
SUSPENDED JUDGMENT

Memories of the British Streptomycin Trial in Tuberculosis

The First Randomized Clinical Trial

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It seems to me that the report published in the British Medical Journal in 1948 [1] of the streptomycin trial in pulmonary tuberculosis is remarkably clear. In this, I perhaps partly flatter myself, for my memory is that the paper was drafted by Philip D'Arcy Hart, by his very able assistant, Mark Daniels, and by myself. The wording is, as I have it in front of me, "The Special Committee of the Medical Research Council 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." Now it may well have been that the decision was reached without too much discussion or great difficulty, but I think its roots went much further back.

In my own situation, I had published my articles in *The Lancet*, which led to my handbook "Principles of Medical Statistics" just 10 years earlier in 1937. In these articles, I had set out the need for controlled experiments in clinical medicine with groups chosen at random. At the outset, I think I pleaded that trials should be made using alternate cases. I suspect if (and its a very large IF) if that, in fact, were done *strictly* they would be random. I deliberately left out the words "randomization" and "random sampling numbers" at that time, because I was trying to persuade the doctors to come into controlled trials in the very simplest form and I might have scared them off. I think the concepts of "randomization" and "random sampling numbers" are slightly odd to the layman, or, for that matter, to the lay doctor, when it comes to statistics. I thought it would be better to get doctors to walk first, before I tried to get them to run. So I had been thinking about controlled trials for all of those 10 years and hoping for an opportunity that might arise. I had already used random sampling numbers in the less emotive field of preventive med-

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icine, e.g. a whooping cough vaccine or anticatarrhal vaccine was given to children in random order [2]. I had not, up to this point, had an opportunity to use treatment assignment by random sampling numbers in the clinical situation. Now the occasion arose and I was, therefore, completely ready for it.

Secondly, the Medical Research Council (MRC) had a tuberculosis research unit under the very able direction of Doctor Philip D'Arcy Hart, who had a distinguished position in the field of tuberculous diseases. He had been frustrated, I think, by some 15 years of using and reading reports on treatment with gold without being able to make a controlled trial to find out whether it really was effective or not. So I think that he himself, if something new came along and there was a chance for making a really good controlled trial, was ready to seize that opportunity [3]. He argued from the medical point of view while I was arguing from the statistical.

A third and dominating feature, which may not have been sufficiently stressed, was that we were extremely limited in the amount of streptomycin we had. The new drug had been discovered in America in 1944. It was just after the Second World War when we were trying to make the trial, in 1946, and Britain literally had no currency. We had exhausted all our supply of dollars in the war and our Treasury was adamant that we could have only a very small amount of streptomycin. This, I think, turned the scales: I could argue with the chairman, Sir Geoffrey Marshall (a good and sensible physician) and he would listen. I could argue that in this situation it would not be immoral to make a trial—it would be immoral *not* to make a trial since the opportunity would never rise again (streptomycin would be synthesized, there would soon be plenty of it, and so on). At that time we were handicapped—we could have enough of the new drug to use on only about 50 patients, and there was said to be no dearth of patients. In point of fact, the planners laid down so many rules there did appear at times to be a bit of a dearth; but when we persisted there were plenty. We were limited to this number, about 50 in the streptomycin-treated arm of the trial, and I thought that was probably enough to get a reliable answer so long as it was strictly controlled and if streptomycin was really effective. And so it proved.

I think there was no doubt it was the first strictly controlled trial—it ushered in the new era of medicine. As I have stressed, the shortage of streptomycin was the dominating feature of the situation in Britain when the trial was under consideration. I wonder if there had not been a shortage of the new drug whether the MRC Committee would have reached the same conclusion to proceed with a controlled trial? I rather doubt it, but I shall never know. I think they would probably have hedged.

Of course, there were no ethical problems in those days: we did not ask the patient's permission or anybody's permission. We did not tell them they were in a trial—we just did it. To tell the truth, all of the discussion today about the *patient's* informed consent still strikes me as absolute rubbish. Personally, I would like to see an ethical committee overlooking the experimenting *doctors*: Is the clinical question worth asking? Is it reasonable to ask patients to enroll? Is the question asked in a way (numbers, duration, drafting of questions, and so on) that will give a valid answer? The patients should be told of the ethical committee's decision and asked whether they will agree

to inclusion in the trial. If patients are intelligent enough to ask questions, they should be answered as clearly as possible (without going into all the details that the ethical committee has dealt with). It could be pointed out that if the treatment is valuable then the controls receiving standard treatment will be in a position immediately to get the benefit of the expanding supplies of the new drug as it becomes available. If, on the other hand, the innovative treatment has undesirable side effects, the experimentally treated group will have been under the specially close supervision of the trial doctors and the treatment-under-test stopped earlier than would be the case in general uncontrolled use.

I think it is wrong to shift the entire consent-giving responsibility onto the shoulders of patients who cannot really be informed or know what weight *relatively* to put upon the technical information provided concerning risks and benefits. The doctors, it seems to me, must weigh all this in the light of their medical training. It is my personal opinion that the responsibility rests with them and their sense of morality.

The reader must realize that I am now into my 93rd year, and all this happened some 44 years ago—but I remember it all very clearly. I do hope this personal account of what went on is of some interest to the readers of *Controlled Clinical Trials*.

REFERENCES

1. Streptomycin in Tuberculosis Trials Committee: Streptomycin treatment of pulmonary tuberculosis. *Br Med J* 2:769–782, 1948
2. Whooping-cough Immunization Committee: The prevention of whooping-cough by vaccination: A Medical Research Council investigation. *Br Med J* 1:1463–1471, 1951
3. Hart PD: Chemotherapy of tuberculosis: Research during the past 100 years. *Br Med J* 2:805–810 and 849–855, 1946