Aspirin in the 21st Century  
Common mechanisms of disease and their modulation by aspirin  

A report from the 2015 Scientific Conference of the International Aspirin Foundation  
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Abstract  

Aspirin has more than one action in its effects on disease. Its acetylation of cyclo-oxygenase 2 (COX-2) in platelets leads to the blockade of pro-inflammatory chemicals and generation of anti-inflammatory mediators, and increase of nitrous oxide (NO) production, which helps to preserve arterial endothelium. But platelets are not its only target. There is now evidence that aspirin has a direct anti-tumour effect on intestinal mucosal cells that block their potential transformation into cancer cells.

Randomized placebo-controlled trials (RCTs) in people with histories of colorectal neoplasia have shown that aspirin reduces the risk of recurrent adenomas, and reduces long term cancer incidence in patients with Lynch syndrome. Among women given aspirin for cardiovascular disease there were fewer cancers than in those given placebo. Epidemiological evidence has suggested that aspirin treatment after cancer is diagnosed reduces the incidence of metastases and prolongs survival, and long term studies of anticancer treatment with aspirin are under way to confirm this.

Apart from cancer studies, aspirin use is now firmly established as treatment for antiphospholipid syndrome (Hughes syndrome), and is being used to prevent and treat the heightened risk of cardiovascular disease in diabetes mellitus and in patients with HIV.

It remains, of course, a first line treatment of choice in acute pain: randomized trials of its use for wisdom tooth extraction pain has shown that it is more effective than placebo and more useful than paracetamol.

Professor Peter Rothwell of Oxford University chaired the annual Scientific Conference of the International Aspirin Foundation in London on 28 August 2015. It took the form of four sessions.

In the opening session, on the mechanisms of action of aspirin, the first speaker, Dr Karsten Schröer of Berlin, explained that aspirin combines a reactive acetyl group with salicylate. Most, perhaps even all, of its pharmacological actions such as prevention of thrombosis and of colorectal cancer are due to target structure acetylation.

The best known of these actions, which occur with the low daily dose of 75mg, is on cyclo-oxygenase-1 (COX-1) in platelets. This is the key to blockade of a cascade of platelet functions, including that of the release of pro-inflammatory chemicals such as sphingosine-1-phosphate (SIP). Aspirin acetylating of COX-2 allows generation of anti-inflammatory mediators. A third aspirin action is acetylation of eNOS, which increases nitrous oxide (NO) production, which directly helps preserve
arterial endothelium (Hennekens C H et al - A randomised trial of aspirin at clinically relevant doses and nitric oxide formation in humans. J Cardiovascular Pharmacol Ther 2010 15(4) 344-8). Professor Schrör’s group is now investigating acetylation targets which will explain its anticancer effects.

Continuing with the mechanism of action theme, Professor Joan Claria, of the University of Barcelona, stated that it may involve the generation of a newly discovered series of eicosanoids called ASA-triggered lipoxins, produced when aspirin acetylates COX-2 (Claria J and Serhan C N - Aspirin triggers previously unrecognized bioactive eicosanoids by human endothelial cell leukocyte interaction. Prof Natl Acad Sci USA 1995 92 9475-79). Other possibilities are ASA-triggered resolvins derived from omega-3 fatty acids. They share anti-inflammatory and ‘pro-resolution’ properties, which are likely to be part of aspirin’s benefits (Servan C N Pro-resolving lipid mediators are leads for resolution physiology. Nature 2014 510 92-101).

Of concern, of course, is the well-known risk of bleeding with aspirin. Why this happens was addressed by Professor Angel Lanas, of the University of Zaragoza. Bleeding in the upper, and to a lesser extent, the lower, gut, is related to interference with the coagulation cascade instituted by platelets. However there are other factors that make people more likely to bleed with aspirin. Important among them are a history of peptic ulcer, older age, combining aspirin with NSAIDs, and higher aspirin dose. Professor Lanas described prevention strategies to lower the risk of bleeding, along with the use of proton pump inhibitors and perhaps H. Pylori eradication (Barkun A S et al - International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2010 152(2) 101-13). The way forward may be with the former, as the benefit of the latter is still to be proven.

Aspirin’s benefits in colorectal cancer may not be solely due to its actions on platelets. Professor Paola Patrignani, of G d’Annunzio University, Chieti, who participated by Skype from Italy, proposed that aspirin has benefits other than those on platelets that add to its effects on carcinogenesis in the bowel (Thun M J Jacobs E J Patrono C - The role of aspirin in cancer prevention Nat Rev Clin Oncol 2012 9(5) 259-67). She admitted that the platelet effect is crucial. Tumours metastasize because cancer cells are transported by the circulation to distant sites by their adherence to platelets. By inactivating platelet ‘stickiness’ this mechanisms is blocked, and circulating leucocytes ‘recognize’ the neoplastic cells and destroy them (Dovizio M Alberti S Guilem-Lobat P Patrigiani P - Role of platelets in inflammation and cancer: novel therapeutic strategies. Basic Clin Pharmacol Toxicol 2014 114(1) 118-27).

