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A controlled trial using a factorial design reported in 1946

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The introduction of randomised controlled experiments in agriculture in the 1920s and 1930s sometimes involved designing studies to make more than one comparison within the same experiment. Partly because of the different circumstances, such studies appear to have been rare in medicine at that time. An apparent early example of such a trial was reported by Wyckoff et al.,[1] who evaluated the effects of digitalis in pneumonia on patients already allocated alternately to anti-pneumococcus serum. Factorial designs, simultaneously testing two or more treatments within the same investigation, can be a more economic form of research than organising several controlled trials to assess separately different treatments for the same condition. In the Wyckoff trial, however, no factorial analysis was envisaged or conducted. The design chosen was simply an efficient means for managing patients and trial procedures conveniently.[2]

Infective hepatitis was one of the most common serious health problems within the armed forces operating in the Mediterranean at that time.[3] There was interest in the potential of protein, and of sulphur-containing amino acids (such as methionine and cysteine) in particular, to alter the clinical course of 'infective' hepatitis in animals and possibly in humans,[4–7] and there were varying opinions about the impact of dietary fat on recovery. The hepatitis/jaundice link with disturbed fat metabolism caused most clinicians to recommend low-fat diets (although it would have been equally logical to increase fat content to compensate for its metabolic deficiencies).

In 1945, Wilson et al.[7] had reported a controlled trial of the effects of supplementary methionine on hepatitis. As cysteine subsequently became more available from the wartime Ministry of Supply, they went on to assess the effects of dietary fat reduction as well as cysteine within a single, factorial trial reported in a paper that also served as a report to the Medical Research Council.[8]

Wilson et al. had formed four comparison groups from the start. They first allocated alternate patients to cysteine supplemented and cysteine unsupplemented groups; then they allocated alternate patients within each of these two groups to high- or low-fat diets. There is no indication in the paper that the authors had considered that there might be an interaction between cysteine and dietary fat, another main reason for using factorial design trials, and so the results of dietary fat and cysteine supplementation were presented separately. In fact, the reason that fat reduction was evaluated as well as supplementation with cysteine appears to have been that it was difficult to maintain calorie input using low-fat diets that were difficult to provide, unpalatable and probably unnecessary in patients who were often anorexic. These patients, while averse to *greasy* foods, were not so reluctant (in wartime-rationed Britain) to consume eggs, butter, cheese, milk and cream, which were rich in another sulphur-rich amino acid: methionine. It made sense to try to sort the matter out.

A modest benefit of cysteine as judged by numbers of relapses was suggested by the data; but the authors judged this to have reflected a higher number of relapses among controls, and 'likely to have arisen merely by chance'. Their conclusions might have differed had they used more modern statistical techniques: the results actually indicate that chance alone was unlikely to have resulted in this difference in relapse rates (2/52 cases vs. 10/51 controls, odds ratio 0.16, 95% confidence limits: 0.03, 0.79, generating a continuity-adjusted p value of 0.029). There was no hint, however, that dietary fat had any effect on cessation of relapses. This is probably just as well because the observation would have been confounded by a substantial difference between groups in the total calorific value of the diets (high fat: 3056 cals/day; low fat: 2025 cals/day), and possibly also with the dietary methionine differences, which were correlated with them. Dietary protein levels did not differ between groups.

The results should anyway be interpreted with caution because unconcealed sequential alternation would have increased the risk that the allocation

schedule would not have been adhered to strictly, a danger that eventually led to the adoption of precautions to conceal allocation schedules the following year.[9,10] Furthermore, in the hepatitis trial, patients in the different dietary fat groups were treated in separate wards housing both cysteine and control patients, an arrangement that researchers might try to avoid nowadays.

For both administrative ease and economic efficiency factorial trials became used to good effect to explore two or more treatments in a single experiment, including further study of the effects of treatments for hepatitis.[11,12] Doll and Pygott[13] used the factorial design to try to sort out the mess of multiple treatment options for patients with gastric ulcers.[14] Not only could they be used to study alternative therapies, but they were sometimes suitable (size and statistical power permitting) for investigating completely independent clinical problems.[15,16] It also became clear that factorial design trials constituted a powerful way of examining combination therapies and synergistic or antagonistic interactions between treatment combinations.[17,18]

The complexities that factorial trials can create are not inconsiderable: assessing statistical power, especially if studying interactions; matching separate inclusion/exclusion criteria; dealing with separate side effects, compliance differences and cross-over problems; and coping with trial stopping decisions. However, all these issues were absent in the early example of a factorial trial reported by Wilson et al. It was an affordable, sensible opportunity to examine two 'separate' clinical management issues in one series of patients. How 'simple' medical research once was . . . !

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