LESSONS FROM THE FIFTEENTH EUROPEAN ASPIRIN FOUNDATION SCIENTIFIC MEETING HELD IN THE ROYAL COLLEGE OF SURGEONS, EDINBURGH, ON 26 OCTOBER 1999

T.C.G. Smith, Medical Correspondent, The Croft, Pinwherry, Girvan, Ayrhsire

In his opening address to the meeting, Professor Peter Elwood, Epidemiologist from the University of Wales College of Medicine, who published the first report on the value of aspirin in the treatment of myocardial infarction, reminded the audience of the following quotation: 'Among the many useful discoveries that this age has made there are few which better deserve the attention of the public than that which I lay before you.' So wrote Reverend Edward Stone of Chipping Norton in 1757 to the President of the Royal Society about his willow bark medicine. The uses of aspirin, the final pharmaceutical outcome of Stone's researches, have spread far beyond the fevers for which he used his bark originally. It is as well known to the public today for its prevention and treatment of heart disease as for treating headache and arthritis. Soon it may become just as well known for its prevention of bowel cancer.

The conference held on 26 October 1999 covered these subjects. It also included a review of Hughes' syndrome, by Dr Graham Hughes himself. Since his 1983 report of the presence of antiphospholipid antibodies in young people with venous and arterial thromboses and recurrent miscarriages, he has shown that they can be treated successfully with aspirin (and in severe cases, warfarin).

As with any effective drug, aspirin has its drawbacks. One of these is Reye's syndrome, still a controversial issue a decade after it led to the withdrawal of medication with aspirin for children in the United States and Great Britain. The conference debated the data that led to its withdrawal. There are no plans to re-prescribe aspirin for children, but there are nagging doubts on whether we may have lost a useful drug in children without good reason.

ASPIRIN IN PREVENTION OF MYOCARDIAL INFARCTION

It is 25 years since the start of the first randomised controlled trial of aspirin in myocardial infarction. It showed a 24% reduction in deaths in men on aspirin (8.3% died on aspirin and 10.9% on placebo).[1] Since then there have been more than 170 published studies of aspirin in the secondary prevention of myocardial infarction and stroke in patients with degenerative vascular disease, more than 140 being randomised controlled trials. They produced remarkably consistent results in all the different patient groups, with around 30 to 40% reduction in vascular events.[2]

The case for secondary prevention is accepted. That for primary prevention (in people at risk of cardiovascular disease but with, as yet, no signs or symptoms) is still debated. According to Gerry Fowkes, Professor of Epidemiology and Head of Public Sciences, the University of Edinburgh, primary prevention gives the same proportionate reduction in cardiovascular events as secondary prevention. There is no significant heterogeneity in its effect in males and females, with and without an association with diabetes, or of different ages. He proposed that the concept that aspirin may be useful in secondary but not primary prevention is misleading. Categorising people as 'primary' or 'secondary' is to do so on past events. It is more appropriate to divide people according to their risk of a future event. Male smokers who are hypertensive and hypercholesterolaemic are obviously at higher risk than those without these risk factors, and whether or not they have had a previous event is a minor part of the clinical decision to prescribe aspirin.

Overall balance between benefit and adverse effects in aspirin prophylaxis varies according to the patient group. Among those at high risk, 30 to 40 per 1,000 on aspirin will avoid a vascular event. This drops to one or two in the lowest risk group. In every 1,000 people on aspirin, around one or two more per 1,000 have a gastro-intestinal bleed on aspirin as compared with placebo (the respective figures are 8/1,000 on aspirin and 6/1,000 on placebo); such bleeds rarely threaten life, unlike myocardial infarctions.

Such statistics mean that in high risk subjects it costs only around £100 to prevent a first event; in those at lowest risk the cost is around £500. These figures are very much less than those for other antiplatelet and cholesterol-lowering agents.

