A Controlled Trial of Individually-Adapted
Short-Course Chemotherapy versus Two-Year
Scheme in Original Treatment of Pulmonary
Tuberculosis*

Report after a Five-Year Follow-Up

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Patients with culture-positive pulmonary tuberculosis
were allocated at random into two groups for a three-
phase regimen in original course chemotherapy. The
first group was given rifampicin (RMP) plus isoniazid
(INH) plus ethambutol until sensitivity tests were com-
pleted, then RMP plus INH until culture conversion,
thereafter INH alone for four months. The second group
received the same drugs until obtaining culture conver-
sion, thereafter INH alone for a period lasting two
years after onset of chemotherapy. One hundred sixty-
eight patients were available for the final assessment
after a five-year follow-up after culture conversion. Two
bacteriologic relapses occurred among the two-year
scheme patients, none in the short-course patients.

A rifampicin (RMP) plus isoniazid (INH)
treatment regimen has been found to achieve
sterility in tuberculous lesions within four
months in mice1,2 and from the fourth month in human

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excised lung tissue.3,4 The above-mentioned results
were in keeping with the absence of relapse in
many patients who refused prematurely to take
drugs after 12 months or even less.5 These experi-
mental and clinical observations suggested that a
shorter treatment period could be considered with-
out adverse results. A controlled trial was therefore
carried out from 1971 to 1975 in order to evaluate
the outcome of a short-course of chemotherapy
for pulmonary tuberculosis.

PATIENTS AND METHOD

Two hundred fifty-two patients were admitted to the
hospital with previously untreated pulmonary tuberculosis
from February, 1971 to February, 1975. Three-quarters
of the patients were natives of Switzerland, and one quarter
from surrounding countries. They were aged between 19
and 79 years (mean: 44.2 years); male/female ratio was
72/28 percent. The patients were eligible for inclusion in
the controlled trial provided they were not known to be
pregnant or to have impaired renal, hepatic, or visual
function. Therefore, six patients were excluded, and two
died within a few weeks. The patients had positive sputum
on smear and culture, except seven who had negative
smear and positive culture results. Cavitation was disclosed
in 195 of the patients. One fourth of the male patients
over 50 presumably were alcoholics. Two hundred forty-
four patients were randomized into two groups. All initially
received RMP (10 mg/kg) plus INH (7 mg/kg) plus

ethambutol (EMB) (25 mg/kg) in one daily dose, half
an hour before breakfast, until sensitivity tests were com-
pleted, ie, for approximately two months. Ethambutol was
added to RMP and INH to prevent emergence of RMP-
resistant organisms in patients with strains initially resistant
to INH. The patients were then given RMP plus INH in
one daily dose until culture conversion, ie, one month after
corresponding sputum collection. Thereafter, the patients
in the first group (A) were treated with INH in one daily
dose for four months, while those of the second group (B)
received INH until two years had passed since the onset
of the regimen with chemotherapy. Antimicrobial drugs
were supplemented with 40 mg pyridoxin daily for the whole
duration of chemotherapy. A total of 244 patients were
consequently included in the controlled trial, which was
carried out on an in- and then an out-patient basis.
Hospitalization was indicated according to socioeconomic,
family, and home conditions. Hospitalization lasted one
month in 86 percent of cases, two months in 26 percent,
three months in 8 percent. It was not considered as playing
a role in the success of the treatment.

Follow-up

After hospital discharge, the patients were given ambu-
latory treatment in which they self-administered drugs.
Compliance was not monitored closely, as the trial was
intended to reflect ordinary conditions of ambulatory self-
given medication with its known drawbacks. Nurses in
the out-patient clinic gave monthly medical supervision of
patients referred to the family doctor, and the remainder
(56 percent) were supervised at the out-patient clinic. The
bacteriologic examinations (smear, culture, sensitivity tests)
and a chest roentgenogram were performed monthly for each
patient up to the time of culture conversion, then every
two to three months until the chemotherapy regimen was
completed. Thereafter during the five-year follow-up period,
bacteriologic and roentgenologic surveillance were carried
out twice a year. Adverse drug reactions were monitored
monthly by the ophthalmologists as long as EMB was given,
by liver function tests (transaminase, alkaline phosphatase,
direct and conjugated bilirubin), kidney function (urinalysis,
blood urea and creatinine) at the time of bacteriologic and
roentgenologic examinations.
RESULTS

Seventy-six of the 244 patients were excluded from the trial for reasons listed in Table 1.

