STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION
Everybody knows about this trial

- So you shouldn’t have any trouble stating whether each of the following statements about it are TRUE or FALSE.

- For each of them, shout “Oooool” if they are TRUE

- And hiss “S-s-s-s-s-s” if they are FALSE
True or False?

1. This was the first trial to randomize patients to different treatments.

“Ooooooo” if it’s true

“Sssssssss” if it’s false

NOW!
False!

1. This was **NOT** the first trial to randomize patients to different treatments.

8 years earlier, Joseph Bell had randomized kids to receive active or placebo pertussis vaccine.
2. Patients allocated to Streptomycin had stopped taking it by the end of the 6 month experimental period.

“Ooooooo” if it’s true

“Sssssssss” if it’s false

NOW!
2. Patients allocated to Streptomycin HAD stopped taking it by the end of the 6 month experimental period.
True or False?

3. Bradford Hill generously shared the credit for the innovations in the trial with 2 others: Philip d’Arcy Hart and Richard Doll.

“Ooooooo” if it’s true

“Ssssssss” if it’s false

NOW!
3. Bradford Hill generously shared the credit for the innovations in the trial with 2 others: Philip d’Arcy Hart and Marc Daniels
True or False?

4. After the trial, experts warned against the widespread use of streptomycin for the treatment of TB.

“Ooooooo” if it’s true

“Sssssssss” if it’s false

NOW!
4. After the trial, experts **DID** warn against the widespread use of streptomycin for the treatment of TB.
5. The consent form for the MRC Trial was only one sentence long.

- by now you know the drill!
False

5. The consent form for the MRC Trial was only one sentence long.

There was no consent form.
6. Two-thirds of experimental pts became giddy from the effects of streptomycin on their sense of balance (vestibular branch of the 8\textsuperscript{th} cranial nerve).
True!

6. Two-thirds of experimental pts **DID** become giddy from the effects of streptomycin on their sense of balance (vestibular branch of the 8\textsuperscript{th} cranial nerve).
True or False?

7. Bradford Hill used randomization to preserve statistical assumptions crucial for the outcome analyses.
False!

7. Bradford Hill **DID NOT** use randomization to preserve statistical assumptions crucial for the outcome analyses.

He used randomization to **conceal the assignment** of patients from the trial clinicians.
True or False?

8. At 6 months into the trial, 85% of patients randomized to streptomycin had live TB in their spit.
8. At 6 months into the trial, 85% of patients randomized to streptomycin **DID** had live TB in their spit.
9. Women were underrepresented in this trial.
False!

9. Women were **NOT** underrepresented in this trial.

\[
\frac{64}{107} = 60\% \text{ of participants were women}
\]
10. Bradford Hill used the risky “sealed envelope” method of allocation in this trial.
True!

10. Bradford Hill **DID** use the risky “sealed envelope” method of allocation in this trial.
True or False?

11. These statements were alternately True and False.
(and that’s how you improved your responses toward the end !)
True and False!

The first 10 **DID** alternate True-False, and that’s probably how you improved your responses toward the end.

But the 10\(^{th}\) and 11\(^{th}\) statements did **NOT** alternate, for **BOTH** of them were true!
TB was a major cause of morbidity and mortality in post-WW II England.

Penicillin (1928) was plentiful but ineffective against TB.

Streptomycin (1943) was scarce and very expensive, but looked promising.

First priorities for scarce streptomycin were the rapidly fatal forms of TB.
TB Meningitis
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First call on Streptomycin: Treat a series of children with TB meningitis
TB Meningitis

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<th>Effect of Streptomycin Rx</th>
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## TB Meningitis

### Effect of Streptomycin Rx

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# TB Meningitis

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<tr>
<td>Treated, early (just positive csf)</td>
<td>46%</td>
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But it remained unclear whether streptomycin was effective against:

- "acute progressive bilateral pulmonary tuberculosis"
  - of presumably recent origin,
  - bacteriologically proved, and
  - unsuitable for collapse therapy
  - among those 15-30 years old"
And so the British MRC struck the Streptomycin in Tuberculosis Trials Committee to answer that question
Streptomycin in Tuberculosis Trials Ctee

• Chair: Geoffrey Marshall
Streptomycin in Tuberculosis Trials Ctee

• Chair: Geoffrey Marshall
• Secretary: Philip d’Arcy Hart
Streptomycin in Tuberculosis Trials Ctee

• Chair: Geoffrey Marshall
• Secretary: Philip d’Arcy Hart
• Clinical Coordinator of Trials: Marc Daniels

• AB Hill: “. . . it is in this development that lies the true memorial to Marc Daniels.”
Streptomycin in Tuberculosis Trials Ctee

• Chair: Geoffrey Marshall
• Secretary: Philip d’Arcy Hart
• Clinical Coordinator of Trials: Marc Daniels
• Member: A. Bradford Hill
Trial Organization

• The Committee created a Multicenter Tuberculosis Hospital Collaboration

• Participating hospitals identified eligible patients and submitted them to a central selection committee.
Trial Participants

• 109 accepted by the committee, but 2 died within a week
• 60% women
• Allocation by “a statistical series based on random sampling numbers” by AB Hill
• Stacks of envelopes for each sex and center
• Envelopes contained a card stating either
  “S” (Streptokinase + Bed Rest), or
  “C” (Bed Rest Alone: no placebos)
With regard to informed consent

• “Patients were not told before admission that they were to get special treatment.”

