

LEADING ARTICLE

COX-2 chronology

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The role of selective cyclooxygenase (COX)-2 inhibitors in medical practice has become controversial since evidence emerged that their use is associated with an increased risk of myocardial infarction. Selective COX-2 inhibitors were seen as successor to non-selective non-steroidal anti-inflammatory drugs, in turn successors to aspirin. The importance of pain relief means that such drugs have always attracted attention. The fact that they work through inhibition of cyclooxygenase, are widespread, and have multiple effects also means that adverse effects that were unanticipated (even though predictable) have always emerged. In this paper I therefore present an historical perspective so that the lessons of the past may be applied to the present.

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- **1859** Hammond Kolbe synthesises salicylic acid, with industrial scale production in 1874.⁷ Salicylic acid is bitter and irritates the mouth and stomach.
- **1863** Friedrich Bayer and Friedrich Wescott found a dye manufacturing company employing six people in Wuppertal-Barmen.⁸
- **1886** Bayer manufacture phenacetin from a waste product of a benzo dye. What starts as a supplement to dye manufacture is to become the company's more profitable and dominant activity^{1 8}

THE ASPIRIN YEARS

- **1897** Motivated by his father's intolerance of salicylic acid, Felix Hoffman synthesises acetyl salicylic acid, named aspirin (derived from Acetyl **Sp**irea).^{1 2 9 10} This had been done before in 1853 (Carl Friedrich Gerhardt) and 1869 (Kraut) but Hoffman's method is quantitative (mixing salicylic acid and acetic hydride 2:3 before adding acetic acid) and yields pure stable aspirin.^{1 2} Aspirin causes less dyspepsia than salicylic acid.
- **1897** Eleven days later Hoffman synthesises another new compound also by acetylation (of di acetyl morphine).^{1 2} Bayer employees try the new substance and find it makes them feel heroic so it is called heroin. Heinrich Dreser prefers to market heroin than aspirin.
- **1898** Aspirin is shown to have a negative inotropic affect on frogs' hearts.^{1 2} Despite this, a secret clinical trial is conducted which shows effectiveness against pain, inflammation, and fever.
- **1899** Aspirin is registered as a tradename.
- **1900** Aspirin is patented in the USA and UK. Patents are refused in Germany. Aspirin rapidly becomes popular, endorsed by Caruso and Kafka (who claimed it eased the unbearable pain of being).¹
- **1903** Bayer production plant is established in Albany, New York. Bootleg sales are rising.
- **1905** Bayer bring lawsuit for patent infringement in England (unsuccessfully) and in the USA (successfully). They lose their patent in England because Kraut had synthesised aspirin in 1869.^{1 2}
- **1911** Aspirin becomes available over the counter.
- **1914–16** In anticipation of loss of patent (1917) Bayer brand aspirin is marketed aggressively with direct to consumer advertisements

1066 AND ALL THAT

When I was 10 years old, history involved learning by rote 150 entries on a date chart. I remember memorising AD 735: Venerable Bede (†) Jarrow, with not even an inkling of what it meant. My history date chart was almost entirely about kings and battles (although individualised with my own birth date of 1947) and contained nothing about medical or drug development apart from the Black Death (1349). In a belated attempt to rectify this, and in recognition that all known non-steroidal anti-inflammatory drugs (NSAIDs) are cyclooxygenase (COX)-2 inhibitors, I present a COX-2 chronology intended to help the reader put current controversies into perspective.

THE CHRONOLOGY

- **1500BC** Ebers papyrus recommends dried myrtle leaves for rheumatic and back pain.^{1–3}
- **C 400BC** Hipocrates (460–377BC) recommends willow tree bark for fever and pain.^{1–3}
- **1763AD** Edward Stone uses willow bark for fever in 50 patients, based on the doctrine of signatures³ (malady and cure—fever and willow—are found in similar places). A misprint means his report to the Royal Society is attributed to the mathematician Edmund Stone.⁴
- **1828** Johann Andreas Buchner prepares salicin, a partially purified extract of willow bark.⁵
- **1838** Raffaele Piria splits salicin to yield salicylic acid.⁶

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Abbreviations: COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors

in the USA. Promotion includes promotional fans with product names printed on them. The American Medical Association objects strongly.

