A Study of 200 Cases of Active, Recent Pulmonary Tuberculosis Treated with Rifampin-Isoniazid

A Follow-up History of One and One-half to Three Years

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Since 1962, rifampin has made possible an advance-ment in the field of antibiostherapy of active pulmonary tuberculosis. Many specialists in France and other European countries consider the new drug as effective, if not more so than isoniazid.

In our previous papers, counting among the first French studies devoted to this subject, we, as well as many others, have stressed the remarkable efficiency of the rifampin-isoniazid double regimen. The present article is an appraisal of this therapy based on a fairly large group of patients. The follow-up periods range from one to three years.

**Material and Methods**

**Patients’ Characteristics**

Almost all adult patients with active and recent pulmonary tuberculosis admitted to our hospital were submitted to this treatment; and in each case all bacteriologic findings were positive both in sputum (fluorescence microscopy) and by culture (Löwenstein’s medium). This group of 200 cases included a large majority of first attacks (85 percent), and a comparatively small number of first relapses, provided no antituberculosis drug had been prescribed during the four prior years.

The prime criterion for selection for these studies was a normal sensitivity of the strains. In order to get a fair and accurate opinion concerning the effectiveness of the rifampin (RMP) isoniazid (INH) regimens, all cases in which bacilli proved to be resistant to INH were rejected.

For statistical purposes, all clinical, biochemical and bacteriologic data have been recorded on punch cards. All chest films have been read by a panel consisting of two of us.

The average patients’ age is 37. Most of them are men (85 percent). Their ethnic cross section is well representative of a tuberculous population in a hospital located in the center of Paris (Table 1).

**Type and Extent of Lesions**

Our 200 cases include 170 initial, untreated patients with tuberculosis (85 percent) (Fig 1) never yet treated, and 30 first relapses (15 percent).

Most of the chest films and tomographs showed severe lesions. They have been divided into four classes according to roentgenographic extension:

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>19</td>
<td>9.5</td>
</tr>
<tr>
<td>Moderately advanced</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>Far advanced</td>
<td>61</td>
<td>30.5</td>
</tr>
<tr>
<td>Very extensive (more than 1/2 lung)</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>

One hundred nineteen patients (59.5 percent) showed at least cavities more than 15 mm in size, while the 81 other patients had cavities of less than 15 mm, or no visible cavity at all.

**Management of Treatment**

The daily dose of INH ranged from 7 to 10 mg/kg, given in a single oral intake before breakfast. The first 100 patients were given 10 mg/kg. For the second lot of 100 patients, the dose was slightly reduced and standardized at 450 mg daily.

A preliminary group of 56 patients were given 900 mg of rifampin daily during the first three months (in other

<table>
<thead>
<tr>
<th>Table 1—Characteristics of the Two Hundred Patients</th>
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<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Age, yr.</td>
</tr>
<tr>
<td>Range: 17 to 82; average 37</td>
</tr>
<tr>
<td>15 to 35</td>
</tr>
<tr>
<td>36 to 50</td>
</tr>
<tr>
<td>51 to 65</td>
</tr>
<tr>
<td>more than 65</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Descent</td>
</tr>
<tr>
<td>French</td>
</tr>
<tr>
<td>European</td>
</tr>
<tr>
<td>Algerian</td>
</tr>
<tr>
<td>Non-white African</td>
</tr>
</tbody>
</table>

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words more than 15 mg/kg). It soon became apparent that this dose was unnecessarily high and liable to induce slight disorders. Consequently, the dosage was reduced and the standard daily intake of rifampin was finally set at 600 mg, or two capsules at a time (about 10 mg/kg); the drug was always given under control and before breakfast. The serum drug level was regularly checked and administered at regular intervals after intake. In cases of underweight (less than 40 kilograms), poor general condition, malnutrition or a history of liver-function disorders, the initial dose of RMP was 300 mg or even less, being progressively increased during the first four weeks following onset of treatment so as to reach 600 mg by the end of the first month.

