we use them. Our total incidence was 11 percent, but only 4 percent were major side effects. The most serious side effect of INH and RIF is on the liver, but the incidence of hepatitis was only 3 percent, and most cases occurred during the daily phase of therapy. The patients recovered uneventfully after stopping the therapy, except in two who were moribund at the start of therapy. Liver toxicity is no more likely in alcoholic than nonalcoholic patients, although it can be more serious. Hepatic cirrhosis does not contraindicate use of RIF and INH or even PZA when indicated for active tuberculosis. The use of two hepatotoxic drugs should be avoided in patients with known active hepatitis, however, by using INH, EMB, and SM until the hepatitis has cleared.

We routinely perform baseline liver function studies before therapy, but repeat these only if symptoms develop suggestive of hepatitis. Patients are asked to report nausea, vomiting, fever, jaundice, or petechiae without delay.

In conclusion, we have now had almost five years of experience with a largely twice-weekly regimen of RIF and INH comprising about 1,000 cases. This report concerns the 585 of this number who met rigid criteria for diagnosis and were cared for under a strict protocol. An overall success rate of 95.4 percent was achieved for those completing therapy.

We have shown this regimen to be effective, safe, and practical under field conditions, even in elderly patients. That this treatment is much less expensive than older, more prolonged regimens is an added dividend in this day of rising medical costs.

References
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Preliminary Results of Six-month Regimens Studied in the United States and in Poland

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The Tuberculosis Control Division of the Centers for Disease Control is involved with two studies of short-course chemotherapy for pulmonary tuberculosis. One is being carried out in the United States and the other in Poland. All short-course regimens being studied are of six months’ duration, and all include rifampin (R) and isoniazid (I) administered daily or intermittently for the entire duration of treatment. Some regimens also included supplemental drugs. This report presents the results of these short-course regimens 18 months after completion of therapy.

The objective of the ongoing U.S. study, the 20th in a series of U.S. Public Health Service cooperative trials, is to compare the efficacy of a six-month regimen with the efficacy of a standard 15-month regimen. Drugs were self-administered throughout. During the first six months, or initial phase, all patients were prescribed R, 600 mg, and I, 300 mg, daily. During the next nine months of therapy, or maintenance phase, patients assigned to the standard 15-month regimen were given I, 300 mg, and ethambutol (E), 15 mg/kg, daily, while those assigned to the six-month regimen were given placebo. Patients who complete this study are to be observed for 36 months from the initiation of therapy.

A total of 838 patients entered the study from 15 participating treatment centers between October 1975 and December 1978. Twenty percent of these patients failed to meet the admission criteria primarily because of negative pretreatment cultures or pretreatment cultures that grew nontuberculous mycobacteria or Mycobacterium tuberculosis resistant to I, R, or E.

Of the 672 eligible patients admitted to the study, 293 (44 percent) were considered not to have completed therapy because they missed more than 14 consecutive days of R-I therapy. Seventeen percent failed to keep appointments and pick up medications. This was the most common reason for failure to complete therapy. Thirty-five patients (5.2 percent) had adverse reactions attributed to R or I or both, 21 had hepatotoxic reactions, and 14 had other types of reactions. Sixteen patients (2.4 percent) experienced adverse reactions (mostly hepatic) which were attributed to alcohol abuse.

Of the 379 patients who completed the initial six months of therapy, 192 were assigned to the standard 15-month regimen, and 187 were assigned to the short-course six-month regimen (Table 1). Of those assigned to the standard regimen, 166 patients (86 percent) were observed at the end of the months of therapy. Only 17 of these patients took less than 70 percent of their assigned nine months of I and E.

Because during the maintenance phase patients in the short-course regimen received no drugs, while those in the standard regimen received I and E, the length of follow-up without drugs for the short-course regimen was nine months longer than that of the standard regimen. Therefore, as of July 31, 1980, more patients assigned to the six-month regimen have had an opportunity to be followed for 18 months after drug therapy ended than those assigned to the standard 15-month regimen (127 vs 89). The cumulative percentage relapsed were estimated by the life table method, which allows patients to be counted for each month.