Early aspirin (at least 300mg soluble aspirin) in the acute stage of myocardial infarction is now standard practice, even when the patient has already been taking 100mg aspirin a day. However, even now some doctors' bags do not contain soluble aspirin, and only a minority of patients reach hospital having had it. In theory a patient who has sustained a myocardial infarct while on prophylactic aspirin has had a flush of fresh platelets into the circulation, and they must be acetylated to prevent their aggregation. The plasma half-life of aspirin is only about 30 minutes, so these fresh platelets can only be acetylated by an added dose of aspirin, and not by the aspirin taken that morning. Within minutes of swallowing it, soluble aspirin will be acetylated and in the circulation. Half of all deaths due to myocardial infarction occur before professional help arrives, and thus patients should be encouraged to take it immediately. The peak time for myocardial infarction is around 4.00 am, when help is slowest to arrive. Small doses of aspirin do work. Former views that high doses of aspirin were needed to reduce inflammation have been revised after the US Physicians Health Study reported that 325mg of aspirin given on alternate days reduced both C-reactive protein and myocardial infarction incidence.

One in five deaths from coronary heart disease occurs unexpectedly in people thought to be at low risk. Preventing these unsuspected deaths is today's main challenge. Much coronary heart disease in the community is unrecognised. Evidence in asymptomatic people may include ECG ischaemia or intracoronary calcium deposits demonstrated on routine chest X-ray. There is a continuum of risk from lower to higher levels that eventually becomes established disease, but many events occur in people who apparently have no cardiovascular disease.

Studies in low risk groups are continuing. In Dundee researchers are following aspirin prophylaxis in diabetes.

In central Scotland the aspirin asymptomatic atherosclerosis trial (AAA) is studying apparently healthy people with some risk of atherosclerotic disease, using early, but asymptomatic, peripheral vascular disease as an entry criterion.

In AAA Professor Fowkes' team is measuring ankle and arm systolic pressures and calculating the ankle-brachial systolic pressure index (ABPI). The normal ABPI distribution is skewed to lower levels, in the presence of atherosclerotic disease. At an ABPI of 0.9 or less, a two- or three-fold increase in risk of heart attack or stroke results regardless of smoking, hypertension or hypercholesterolaemia. It is a good predictor of future risk. The AAA team is randomly allocating people with low ABPI to aspirin or placebo to see if a difference can be demonstrated to their cardiovascular death rate.

Professor Fowkes estimates that aspirin must be taken daily by 100 people at high risk or by 700 people at low risk to save one life per year in each category. He sees no reason for it to be taken by the population at large, but higher risk groups without vascular symptoms may benefit, mainly by reductions in non-fatal myocardial infarctions.

Aspirin 75mg daily is effective in the secondary prevention of strokes and heart attacks in people with past myocardial infarctions. There is good reason to believe it will also prevent them in people at high risk (smokers, with hypertension and/or hypercholesterolaemia) who have, as yet, no cardiac symptoms. Ankle-brachial systolic pressure difference is a good measure of risk.

ASPIRIN IN BOWEL CANCER

Aspirin may prevent large bowel cancer by inducing apoptosis in cells undergoing malignant change. Chris Paraskeva, Professor of Experimental Oncology, and Director of the CRC Colorectal Tumour Biology Research Group, the University of Bristol, forecasts that it may well be used in future alongside novel anti-cancer treatments.

One target disease for aspirin is familial adenomatous polyposis (FAP). Inheriting a single mutation for FAP in one gene leads to a near 100% risk of colonic adenocarcinoma.

The evidence that aspirin and non-steroid anti-inflammatory drugs (NSAIDs) may prevent cancer is epidemiological, experimental and clinical. In each of 15 studies published since 1991 aspirin reduced the incidence of colonic polyps or colorectal cancer, the relative risk (RR) ranging from 0.5 to 0.8.

Some carcinogenic gene mutations increase cell proliferation, some prevent apoptosis, yet others increase cell invasion into other tissues. In experimental models aspirin restricts colorectal cell proliferation and inhibits tumour vasculature formation by blocking angiogenesis. The Bristol group added salicylate to benign and malignant colonic tumour cells; apoptosis was stimulated in both groups of cells, the carcinoma cells being more sensitive to the salicylate than the non-malignant cells.

Aspirin's effect on prostaglandin synthesis may also be important. Many tumour cells contain high levels of prostaglandins, and aspirin may inhibit their production, with the potential to block many other biochemical pathways. Cyclo-oxygenase, itself blocked by aspirin, may produce carcinogenic compounds.

Two studies are currently in progress on aspirin in bowel cancer. The Newcastle team is co-ordinating the use of aspirin in FAP to establish if it will reduce polyposis. In the hereditary non-polyposis colon cancer study, aspirin and dietary changes are being compared for their effects on tumour development. American experimental data support the epidemiological data: the British clinical data will soon be forthcoming.