- **1917** Marketing of aspirin by Montsanto provokes legal battle, leading to US Supreme Court verdict that the name aspirin is now so widespread that Bayer do not own it.^{1 2}
 - Bayer USA essentially separates from Bayer, Leverkusen to avoid anticipated war related sanctions. One week later, USA enters the first World War
 - Six months later “Trading with the Enemy” Act creates the Office of Alien Property Custodian to take over German assets and hold in trust during the war.¹
- **1918** Bayer, USA accused of having subsidiary, secretly poisoning Americans with contaminated dye.¹
 - Sales of Bayer aspirin collapse in USA
 - “Trading with the Enemy” Act amended to allow German property to be sold to Americans.
 - Bayer US is sold for \$5.31 million to Sterling Products who add it to their portfolio of laxatives, dandruff treatments, and impotence cures (advertisement: “Makes old men boys again”).¹
- **1920s** Sterling reach agreement with Bayer, Leverkusen to market Bayer aspirin in the USA. Advertisements claim that aspirin “does not affect the heart”. US administration forces company to withdraw this claim.¹
- **1938** Douthwaite and Lintott use rigid endoscopy to show gastric damage with aspirin, illustrating their *Lancet* paper with watercolour paintings.¹¹
- **1940** Nana Svartz develops sulphasalazine for arthritis on spurious theoretical grounds (sulpapyridine for bacteria, a salicylate to penetrate connective tissue), thereby inadvertently recreating an[azo] dye in the process. Sulphasalazine has little obvious effect on arthritis but Svartz is an observant physician who notices improvements in the underlying bowel symptoms of patients with enteropathic arthritis.¹²
- **1940** Karl Link shows aspirin increases bleeding and advises caution in his article “Is aspirin a safe medicine?” in the *Journal of the American Medical Association*.¹³
- **1948** In the *Lancet*, cardiologist Paul Gibson recommends aspirin for prevention of coronary thrombosis.¹⁴
- **1950** Lawrence Craven recommends aspirin, having given it to more than 400 male patients, none of whom has a heart attack. Craven’s recommendation is ignored.¹⁵
- **1953** Writing in the *Mississippi Valley Medical Journal*, Craven reports on the use of aspirin in 8000 patients and concludes “Aspirin provides a safe and effective method of preventing coronary thrombosis”.¹⁶

THE NSAID YEARS

- **1959** John Nicholson (Boots), collaborating with Stuart Adams, synthesises drug 10335 which causes rashes in animals. Unconvinced of the result, three members of staff take drug 10335 and one gets a severe rash.^{1 17}
- **1961** Adams and Nicholson identify ibuprofen.¹⁷
- **1960s** Numerous theories about the mode of action of aspirin and NSAIDs abound, most of them wrong, being based on experiments with high doses.
- **1967** Aspirin shown to inhibit platelet aggregation.¹⁸
- **1969** Ibuprofen marketed as Brufen. A clinical trial (n = 18) shows the marketed dose is no better than placebo.¹⁹

