How long? how short?

TB treatment, 1948-2018, getting the duration right

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Outline

Streptomycin

The fifties and sixties
- Streptomycin, PAS and isoniazid
- Thiacetazone

Rifampicin and the advent of short course chemotherapy
The streptomycin era

Streptomycin, the first effective drug in the treatment of TB, was discovered in 1943 by Selman Waksman.

Following successful *in vitro* and animal experiments an investigation into its effects in man was initiated in 1945 in multiple sites in the USA using a common protocol.
A daily dosage of 1.8g was agreed upon, being injected intramuscularly every four hours, day and night. All patients were to receive streptomycin for 120 days.

“These decisions .... were admittedly arbitrary for there was no information on which to base informed judgement but in order that the study have any statistical significance it was considered essential that this first group of patients be treated in accordance with a single regimen”
Streptomycin: the American studies

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Preliminary Report of a Cooperative Study of 223 Patients by the Army, Navy and Veterans Administration
The MRC streptomycin trial

- In September 1946 a special committee of the British Medical Research Council (MRC) agreed to plan clinical trials of streptomycin in tuberculosis.

- The committee decided that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

- A landmark not just for tuberculosis but for the whole of medicine; the first properly conducted randomised trial.
MRC streptomycin protocol

- Patients were given 2g. streptomycin daily; four injections at six-hourly intervals.

- No loss of hearing was reported, except for two cases of high-tone deafness.

- The original intention was to continue streptomycin treatment for six months. However, reports from the U.S.A., and a growing impression in our own centres, indicated that the **maximum effect of streptomycin was reached within the first three or four months**, and it was therefore decided in July, 1947, to treat patients for four months only.
Streptomycin trial: Radiographic appearances at 6 months compared with baseline

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<th>Bed rest group</th>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Considerable improvement</td>
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<td>51%</td>
</tr>
<tr>
<td>Moderate or slight improvement</td>
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<tr>
<td>No material change</td>
<td>2</td>
<td>4%</td>
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<tr>
<td>Moderate or slight deterioration</td>
<td>5</td>
<td>9%</td>
</tr>
<tr>
<td>Considerable deterioration</td>
<td>6</td>
<td>11%</td>
</tr>
<tr>
<td>Died</td>
<td>4</td>
<td>7%</td>
</tr>
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<td><strong>55</strong></td>
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MRC, BMJ 1948
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P < 0.01 for difference between the two groups

MRC, BMJ 1948
Was 4 months too short?

“The major improvement in patients treated with streptomycin was seen in the first two to three months; in the latter half of the six-month period numbers of them began to deteriorate. Streptomycin therapy had been stopped at the end of four months, and it is natural to ask whether the deterioration is attributable to stoppage of treatment. This seems unlikely for the majority; most had begun to deteriorate radiologically before the end of four months.”

MRC, BMJ, 1948
Streptomycin trial: percentage survival in 5 years

W Fox et al, Q J Med 1954
Streptomycin & PAS study (5 year follow-up)

- Patients received 3 months treatment of S, P or SP - after three months the clinician was free to institute additional treatment if it was considered it might be of benefit.

- During the first two years 25% S, 57% P and 44% of SP patients had additional chemotherapy.

- ‘These differences must be borne in mind when assessing the findings for the five-year period’

- Of survivors at three months, 62% S, 81% P and 69% SP patients had collapse therapy or resection.

- No mention of whether longer treatment would have been beneficial.

Fox and Sutherland, QJM 1956
Deaths in the first two studies (long term follow-up)

<table>
<thead>
<tr>
<th>Trial</th>
<th>5 year mortality</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No Rx</td>
<td>S alone</td>
<td>P alone</td>
<td>SP</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>67%</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin &amp; PAS</td>
<td>31%</td>
<td>36%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

A comparison, as regards five-year progress, of the 54 patients initially treated with streptomycin alone in this trial with the 55 like patients treated similarly in the first Medical Research Council trial, shows a considerable benefit to the later series, attributable to more additional chemotherapy and major surgical measures, as well as to a fuller understanding in the second trial of the applications of chemotherapy and surgery.
Isoniazid study (SP, H & SH)

- Commenced in 1952, 3 months’ Rx
- Cases were admitted to the trial in one of three main groups:
  1. acute rapidly progressive pulmonary tuberculosis believed to be of recent origin;
  2. other forms of pulmonary tuberculosis considered suitable for chemotherapy: this group included a wide range of disease, and contained both acute and chronic cases;
  3. chronic forms of pulmonary tuberculosis expected to make only a limited response to streptomycin plus PAS
- From 4-6 months treatment was continued for patients in disease group 3, and for other patients selected by the clinician.
East African trials

- The first RCT of anti-TB treatment in East Africa was initiated in Uganda in 1953, patients were randomised to a three month regimen of SH or SP – ‘when the satisfactory response of the early cases was observed it was decided to study the effects of more prolonged chemotherapy ... and extend the period of uninterrupted chemotherapy ... to 24 weeks.’