Aspirin 300mg daily lowers cancer rates by between a fifth and a half in patients with familial polyposis coli. It may do so by inducing apoptosis in cells undergoing malignant change. Non-polypotic bowel cancer may also respond to aspirin: trials are under way to test this.

ASPIRIN IN ACUTE STROKE

Aspirin is far less accepted as part of the emergency treament for acute stroke, even though the evidence for it is just as good as in myocardial infarct. This was the main theme of Peter Sandercock, Professor of Medical Neurology at the University of Edinburgh.

A patient with acute stroke requires a brain scan; if it shows haemorrhage, aspirin should not be given. Most strokes, however, are ischaemic, and the brain in ischaemic stroke appears normal on CT; MR scan may show absence of flowing blood. Aspirin will not unblock the artery: this needs thrombolitic drug, but it may help a self-unblocking artery to stay unblocked, and may keep arteries in the penumbra open, thereby minimising ischaemic damage.

Two large trials have studied the effects of aspirin in the first 48 hours of stroke. Patients in the Chinese and International stroke trials (around 20,000 patients in each trial) were all seen within 48 hours and randomised to aspirin and subcutaneous heparin for 14 days, after which all were given aspirin long term. The International trial was in four continents, 36 countries, 467 hospitals and 19,436 patients, 68% undergoing CT scan pre-treatment. The Chinese acute stroke trial followed 10,000 patients on aspirin and 10,000 on placebo in 413 hospitals across China; 87% had pre-treatment CT scans. Sadly the United Kingdom was the country with the lowest scan rate. British radiologists resisted requests for CTs in stroke patients, yet, when asked whether they would want a scan themselves before stroke treatment, they all said that they would. The final CT scan rates, to define the diagnoses, were around 97% in both trials.

In both trials aspirin reduced recurrent ischaemic stroke rates. It caused one or two extra bleeds in the brain per 1,000 cases of haemorrhagic stroke. Overall the risks of death or non-fatal stroke were reduced by 11%. For every 1,000 patients treated with aspirin, nine lives were saved. Aspirin reduced the incidence of post-stroke dependence by 5%: the effect was small, but definite. It also improved the chances of a complete recovery.

Professor Sandercock concluded that in the first six hours after an acute stroke aspirin is beneficial. If a scan cannot be performed in that time, aspirin should be started and

continued until the scan result dictates otherwise. No particular category of patient reacts to aspirin differently from the rest. Heparin is not more effective than aspirin, even in patients with atrial fibrillation. Aspirin is associated with a small excess of bleeds but the risk is very low particularly if heparin is co-prescribed.

CT scans are needed to determine the cause, as the clinical signs do not distinguish well enough between ischaemic and haemorrhagic stroke. There is strong evidence of benefit in using organised stroke services and routine early aspirin, but further trials are needed to establish the benefits of thrombolysis and anticoagulants. Today, 5,000,000 people world-wide have acute ischaemic strokes each year. Only 1,000,000 get medical attention and aspirin and this surely needs to change.

Aspirin should not be withheld from patients with acute stroke because of fears about bleeding. Two large trials have shown that it is beneficial (reducing mortality and post-stroke morbidity) in acute stroke – extra bleeding due to aspirin occurs in only one or two per 1,000 cases. The benefits far outweigh the risks. However, more CT scans (the only sure way to distinguish between ischaemic and haemorrhagic stroke) should be done in acute stroke patients, so that those with haemorrhage can avoid even this small risk.

ASPIRIN IN PULMONARY EMBOLISM PREVENTION

Platelet activation and aggregation are not considered among the prime causes of venous thrombosis and pulmonary embolism, yet Colin Prentice, Professor of Medicine, the University of Leeds, reported that aspirin prevents them.

He proposed that aspirin works in venous thrombosis and embolism by inhibiting the platelet surface phospholipids that produce thrombin.

He described the pulmonary embolism prevention trial (PEP), a study of thrombotic complications after hip fracture in 140 centres.[3] PEP randomised 13,356 patients undergoing surgery for fractured hip to daily aspirin 162 mg or placebo for five weeks. The surgeons could add heparin or other anticoagulation as they wished. The primary endpoints were mortality from fatal pulmonary embolism and cardiovascular diseases. Other endpoints were morbidity during hospital stay from pulmonary embolism, deep vein thrombosis and cardiovascular diseases, and total mortality at five weeks.