- **1971** Sir John Vane shows inhibition of prostaglandin synthesis to be the mode of action of aspirin and NSAIDs.²⁰
- **1970s** Numerous experiments show that prostaglandins protect the stomach even against boiling water.²¹
 - Systematic data showing that aspirin use is associated with a reduction in myocardial infarction and stroke emerge.²²
 - New possibly safer NSAIDs are launched. They include azapropazone and piroxicam. Use is later restricted when they are associated with a particularly high level of ulcer complications.²³ The problem with piroxicam is thought to be that its long half life precludes recovery of gastric cyclooxygenase activity.
- **1980s** FDA announce that one aspirin a day helps prevent a second heart attacks but objects to Sterling advertising claims to that effect.^{1 2}
- **1989** Phillip Needleman identifies a steroid suppressible cyclooxygenase—COX-2.²⁴ In the same year molecular biologists identify an immediate early gene, with homology to COX-1 that is responsible for this activity.^{25 26} When told by an excited researcher that they have identified a cyclooxygenase, one of them (Herschman) retires to his room and consults a student textbook to find out what a cyclooxygenase is.^{27–29}
- **1991–93** Intensive drug development activity results in first generation of selective COX-2 inhibitors. The pharmacology is unusual because inhibition shows delayed onset and is semi irreversible.^{27 28} At least one company misses out on a blockbuster because their pharmacological screening does not take account of these properties
- **1992** Non-selective NSAIDs and selective COX-2 inhibitors shown to act by obstructing entrance of precursor arachidonic acid.²⁸
- **1994** Bayer takes over Sterling Winthrop and is able to sell Bayer aspirin in the USA for the first time in 75 years.²
- **1994** Crystal structure of COX-1 published.²⁹

THE COX-2 YEARS

- **1995** First generation of selective COX-2 inhibitors enter clinical trials, with celecoxib (made by Montsanto) and rofecoxib (made by Merck). Over the next four years numerous trials show selective COX-2 inhibitors to reduce pain and inflammation both acutely and chronically and to be as effective as NSAIDs in this activity.³⁰ In the same and parallel trials they are shown to lack the ability of non-selective NSAIDs to cause a fourfold enhancement of gastroduodenal ulcers.³¹ Gastrointestinal safety enables new indications such as perioperative analgesia to be investigated.³² The drugs appear to be a major therapeutic advance.
- **1996** Crystal structure of COX-2 published.³³
- **1998** Acid suppression shown to protect against NSAID ulcers.^{34 35} Publications recognise a potential difference between selective COX-2 inhibitors and non-selective NSAIDs with regard to possible cardiovascular thrombosis but emphasise the complexity of effects makes it possible they could have a higher or lower thrombotic tendency.³⁶ An abstract suggests fewer cardiovascular deaths on rofecoxib than NSAIDs³⁷
 - Celecoxib approved
- **1999** Most whole body prostacyclin production is shown to be inhibitable by COX-2 inhibitors.³⁸

