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

D B E C GILL

MRC health services research fellow

University of Oxford Institute of Health Sciences,
Oxford OX3 7LF

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...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.

MIKE CLARKE

Sydney Breast Cancer Institute visiting fellow

National Health and Medical Research Council
Clinical Trials Centre,
University of Sydney,
Sydney, NSW 2006,
Australia

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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.

HANNO PIJL

Senior investigator

ARNOUD C TOORNVIET

PhD student

A EDO MEINDERS

Professor of general internal medicine

Department of General Internal Medicine,
Leiden University Hospital,
PO Box 9600,
2300 RC Leiden,
Netherlands

JAN A GEVERS LEUVEN

Senior investigator

Gaubius Laboratory,
TNO-PG,
PO Box 2215,
2301 CE Leiden,
Netherlands

G M J VAN KEMPEN

Professor of biochemical aspects of psychiatry

Department of Psychiatry,
Leiden University,
2340 BG Oegstgeest,
Netherlands

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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.

Table 1—Logistic regression model testing adjusted association between serum cholesterol group and depression (defined as score on geriatric depression scale >10) in 476 elderly hospital patients

	No of patients	Odds ratio (95% confidence interval)
Serum cholesterol (mmol/l):		
≥6.20	60	1.0*
4.14-6.19	313	2.0 (1.1 to 3.6)
≤4.13	103	2.7 (1.3 to 5.5)
Age ≥80	215	1.1 (0.7 to 1.6)
Women	333	1.8 (1.1 to 2.7)
Living alone	163	1.0 (0.7 to 1.5)
≥6 Diseases	279	0.7 (0.4 to 1.1)
Impaired function†	224	1.7 (1.1 to 2.5)
Cognitive impairment‡	172	1.9 (1.2 to 2.9)
Malnutrition§	260	0.7 (0.5 to 1.2)

*Reference group.

†Score on Tinetti scale <18. ‡Score on minimal state examination <22. §Score on prognostic nutritional index >35.

Data in this study were taken from 476 elderly patients consecutively admitted to our unit over 12 months (mean age 78.8 (SD 7.4); 70% women). A multidimensional evaluation, including information on demographics, physical health, cognitive and affective status, functional ability, and social support, was performed on the third day after admission with a standard protocol. Cognitive status was evaluated by the Folstein mini-mental state examination, depressive symptoms with the geriatric depression scale,² and functional disability with the Tinetti balance and gait scale. Nutritional status was assessed by Mullin's prognostic nutritional index, which considers the serum albumin concentration, triceps skinfold thickness, serum transferrin concentration, and results of skin sensitisation tests. Somatic health was assessed as the number of diseases.

The patients were stratified in three groups of decreasing serum cholesterol concentrations: ≥6.20, 4.14-6.19, and ≤4.13 mmol/l. Mean scores on the geriatric depression scale across the three groups were, respectively, 11.3 (6.5), 13.3 (6.3), and 14.1 (6.9) mmol/l ($P=0.025$ on analysis of variance). The association of serum cholesterol groups with depression (defined as a score on the geriatric depression scale of >10) was tested in a multiple logistic regression model in which confounding by age, sex, somatic health, poor cognition, malnutrition, disability, and living alone could be controlled for. Table 1 shows that the risk of depression was greater in the group with the lowest serum cholesterol concentration even after the potential confounders were considered.

Although these results cannot confirm the mechanism proposed by Steegmans and colleagues to explain the relation between low serum cholesterol concentration and depression, the strength of the association that we found suggests that it may be clinically relevant in elderly people. Our data and those of Steegmans and colleagues need further confirmation, particularly in the light of previously reported conflicting data.³

RENZO ROZZINI
Chief
BRUNO BERTOZZI
Assistant
PIERA BARBISONI
Assistant

Geriatric Evaluation and Rehabilitation Unit,
P Richiedei Hospital,
Gussago, Brescia,
Italy

MARCO TRABUCCHI
Chief

Geriatric Research Group,
25122 Brescia,
Italy

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 February.)

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Other studies have been done in humans and monkeys

EDITOR.—Paul H A Steegmans and colleagues assert that theirs was the first study in humans to investigate the relation of serum cholesterol concentration to metabolism of serotonin and that only one study in monkeys has done so.¹ However, two studies in humans bear on this issue, as does one study in primates that they fail to cite.