The patients ranged in age from 65 to 104. After 35 days, 82% were discharged from hospital and alive, 11% were still in hospital, and 7% had died. Pulmonary embolism was a relatively small proportion of total mortality (52 patients, 6%). In the aspirin group deaths from pulmonary embolism were half those in the placebo group. Non-fatal pulmonary emboli and deep vein thromboses were reduced by a third in the aspirin group, the main reduction in thromboses being in the femoral and iliac veins ($p = 0.0006$). Adding heparin to aspirin made no difference to thromboembolism.

Aspirin had no effect on local bleeding, such as haematomas. Wound bleeding was graded by blood transfusion; there was a very small difference in transfusion volumes. All the serious bleeds (six per 1,000) were easily treated by transfusion. Professor Prentice regards these data as substantiating the use of aspirin as an antithrombotic after hip surgery. It causes less bleeding than heparin, the treatment is easily continued post-discharge, and is inexpensive.

Aspirin has a reputation for working in arterial, but not venous, thrombosis. The Pulmonary Embolism Prevention (PEP) trial showed that in patients with hip fractures treated surgically, it reduced deaths from pulmonary embolism by half. It caused no serious or unmanageable bleeding. PEP also showed that with modern surgery, deep vein thrombosis and pulmonary embolism are now very rare.

REYE'S SYNDROME – THE ASPIRIN ENIGMA

Aspirin and Reye's syndrome were linked in the 1980s, culminating with the withdrawal of the drug from use in children up to 12 years old in 1986. Dr Peter Lewis, Senior Lecturer in Bio-statistics at the School of Postgraduate Medicine, the University of Bath, and Ken MacRae, Professor of Medical Statistics at the European Institute of Health and Medical Sciences at the University of Surrey, doubted that this was the right decision.

It was made on case control and cohort studies. Much was made of the fact that there were four case control studies, but they were all in the same population, so that it was one case control study repeated three times. There is still no plausible biological model to explain Reye's link with aspirin, and no good case definition. Experts in Reye's syndrome would disagree on the diagnosis in at least 30 % of the cases reported.

The one type of study that would have resolved the doubts, a randomised controlled trial, was not possible in the American population, as it would involve withholding non-prescription medicines from patient groups. A comparative cohort study with historical controls was chosen instead. For this to be acceptable, the cohorts must be identical except for the use of aspirin in young children. That needed a sudden cessation of aspirin prescribing. This did not happen. There was a gradual drift away from aspirin in North America and other countries, so that it is impossible to tell when it stopped. The change took about 15 years to happen, from the early Eighties onwards.

The way of making the diagnosis should have remained constant before and after the end of aspirin prescribing. This, too, did not happen. Many doctors only diagnosed Reye's syndrome when aspirin had been prescribed; if the symptoms occurred without it, another diagnosis was made. Surveillance of Reye's cases was poor: there was no national support for the study. It is probable that only 20% of all illnesses fitting the diagnosis of Reye's were reported. Since 1994 there have been none.

Different centres reported vastly different relationships between aspirin and Reye's. In some, 100% of the Reye's cases had had aspirin: Japanese centres reported much lower percentages, and in Australia the figure was 5%. In the United Kingdom study, the cases came from all over the country, but the controls were from a few hospitals in the south of England. Was this truly one disease, or were there

several diseases, and why were there such differences?

Control groups were taken from emergency rooms, schools, communities and in-patients and they did not match the cases. Their use of aspirin ranged widely; in some cases, the aspirin may have been started after the onset of Reye's. An early sign of Reye's is vomiting; some children took the aspirin after it started, yet the drug was blamed for their illness. Typical Reye's syndrome is biphasic, with a flu-like syndrome followed by the second phase of brain and liver disease. Drs MacRae and Lewis would be more confident of the link if the aspirin had been taken in phase one.

Most people take aspirin for fever, so that cases should have been matched to controls with an equal indication for taking it, such as a fever, but there is little evidence that this happened. There may have been bias in recall, too. Many patients and their parents could not recall if they had taken aspirin for certain, and recall was particularly difficult when the child had died. There was also evidence of diagnostic bias, in that the decision to call the illness Reye's was influenced by knowledge of aspirin exposure, and of reporting bias, when the diagnosis was made from recorded reviews, non-tertiary care hospitals, and by expert panel review.

