

Early controlled trials

Randomised mental health trial began in 1935...

EDITOR,—The British have been very ready to proclaim that they have the best police service, the best television service, and so forth, and I wonder whether this national complacency has contributed to our longstanding belief in the primacy of the Medical Research Council's trial of streptomycin,¹ as discussed by P D'Arcy Hart.²

I have become aware of a randomised trial of counselling and social work support in adolescents, which began in 1935 in the United States. It set quality standards that have been matched by few later trials in mental health, with over 500 patients randomised and 30 year follow up.³ Conceivably there is a connection between its being little known and the worse results reported in the intervention group for various outcomes including death, disease, and criminal behaviour. Indeed, when McCord's heroic efforts at tracing subjects were reported, an accompanying paper was published criticising the study, with the subtitle "The hazards of follow-up research."⁴

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- 1 Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;iii:373-5.
- 2 D'Arcy Hart P. Early controlled clinical trials. *BMJ* 1996;312:379. (10 February.)
- 3 McCord J. A thirty year follow-up of treatment effects. *Am Psychol* 1978;33:284-9.
- 4 Sobel S. Throwing the baby out with the bathwater: the hazards of follow-up research. *Am Psychol* 1978;33:290-1.

...but "quasirandom allocation" of treatment was reported in 1930

EDITOR,—P D'Arcy Hart rightly points out¹ that the history of controlled clinical trials predates the publications in 1948 of the Medical Research Council's trial of streptomycin² and the Dutch trial of paludrine in malaria.³ In their study Carla van der Wijden and John A Overbeke do not seem to have searched issues of *Nederlands Tijdschrift voor Geneeskunde* before that year,⁴ and, if that is so, it is not surprising that they did not find any randomised trials.

As D'Arcy Hart notes, the large patulin trial, with which he was involved,⁵ deserves a place in the history of controlled trials, and prior examples also exist. The 1944 report of the patulin study itself cited an earlier, smaller, study of the same treatment.⁶ Both of these studies used a "quasirandom" system of allocating treatment (alternate assignment), which is potentially open to bias because of the possibility of prior knowledge of the treatment to be allocated; other such trials were reported in the previous decade.⁷ In fact, the issue of the *BMJ* published on 11 December 1937 contained two such studies.^{8,9} However, controlled trials in which the allocation was based on a random system also appear in the medical literature of the 1930s, although the method of randomisation is not so well described as it was in the streptomycin report. For example, Diehl and Cowan reported their investigation of vaccines for the common cold, in which university students were assigned "at random" to treatment or control groups,¹⁰ and Amberson *et al* flipped a coin to allocate groups of patients to sanocrysin or placebo in their study of pulmonary tuberculosis.¹¹

These may prove to be isolated examples, but, without a thorough search, one cannot know how isolated—or common—this trial methodology was in the 1930s and 1940s, or even earlier. If you do not look you will not find. As an illustration, a hand search that I did of each issue of

the *Lancet* for the six months from July to December 1947 yielded two trials of the treatment of breast feeding problems in which the women were, respectively, "randomly distributed" to the different treatments and "treated at random."^{12,13}

I would be interested to receive details of any other randomised or quasirandomised trials dating from before 1948 of which readers are aware, whether or not they have been found by a systematic search of the literature.

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- 1 D'Arcy Hart P. Early controlled clinical trials. *BMJ* 1996;312:378-9. (10 February.)
- 2 Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;iii:769-83.
- 3 Kloppe S, Slop D, op 't Land C. Een onderzoek naar de suppressieve werking van paludrine bij malaria tertiana. [A study of the suppressive action of paludrine in tertian malaria.] *Ned Tijdschr Geneesk* 1948;92:3922-9.
- 4 Van der Wijden CL, Overbeke JA. Audit of reports of randomised clinical trials published in one journal over 45 years. *BMJ* 1995;311:918.
- 5 Medical Research Council. Clinical trial of patulin in the common cold. *Lancet* 1944;iii:373-5.
- 6 Hopkins WA. Patulin in the common cold. Biological properties: extended in the common cold. *Lancet* 1943;iii:631-4.
- 7 Wyckoff J, Du Bois EF, Woodruff IO. The therapeutic value of digitalis in pneumonia. *JAMA* 1930;95:1243-9.
- 8 Snodgrass WR, Anderson T. Sulphanilamide in the treatment of erysipelas: a controlled series of 270 cases. *BMJ* 1937;11:1156-9.
- 9 Hogarth JC. Para-benzylaminobenzenesulphonamide in the treatment of scarlet fever. *BMJ* 1937;iii:1160-2.
- 10 Diehl HS, Cowan DW. Cold vaccines: an evaluation based on a controlled study. *JAMA* 1938;111:1168-73.
- 11 Amberson JB, McMahon BT, Pinner M. A clinical trial of sanocrysin in pulmonary tuberculosis. *Am Rev Tuberc* 1931;24:401-31.
- 12 Robinson M. Hormonal treatment of deficient lactation. *Lancet* 1947;iii:90-2.
- 13 Robinson M. Hormones and lactation. *Lancet* 1947;iii:385-7.