• “C Patients did not know throughout their stay in hospital that they were control patients in a special study.”
Ethics were of great concern

1. “The meteoric rise and regrettably slower fall of many a form of treatment bear eloquent witness to the lack of the controlled trial in medicine.”

2. “Application of trials ... subject to the fundamental ethical problem inherent in using human beings as the subject of an experiment.”
Ethics were of great concern

3. “In developing the trial . . . The MRC committee was relieved of this particular moral responsibility. “

4. “It had a quite insufficient supply [of streptomycin] to treat all possible cases of pulmonary tuberculosis.”

5. Determined that it was unethical NOT to do the trial. (BMJ 1948;2:791-2)
AB Hill on the trial’s ethics

• It could not for ethical reasons insist upon an exact equality between the groups, the full double-blind procedure [eg, placebo injections].

• Nor in this instance do I myself believe that procedure to have been required when the success or failure of the treatment rested upon life or death, or in the assessment of x-ray changes by persons kept unaware of the treatment given to the patient.
AB Hill on the trial’s ethics

• In a controlled trial, as in all experimental work, there is no need in the search for precision to throw common sense out of the window.

(BMJ 1963;1:1043)
Conduct of the Trial

• S and C patients usually on separate wards.
• S patients received 0.5 grams Streptomycin I-M q6h.
• Submitted periodic clinical and lab reports
• Periodic chest xrays read by 3 experts (2 radiologists and 1 physician), blind to Rx and timing.
• Collapse therapy permitted in deteriorating patients (early in 21% of C; later in 21% of S)
Collapse Therapy
Collapse Therapy
Results at 6 months
## Results at 6 months

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RRR for death = 74%
P of chance = “less than one in a hundred”
Xray improvement showing a “reasonable prospect of recovery”
April 2, 1947
Xray improvement showing a “reasonable prospect of recovery”

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X-ray improvement showing a "reasonable prospect of recovery"

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7 X as likely to show a “reasonable prospect”

P of chance = “less than one in a million”
And the protocol permitted the identification of harm as well as benefit

- After 4-5 weeks of Streptomycin, 2/3 of patients started developing “giddiness” (vertigo), and many went on to unsteadiness when walking (ataxia).

- This was toxicity to the (vestibular branch of the 8th cranial) nerve that serves the semi-circular canals
And the protocol permitted the identification of the loss of drug efficacy

- Strains of streptomycin-resistant Tubercle bacilli rapidly developed
And not all the news was good

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13 patients developed highly resistant bacilli. 8 of these patients deteriorated. 3 of them died.
And not all the news was good

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13 streptomycin patients developed highly resistant bacilli.
8 of these patients deteriorated.
3 of these patients died.
Which led to a note of caution

“From the point of view of the community . . . there is the risk that patients with unsuitable lesions ineffectively treated . . . may disseminate streptomycin-resistant organisms, so that an increasing number of new cases of all forms of tuberculosis may in future be found to be unresponsive to streptomycin.”

-accompanying BMJ editorial
AB Hill on the introduction of RCTs

“What, therefore, is new in the development of the last 20 years is . . . the most careful planning of the experiment in advance, and an experiment that usually, though not invariably, makes the following demands:

(a) the construction of two (or more) closely similar groups of patients observed at the same time and differing in their treatment;
AB Hill on the introduction of RCTs

(b) the construction of these groups by some process of random allocation; and

(c) the withholding of a form of treatment from one or other of these groups.
The Commissariat struck in 1962

Ethics committee of the WMA:

• No objection to mindless, uncontrolled Rx in routine clinical care
• But must have individual informed consent for all patients in RCTs
• Prohibited RCTs in children “not under the care of relatives”
• Prohibited RCTs among “mental defectives” and “persons retained in mental hospitals.”
Leading to AB Hill’s prophesy 47 years ago!

- These are just a handful of examples of the proposed "should and should not" that come from high authority.

- It is said that they are only a "guide to doctors in different parts of the world,"

- but once so formulated and promulgated it would, I suggest, be difficult, if not even sometimes legally hazardous, for a doctor to act counter to them.
It is my belief that they may hamper, if not prevent,
- much research through clinical trials
- that not only is entirely ethical
- but can, indeed, be more ethical
- than the unthinking use of unproved treatments.
Spring time at the Trout Centre
Radiological Assessments

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<td>10 18%</td>
<td>13 25%</td>
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<tr>
<td>No material change</td>
<td>2 4%</td>
<td>3 6%</td>
</tr>
<tr>
<td>Moderate or slight deterioration</td>
<td>5 9%</td>
<td>12 23%</td>
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<td><strong>Total</strong></td>
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