It is well known that a double treatment with RMP and INH alone may become ineffective where bacilli show primary resistance to INH, thus leading to an early onset of resistance to RMP. For this reason we now regularly start the treatment with three drugs during the testing period, until evidence is obtained that the strain is normally sensitive to INH. Among the 200 patients of these series, 67 have been treated from the beginning with RMP and INH alone, while 133 have been treated initially with a third additional drug (71 with streptomycin [SMY], 62 with ethambutol [EMB]).

The minimal period of RMP treatment has been fixed at six months; the regimen has then been continued with INH-EMB, or sometimes even with INH alone, for a total duration of 15 to 18 months. From the sixth month, the decision to continue the rifampin treatment was made on an individual or particular basis. Three subgroups may be considered:

- 6 months treatment with RMP
- 6 to 9 months
- more than 9 months

The total time spent in hospital and/or sanatorium extended to an average of five to seven months:

<table>
<thead>
<tr>
<th>Duration</th>
<th>Cases</th>
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<tbody>
<tr>
<td>6 months</td>
<td>42</td>
</tr>
<tr>
<td>6 to 9 months</td>
<td>105</td>
</tr>
<tr>
<td>9 to 12 months</td>
<td>35</td>
</tr>
<tr>
<td>more than 12 months</td>
<td>18</td>
</tr>
<tr>
<td>200 cases</td>
<td></td>
</tr>
</tbody>
</table>

**Supervision during and after Treatment**

Weight, temperature and physical findings were regularly controlled.

Chest roentgenograms were taken monthly during the three first months, then every three months thereafter. Tomographs of the chest were made every three months.

Bacteriologic status was checked monthly by microscopy as well as by culture. The first 60 patients underwent sputum examination every week. The tests for drug-resistance were performed on the first and the last positive culture and on solid medium according to the "proportion method" as it has been codified by Canetti, Rist and Grosset.

The biologic survey included: serum bilirubin, serum glutamic-pyruvic and glutamic-oxaloacetic transaminases (SGPT and SCOT), serum alkaline phosphatases, serum albumin and globulins with protein electrophoresis, blood urea nitrogen, blood sugar, erythrocyte and leukocyte count, sedimentation rate and the usual urinalysis.

The serum investigations and controls took place monthly for all patients during the three first months. They were even more frequent for the first 60 patients of our series, as well as in cases of any confirmed or suspected slight abnormalities.

After discharge, the follow-up with regular control lasted:

<table>
<thead>
<tr>
<th>Duration</th>
<th>Cases</th>
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<tbody>
<tr>
<td>at least 1 year</td>
<td>37 + 1*</td>
</tr>
<tr>
<td>1 Â½ years</td>
<td>35</td>
</tr>
<tr>
<td>2 years</td>
<td>81</td>
</tr>
<tr>
<td>3 years</td>
<td>46</td>
</tr>
<tr>
<td>200 cases</td>
<td></td>
</tr>
</tbody>
</table>

**Bacteriologic Findings**

Negativation of sputum. This report will be restricted to the final results from sputum cultures on Löwenstein's medium. Figure 2 demonstrates the proportion of those among the 200 patients whose sputum contained Mycobacterium tuberculosis recoverable at monthly intervals. The date indicated is that of the last culture which yielded one colony only.

The regimen instituted has proved to be particularly effective. These significant results are demonstrated by

*One patient died during the seventh month of regimen, from an invasive carcinoma of the larynx. Pre and postmortem investigations and controls gave evidence of a total bacteriologic and anatomical healing of the tuberculous lesions.
CULTURES OF SPUTUM
(200 CASES)

% POSITIVES CULTURES

100.
75.
50.
25.
0.

1 2 3 4 MONTHS

FiguRe 2

the fact that the sputum has become definitely negative in 100 percent of the cases by 120 days, in 97.5 percent by 90 days; even in patients with highly extensive lesions or whose sputum microscopy and cultures showed initially the highest density of bacilli.

Our group, which only included patients with normal sensitivity to both INH and RMP, showed no difference in the rate and speed of sputum conversion whether or not a third drug (EMB or SMY) was added to the basic double regimen of RMP and INH. On the whole, the decreasing curve of microscopy findings is parallel to that of cultures, but somewhat different in the case of very extensive and highly bacillary lesions.

