# A 1955 clinical trial report that changed my career

David Sackett

*J R Soc Med* 2010 103: 254
DOI: 10.1258/jrsm.2010.10k003

# A 1955 clinical trial report that changed my career

David Sackett

#303, 28 Duke Street, Hamilton, Ontario L8P 1X1, Canada
E-mail: sackett@bmts.com

DECLARATIONS

**Competing interests**
None declared

**Funding**
None

**Ethical approval**
Not applicable

**Guarantor**
DS

**Contributorship**
DS is the sole contributor

**Acknowledgements**
Additional material for this article is available from the James Lind Library website (www.jameslindlibrary.org), where it was originally published

In 1955, during the dawn of the modern era of randomized clinical trials, Thomas Chalmers and his colleagues published a remarkable paper.[1] It was then and probably remains one of the most detailed reports of clinical trials ever published: it begins with a Table of Contents and runs on to a further 71 pages of small type. It is a model of how randomized trials should be reported, reflecting Marc Daniels' call for better reporting of clinical trials five years earlier,[2] and anticipating by over four decades the reporting standards agreed and promulgated by the CONSORT Group.[3]

Tom Chalmers and his colleagues described the eligibility criteria of participants clearly, and their random allocation (with concealment of the next participant's assignment) into their 2 × 2 factorial trials,[4] thus permitting comparisons of two regimens per trial. The similarity between treatment groups in respect of 34 other variables that might affect patient prognosis was confirmed. Experimental and control regimens were precisely defined, and compliance with them was closely monitored and reinforced. All patients were accounted for at the end of the trials. Analyses were clearly described and transparent. The 'external validity' of the trial results was tested by comparison with another, independent control group of patients. Finally, late effects of the treatment regimens were assessed in a 10-year follow-up study.

I first came across this report in 1959. Although I failed to appreciate many of its methodological strategies and strengths at that time, it changed my career. I was a final-year medical student on a medical ward, where a teenager with 'infectious hepatitis' (now called 'Type-A hepatitis') was admitted to my care. He presented with severe malaise, an enlarged and tender liver, and a colourful demonstration of deranged bilirubin metabolism that made me the envy of my fellow clerks. However, after a few days of total bed rest his spirits and energy returned and he asked me to let him get up and around.

In the 1950s, everybody 'knew' that such patients, if they were to avoid permanent liver damage, must be kept at bed rest until their enlarged liver receded and their bilirubin and enzymes returned to normal. And if, after getting up and around, their enzymes rose again, back to bed they went. This conventional wisdom formed the basis for daily confrontations between an increasingly restless and resentful patient and an increasingly adamant and doom-predicting clinical clerk.

We clinical clerks were expected to read material relevant to the care of our patients. I wanted to understand (for both of us) how letting him out of bed would exacerbate his pathophysiology. After exhausting several unhelpful texts, I turned to the journals. PubMed was decades away, and the National Library of Medicine hadn't yet begun to help the Armed Forces Medical Library with its *Current List of the Medical Literature*. Nonetheless, it directed me to a citation in the *Journal of Clinical Investigation* (back in the days when it was a real clinical journal) for: 'The treatment of acute infectious hepatitis. Controlled studies of the effects of diet, rest, and physical reconditioning on the acute course of the disease and on the incidence of relapses and residual abnormalities.'[1] Reading this paper not only changed my treatment plan for my patient, it forever changed my attitude toward conventional wisdom, uncovered my latent iconoclasm, and inaugurated my career in what I later labelled 'clinical epidemiology'.

The paper introduced me to Tom Chalmers, who quickly became my hero and, a decade later, my friend. Tom was a US Army gastroenterologist

in the Korean War, and had become involved in a major outbreak of 'infectious' hepatitis among American recruits. The application of conventional wisdom on enforced bed rest was keeping affected soldiers in hospital for about two months and requiring another month's convalescence. Tom wrote: 'This drain on military manpower, along with more recent [short-term metabolic] observations suggesting that strict bed rest might not be as essential as heretofore thought, emphasized the need for a controlled study to determine the safety of a more liberal regimen of rest and less prolonged hospitalization'.

Employing what I increasingly came to recognize as 'elegant simplicity', Tom and his colleagues allocated soldiers who met pre-defined hepatitis criteria at random either to bed rest (continuously in bed, save for one trip daily to the bathroom and one trip to the shower weekly), or to be up and about as much as the patients wanted (with no effort made to control their activity save 1-hour rests after meals) throughout their hospital stay. The time to recovery (as judged by liver function testing) was indistinguishable between the comparison groups, and no recurrent jaundice was observed.

Armed with this evidence, I convinced my supervisors to let me apologize to my patient and let him be up and about as much as he wished. He did, and his clinical course was uneventful.

My subsequent 'clinical course' was far from uneventful. I became a 'trouble-maker', constantly questioning conventional therapeutic wisdom, and offending especially the subspecialists when they pontificated (I thought) about how I ought to be treating my patients. I had a stormy time in obstetrics, where I questioned why patients with severe pre-eclampsia received intravenous morphine until their respirations fell below 12 per minute. I gained unfavourable notoriety on the medical ward, where I challenged a consultant's recommendation that I should ignore my patient's diastolic blood pressure of 125 mmHg 'because it was essential for his brain perfusion'. And I deeply offended a professor of paediatrics by publicly correcting him on the number of human chromosomes (they had fallen from 48 to 46 the previous month!).

Tom Chalmers, along with Ed Fries (who answered the question about whether diastolic blood pressure should be ignored) and Archie Cochrane, became my role models. Ten years after I discharged my hepatitis patient, armed with some book-learning and blessed with brilliant colleagues, I began to emulate these mentors by converting my passive skepticism into active inquiry, addressing such questions as: Why do you have to be a physician in order to provide first-contact primary care?[5] Are the 'experts' correct that teaching people with raised blood pressure all about their illness really makes them more likely to take their medicine?[6] Just because the aorto-coronary arterial bypass is good for ischaemic hearts, should we accept claims that extracranial–intracranial arterial bypass is good for ischaemic brains?[7]

In the year that the paper by Tom Chalmers and his colleagues was published, there were only 347 reports of randomized trials. Half a century later, about 50,000 reports of randomized trials were being published every year, with the total number of trial reports by then exceeding half a million. I am proud to have contributed to this development, to the skepticism that drives it, and to the better informed treatment decisions and choices which have been made possible as a result.

## References


1 Chalmers TC, Eckhardt RD, Reynolds WE, *et al*. The treatment of acute infectious hepatitis. Controlled studies of the effects of diet, rest, and physical reconditioning on the acute course of the disease and on the incidence of relapses and residual abnormalities. *J Clin Investig* 1955;**34**:1163–235

2 Daniels M. Scientific appraisement of new drugs in tuberculosis. *Am Rev Tubercul* 1950;**61**:751–6

3 See http://www.consort-statement.org/

4 Doll R. Controlled trials testing two or more treatments simultaneously. *The James Lind Library* 2003

5 Sackett DL, Spitzer WO, Gent M, Roberts RS. The Burlington randomized trial of the nurse practitioner. *Ann Intern Med* 1974;**80**:137–42

6 Sackett DL, Haynes RB, Gibson ES, *et al*. Randomized clinical trial of strategies for improving medication compliance in primary hypertension. *Lancet* 1975;**1**:1205–7

7 The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. *N Engl J Med* 1985;**313**:1193–200