A change in treatment program was made in 23 cases. Some physicians prolonged the monotherapy with INH in 18 patients of group A for longer than four months, or curtailed the monotherapy with INH prematurely in five patients of group B, for personal reasons. The bacteriologic control was unsatisfactory in 26 cases—either the patients failed to deliver the sputum on the specified time, or the doctor failed to ask for culture. Thirteen patients moved to another location out of reach or absconded. Eight deaths occurred, four from malignant diseases, (some possibly overlooked at admission), although three sputum specimens were collected initially for cytopathologic examination for all smokers over age 50. There were bronchial carcinoma (two), relapse of melanoma (one), and carcinoma of the pancreas (one). Two elderly patients died from stroke, two others from coronary disease. The adverse reactions were defined, as far as the observed cases are concerned, as a marked increase in transaminase values (ie, over 100 IU), or as moderate but increasing values over a two-month period. There were three increases in transaminase after 11, 21 and 23 months respectively in patients of group B. A total of 168 patients remained available for the final assessment. The age and sex distribution is shown in Table 2.

Roentgenologic Data

Cavitation was found in 71 of 89 (79.8 percent) of group A, and in 64 of 79 (81.0 percent) of group B patients.

Bacteriologic Results

One hundred sixty-eight case records were compiled. Each case was closed five years after culture conversion took place, 89 in group A (86 initially positive on sputum smear) and 79 in group B (initially 77 positive on smear). The progress in culture conversion is indicated in Table 3.

According to the treatment program, INH alone was given after culture conversion. In group A (INH alone for four months after culture conversion), the total duration of treatment was six months (21 cases, 23.6 percent), seven months (32, 36 percent), eight months (24, 27 percent), nine months (11, 12.4 percent) and ten months (1, 1 percent). In group B (two-year treatment), INH alone was given for 22 months (18 cases, 22.8 percent), 21 months (27, 34.2 percent), 20 months (22, 27.8 percent), 19 months (9, 11.4 percent) and 18 months (3, 3.5 percent).

It is noteworthy that 21 patients of group A and 18 patients of group B went directly onto INH monotherapy after the three-drug regimen at the end of the 2nd month, ie, when the negative result of the culture initiated at the end of the first month was known. As stated above, the onset of monotherapy with INH was calculated solely on the basis of culture conversion. It must be emphasized, therefore, that the 21 patients of group A and the 18 patients of group B with early conversion were put on INH alone, during 4 and 22 months respectively, whatever the general condition, the initial extension of the disease and the roentgenologic changes. The overall treatment scheme is depicted in Figure 1.

Relapse Rate

Relapse was defined as the presence of one or more positive cultures during the follow-up period, as far as quiescence was achieved and confirmed on monthly intervals during chemotherapy. During the five-year follow-up which started from the culture conversion, one bacteriologic relapse was observed during the fourth year after culture conversion in a

Table 1—Reasons for 76 Exclusions from the Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in Treatment Scheme</th>
<th>Primary Resistance to INH</th>
<th>Unsatisfactory Bacteriologic Report</th>
<th>Emigrated or Absconded</th>
<th>Adverse Drug Reactions</th>
<th>Deaths</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>18</td>
<td>1</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>2</td>
<td>16</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 2—Age and Sex Distribution of 121 Male and 47 Female Patients Available for Final Assessment

<table>
<thead>
<tr>
<th>Group</th>
<th>M/F</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>16/3</td>
<td>7/5</td>
<td>9/4</td>
<td>8/3</td>
</tr>
<tr>
<td>B</td>
<td>11/2</td>
<td>9/2</td>
<td>12/4</td>
<td>13/6</td>
</tr>
</tbody>
</table>

