The first randomized trial of aspirin for heart attack and the advent of systematic overviews of trials

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THE FIRST RANDOMIZED TRIAL OF ASPIRIN FOR HEART ATTACK

Archie Cochrane, my predecessor as director of the UK Medical Research Council's Epidemiology Research Unit in Cardiff, was inclined to play down his own work and to encourage others. Around 1969, he was very encouraging to me when I proposed a randomized controlled trial of aspirin in patients after heart attack (myocardial infarction).

The idea that aspirin might be helpful in these circumstances was not my own. John O'Brien, a haematologist in Portsmouth, England, had concluded that aspirin might be protective in a number of thrombotic conditions.[1] He was one of the first to call for a trial of aspirin after a thrombotic event such as a heart attack,[2] and to show that low doses of the drug were likely to be effective.[3] This work had led me to be interested in platelets as a possible key factor in myocardial infarction. Every other epidemiologist seemed to be working on lipids and cholesterol, so I thought I could make a contribution if I investigated thrombotic mechanisms. My interest focused on platelets and my idea was to examine dietary and life-style determinants of platelet activity.

I recognized that we needed to show first that platelets are relevant to heart disease. I talked to a number of haematologists and plateletologists, asking if there was a test of platelet function which we could use in a large prospective field study. I was advised that the test of platelet adhesiveness used in laboratories at that time was so poorly reproducible that it was almost worthless. When James Graham, a colleague in the Department of Therapeutics in the Welsh National School of Medicine, suggested a clinical trial of aspirin I recognized that, by 'clobbering' platelets rather than by measuring their function, we could test their relevance to infarction.

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O'Brien and Graham were not the only people to call for such a trial at that time, however. In the United States another haematologist, Harvey Weiss, wrote similar letters to the journals.[4] As it happens, all these men had been anticipated during the 1950s by a general practitioner in Mississippi. Dr LL Craven described how he 'urged friends and patients to adopt the practice of taking aspirin, one or two 5 grain tablets daily.' His report goes on to state: 'Approximately 8000 men and women adopted the regime . . . not a single case of detectable coronary or cerebral thrombosis occurred among patients who faithfully adhered to this regime during a period of eight years.'[5]

It was against this background that the Epidemiology Research Unit in Cardiff warmed to the idea of a randomized controlled trial of low dose aspirin. We co-opted James Graham, and Ross Renton and others in Aspro-Nicholas, a pharmaceutical firm which agreed to supply the aspirin and matching placebo (these were produced in capsule form to disguise the taste of the aspirin).

The first patients were approached in 1970. Men diagnosed as having had a myocardial infarction were identified immediately after discharge from one of a number of local hospitals. After their general practitioners had been contacted to ensure that there were no contraindications, each man was visited in his own home, the trial was explained, and his cooperation was sought. A copy of the randomization code was kept by Peter Sweetnam, the statistician in the Unit, and the code was broken only if a physician or general practitioner required to know what his or her patient was receiving.

The dose of aspirin which was used in this trial had been long debated. Inhibition of platelet aggregation was judged to be the effect of aspirin relevant to heart attack; studies by O'Brien and others strongly indicated that a single tablet (then 5 grains or 330 mg) daily would be more than adequate. Moreover a small dose was attractive because undesirable side effects would be less likely to occur. In spite of the evidence, others recommended larger, multiple daily doses, and all the later trials reflected the persuasiveness of these opinions.

Our trial received general support from our local colleagues, some of whom were rather amused by the

notion that aspirin might be helpful in heart attack. Further afield, however, the reception was rather different. Several aspects of our work came under attack, not only the low dose of aspirin we were using. Aspirin was also under something of a cloud because high doses caused gastric irritation. For these and other reasons, many physicians were reluctant to allow their patients to be included in the trial. Many patients were also reluctant to become involved. The idea that aspirin might actually be beneficial was quite novel to them. Indeed, it seemed bizarre to some. At the end of an explanation about the trial, patients would sometimes ask: 'Come off it, Doc, what do these capsules really contain?'