However, aspirin almost certainly also acts directly on the colorectal mucosal cells. Professor Patrignani and her colleagues have developed a new assay of four different molecular biomarkers of pathways implicated in the genesis of cancer in colorectal epithelial cells (Patrignani P et al - Reappraisal of the clinical pharmacology of low dose aspirin by comparing novel direct and traditional indirect biomarkers of drug action. J Thromb Haemost 2014 12(8) 1320-30). They showed that aspirin changes the rectal mucosal phenotype in a way that would delay or prevent the early development of colorectal cancer.

Session Two concentrated on the clinical evidence of the effect of aspirin on cancer. The first speaker, Professor Andrew Chan, of Massachusetts General Hospital, said that the evidence that it is linked to a lower risk of colorectal cancer is remarkably consistent. Five placebo-controlled randomized trials (RCTs) in people with histories of colorectal neoplasia showed that it reduced the risk of recurrent adenomas, which are the precursors of most cancers. Other RCT confirmation of aspirin’s protection comes from long term follow-up of people with the Lynch hereditary colorectal cancer syndrome. And In women randomized to aspirin or placebo for primary prevention of
cardiovascular disease there were fewer colorectal cancers among those given aspirin than among those taking placebo.

The most recent results in a secondary cardiovascular event prevention trial even suggest that the cancer prevention extends to cancers beyond the colorectal area. Professor Chan concluded that there may well be a role for aspirin in the prevention of other cancers.

Dr Farhat Din, of Edinburgh University, accepts the epidemiological and RCT evidence that aspirin has striking chemoprotective properties against colorectal cancer. Not only does it reduce incidence and mortality but it also improves survival in patients who already have the disease. She set herself the task of understanding why it does so. Environmental factors account for more than half the variation in colorectal cancer risk, one of which is obesity. The risk of developing colorectal cancer is 30% lower with regular physical activity, and around 10% higher in the obese overall. This obesity-related risk is even higher in men in whom it is raised by from 30% to 70%. Dr Din’s team therefore concluded that imbalance of energy and of metabolism may initiate and then promote colorectal cancer.

Dr Din’s team have therefore studied the mTOR pathway which is pivotal in controlling cell survival, the regulation of metabolism and energy homeostasis. mTOR integrates stimuli in the cell from growth factors, nutrient and signalling pathways, so that in energy imbalance both environmental and genetic risks converge on abnormal signalling pathways. These alter colorectal crypt metabolism and growth towards adenoma, and then to carcinoma. Aspirin targets several of these pathways.

Dr Din’s group attribute the anti-tumour activity of aspirin to its potent inhibition of mTOR signalling and of its activation of AMP kinase phosphorylation, which also inhibits mTOR. An early stage of induction of cancer is initiation of protein translation: Dr Din showed that aspirin is key to blocking translation elongation, a novel insight into the effects of aspirin in colorectal cancer.

The second session concluded with a combined presentation by Dr Ruth Langley of London and Professor Peter Elwood of Cardiff on the opportunities for using aspirin to treat cancer. They reviewed the epidemiological evidence showing the benefits of aspirin after cancer is diagnosed in preventing metastases and prolonging survival. They discussed the evidence for there being specific tumour mutations that would be biomarkers of response to aspirin. They also discussed the frequency of gastro-intestinal bleeding and an absence of evidence that fatal gastro-intestinal bleeding is increased by low-dose aspirin – an important factor of relevance to the reluctance of doctors to prescribe low-dose aspirin. Finally they presented planned and ongoing clinical trials aiming to establish a role (or not) for aspirin in the treatment of colorectal cancer.

The third session moved away from cancer to other diseases in which aspirin has profound effects. More than 30 years ago Professor Graham Hughes, of London described antiphospholipid syndrome (APLS) for the first time: it has been named after him as Hughes syndrome. Unfortunately Professor Hughes had been taken ill and was unable to attend, but in his notes he explained that it is an autoimmune disease that causes venous and arterial thrombosis. Commonly it causes migraine, memory loss, epilepsy, angina and recurrent miscarriage. It is the commonest treatable cause of pregnancy loss.