Table 3—Number of Culture Conversions and Monthly Accumulated Percentages

<table>
<thead>
<tr>
<th>Group</th>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>21(23.6%)</td>
<td>32(39.6%)</td>
<td>24(86.6%)</td>
<td>11(99%)</td>
<td>1(100%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>18(22.8%)</td>
<td>27(37.0%)</td>
<td>22(84.8%)</td>
<td>9(96.2%)</td>
<td>3(100%)</td>
<td></td>
</tr>
</tbody>
</table>
male patient allocated to the two-year program. It should be mentioned that a woman who initially had circumscribed apical nodules with a positive smear, allocated to the two-year program, suffered relapse seven years after culture conversion (two years after closure of the controlled trial) with a positive culture, and negative smear. Both patients had a fully sensitive strain.

**DISCUSSION**

The experimental, pharmacologic and bacteriologic observations referred to above1-4 have reasonably led to the belief that antitycobacterial properties of RMP, INH and EMB could favorably shorten the previous two-year treatment scheme of pulmonary tuberculosis.6 The present study was designed in 1971 to explore the effectiveness of a short-course of chemotherapy. A three-phase regimen6 was planned: RMP-INH-EMB until sensitivity tests were completed, then RMP-INH until culture conversion was known, i.e., one month after sputum collection, thereafter INH alone. The duration of the whole treatment thus depended upon individual culture conversion time for the patients allocated to the short-course group A. In order to evaluate the effectiveness of the program, the bacteriologic follow-up was extended for five years. It has been noticed indeed that results obtained in shorter term controlled trials have been sometimes contradicted by subsequent relapses.6

The five-year follow-up failed to show any statistical difference between the short-course and the two-year program, as far as relapse rate is concerned. Comparable results were obtained in controlled trials by the British Thoracic and Tuberculosis Association, investigating short-course chemotherapy.7-12 A relapse rate as low as 2 percent was noticed in regimens including daily RMP plus isoniazid and/or pyrazinamide for nine months.5,9,13 In the present study, one relapse occurred four years after culture conversion. Another relapse was observed seven years after culture conversion, after the final assessment. Both patients who had been allocated to group B had fully sensitive strains. Culture conversion rate (Table 3) was assigned to the bactericidal properties of RMP and isoniazid on fast multiplying organisms.13,14 The low relapse rate may be attributed to the effect of these drugs on intermittently multiplying organisms.13,14

A considerable decrease in the population of mycobacteria was considered to be achieved after the initial multiple-drug regimen.15,16 The subsequent monotherapy with INH was not supposed to enhance multiplication of the few remaining INH-resistant organisms. Considering the results of the present study, it is doubtful that any other bactericidal drug associated with INH up to the end of chemotherapy would have provided an additional benefit. The Singapore and the Mexican controlled trials have successfully applied monotherapy after quiescence was achieved by an initial multiple-drug regimen.18-20

In group A, chemotherapy was given for six months in 21 patients, seven in 32, eight in 24, nine in 11, and ten in one (Fig 1). The duration lasted less than the nine-month course which has been
recommended, in 86.5 percent of the cases. No relapse was observed in the 21 patients treated for six months, whereas a six-month course produced a relapse rate of 5 percent in a British trial. The discrepancy may be explained, in part at least, by the individual adaptation to the duration of treatment, which was dependent upon the time required for culture conversion. Nevertheless, a six-month course seems to be the minimum limit of duration of treatment, as a four-month course gave deceptive results.

No adverse reactions were observed in patients in group A. The advantages of short-course chemotherapy is now widely recognized.

Sixty-six percent of the patients self-administered the drugs after one month, 26 percent after two and 8 percent after three months. According to the results observed so far in this study, closer supervision probably would have diminished the number of exclusions. Taking into account this kind of disadvantage, Iseman et al have nevertheless considered self-given medication an acceptable procedure in ambulatory patients. The British Thoracic and Tuberculosis Association trials have shown that the initial size of the cavitation does not play a role in the results of chemotherapy; therefore, cavitation size was not looked upon in the final assessment of this study. No importance was attached to roentgenologic changes.

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