How long? how short?

TB treatment, 1948-2018, getting the duration right

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Outline

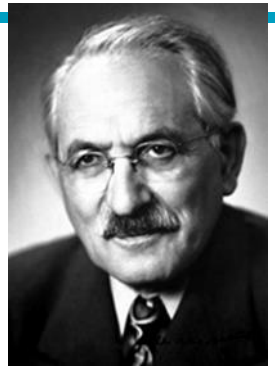
Streptomycin

The fifties and sixties

- Streptomycin, PAS and isoniazid
- Thiacetazone

Rifampicin and the advent of short course chemotherapy

The streptomycin era



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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.

Streptomycin: the American studies

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”

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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

Radiological outcome at 6 months	Streptomycin group		Bed rest group	
	N	%	N	%
Considerable improvement	28	51%	4	8%
Moderate or slight improvement	10	18%	13	25%
No material change	2	4%	3	6%
Moderate or slight deterioration	5	9%	12	23%
Considerable deterioration	6	11%	6	11%
Died	4	7%	14	27%
Total	55	100%	52	100%

MRC, BMJ 1948

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$P < 0.01$ for difference between the two groups

Was 4 months too short?

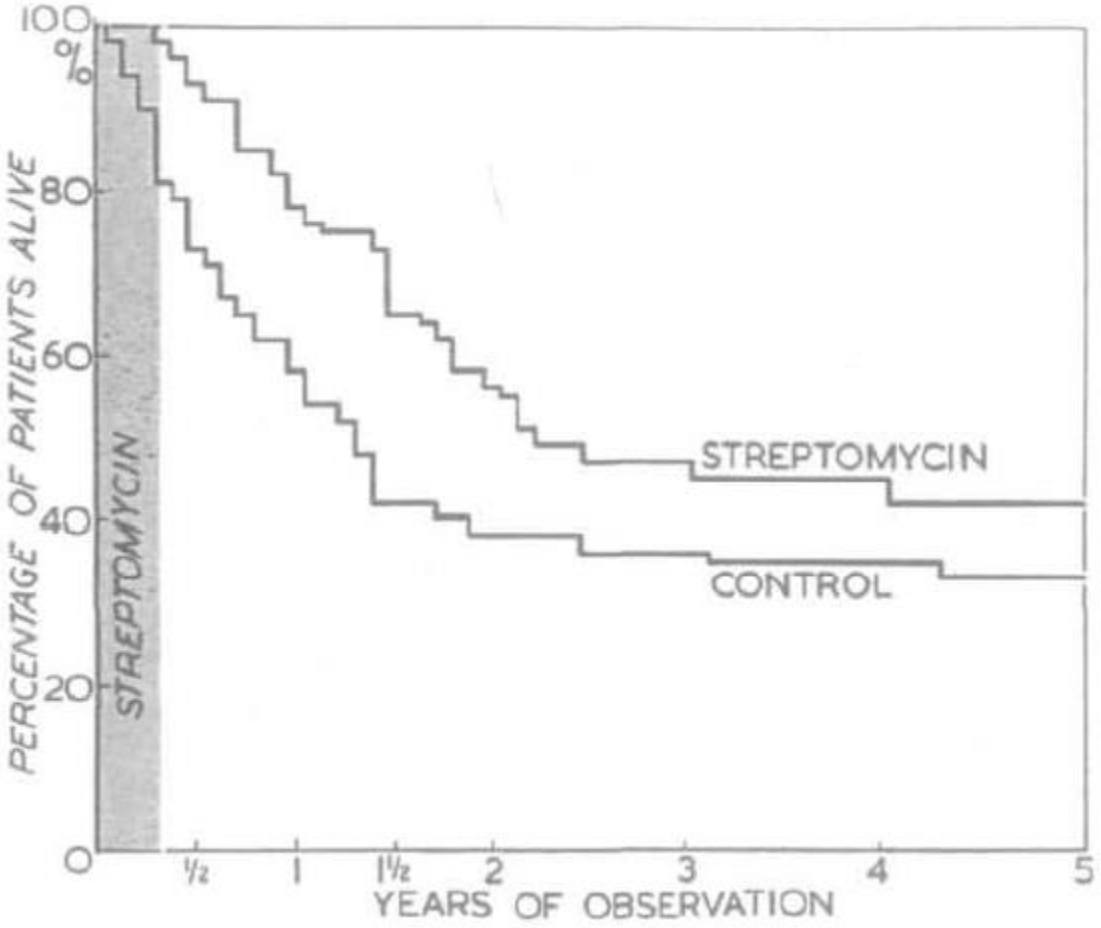
"The major improvement in patients treated with streptomycin was seen in the first two to three months; in the latter half of the six-month period numbers of them began to deteriorate.