Studies in Short-course Chemotherapy for TB

727
they have been taking no drugs. Patients were considered to have relapsed if they had two or more M tuberculosis cultures after their assigned therapy was completed. During the 18-month follow-up, significantly more patients (F=.0008) relapsed in the short-course regimen than in the standard regimen (9 percent vs 0 percent). All 16 relapses among patients in the short-course regimen occurred in the first six months after discontinuing drug therapy. No patient treated for 15 months relapsed.

From this study we can conclude that R and I given daily for six months can cure about 91 percent of patients, but an even higher cure rate is desirable. This can be accomplished in two ways: (1) lengthen treatment to nine months or longer and (2) supplement the "core regimen" of I and R with additional drugs.

Studies conducted in Poland in collaboration with the National Institute for Tuberculosis Research have allowed us to examine the effect of adding certain supplemental drugs to such a core regimen of I and R given for six months. The five regimens studied are shown in Table 2.

A total of 530 patients between the ages of 15 and 70 years with smear-positive pulmonary tuberculosis were admitted to this study.

All patients were hospitalized for the first two months of daily therapy and received the remaining four months of supervised therapy as outpatients.

Daily drug dosages were as follows: I, 300 mg, R, 600 mg (450 mg for those <50 kg), E, 25 mg/kg, streptomycin (S), 1 g (0.75 g for those older than 50 years) and pyrazinamide (Z), 2 g (1.5 g <50 kg). Intermittent dosages were I, 15 mg/kg, R, 600 mg, and E, 50 mg/kg.

The treatment was generally well accepted in all five regimens; only 16 percent of the 530 patients failed to complete the six months of treatment. Common reasons for failure to complete treatment were delinquency and concomitant disease interfering with therapy. Drug toxicity was not a major problem, but was higher among those assigned 2 IRSZ/I,R than among those assigned to the other four regimens. The higher toxicity of this regimen was attributed to streptomycin, not to pyrazinamide. All patients assigned to the four regimens that contained E were culture-negative by the fifth month of therapy. Patients assigned to 2 IRSZ/I,R showed much better, all achieving sputum negativity by the third month.

The four regimens that included ethambutol yielded relapse rates of 7 to 20 percent during the 18 months after treatment was completed (Table 2).

The highest relapse rate (20 percent) occurred in regimen 2 IRE/I,R,E,. This suggests that once-weekly drug administration during the continuation phase may be inferior to daily or twice-weekly administration of drugs. Relapse rates for regimens 6 IRE, 2 IRE/I,R,E, and 2 IRE/I,R,E, were 12 percent, 17 percent, and 7 percent respectively. Thus, the study provides no evidence that daily drug administration is superior to twice-weekly administration during the continuation phase. The 12 percent relapse rate among Polish patients given 6 IRE was similar to the 9 percent relapse rate experienced by the U.S. patients given daily I and R in Study 20. This suggests that ethambutol adds very little to the potency of the I–R six-month regimen. On the other hand, the addition of S and Z during the initial two-month daily phase had a dramatic effect. No relapses occurred among the patients treated with 2 IRSZ/I,R.

Were it not for the toxicity of S, 2 IRSZ/I,R would

Table 2—Polish National Institute for Tuberculosis Research Study: Relapse Analysis

<table>
<thead>
<tr>
<th>6-Month Regimens</th>
<th>Completed 6 Months of Therapy</th>
<th>Observed 18 Months After Therapy</th>
<th>No. Relapsed</th>
<th>Cumulative Percentage Relapsed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen 6 IRE</td>
<td>93</td>
<td>90</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Regimen 2 IRE/I,R,E</td>
<td>90</td>
<td>88</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Regimen 2 IRE/I,R,E</td>
<td>89</td>
<td>87</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Regimen 2 IRE/I,R,E</td>
<td>91</td>
<td>87</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Regimen 2 IRSZ/I,R</td>
<td>85</td>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Cumulative percentage relapsed at 18 months after discontinuation of drug therapy. Relapse is calculated at 6-month intervals by life table method. I=isoniazid, R=rifampin, E=ethambutol, S=streptomycin, and Z=pyrazinamide.
appeared to be a nearly ideal regimen. It may be that S
does not add substantially to the efficacy of this regi-
men. To answer this question, a new study has been
undertaken in Poland, one group of patients being
given 2 IRSZ/I, the second group being given 2 IRZ/I.

