of whom had bacteriologically-positive advanced cavitary tuberculosis and who are being treated the first time in 19 participating hospitals. Preliminary conclusions from this coop-
Editorial study (which is now being prepared for publication) are:

1. Rifampin-isoniazid produced sputum conversion two weeks earlier than streptomycin-isoniazid-ethambutol and the addition of ethambutol to the rifampin-isoniazid regimen had no advantage. It is important to recognize that the presence of a positive smear at 16 weeks was not always an indication of treatment failure, since in 85 percent of the positive smear specimens, the culture was negative. A negative smear was a reliable indicator of a negative culture as early as the tenth week.

2. As early as the eighth week, 58 percent of the patients (5 of whom had far-advanced cavitary disease) had negative cultures; at 12 weeks, 85 percent; and at 16 weeks, 95 percent.

3. Rifampin was well tolerated. Less than 2 percent of the patients had to stop drugs because of symptoms, usually gastrointestinal complaints.

4. Serial laboratory tests were performed to monitor renal and hepatic function. The only abnormalities during treatment were found in the serum glutamic pyruvic transaminase levels. Five percent of patients on each rifampin regimen had an elevation over 100 units during treatment. Usually the elevation occurred only one time with no clinical symptoms. The serum glutamic pyruvic transaminase decreased both for patients who continued on rifampin and for those who discontinued.

5. The two drug regimen of rifampin is more effective and less toxic than the three-drug or four-drug alternating regimens previously used for far-advanced cavitary cases. These regimens contained streptomycin and either pyrazinamide or para-PAS, all of which are quite toxic.

Earlier Public Health Service trials have brought together material which reflects the improvement in the treatment of cavitary tuberculosis over the past two decades in terms of reduced toxicity and rapidity of sputum conversion. The first line of Table 1 shows the percentage of patients with reactions severe enough to force discontinuance of the regimen. The next two lines show the percentage of patients whose sputum grew M tuberculosis after eight and twelve weeks of treatment.

The combination of rifampin-isoniazid is superior on all points. Toxicity is reduced to a minimum level—only two patients per hundred. By eight weeks, only 42 percent of the patients had a positive sputum culture, a level not reached with streptomycin-isoniazid-ethambutol until ten weeks. In addition, reversal of potential infectiousness was advanced by two weeks.

It is of great importance that rifampin and isoniazid are both oral agents and remarkably nontoxic in relation to the other drugs available. With appropriate safeguards to be sure the patient is taking his drugs and has no symptom of toxicity, it provides an ideal outpatient regimen. Thus, the combination of rifampin-isoniazid in the initial treatment of tuberculosis appears to be the optimum regimen at present. Outpatient treatment is feasible, and, for those hospitalized, it does make possible earlier discharge of the patient from impatient to ambulatory treatment. Even though rifampin is expensive at the present time, its cost is only a small fraction of the hospital per diem cost.

The public and voluntary organizations must educate the controllers of the budgets to support ambulatory care with some of the monies that do not have to be spent for hospital care as the result of reduction in the duration of hospitalization.

In my opinion, the initial course of rifampin-isoniazid at present should probably be 12 to 16 weeks, then switch to a less expensive regimen such as isoniazid-ethambutol for the completion of chemotherapy. The optimum duration of the total chemotherapy is now under investigation in another cooperative study of the Public Health Service. If in fact the total duration of chemotherapy can be reduced by even as much as six months, or possibly a year, the cost of rifampin may more easily be justified. Maybe rifampin is too good to be reserved for retreatment tuberculosis.

The Public Health Service experience with rifampin is in daily treatment. We have had no experience with intermittent treatment at higher doses, but have noted the reports on toxicity with these regimens. Continued investigation of this observation is mandatory; but it also emphasizes the necessity at this time for continuous medication by the patient and an understanding by the patient that he must take his medication every day for as long as recommended and not sporadically.

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CHEST, VOL. 61, NO. 6, JUNE 1972

SPECIAL ISSUE

Table 1—Optimum Drug Regimen for Treatment of Cavitary Tuberculosis, 1953 to 1971

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Drug discontinued
for adverse reactions
(percent) 22 13 11 2

Culture positive
(percent)
At 8 weeks 59 62 61 42
At 12 weeks 35 24 31 15