Professor Peter Rothwell

First Winner of the International Aspirin Foundation Senior Science Award

Academics and medical researchers met together at The Caledonian Club, in London, on Tuesday 9th December 2014 to honour the winner of the first Senior Science Award given by the International Aspirin Foundation. The Foundation, set up in 1974 to co-ordinate world-wide understanding of, and research into, the uses of aspirin, has marked its 40th anniversary by its decision to initiate a series of awards to clinicians and scientists who have made outstanding contributions to our knowledge of this amazing medicine.

Aspirin, brought into medical practice in 1899, was the first synthetic medicine to achieve worldwide use, initially as an analgesic and anti-inflammatory agent. More than a century later it is still widely popular for pain and fevers, but that is by no means its only use. Since Sir John Vane and colleagues discovered its effects on platelet function, aspirin found a second use in preventing arterial thrombosis, so that it is now just as well known to the general public for its ability to prevent strokes and heart attacks as for its action on pain. The continuing decline in serious cardiac and cerebrovascular events and deaths among people over 50 years of age is in part to its use in the secondary prevention among men and women at risk.

Yet both of these uses of aspirin may now be eclipsed by its new use in cancer. It is for this that Professor Rothwell was chosen by the International Aspirin Foundation as the clinician most deserving of the First Senior Science Award.

This report of the Award ceremony describes his work and the current status of aspirin research, particularly into its uses in preventing, and possibly, in future, treating cancer metastases.

Professor Peter Rothwell

Professor Rothwell is the Action Research Professor of Neurology in the Nuffield Department of Clinical Neuroscience, Oxford University. In 2000 he established the Stroke Prevention Research Unit that now employs more than 40 research staff. He has published more than 400 scientific papers and several books, covering aspects of primary and secondary prevention of stroke, the effects of high blood pressure on the brain, and the risks and benefits of aspirin.

This is by no means his only award. Among the others have been the first British Medical Journal Award for Outstanding Contribution to Clinical Research, the Foulkes Foundation Medal of the Academy of Medical Sciences, the World Stroke Organisation President’s Biennial Award for Outstanding Research, and the Kinmouth Medal of the Royal College of Surgeons.
He combines his research responsibilities with clinical practice as a consultant neurologist for the Oxford University Hospitals Trust, but his research interests now range beyond that of vascular disease in neurology. For over a decade they have included the effects of aspirin on cancer, and in particular in cancer of the bowel, its incidence, its metastases and mortality. It is for this seminal work, and the interest this has generated in the medical research and clinical communities around the world that the International Aspirin Foundation selected him as the well-deserved winner of its inaugural award.

**The award presentation – The International Aspirin Foundation**

**Nick Henderson and Pippa Hutchison**

Nick Henderson, the driving force behind the Foundation since its inception in 1974, welcomed the audience. He announced that he was passing on the post of Executive Director to Pippa Hutchison, until now his co-director. She briefly reviewed the work done with aspirin since 1974, and the decision to celebrate the 40 years with the introduction of two awards, the first a Senior Award for researchers with a proven record of excellence, which would alternate each year with a Junior Award.

Why should aspirin take up so much research time and effort? Pippa explained that its uses have spread widely since its effects on platelets became widely known in the 1960s. Its history goes back much further. Hippocrates used extracts of willow (Salix) leaves to ease childbirth pain and fever as long ago as in 400 BC, since when salicylates have since been in continual use. From their active principle aspirin was synthesized 115 years ago and it has become inexpensive, easy to administer, and available all over the world. It has been unrivalled as an analgesic for 100 years and for thrombosis prevention agent for more than 40, and in the last twenty years it has generated great interest in its place in oncology. Mrs Hutchison introduced Professor Peter Elwood, of Cardiff, to explain this unexpected aspect of its use. Professor Elwood has been active in research into aspirin for more than 40 years.

**Professor Peter Elwood**

Professor Elwood first spoke of his valued friendship with and affection for Nick Henderson, who he said has played a key role in the development of aspirin. He added to Pippa’s history of aspirin by mentioning that plant sources (that would have contained salicylates) had been mentioned in medical texts long before the time of Hippocrates – the great man was only continuing a regimen that had been effective for generations before him.