The initial studies of aspirin in APLS-affected women increased the previous successful pregnancy rate from under 20% to over 90%. It is now combined with low molecular weight heparin for APLS-positive women with severe miscarriage histories and/or previous thrombosis (Wong L F Porter T F de Jesus G R - Recurrent early pregnancy loss and antiphospholipid antibodies. Where do we stand?
Professor Carlo Patrono, of the Catholic University School of Medicine, Rome, took over the theme of aspirin in diseases other than cancer with a report on his research into its use in diabetes mellitus. He explained that in both types 1 and 2 diabetes there is particularly high thromboxane synthesis, so that platelets are primed to over-react to coronary plaque fissuring or rupture, greatly increasing thrombosis risk (Davi G et al - Thromboxane biosynthesis and platelet function in Type II diabetes mellitus. N Engl J Med 1990 322 1769-74). There is however evidence that in some type 2 diabetic patients, the level of thromboxane may recover rapidly after a dose of aspirin and a once daily regime may be sub-optimal for such patients. Professor Patrono asked for RCTs to test a personalised anti-platelet regimen (such as twice daily doses). Even with dual or triple anti-platelet regimens given for acute coronary syndromes the residual risk of further events is substantial (Patrano C - The multifaceted clinical read-outs of platelet inhibition by low dose aspirin. J Am Coll Cardiol 2015 In Press). We need further investigation to find ways of reducing such risks.

Dr Andrew Freedman, of Cardiff Medical School, highlighted an aspect of HIV that is perhaps underestimated by clinicians. Before anti-HIV combination therapy (HAART) started in the 1990s patients with it progressed to terminal disease in around 10 years, and it was always fatal. However now, if it is not diagnosed too late, most HIV patients can expect to live into old age. Nevertheless they still have a higher than normal death rate from other diseases, such as malignancies, cardiovascular disease, renal, hepatic or neurological diseases (Triant V A et al - Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease J Clin Endocrinol Metab 2007 92(7) 2506-12). They are becoming commoner in HIV patients as with their longer survival and older age.

The evidence suggests that people on HAART are in a state of heightened immune activation and inflammation, both of which probably contribute to their higher morbidity and mortality (Lyons H et al - Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning domains in HIV infections. Acquired Immune Defic Syndrome 2011 57(5) 371-9). As aspirin may well be beneficial in such circumstances, Dr Freedman instituted a short pilot study in which aspirin was given for one week to patients with HIV and to controls. The HIV patients had at baseline significantly higher platelet activation than the controls (Gresele P et al - Endothelial and platelet function alterations in HIV-infected patients Thromb Res 2012 129(3) 301-8). With aspirin platelet aggregation and markers of cellular activation both diminished. The latter included sCD14, lowering of which protects the colorectal mucosal barrier against the action of gram negative bacteria.

Serum levels of sCD14 and other inflammatory markers are independent predictors of mortality from non-AIDS events such as myocardial infarction, stroke, malignancies and serious bacterial infections, and of overall mortality. Dr Freedman described 3 trials, one complete and 2 ongoing, which should soon indicate the value of aspirin in surviving HIV patients.

The session ended with the use of aspirin in its original indication – acute pain. Professor Ron Eccles of the Common Cold Centre, Cardiff explained that as aspirin has been freely available for more than 100 years as an analgesic with unquestioned efficacy and lack of addictive properties, there has been little demand to show its effects in clinical trials. However RCTs of aspirin in acute pain, in headache and migraine, common cold and ‘flu, muscle aches and pains, menstrual pain, toothache and post-tooth extraction pain, and the pains of arthritis together provide hard clinical evidence for its efficacy (Lampl C et al - Aspirin is first line treatment for migraine and episodic tension type headache regardless of headache intensity. Headache 2012 52(1) 48-56).
One pain model that has been standardized for clinical trials is that following wisdom tooth extraction: Its timing and intensity is predictable and it is a common dental procedure. These studies have shown that aspirin is more effective than placebo and more useful than paracetamol (Seymour R A et al - An investigation into the comparative efficacy of soluble aspirin and solid paracetamol in postoperative pain after third molar surgery. Br Dent J2003 194(3) 153-7).

Professor Eccles added that the formulation of aspirin products markedly changes its absorption and pharmacokinetics. Simple aspirin is absorbed more slowly than effervescent and buffered aspirin. Times to peak concentration vary from 33 to 83 minutes with the standard tablet to only 18 minutes in the case of micronized tablets with an effervescent nucleus, giving the prescriber an extra choice in the case of acute and severe pain.

**Conclusion**

Although aspirin has been in clinical use for more than a century there is still much to be learned about its future uses, particularly in cancer and in patients who are at particularly high risk of cardio- and cerebrovascular diseases – such as those with diabetes mellitus and long term survivors of HIV infection. This conference has mapped out its future uses. We await the results of the current clinical trials with some hope and optimism.