Low serum cholesterol and serotonin metabolism

Results may have been affected by confounding

EDITOR,—Paul H A Steegmans and colleagues report that plasma concentrations of serotonin are lower in men with persistently low serum cholesterol concentrations than in a reference group of men. They point out that this indicates that low serum cholesterol concentrations are associated with altered metabolism of serotonin, which could explain the observed association between low serum cholesterol concentrations and suicide.¹

We believe that their finding may be confounded by at least two factors. Firstly, more than 95% of serotonin in plasma is in platelets. As soon as platelets are activated they are likely to release serotonin, thereby increasing free plasma concentrations. Alcohol is one of the factors known to induce release of serotonin by platelets.² The reference group in Steegmans and colleagues' study consumed significantly more alcohol. Secondly, plasma free serotonin concentrations are raised in peripheral vascular disease, probably because of platelet hyperactivity.³ The reference group is likely to have had more pronounced vascular derangements than the study group as a result of its persistent higher cholesterol concentrations. Furthermore, it would have been interesting to know the platelet count in the groups as this might be expected to correlate positively with total platelet serotonin uptake and negatively with plasma serotonin concentrations.

Although platelet serotonin uptake and content may serve as a model for central serotonin membrane transport, there is no reason to assume that the plasma free serotonin concentration reflects central metabolism of serotonin. The concerted effects of synthesis, release, and degradation of serotonin determine its concentration in various tissues. The rate of synthesis of serotonin depends on the availability of its precursor, tryptophan, in both enterochromaffin cells and neurones. The mechanisms responsible for release and degradation, however, differ considerably between the periphery and brain. The release from enterochromaffin cells depends on several stimuli (for example, ingestion of glucose), while synaptic release is brought about by serotonin. Degradation of peripheral serotonin takes place in liver and lung tissue.⁴

Removal of serotonin from the synaptic cleft occurs through reuptake and by breakdown in neuroglial cells. Peripheral serotonin concentrations do not affect brain synaptic concentrations, as serotonin does not cross the blood-brain barrier.⁵ Thus we believe that Steegmans and colleagues' findings indicate only that serotonin transport mechanisms in the brain do not differ between men with high and men with low serum cholesterol concentrations. The plasma free serotonin concentration is probably determined by factors other than cholesterol and does not reflect synaptic availability. In our opinion, the results do not explain the association between low serum cholesterol concentrations and suicide.

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- 1 Steegmans PHA, Fekkes D, Hoes AW, Bak AAA, van der Does E, Grobbee DE. Low serum cholesterol concentration and serotonin metabolism in men. *BMJ* 1996;312:221. (27 January.)
- 2 Linjaerde O. Inhibitory effect of ethanol on 5-hydroxytryptamine (serotonin) uptake in human blood platelets in vitro. *Acta Pharmacol Toxicol* 1979;45:394-8.
- 3 Barradas MA, Gill DS, Fonseca VA, Mikhailidis DP, Dandona P. Intraplatelet serotonin in patients with diabetes mellitus and peripheral vascular disease. *Eur J Clin Invest* 1988;18:399-404.
- 4 Tyce GM. Origin and metabolism of serotonin. *J Cardiovasc Pharmacol* 1990;16:S1-7.
- 5 Verbeuren TJ. 5-Hydroxytryptamine: distribution, synthesis, metabolism, release, uptake and passage across body membranes in cardiovascular tissues, including blood brain barrier. In: Olesen J, Saxena PR, eds. *5-Hydroxytryptamine mechanisms in primary headache*. New York: Raven Press, 1992:29-39.

Risk of depression is higher in elderly patients with lowest serum cholesterol values

EDITOR,—We read with interest Paul H A Steegmans and colleagues' short report on serum cholesterol concentration and serotonin metabolism.¹ We would like to add support to the hypothesis of an association between low serum cholesterol concentration and depression with data obtained in our geriatric evaluation and rehabilitation unit.