Ringo *et al* found a non-significant trend towards an increased cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid (a central metabolite of serotonin thought to gauge turnover of serotonin) with high cholesterol concentration in psychiatric patients and staff.² The 23% higher mean 5-hydroxyindoleacetic acid concentration in subjects with a high cholesterol concentration is comparable in size, though not significance, to the 19% higher (arithmetic) mean peripheral serotonin concentration in Steegmans and colleagues' study. Anderson *et al* found significantly reduced plasma tryptophan concentrations in people placed on diets to induce weight loss.³ Women, who were placed on a lower fat diet than men (25% energy from fat *v* 35%), showed a greater reduction in tryptophan concentrations and a significant change in hormonal measures of central serotonin.

In primates Muldoon *et al* documented a 31% higher prolactin response to fenfluramine (a hormonal measure of combined presynaptic and post-synaptic central serotonin activity) in monkeys with high cholesterol concentrations than in those with low cholesterol concentrations due to dietary intervention. This effect was significant.⁴

Rather than being the first study in humans and the second in primates, the study by Steegmans and colleagues is an important addition to a growing body of evidence suggesting a connection between cholesterol and central serotonin that may help to mediate an association between low(ered) cholesterol and violence.

BEATRICE A GOLOMB

Robert Wood Johnson clinical scholar

Division of General Internal Medicine and Health Services Research,
Department of Medicine,
UCLA Medical Center,
University of California, Los Angeles,
Los Angeles, CA 90095-1736,
USA

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.)

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Authors' reply

EDITOR.—Hanno Pijl and colleagues suggest that the higher alcohol intake in our reference group could explain the higher plasma serotonin concentration in the group. The study they refer to, however, is an *in vitro* study. Although platelet serotonin concentrations are generally decreased in alcoholic subjects,^{1,2} the effects on plasma sero-

tonin concentrations are unknown. In one study platelet uptake of serotonin was increased in alcoholic subjects, without modifications of the paroxetine binding site.³ The results are therefore equivocal. Importantly, adjustment for use of alcohol did not materially change our findings.

Although plasma free serotonin concentrations are increased in peripheral vascular disease, this disease cannot have been responsible for the observed association between low cholesterol and serotonin concentrations in our study: the prevalence of cardiovascular disease (including symptomatic peripheral vascular disease) was even lower in the reference group (4%) than the group with low cholesterol concentrations (9%). Furthermore, the prevalence of cardiovascular risk factors (hypertension) was similar in the two groups.

Pijl and colleagues state that the mechanisms responsible for the release and degradation of serotonin differ considerably between peripheral tissue and brain. This may be true for release of serotonin but is not for its degradation. Removal of free serotonin from the plasma or the synaptic cleft occurs through uptake by platelets or the neurone, respectively. The degradation in both instances takes place mainly in other cells—namely, the cells of the liver and lung and the neuroglial cells, respectively. Thus similarities exist in the mechanisms by which the periphery and the brain regulate the action of serotonin.

Pijl and colleagues conclude that the plasma free serotonin concentration is probably determined by factors other than cholesterol and does not reflect synaptic availability. As we mentioned, however, the finding of lower plasma serotonin concentrations in men with low cholesterol concentrations indicates that the metabolism of serotonin is altered in these subjects, especially as no alternative explanation for the observed association exists. If plasma serotonin concentrations do correlate with the concentrations in the synaptic cleft, this may explain the higher incidence of suicide in people with low cholesterol concentrations.

The study by Renzo Rozzini and colleagues provides important additional evidence for the association between naturally occurring cholesterol concentrations and depression in elderly people. It would have been even more interesting if they had studied measures of serotonin metabolism.

The findings of Ringo *et al*, mentioned by Beatrice Golomb, are in line with our results. In contrast to our population based study, their study was restricted to psychiatric patients. The study by Anderson *et al* did not address the relations between naturally occurring cholesterol concentrations and metabolism of serotonin.

P H A STEEGMANS

Research associate

D E GROBBEE

Professor

Department of Epidemiology and Biostatistics,
Erasmus University Medical School,
PO Box 1738,
3000 DR Rotterdam,
Netherlands

D FEKKES

Assistant professor

Section Pathophysiology of Behaviour,
Erasmus University Medical School

A W HOES

Assistant professor

Department of General Practice,
Erasmus University Medical School

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