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What is This?
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THE FIRST RANDOMIZED TRIAL OF ASPIDRIN 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. He was one of the first to call for a trial of aspirin after a thrombotic event such as a heart attack, and to show that low doses of the drug were likely to be effective. 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 lifestyle 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.

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. 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.’

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
field, 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.8

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 Herschel 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Reduction (%) in all-cause mortality with aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC I (1974)</td>
<td>1239</td>
<td>26 NS</td>
</tr>
<tr>
<td>CDP (1976)</td>
<td>1529</td>
<td>30 NS</td>
</tr>
<tr>
<td>MRC II (1976)</td>
<td>1725</td>
<td>30 NS</td>
</tr>
<tr>
<td>German (1978)</td>
<td>626</td>
<td>18 NS</td>
</tr>
<tr>
<td>AMIS (1980)</td>
<td>4524</td>
<td>10 NS</td>
</tr>
<tr>
<td>PARIS (1980)</td>
<td>1216</td>
<td>18 NS</td>
</tr>
</tbody>
</table>

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

recognition of the need for systematic overviews of
evidence from all relevant trials we would now judge the
cautious of the Editor to have been commendable.

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.

REFERENCES

3 O’Brien JR. Two in-vivo studies comparing high and low aspirin dosage. Lancet 1971;206:399–400