But for Professor MacRae, the most telling evidence that aspirin was not responsible for Reye's comes from the Yale study that led to its ban. Reye's syndrome is staged according to severity. Paradoxically its association with aspirin was weaker in the more severe cases and in the most severe cases the link was weakest of all. This inverse dose response strongly argues against the link.

Professor MacRae concluded that Reye's syndrome is probably a heterogeneous group of illnesses of toxic or metabolic origin and that its positive relationship with aspirin is as untenable as the negative association proposed with paracetamol.

Doubts remain about the diagnosis of Reye's syndrome and whether aspirin was actually its cause in the cases described mainly in the 1980s. How can the apparent inverse dose relationship between the drug and the severity of the disease be explained? Were the trials properly controlled, were the diagnoses unbiased, and were the epidemiological studies flawed because not all cases in the communities concerned were reported? Aspirin will not be used again in children – but have we lost a good drug on poor evidence? The debate continues.

ASPIRIN AND THE ANTI-PHOSPHOLIPID SYNDROME

Graham Hughes is consultant rheumatologist at the Guy's and St Thomas' Hospital Trust, where he set up, in the Rayne Institute, the Lupus Arthritis Research Unit. He is editor of the journal *Lupus*. His main research interest is in systemic lupus erythematosus (SLE), not in itself a rare disease. However, he is seeing more and more people with anti-phospholipid syndrome, named internationally in 1992 as Hughes' syndrome.

Women with it have recurrent spontaneous abortions, arterial and venous thromboses, and early myocardial infarctions. His interest in the disease started in 1975, in Jamaica, where he found women with 'Jamaican neuropathy', with meningomyelopathy, false positive syphilis tests, and thromboses in veins and arteries. In 1983 he wrote of recurrent thrombosis, abortion, cerebral disease, lupus and a circulating protein pro-coagulant co-factor, as the anti-phospholipid syndrome.[4] Later in 1983 he added thrombocytopenia, livido reticularis, teenage migraine, demyelinating disease, Budd Chiari syndrome and dementia to the list of signs and symptoms. His colleague, Nigel Harris, developed the tests and the offending pro-coagulant protein beta-2GP-1 is now well studied. Other protein co-factors that promote clotting include prothrombin. Dr Hughes' group showed that people who possess anti-phospholipid antibodies and prothrombin antibodies have a 60% risk of thrombosis, and that many develop dementia. Many patients with Hughes' syndrome have memory loss and fail to report it, perhaps because they also have cognitive disorders. They improve neurologically when they start anticoagulants; indeed they know precisely, because they feel worse, when their INR has fallen. Among their neurological problems are choreo-athetosis and transverse myelopathy, and some are diagnosed as having multiple sclerosis. Most respond to warfarin.

Antiphospholipid antibodies bind to platelets, alter clotting factors and directly affect endothelial cell function. Aspirin is the mainstay of treatment. The best data for its use are from pregnancy, in which Hughes' syndrome is the more important thrombotic cause of recurrent pregnancy loss, which may occur as late as the seventh month. Simply explained, the placenta thromboses. Treatment with aspirin alone is remarkably successful. Among women with anti-phospholipid syndrome, whose previous pregnancies had a 19% live birth rate, the current rate on aspirin is more than 70%. Adding heparin may help further. There may be different subsets of the disease, depending on whether patients have arterial or venous thrombosis.

Perhaps the United States might not have existed had it not been for a case of Hughes' syndrome. From 1683 onwards, Queen Anne had 18 miscarriages, a facial rash and arthritis. Her lack of an heir led to the invitation to the Hanoverians to take the throne, and it could be argued that their incompetence in managing their colonies led to the establishment of the USA.

Hughes' syndrome causes many of the strokes that affect people under 45 years old. It is preventable, as are many cases of migraine, memory loss, deep vein thrombosis on the contraceptive pill, and some cases of Alzheimer's disease. Any woman who has had one miscarriage, recurrent migraine, an early vascular event and is under 40 should be tested for it. Dr Hughes estimated that there are probably ten such women in each average-sized general practice.

Anti-phospholipid syndrome is not uncommon – but do doctors recognise it? Young women with migraine, a facial rash, deep vein thrombosis on the pill and recurrent miscarriages should be tested for anti-phospholipid antibodies. The test is not expensive. Aspirin, with perhaps added heparin, helps them greatly, may allow them to complete their pregnancies, and avoid mid-life onset of stroke or dementia.

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