Some Thoughts on Results Following Intermittent Streptomycin in Pulmonary Tuberculosis

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The contribution made by streptomycin (SM) towards the success of antituberculous chemotherapy is by now well established. It is not an "all safe, all powerful" drug, as its use can lead to serious consequences. There appears to be some danger from toxicity of the drug itself, but in our experience this has been relatively low. However, the dosage of streptomycin when used intermittently (two or three injections per week) in combination with daily INH and/or PAS is generally inadequate and invites therapeutic failure. This results in the patient's excreting organisms resistant to one or more of the principal antimicrobial agents. Retreatment is rather difficult, the percentage of success being comparatively low; and surgery in these patients carries a definite risk of postoperative complications such as bronchopleural fistula and empyema.

One sees a number of private physicians and chest hospitals throughout the country using combinations of drugs including biweekly streptomycin, believing this to be "adequate" initial treatment in tuberculosis. The reason is difficult to understand. Papers have been published to confirm the earlier findings of the British Medical Research Council—that intermittent SM with daily INH or PAS is not the treatment of choice in tuberculosis.^

We have reviewed 108 cases who were admitted to National Jewish Hospital consecutively since 1956, whose sputum was initially positive for typical M. Tuberculosis, and whose previous chemotherapy had included intermittent SM (1 gm. two or three times per week). Positive culture on admission was found in 79 per cent of these cases, and all but five of these were excreting high proportions of tubercle bacilli resistant to SM and/or INH. In 21 per cent of these cases the treatment had been apparently successful and their sputum tests were consistently negative for tubercle bacilli.

An additional group of 46 cases was studied whose initial chemotherapy including intermittent SM was started after January 1955 (i.e. after the publication of the M.R.C. findings). Thirty three per cent of these patients were found positive for tubercle bacilli on admission, and all but three were resistant to SM and/or INH (Table 1). The treatment was started at home for 14 of these patients, and in hospital for 32.

Many factors may explain why certain principles are not more widely accepted in the United States, and among these is the fact that reports observed by us in the American literature do not sufficiently stress the superiority of the regimens containing daily SM over all others. One argu-

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ment presented in favor of other regimens is the idea of holding one's 'major' drug for future needs. Of course this is not necessary if one can achieve a conversion rate of approximately 99 per cent in previously untreated cases by applying appropriate and adequate chemotherapy. 5

One of the writers has had some experience in chest work in England and Australia, and certain groups there, too, at one time believed biweekly SM with daily INH or PAS to be good treatment. This practice has become much less frequent in the last two years or so, though such a combination is occasionally used at the tail end of the initial treatment with daily SM plus INH and/or PAS. Lately the use of intermittent SM is being abandoned in preference to daily INH plus PAS. One can also mention that in these countries practically every case picked up by private practitioner, mobile survey, etc., is referred to the area chest clinic for investigation and appropriate treatment. Therefore there is a better chance for such treatment to be applied according to uniform standards.

Several reports have been published dealing with studies carried out by the M.R.C. in England, 1-3 to assess the clinical potentialities of SM, INH and PAS. This comprehensive work outlined the results of the principal controlled trials. Some of the most important findings were as follows: (1) At six months, only two of the 12 positive cultures from patients treated with daily SM plus INH contained organisms highly resistant to INH, compared with eight out of nine from those treated with biweekly SM plus daily INH; (2) There was substantial bacteriologic and radiographic evidence.

It was clearly established that biweekly SM with daily INH was much less satisfactory in preventing the emergence of INH resistant organisms. In addition the M.R.C. showed that daily SM with INH was superior to all dual drug combinations at the six month period. Since then other independent groups, including National Jewish Hospital, have confirmed these findings. 1, 10

It is our opinion that intermittent streptomycin should not be used in moderately advanced or far advanced tuberculosis. If it is desirable to avoid daily injections in minimal disease, then one should use daily INH with PAS since this combination has been proved more effective than intermittent SM with INH or PAS. One should not be lulled into believing that high dosage INH might permit the use of intermittent SM. Biehl et al., 11 has shown that such a combination has an equal number of treatment failures.

The therapeutic drive against tuberculosis cannot approach 100 per cent success if inadequate treatment is given initially. It is generally felt that

<p>| TABLE I |
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<table>
<thead>
<tr>
<th>YEAR</th>
<th>DISEASE CLASSIFICATION</th>
<th>PREVIOUS THERAPY</th>
<th>SPUTUM CULTURE ON ADMISSION</th>
<th>DRUG RESISTANCE</th>
<th>DRUG SUSCEPTIBILITY</th>
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<tbody>
<tr>
<td>1955</td>
<td>8 6</td>
<td>14 14 9</td>
<td>13 1</td>
<td>11 13 5</td>
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<tr>
<td>1956</td>
<td>11 14</td>
<td>25 21 14</td>
<td>17 8</td>
<td>13 14 4</td>
<td>2</td>
</tr>
<tr>
<td>1957</td>
<td>4 3</td>
<td>7 6 4</td>
<td>2 5</td>
<td>1 1 1</td>
<td>1</td>
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<tr>
<td>Totals</td>
<td>46 46</td>
<td>32 14</td>
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early institutional treatment is to be preferred for the majority of patients suffering from pulmonary tuberculosis.

SUMMARY

1. A review of National Jewish Hospital cases is presented, showing an incidence of drug resistance of over 65 per cent in those cases admitted, whose initial treatment elsewhere had included intermittent streptomycin.
2. The importance of initial "adequate" therapy is emphasized. It is our opinion that intermittent streptomycin should not be included in any initial treatment regimen.

RESUMEN

1. Se presenta una revisión de los casos del Hospital Israelita mostrando una frecuencia de la resistencia a las drogas de más de 60 por ciento en los casos admitidos que habían sido tratados antes en otra parte de manera inicial incluyendo el uso de la estreptomicina intermitente.
2. Se recalca la importancia de hacer un tratamiento inicial "adecuado." En nuestro concepto la estreptomicina intermitente no debe ser usada en cualquier régimen de tratamiento inicial.

RESUME

1. —L'auteur passant en revue les cas de l'Hôpital National Juif montre la fréquence bactérienne atteint 65% des malades hospitalisés, dont le traitement initial avait comporté en tout cas de la streptomycine administrée de façon intermittente.
2. —L'auteur souligne l'importance de la thérapeutique convenable appliquée dès le début de la maladie. À son opinion, la streptomycine administrée de façon intermitente ne devrait pas être admise dans le programme thérapeutique du début de l'affection.

ZUSAMMENFASSUNG

1. Es wird eine Übersicht des Nationalen Jüdischen Krankenhauses vorgelegt, die ein Vorkommen von Arzneimittel-Resistenz nachweist bei mehr als 63% solcher Zugänge, bei denen auswärts eingeleitete Behandlung intermittierendes Streptomycin einbegriffen war.

REFERENCES