However it took the expertise of a 19th century pharmaceutical company, Bayer AG, to convert the plant based remedies into a synthetic compound that could be produced on an industrial scale for a mass market. It became the first synthetic drug and played a great part in establishing the modern pharmaceutical industry.

Professor Elwood’s team conducted the first randomised trial of aspirin 40 years ago. It introduced the principle of the use of aspirin in cardiovascular disease. It was followed by Richard Peto’s overview of six trials for the same indications. Today the risks and benefits of aspirin are hotly debated. Professor Elwood stressed that its risks are grossly exaggerated, and that this may help
explain why the role of aspirin in vascular disease is being eroded by other drugs. This steady diminution of its use was predicted by Professor Rothwell.

Cancer prevention may therefore become aspirin’s main use. Animal studies were the pointer to it in the 1960s, then at the turn of the century the idea was reinforced by studies of apoptosis and of mismatched DNA repair. Professor Elwood’s team brought together all the evidence of aspirin’s effect in cancer, including Mendelian randomization which produced highly favourable evidence. At the time Professor Elwood felt that although the evidence was extremely persuasive it was unlikely that there could be a randomised trial involving placebo comparison, and that clinicians would have to depend for evidence of its effect in other, less acceptable or persuasive studies.

He could not have been more wrong. In the same year Professor Rothwell’s team published six RCTs on the subject! He had gone back to the old vascular randomised trials and followed up the patients with a view to seeking an effect on cancer. He found it. There was significant evidence of protection against cancer among those who had been randomised to aspirin.

Why, then, is aspirin not promoted more fully for cancer prevention? The main reason is that it is perceived to cause bleeding. Professor Elwood insisted that the bleeding has been greatly exaggerated – although it is around twice as common among those taking aspirin as in those not taking it. However, the bleeds on aspirin are very much less serious than alleged.

Professor Carlo Patrono’s work in Rome shows that people who bleed have evidence of active stomach pathology, such as *Helicobacter pylori* infection or other causes of irritation, that when eradicated avoids the risk of bleeding. The risks of bleeds fall with the years, so that after 4-5 years of aspirin treatment there is no evidence of excess gastrointestinal bleeds. As for cerebral bleeding there was no evidence of any increase over 10 years in patients who have well controlled hypertension.

Although there is no valid evidence of an increase in fatal bleeds on aspirin (in the trials fatal bleeds are the same as or lower on aspirin than on placebo), medical colleagues still believe that aspirin can be responsible for bleeding. This is a problem that Professor Elwood says must be overcome.

The benefits of aspirin do not stop with its cardiovascular effects. In the Rothwell randomised trials the patients on aspirin survived for longer and metastatic spreads of cancers decreased. However, this is only overview evidence: these benefits may apply to specific subgroups of cancer who will respond and not to others. That is why we should all be pleased by the large randomised trial about to be undertaken by Dr Ruth Langley and her colleagues.

Professor Elwood pleaded that all the evidence should be made freely available by consultants to patients so that they can make up their own minds on whether or not to take aspirin. A few years ago Professor Elwood held a ‘citizen’s jury’ under the title of ‘My health and responsibility’. The members of the public, who acted as jurors, were unanimous in wanting to know the results of research ...’even before there was agreement amongst doctors.’

Summing up the present state of aspirin prescribing, Professor Elwood said that it:

- Is effective in heart attacks and strokes but other drugs are now competing for its place.
- Is effective in reduction in cancer according to Professor Rothwell’s 6 follow up papers.
- May be effective in increasing survival of patients with cancer.
- Side effects do exist but they are exaggerated.
- His botanist friends say there is much more to discover about the molecule.

Peter Rothwell, said Professor Elwood, is being celebrated for his work on bringing the news about aspirin in cancer to the world. It is, he added, ‘The work of a genius.’

He then presented Professor Rothwell with a framed statement of the award, a crystal claret jug engraved with the crest of the Foundation, and a cheque.