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



42%

33%

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)

Trial	5 year mortality			
	No Rx	S alone	P alone	SP
Streptomycin	67%	58%		
Streptomycin & PAS		31%	36%	19%

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.

Opinions vary from eighteen months to two years (American Trudeau Society 1958, Ross et al. 1958, Tucker 1958, Ross 1959, Crofton 1960) to indefinitely prolonged chemotherapy (Dooneief et al. 1955, Pfeutze et al. 1960, Worbec et al. 1960), or even, in selected cases, to chemotherapy for life (Lancet 1953, Hyde 1960, American Thoracic Society 1961a)".

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

Rx(m)	N	% Relapsing
< 3	14	36%
3-5	12	17%
6-8	31	7%
9-11	48	8%
12-17	73	2%
18-23	26	0%
> 23	37	0%
Resis	18	22%

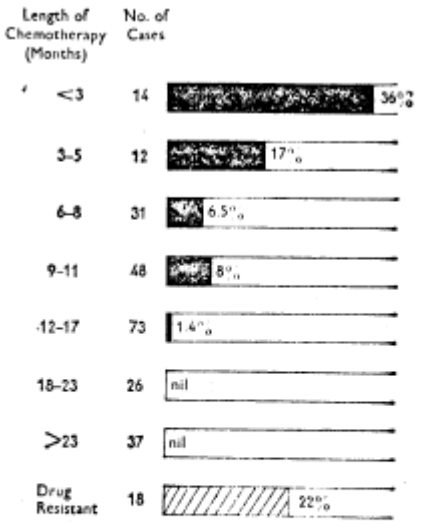


FIG. 4.—Length of chemotherapy and release in 259 cases of pulmonary tuberculosis admitted in 1953. Follow-up, December, 1956. The figures are derived from Ross *et al.* (1958). They comprise all patients admitted to Edinburgh hospitals with pulmonary tuberculosis in the year 1953.

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.

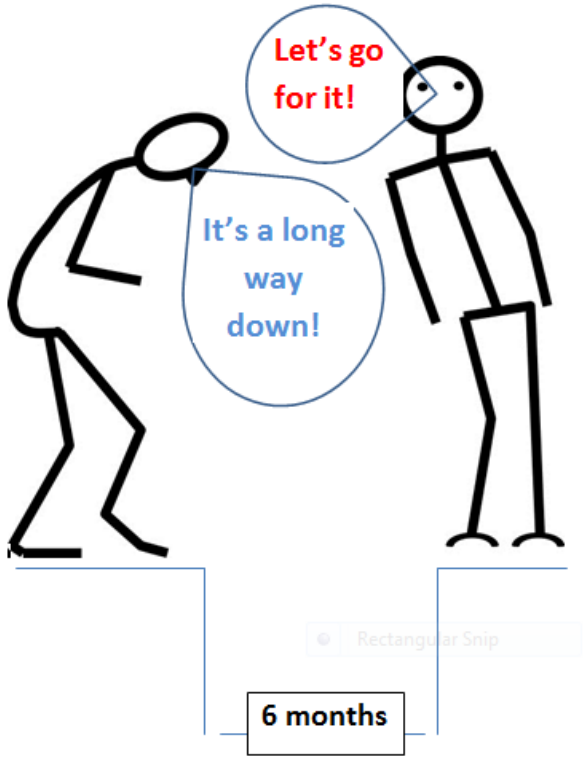
Of mice and men

- 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

Reprinted from THE LANCET, *May* 20, 1972, *pp.* 1079-1085

CONTROLLED CLINICAL TRIAL OF SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PULMONARY TUBERCULOSIS

EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCILS

Summary A comparison has been made between four 6-month daily regimens, all containing streptomycin plus isoniazid, and 3 of them a third drug—rifampicin, pyrazinamide, or thiacetazone—and a standard 18-month regimen in the treatment of newly diagnosed extensive smear-positive pulmonary tuberculosis. At 6 months all except 2 of 450 patients (both of them on streptomycin plus isoniazid) had a favourable response. There was also very little drug toxicity. The bacteriological relapse-rates between 6 and 12 months were 18% of 94 patients on the two-drug combination, 4% of 99 on the rifampicin, 6% of 88 on the pyrazinamide, 21% of 84 on the thiacetazone, and 2% of 83 patients on the standard regimen. Most of the relapses occurred by 9 months and nearly every patient who relapsed did so with drug-sensitive organisms. It is concluded that both the rifampicin-containing and pyrazinamide-containing 6-month regimens are highly effective, especially considering the very severe disease under study, and that the prospects of developing effective and practicable short-course regimens are excellent.

Thank you!