

Hemminki E (2005). Commentary on an early placebo controlled trial in Finland.



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Despite its title, *Observations on preoperative treatment with strophanthin* (a cardiac glycoside used as a 'cardiotonic' drug) is a report of a controlled trial done in a city hospital in Helsinki, Finland, between 1945 and 1947. The authors, Eino Elovainio and Gustaf Östling, wanted to assess whether giving the drug intravenously to elderly patients for three days pre-operatively could prevent peri-operative cardiovascular complications and death. The issue was important because differing clinical opinions about the value of 'strengthening the heart' before surgery in this way were reflected in practices ranging from routine use to total rejection because of the treatment's alleged dangers. In the event, no effect on mortality was detected in the study. The drug is still marketed in some countries, although not in Finland since the 1970s.

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In some respects the report of Elovainio's and Östling's trial is very modern. Their introduction rehearses the arguments for doing the trial, reviewing the animal and human literature, and discusses the timing problem (is it too late to do a trial?). They also note the possible beneficial effect of being in the trial - having a rest in hospital for three days preoperatively – although it is not clear whether patients were aware that they were participating in a placebo controlled trial. The investigators used alternate allocation to generate the comparison groups, and endeavoured to achieve double blinding by using drugs and placebos donated by a pharmaceutical company. Analysis of the results was fairly basic, but reasonable for the era in which it was done. Today, an adjustment might have been made for some imbalance in the age distribution of the patients in the two groups.

Why has the report of this trial come to notice only now? The report was identified through hand searches of journals done by Finnish contributors to the Cochrane Collaboration, and then added to the register of reports of trials published in *The Cochrane Library*. It is one of 5 reports of controlled trials in Finland published before 1950. The fact that it was not recognised before this systematic search may have been because the results suggested that the drug was no better than placebo. The relative obscurity of the MRC patulin trial ([MRC 1944](#)) compared with the celebrated MRC report of its randomized trial of streptomycin for pulmonary tuberculosis published four years later ([MRC 1948a](#)) has been attributed to the fact that the former did not find any advantage of the drug tested, whereas the latter did.

Another factor likely to be relevant is that, although Elovainio's and Östling's study was reported in English (now the *lingua franca* of medical research), it was published in a local Finnish journal established in 1946 by Duodecim, the Finnish Medical Society. At that time, the name of the journal was *Annales Chirurgiae et Gynaecologiae Fenniae*, and it was probably not widely read outside Finland. In 1976 it became a Scandinavian journal and dropped 'Fenniae' from the title; and in 2002 the name was changed to the *Scandinavian Journal of Surgery*.

Even though the report of Elovainio's and Östling's trial appears to have been largely overlooked, it is possible that, in its time, it had an impact on the use of preoperative treatments. I do not know whether the authors influenced future research and practice. Neither of them had an academic career, and their biographies are very short and formal in the *Finnish Physicians' Register*. When the trial started in 1945, just after a devastating war, Eino Elovainio was 48 years old and working as the temporary chief surgeon at the Maria Hospital in Helsinki. Although he had defended his thesis on kidney diseases in 1938, he did not subsequently have an academic career. He worked in various hospitals and ended his career as the chief physician of a Helsinki city hospital.

Gustaf Östling was 31 at the start of the trial and had finished his medical studies two years before. He defended his pharmacological thesis on strophanthin in 1946. He specialised in pharmacology and internal medicine, and worked in Helsinki University and its hospital for a few years. He then moved to the drug industry, initially as the medical director of a small Finnish company, later moved to Sweden, and retiring in 1977 from the position of medical director of Pharmacia.

On the basis of the article and the biographies it is difficult to judge who was behind the idea of the controlled trial.

Knowing the hierarchical staffing structure in Finnish hospitals at that time, it is clear that Elovainio's support would have been needed for permission to use alternation to allocate treatment. But who insisted on placebo controls? Was it one of the two authors or was it suggested by Professor Vartiainen, in the company (Orion) that supplied the drugs and placebos? So long after both men have died it may never be known, but there is clearly scope for research to learn more about the adoption of controlled trials in Finland during the 1940s.

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