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NEWS BRIEFS from the Aspirin Foundation

Aspirin - too good for its own good?

Is it possible for a drug to be so useful that its value to society could obstruct research into future uses? Possibly so in the case of aspirin, according to writer and broadcaster Diarmuid Jeffreys, whose book *Aspirin: the remarkable story of a wonder drug* is published by Bloomsbury.

Writing in *The Guardian*, (8th July) Mr Jeffreys argues that placebo-controlled trials will become more difficult to carry out in the light of recent findings that aspirin may protect against some cancers and reduce the risk of dementia, in addition to its established roles as an analgesic, anti-inflammatory and antiplatelet agent.

It was hard enough to prove what is now considered incontrovertible. Early clinical trials in the 1970s to determine whether aspirin reduces the risk of cardiovascular events were not conclusive and only very large studies of secondary prevention proved capable of providing convincing evidence. Since then, observational studies have found strong statistical links between regular aspirin consumption and a lower incidence of cancers of the breast, lung and colon and possibly a protective effect against Alzheimer's disease. As a result, some epidemiologists now believe that many - or perhaps all - people aged 50 or older should be taking low-dose aspirin prophylactically.

A causal relationship between aspirin and these remarkable observations can only be

proved by the tried and tested method of randomised, placebo-controlled trials. But this would mean denying participants access to a drug which might reduce their risk of developing some very unpleasant problems and would lower their risk of a heart attack by up to a third. How would the investigators obtain ethical approval, and how would they obtain informed consent?

If interventional studies are not feasible, observational studies may plug the gap. As we reported in the last newsletter, Professor Peter Elwood and colleagues at the Department of Epidemiology, University of Wales School of Medicine, have floated the idea of aspirin prophylaxis for everyone over 50 - around one million people in Wales. This would provide such a large database to explore the relationship between aspirin and disease that confounding and bias would not be significant problems.

There is, however, another fly in the ointment. A new EU directive requires a single sponsor to accept legal and ethical responsibility for a clinical trial. Public organisations such as hospitals and universities used to spread the costs and risks between them; now, no-one outside the private sector could afford to carry the burden alone. This bureaucratic obstacle, reports Diarmuid Jeffreys, has prompted Professor Elwood to investigate natural sources of salicylate: organic fruit and vegetables are rich in salicylates, he says, and there are no liability issues in promoting them.

Kick-off with an aspirin

Medical columnist Dr Thomas Stuttford has drawn attention to the increased risk of myocardial infarction (MI) among men during important football matches (The Times, July 26th), citing research from The Netherlands which showed that mortality from MI and stroke increased by 50 percent on the day the Dutch team was eliminated from the 1996 European championship. In fact, several studies have reported similar findings: a 28 percent increase in fatal MI and stroke on match days in the North-East of England and a 25 percent increase in admissions for MI in Birmingham when England lost to Argentina in a penalty shoot-out in 1998. (The opposite is also true: when France won the World Cup in 1998, fatal MI was 30 percent lower.)

But Dr Stuttford's point is a serious one, and he neatly summarises the relevant targets from the National Service Framework for Coronary Heart Disease. A single 300 mg dose of aspirin should be given as soon as possible after a suspected MI, and anyone at risk of an MI should carry an aspirin tablet at all times. In the event of cardiac arrest, paramedics should aim to restore cardiac rhythm within 8 minutes; treatment with a fibrinolytic agent ('clot-buster') should be given within 60 minutes; and subsequent management should include treatment with low-dose aspirin, a beta-blocker, a statin and possibly an ACE inhibitor. Prompt intervention is essential: treatment within the first hour can save an additional 65 lives per 1000 patients whereas a delay of up to 4 hours means this figure falls to 25 per 1000.

Coronary protection gives aspirin the edge over coxib

Aspirin offers more quality-adjusted life years (QALYs) and is cheaper than a selective COX-2 inhibitor as prophylaxis of colorectal carcinoma, according to an analysis by US investigators (*Cancer 2004;101:189-97*).

They developed a computer model to simulate the effects in healthy 50 year-old men of taking enteric-coated aspirin 325 mg/day or celecoxib 400 mg/day for 10 years to prevent the development of colorectal cancer. They assumed the drugs were equally effective in preventing cancer and

included in their calculations the risk of adverse effects for each. However, celecoxib does not reduce the risk of coronary events and the benefits of cardioprotection were therefore incorporated only for men taking aspirin.

Compared with celecoxib, aspirin therapy resulted in an extra 0.03 QALYs and cost \$23,000 less per person over the 10-year period. Complications were more frequent with celecoxib (by 3.9 percent) and more often fatal (deaths were 0.17 percent more frequent). This is equivalent to one additional complication for every 26 people taking celecoxib, and one additional death for every 588 coxib users.

Aspirin cuts daily ischaemic episodes by 25%

Low-dose aspirin reduces both the frequency and total duration of daily ischaemic episodes in patients with chronic stable artery disease, say Greek investigators (*Heart 2004;90:389-3*).

In a double-blind crossover study, they studied the effect of 3 weeks' treatment with aspirin 300 mg/day in 40 patients with myocardial ischaemia (confirmed by 24-hour Holter monitoring). There were 251 ischaemic episodes after aspirin use compared with 339 after placebo (a 26 percent reduction) and the total duration of ischaemia was 1365 and 1765 minutes respectively (a 23 percent reduction). Markers of platelet activation, thrombin generation and inflammation - such as macrophage colony stimulating factor (MCSF) interleukin-6 and urinary thromboxane B2 and its metabolite - were also significantly reduced following aspirin use.

The investigators found that the proportional reduction in MCSF correlated with the reduction in the ischaemic burden, and concluded that the link between the markers of inflammation and reduced platelet activation is important. Aspirin may prevent transient reductions in coronary flow and improve daily ischaemia via inhibition of platelets, thrombin and cytokines, they conclude.

AF Prof