**Professor Rothwell**

In response Professor Rothwell was modest about his contribution, saying that the introduction was over generous. In thanking the committee of the Foundation for selecting him, he said that the research effort so far had only scratched the surface of what aspirin does. It will perhaps take another 40 years before we will get to the bottom of some of the effects of aspirin on non-vascular outcomes. He hoped that the awards will continue biennially, and thanked his colleagues, who included Sir Richard Doll and Richard Peto, Tom Meade, Jill Belch, Jackie Price and other collaborators, numbering over fifty in all, without whom the research would have been impossible. The next forty years of research will be into understanding the effects of aspirin on non-vascular outcomes.

**The interview**

Professor Elwood then interviewed Professor Rothwell in front of the audience about his work: the conversation is reported here:

Elwood: You are primarily a neurologist. What stimulated your interest in aspirin in cancer?

Rothwell: My main interest is in stroke: we have given aspirin to more than 20,000 people with TIA and stroke in the clinical service that I am involved in and so I inevitably became interested in the effects of aspirin. In addition, my mentors such as Charles Warlow in Edinburgh, Professors Doll and Peto in Oxford, and Henry Barnett in Canada were all involved in randomised trials of aspirin and encouraged my interest. There were hints from these trials that aspirin had effects on non-vascular outcomes as well as vascular ones. In particular there was a signal in the old stroke prevention trials that aspirin reduced non-vascular deaths.

Elwood: I am envious that you had the idea of following up the vascular trials.

Rothwell: We were not the first to do it. The US Physicians Health Study and the Women’s Health study had already done it but found no reduction in cancer incidence in the aspirin groups up to ten years after enrolment. We decided to follow up for longer than that to see if there might be a signal beyond ten years. It was partly our good fortune that we were initially following up UK trials that had started earlier than the US trials and could therefore address the question of possible longer-term effects.

Elwood: That delay had been predicted before your results were known. Did you have difficulties in putting the studies together?
Rothwell: Yes, previous observational studies had suggested that effects of aspirin on cancer incidence might be delayed for more than 10 years. It did take us some time to get approval to do post-trial follow-up for some of the trials. For example, when we applied to get ethics approval to get cancer registration data for participants in the UK-TIA Aspirin trial the local Ethics Committee said that we should first try to trace the individuals from the trial or to contact their living relatives in order to get consent to access any centralised cancer registrations. This would have been an enormous logistical and administrative task and was well beyond our funding. Eventually we persuaded the ethics committee and two subsequent national committees that the project was ethical and scientifically sound and we were allowed to access centralised cancer registrations. Sadly the process was so long-winded that Richard Doll had died before we finally got the results. It was sad that he didn’t get to know the fruits of the project that he had strongly supported.

Elwood: How convincing is the evidence now? We know about cancer of the bowel and breast: what about other types of cancer, such as of the blood?

Rothwell: Broadly speaking, there are two separate effects of aspirin: a shorter-term reduction in blood-borne metastasis, which seemed most marked for colorectal cancer but which might be present for several cancers; and the longer-term reduction in cancer incidence. In terms of the effect on metastasis, we have to say that we only know about cancers developing while the patient is already on aspirin i.e. in the old trials of aspirin. Starting aspirin after diagnosis of cancer is a different question and that is why new trials of aspirin as an adjuvant treatment for cancer are starting. In terms of the longer-term effect on cancer incidence the effect on colorectal cancer is now proven for low dose aspirin, and there is now increasingly strong evidence of a reduction in risk of oesophageal and gastric cancer with low-dose aspirin. The evidence for other types of cancer is less convincing. There may not be startling effects of low-dose aspirin on incidence of non-gastrointestinal cancers and we are still working on the effects of high-dose aspirin.

Elwood: Should aspirin be actively promoted to the general public?

Rothwell: We need more data on daily low dose aspirin in women. As gastrointestinal cancers account for less than 10% of all cancers in women in many cohorts, a reduction of half in incidence would make little difference to overall cancer incidence and mortality. But in men gastrointestinal cancers account for around one quarter of all cancers and so the overall impact of low-dose aspirin is greater.