ACKNOWLEDGMENT: The authors wish to express their
deep appreciation for the work of the staff in the cooperat-
ing clinics, both in the United States and in Poland, with-
out whom these studies could not have been performed. We
also are grateful for the help of our co-workers at the Center
for Disease Control in Atlanta and at the National Institute
for Tuberculosis Research in Poland.

Summary of Symposium

Robert G. Loudon, M.B., F.C.C.P.*

DISCUSSION

In the discussion that followed the presentations, a
number of questions were asked: some evoked
agreement, some did not. Panel members agreed that
short-course chemotherapy should not be limited to pa-
tients who may have difficulty in cooperating with
treatment. A patient with no financial difficulties,
anxious to have the best treatment available, and will-
ing to accept a long duration of treatment, would
appropriately be given the same recommendations as
any other patient; for example, a nine-month course
of isoniazid, rifampin, and ethambutol, with etham-
butol being given for the first two months only. The
inclusion of ethambutol was questioned, and defended
on the grounds, among others, that it would benefit
any patients harboring organisms resistant to isoniazid.
Patients likely to abscond might best be given as many
drugs as they can tolerate—perhaps a four-drug regi-
men. Dr. Pilheu preferred as a routine regimen to
give four drugs, I, R, S, Z for two months, followed by
another four months of I-R.

The question was asked: "Does rifampin alone cause
hepatitis, apart from the elevation in bilirubin?" Pro-
fessor Grosse felt that the hepatotoxicity of rifampin
itself is very low; in some way it seems to change the
metabolism of INH and increase its toxicity. Dr. Pilheu
commented that RMP in rare cases causes cholestasis,
but does not tend to cause hepatic dysfunction in those
who initially have normal function, even in alcoholic

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patients. Liver biopsy specimens from patients receiv-
ing RMP who get "hepatitis" show only cholestasis.
This will disappear as soon as the rifampin therapy is
stopped; if rifampin is resumed two or three weeks
later, the cholestasis does not reappear.

The panel in general favored short-course chemother-
apy over longer regimens. An official recommendation
was quoted as advising nine months of an isonia-
zid-rifampin regimen as one of the accepted approaches
to treatment of tuberculosis, but the opinion was that
this should be the preferred, not simply an accepted,
approach. But the panel agreed that there is no one
ideal regimen. If regimens are too long, patients are
lost to treatment; if more potent drugs are used, there
may be increased side effects.

While the literature on the subject is meager, there
are good reasons for believing that a regimen adequate
for the treatment of pulmonary tuberculosis will be
adequate or more than adequate for the treatment of
extrapulmonary or miliary tuberculosis, or tuberculosis
in children.

It was agreed that pyrazinamide is likely to play a
more important role in chemotherapy in the future.
Reducing the duration of regimens to six months is
likely to be dependent on its use. It may be of special
value in certain categories of patients, such as in refu-
gees, a high proportion of whom may harbor drug-
resistant organisms. In Arkansas, for example, the need
for adding ethambutol routinely to isoniazid-rifampin
is questioned; but if a patient has been exposed to
isoniazid in the past as prophylaxis or treatment, or
comes from abroad, four drugs are given in combina-
tion until drug-susceptibility results are available. If
the organisms grown from the patient are drug-sus-
ceptible, isoniazid-rifampin is given to a total of nine
months. If isoniazid resistance is present, rifampin-
ethambutol has proved unsatisfactory, and the regimen
is changed to streptomycin-rifampin-pyrazinamide
twice weekly to a total of nine months. So far this has
proved satisfactory. An alternative recommendation, for
Indochina refugees, is to start with isoniazid-rifampin-
ethambutol.

In summary, Dr. Rubin commented that we have not
yet resolved the problem of the best regimen or dura-
tion, but the consensus seems to be moving toward
nine months of a regimen containing at least isoniazid
and rifampin. The problem of delinquency among pa-
tients represents a point where the art and science of
medicine come together—where we teach patients com-
pliance, treat them as individuals, and sell them on
what they need, we and they do better.