After the trial had been running for about a year, a most dramatic series of events occurred. On a Saturday morning early in 1972, one of us received a telephone call from a pharmacologist in Boston, Herschel Jick. Jick had learned about our research from Martin Vessey, an Oxford epidemiologist who was working with him at the time.[6] To identify previously unsuspected harmful effects of drugs, Jick and his colleagues had been interviewing patients admitted to several hospitals in and around Boston, asking them about the drugs they had taken during the week before admission. They found that patients who had survived to be discharged from hospital after heart attacks were less likely than others to have taken aspirin before admission to hospital.[7]

This evidence put us in a most serious dilemma! There were two possible explanations for the Boston findings: either aspirin could be harmful, killing patients before they could be interviewed; or it could be protective, reducing the chances of admission to hospital with a heart attack. If the first was true, then the sooner our trial was stopped the better. If the second was true, we would have to consider expediting our trial by expanding it rapidly.

Intensive discussions took place, and with considerable reluctance, we decided that we should break the code of our trial. We expected nothing conclusive from the results because the numbers of participants in the trial at that stage were still quite small. In the event, we found that six men taking aspirin had died compared with eleven taking placebo. We were reassured sufficiently to expand the trial.

When the trial had run its course there had been 47 deaths among patients taking aspirin and 61 among those taking placebo, but this difference was not statistically significant at conventional levels of significance. We did not report the fact that, had we added 10 and 15 non-fatal heart attacks, the difference between aspirin and placebo would have been statistically significant. Our report was published in the *BMJ*,[8] alongside a paper reporting the observations made by Hershel Jick and his colleagues.[7] Both were in a section of the journal entitled 'For Debate'. At the time we felt somewhat miffed by this, but in view of the later recognition of the need for systematic overviews of evidence from all relevant trials we would now judge the caution of the Editor to have been commendable.

Table 1

Trial	*Number of patients*	*Reduction (%) in all-cause mortality with aspirin*
MRC I (1974)	1239	26 NS
CDP (1976)	1529	30 NS
MRC II (1976)	1725	30 NS
German (1978)	626	18 NS
AMIS (1980)	4524	10 NS
PARIS (1980)	1216	18 NS

All six trials: 10 859 patients
Weighted overall effect of aspirin: 23% reduction, $P<0.0001$

THE ADVENT OF SYSTEMATIC OVERVIEWS OF TRIALS

The findings in our trial led us and others to set up and report further randomized controlled trials. In all of these, mortality was lower in the aspirin groups than in the placebo groups, but in none were these differences statistically significant. We found the consistency of the results of the six trials that were available impressive, and believed that they were virtually conclusive in support of aspirin. However, two developments in the wider scene alarmed us. One was a claim based on the results of a small trial in which statistically significant differences were interpreted as evidence that aspirin was of value only in unstable angina, and not in heart attack;[9] the other reason for our concern was another claim based on small numbers that aspirin was useful in men but not in women.[10]

These retrospective conclusions based on small numbers seemed to us to be untenable, and likely to reflect the play of chance, so we conducted our own, somewhat primitive, meta-analysis of all the evidence available at that time.

Table 1 is taken from a slide that Archie Cochrane and I prepared and showed at many meetings in the very early 1980s, in the United Kingdom and elsewhere. We were very pleased when Richard Peto presented a considerably more elegant overview of these six trials to the first meeting of the Society for Clinical Trials in Philadelphia, and drew attention to the strength of the evidence in a *Lancet* editorial.[11] After this, Peto and his colleagues began to conduct a series of overviews that have become truly monumental in the history of medical research.[12] As a result of all this work, the beneficial effects of aspirin have probably been more conclusively established than those of any other drug.

Note A more extensive account of this story is available in Elwood PC. Cochrane and the benefits of aspirin. In: Maynard A, Chalmers I (eds). *Non-Random Reflections on Health Services Research: On the 25th Anniversary of Archie Cochrane's 'Effectiveness and Efficiency'*. London: BMJ Books, 1997:107–121.

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