- In the second trial, which commenced in 1956, treatment (isoniazid plus sulphone or PAS) was given for six months after which ‘the clinician was free to undertake any treatment he wished.’

- In the third trial, starting in 1958, treatment duration had advanced to one year.
Madras home/sanatorium: duration comparison

• A lesser known aspect of the Madras home sanatorium trial was the assessment of whether there was benefit to be had by extending treatment beyond one year
• Patients were randomly allocated to receive either isoniazid or calcium gluconate in year two
• “Relapses at the end of the second year were small in number and similar between the two regimens”

Bulletin WHO 1960
Writing in 1962 Wallace Fox said:

“Although, in medically advanced countries, chemotherapy has been used extensively for pulmonary tuberculosis for more than ten years, the optimum duration of chemotherapy is still uncertain, especially for the more extensive lesions.

Treatment for life?

- Commenting on the results of a trial conducted at Guy’s hospital in patients with ‘long standing tuberculosis, often with extensive irreparable lung damage’ a Lancet leader writer said:

  “As the sputum commonly became positive again when the drugs were stopped treatment of these patients for a long time – perhaps indeed for life – may be justified”

Lancet 1953, ii, 237
How long?

• In the early MRC trials treatment was administered for 3 months, ‘anything longer was regarded as undesirable’

• By the mid-50s some clinicians were advocating six months, a year or even longer. The MRC’s chronic trial set out to assess how long patients needed to be treated.
MRC chronic trial - how chronic was it?

Eligible patients:

(a) were aged between 20 and 70 years;
(b) had bilateral disease (or unilateral in patients over 40 years of age);
(c) had cavitation in one or both lungs with a minimum total diameter of 5 cm on a PA radiograph
(d) had sputum positive for acid-fast bacilli on two consecutive direct smear examinations;
(e) had received no previous anti-tuberculosis treatment
MRC Chronic trial: how long to treat?

- To meet the wide range of views on the optimum duration of chemotherapy current at the start of the study (1956), participating clinicians were offered a choice of randomisations, either:
  1. six months, one year, or two years
  2. one, two or three years
  3. two, three, or four years (one centre)
- Patients were also randomised to an initial streptomycin supplement or not
- Initially group 1 was the preferred choice of most clinicians, by mid-1957 their preference had shifted to group 2 as doubts arose as to the efficacy of the 6 month regimen
MRC Chronic trial: results

- Relapse occurred in 62% in patients treated for only 6 months, 19% treated for 1 year, and only 4% in those who were treated for 2 or more years.

- The streptomycin supplement reduced the percent unfavourable at one year from 16% to 3%

MRC Tubercle 1962
Edinburgh experience

<table>
<thead>
<tr>
<th>Rx(m)</th>
<th>N</th>
<th>% Relapsing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>14</td>
<td>36%</td>
</tr>
<tr>
<td>3-5</td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td>6-8</td>
<td>31</td>
<td>7%</td>
</tr>
<tr>
<td>9-11</td>
<td>48</td>
<td>8%</td>
</tr>
<tr>
<td>12-17</td>
<td>73</td>
<td>2%</td>
</tr>
<tr>
<td>18-23</td>
<td>26</td>
<td>0%</td>
</tr>
<tr>
<td>&gt; 23</td>
<td>37</td>
<td>0%</td>
</tr>
<tr>
<td>Resis</td>
<td>18</td>
<td>22%</td>
</tr>
</tbody>
</table>

Fig. 4 — Length of chemotherapy and release in 259 cases of pulmonary tuberculosis admitted in 1953. Follow-up, December, 1956. The figures are derived from Ross et al. (1958). They comprise all patients admitted to Edinburgh hospitals with pulmonary tuberculosis in the year 1953.

Crofton BMJ 1959
“It is our view that all patients with tuberculosis require to continue chemotherapy for at least one year, those with severe disease up to two years - occasionally longer. If we accept that we should convert the sputum in all cases of tuberculosis with initially sensitive organisms, it is clear that our aim must be to continue chemotherapy for long enough to prevent relapse.”

Crofton BMJ 1959
And so it was ....

- By the end of the ‘60s the standard regimen in much of the developed world was PAS and isoniazid given for 18 months, or more, supplemented by three months’ of streptomycin.

- In the developing world a similar, but cheaper, regimen was given, with thiacetazone replacing PAS.
• The advent of rifampicin offered the possibility of an alternative to the unpleasant gastric side effects of PAS

• But much more important were the studies which demonstrated the effectiveness of the isoniazid/rifampicin combination in sterilising murine tuberculosis and showed the combination to be effective in rapid sputum conversion in man
A serendipitous choice?

- Who was it who decided that the duration to be studied in that first short course trial should be 6 months?

- What was the basis of the choice?

- None of the publications tell us
And the rest - is history

The best part of 50 years has past since the first publication – and despite repeated attempts we have so far failed to better the results of that very first study.

In 2010, following publication of Study A, WHO had to reverse its earlier recommendations – and today most drug sensitive TB is still treated with six months of isoniazid and rifampicin.
Thank you!