Elwood: What about promoting it for men over 50 years old?

Rothwell: Taking aspirin for 5 years is likely to do more good than harm for men aged 45-65 years. The benefit is already established for vascular risk in otherwise healthy men with vascular risk factors: the cancer story adds to that benefit. There are risks of course, but it would help if we had a simple measure of the overall balance of risk and benefit. For example, if we could say that taking low dose aspirin for 5 years in one’s 40s or 50s would prolong a good quality of life by perhaps a year it would help people to understand the decision better. The ASPREE trial in Australia and the 
US will also give us useful insights into the effects of aspirin at older ages and is also looking at simple overall measures of risk and benefits. If we could say that people will live longer if they take aspirin and remain in a healthy state with reduced disability the risk message would be clearer and simpler.

Elwood: It has been shown that healthy behaviours – five healthy lifestyle factors plus low dose aspirin – reduces dementia and improves quality of life by reducing illnesses by 60% in later life. That is a good theme on which to end.

Addendum

Your reporter (Dr Tom Smith) was privileged to be able to chat with some of the prime movers in the aspirin story after the interview. Prime among them was Professor Carlo Patrono, of Rome, whose research into the biochemistry and function of platelets has clarified the action of aspirin and other drugs upon them. In particular he is interested in the bone marrow precursors of platelets, the megakaryocytes. Low dose aspirin has a four-hour life in the bloodstream yet once a day aspirin is enough to keep platelets inactive for more than a day. Aspirin must therefore have a more lasting effect on megakaryocytes for its effect on platelet aggregation to continue beyond its presence in the blood. Some of Professor Patrono’s current research is therefore targeted on megakaryocyte function, a much more difficult proposition than studying platelets as of course megakaryocytes exist only in bone marrow and not in the circulation.

Asked if aspirin’s effects are possibly due to its actions on other cells apart from platelets, Professor Patrono firmly believes that the principal action of aspirin, for all its benefits, is to do with platelet function. We do not yet know all the complex actions of platelets, but he is sure that we will learn much more about them in the near future. Platelet aggregation and adhesion appears to be the basis for aspirin’s preventive effect against metastases. A main method of spread of primary cancers depends on the ‘stickiness’ or platelets. Cells that break off from the primary cancer and enter the bloodstream stick to platelets, which carry them to distant sites. There, the platelet/cancer cell combination adheres to the walls of smaller arteries, initiating metastases. By reducing platelet adhesiveness aspirin prevents cancer cells from combining with platelets. Circulating white blood cells can then recognize and destroy them (they do not ‘see’ the cancer cell when it is attached to a platelet), making their spread very much less likely.

Asked which diseases might be the future targets for aspirin research, the group (Elwood, Rothwell, Langley and Patrono) agreed that pre-eclampsia may be one: there is already evidence of benefit. Dementia may be another, but today’s focus must be to complete the trials in cancer.

On that subject, I was pleased to talk to Dr Christopher Coyle, research registrar to Professor Langley’s group, and to Marta Compo, the research scientist responsible for organising and supervising their ADD-Aspirin trial that is about to start in early 2015. Patients with breast, colorectal, gastro-oesophageal or prostate cancers will be enrolled in this double blind randomised trial of aspirin and placebo. Follow up will be at least 10 years from randomisation. One hundred centres, initially in the United Kingdom, with four principle investigators in each centre, will be involved. There are plans for the trial to be established in India, later.
I felt privileged to be in the company of all these dedicated clinicians and scientists. Their work has been, in the main, unsung and hardly known about by the medical profession and is certainly not known by the public at large. Perhaps this is because aspirin is an old drug that is, to most people, just an ordinary over-the-counter remedy. Partly it is because it has had a bad press because of the claims about its ability to cause bleeding. Partly it is because of the media’s hunger for the new ‘magic bullet’ that will cure complex diseases. Aspirin doesn’t fit that profile, yet it has had a memorable history, and its future may be even more amazing.

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