In a previous paper we have emphasized how frequently the sputum from extensive lesions yielded non-cultivatable bacilli during the course of RMP treatment.

For comparative purposes, Figure 3 shows the rate of bacillary conversion in groups of similar patients treated with or without rifampin.

Onset of resistance to RMP. One hundred ninety-six patients have been completely tested for drug-resistance on the initial as well as on the last positive culture. In four other patients, the first test only could be performed owing to an early negativation of the cultures (as early as the 15th day).

In all of our cases, the strains' susceptibility to RMP remained normal until the final negativation. No onset of resistance was observed.

Pathologic findings. As a token and confirmation of the excellent bactericidal action of the combined RMP-INH treatment, we suggest that one might take into account ten personal cases in which a pathologic investigation of pulmonary specimens was made possible following surgical operation or necropsy after incidental death. Six of these cases belong to another series.

In all of the ten cases treated for more than three months (in nine cases, from 95 days to ten months), cultures of the specimens for M tuberculosis were negative. In some cases, acid-fast bacilli appeared on microscopic investigation of the samples, but none was cultivatable nor transmissible to the guinea-pig.

Roentgenographic Evaluation

Roentgenologic improvement is often a difficult matter to evaluate (Table 2). In the present series, three groups only are to be considered, characterized as follows:

- insignificant, implying slight or no change;
- satisfactory, meaning a progressive regression at the usual rate, with remaining scars of more or less importance;
- very satisfactory, meaning cases with fast improvement followed by total disappearance or conversion of cavities (on tomographs), leaving no, or only slight, scars.

Radiologic improvement appears to take place somewhat earlier than with the other classic drug combinations. Concerning the radiologic evolution of the case history, it is worthwhile pointing out the high rate of
Table 2—Roentgenographic Improvement During Treatment*

<table>
<thead>
<tr>
<th>Mo.</th>
<th>Slight</th>
<th>Improvement Rate</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd</td>
<td>33</td>
<td>129</td>
<td>38</td>
</tr>
<tr>
<td>6th</td>
<td>7</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>12th</td>
<td>5</td>
<td>52</td>
<td>142</td>
</tr>
<tr>
<td>Total, %</td>
<td>2.5</td>
<td>26</td>
<td>71.5</td>
</tr>
</tbody>
</table>

cavitary conversion leading to residual cystic epithelialization.

Tolerance of Treatment

The tolerance of the RMP-INH regimen has been generally very good: since in only one patient out of 200, the treatment had to be stopped. Some patients received rifampin for 18 months without experiencing any difficulty. On the whole, a tolerance evaluation could be stated as follows:

perfect tolerance throughout treatment 177 patients (88.5 percent)
transient disturbance (sometimes leading to temporary interruption and once only to complete and final interruption) 23 patients (11.5 percent)
200 patients

Clinical findings (Table 3). On the whole, the clinical acceptance proved to be very satisfactory; 20 patients occasionally complained of some digestive troubles such as slight loss of appetite, nausea or gastric pains lasting a few days only. These difficulties were often in coincidence or connected with slight or moderate biologic abnormalities.

Of the group of 200, seven patients had clinical jaundice (3.5 percent). But two of these were obviously affected with incidental epidemic infectious hepatitis. In the other cases, the jaundice always developed during the first three weeks of treatment.

The serum bilirubin level was moderately increased (from 2 to 6 mg/100 ml). Serum alkaline phosphatases often reached twice the normal level. Serum transaminase levels remained normal or increased moderately (not higher than 200 units SGPT). The other hepatic biologic tests remained within a normal range. In no case did a liver biopsy appear necessary. In one of the last cases immunology was positive with “Australia” antigen, while in older patients this test was not performed.

The jaundice always faded spontaneously in less than two weeks. In five cases, the RMP-INH treatment has been temporarily discontinued for a few days, and then resumed without any further or new disturbance. In four other cases, while the therapy had not been modified, the jaundice also healed without showing any sign of gravity. With one single patient we felt it would be wiser to suppress definitively the intake of RMP; we now feel this was an unnecessary precaution.

Thus, in all our cases but one, the therapy was continued after remission of the jaundice and lasted for a long period (six to ten months) without leading to any incident. As has already been said, the liver function tests became and remained normal. These icteric incidents did not appear more frequent than with other combined anti-tuberculosis regimens involving INH (such as INH and ethionamide or prothionamide, for instance). Causes and management of such temporary icteric incidents will be discussed later.

Biologic findings. After weekly biochemical checkings, some transient and very slightly abnormal liver tests were noticed in less than 10 percent of cases. They appeared not later than the first weeks of treatment and lasted a few days only.

—Eight patients had an increase of serum transaminase levels (not exceeding 20 μg/ml); the rate became normal again in less than 30 days without any change in the treatment.

—Ten patients had a transient increase in serum bilirubin (one sample or more exceeding 1 mg/100 ml); they include the seven cases with clinical icterus already mentioned. For nine of these patients, the regimen was maintained or resumed after a brief interruption without further incident. In none of the cases under discussion were any blood, kidney, nervous, mental or skin disorders recorded.

Discussion

The most impressive result of this trial lies in the early bactericidal effect of the RMP-INH regimen: no failure or relapse occurred during the follow-up period. The exceptionally high rate of 100 percent conversion of sputum-cultures before the end of the fourth month in patients with initially far-extensive and highly bacillary lesions is rarely, if ever, attainable with other antituberculosis regimens.

In France, and in some other European countries where the INH primary-resistance index is about 4.5 percent, it seems safer to include a third drug during the first weeks of treatment, as long as the resistance-tests are not available. As soon as the normal sensitivity of the strain to INH is ascertained, the additional drug may be suppressed.

Roentgenologic improvement is at least as good and even somewhat faster than with other drug regimens. The few poor or moderate results occur in particular
cases such as solid tuberculomas, bronchial stenosis, old scars or fibrous foci, etc. The high rate of cavitory reduction or closing, with or without conversion to residual cysts, is additional evidence of the fast and early bactericidal effect of this type of therapy.

The main lines of our trial are in keeping with most of the papers published so far in various European countries, as well as with the first American trials, such as the one recently published by Newman and co-workers on behalf of the U.S. Public Health Service.

The overall tolerance to the regimen is generally of the best. It should be kept in mind that the present group history, involving as it did a long post-therapy follow-up period included many early cases, among which were the first patients we had ever treated with the RMP. At that time, our control and selection of patients with histories of liver malfunction was perhaps not as precise as it is now; and additionally we then used a fairly high dosage of RMP. This background could account for the 5 percent of cases with increased bilirubinemia.

In a more recent series (yet to be published), numbering 1,420 patients treated with RMP at a dosage level of 10 mg/kg, the frequency of clinical jaundice possibly related to the drug has fallen as low as 2.18 percent (Table 4).

Apart from past or recent liver malfunction, cirrhosis, severe alcoholism or malnutrition, etc a favoring or predisposing factor appears to be associated with high dosage levels of INH; it is evident the RMP alone rarely induces jaundice. In such cases, we suggest starting the treatment with a low and progressively larger dosage of RMP as well as of INH, before reaching the final standard dosage. If a biologic and/or clinically confirmed jaundice appears in spite of these precautions, it seems advisable to interrupt the treatment temporarily, with the intention of resuming cautiously the same therapy after remission. In the even milder cases, provided a strict and repeated biologic control is maintained, treatment may often be continued without any damage.

The total duration of the RMP-INH regimen cannot yet be definitely established until the results of long and extensive inquiries become available; some are already under way in our country. For the present time, it may be assumed that RMP should be prescribed for a period of nine months at least, out of a total antituberculosis therapy of about 12 months.

It is nevertheless to be hoped that owing to this new, powerful, and well tolerated regimen, the treatment may in the future be shortened, or its overall duration more factually adapted to the significance of the initial bacillary density or extension of lesions. There lies a problem of tremendous economic and social importance— but one requiring more experience and background than we have at present.

**BIBLIOGRAPHY**


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