- Rofecoxib approved
 - FDA require outcome studies to use suprathreshold doses to prove robustness of safety data. Unfortunately when toxicities emerge converse reasoning is not applied.
 - **2000** Outcome studies of celecoxib and rofecoxib are published.^{39 40} Celecoxib wins the battle to be first (by three months) but observers are puzzled by publication of six month data from a trial widely known to have lasted over one year. *JAMA* does not publish discussion of this issue until 2002.⁴¹ Meanwhile, the obvious proposal that journals should see all protocols of clinical trials that they publish is reiterated.⁴²
 - **2000** Both CLASS and VIGOR trials show that the use of selective COX-2 inhibitors essentially abolishes the risk of a perforation ulcer or bleed in patients without risk factors but residual rates are high in patients with risk factors.^{39 46} There are more heart attacks in patients on rofecoxib than on naproxen in the VIGOR study.³⁹ Regulatory authorities recommend COX-2 inhibitors are used preferentially in patients with risk factors, including “serious co-morbidity, such as cardio-vascular disease...and hypertension”.^{43 44}
 - Arguments continue about whether the data reflect a harmful effect of rofecoxib, an antithrombotic aspirin-like effect of naproxen, a mixture of the two, or the play of chance.
 - Increasing use of aspirin makes it a bigger cause of ulcer bleeding than NSAIDs.⁴⁵ It seems aspirin abrogated all or most of the benefits of COX-2 inhibitors.³⁸ There are warnings that aspirin is overused for primary prevention.⁴⁶
 - Monsanto merges with Pharmacia and Upjohn, maintaining the name Pharmacia.
 - Sales of COX-2 inhibitors soar, boosted by intense direct to consumer marketing (\$161 million spent on rofecoxib).⁴⁷
 - Celecoxib is reported to reduce polyps in familial adenomatous polyposis.⁴⁸
 - Merck and Searle launch placebo controlled studies on the prevention of sporadic polyps, convinced that these placebo controlled studies will clear selective COX-2 inhibitors of the implication that they cause heart attacks.
 - Theories about the effects of aspirin, NSAIDs, and COX-2 inhibitors on cancer development abound, most of them wrong, based on experiments with high doses. Only a few explain how aspirin, a highly selective COX-1 inhibitor, might also reduce cancer development.⁴⁹
 - **2001** Effect of proton pump inhibitors (PPIs) on outcomes is assessed in high risk population of patients who have experienced life threatening ulcer haemorrhage. PPIs reduce recurrent haemorrhage fourfold.⁵⁰
 - **2002** Pharmacia taken over by Pfizer who add celecoxib to their portfolio which includes antiseptic mouthwash, denture adhesive cream, and impotence treatment (advertisement: “Get back to mischief”).⁵¹
 - **2003** European Medicines Agency (EMA) orders review of cardiovascular safety of COX-2 inhibitors. Their report points out that because selective COX-2 inhibitors do “not inhibit platelet aggregation, anti platelet therapies ... should not be discontinued...”, that “COX-2 selective inhibitors reduce the formation of ... prostacyclin” but that “the clinical relevance of these observations has not been established”. EMA declares itself broadly satisfied and maintains licences of current drugs.⁵²
 - USA goes to war with Iraq over alleged concealed weapons of mass destruction.
 - **2004** The largest ever trial with gastrointestinal outcomes (TARGET) is published.^{53 54} It shows clear cut fourfold reduction in ulcer complications with lumiracoxib compared with ibuprofen or naproxen. Rates of myocardial infarction on lumiracoxib are lower than on ibuprofen but higher than on naproxen. Unfortunately, neither result is statistically significant because the 18 500 patient study is too small!
 - Meanwhile, meeting presentations, word of mouth, and web based items highlight a study sponsored by the FDA that is said to show an increased risk of myocardial infarction with rofecoxib. The whistle blower accuses the FDA of covering up data.⁵⁵
 - **29 September 2004** First public presentation of TARGET data.⁵⁶
 - **30 September 2004** Merck withdraws rofecoxib.⁵⁷ In the APPROVe trial of rofecoxib versus placebo for polyp prevention, there is a doubling of myocardial infarction rate on rofecoxib.⁵⁸
 - Overnight, direct to consumer advertising is replaced by direct to litigant advertising.⁵⁹ COX-2 inhibitor market collapses.
 - The problem of whether the cardiovascular effects of VIOXX are unique (in an undefined way) or a class effect are hotly debated. Proponents feel the problem with rofecoxib is that its long half life precludes recovery of vascular COX-2 activity.
 - **December 2004** A sequential meta analysis by Juni and colleagues shows a significant association between rofecoxib and myocardial infarction had developed by the year 2000.⁶⁰ Merck is effectively accused of concealing weapons of mass destruction. However, the result that established the association, the VIGOR study, has been openly discussed since 2000. Juni’s paper shows no significant association with normal doses of rofecoxib or in data which excluded VIGOR.
 - **January 2005** Kaiser Permanente study published in the *Lancet*.⁶¹ Statistically, the strongest association is between non-selective NSAIDs and myocardial infarction rather than between rofecoxib and myocardial infarction (although the odds ratio is somewhat higher for the latter). Astonishingly, neither the paper nor the accompanying editorial about drug safety discusses this result.
 - **16–18 February 2005** FDA reviews cardiovascular safety of selective COX-2 inhibitors and by various margins vote to allow their continued use. Merck announces that it may re-launch VIOXX. Three papers are published showing enhanced, almost certainly dose dependent, cardiovascular risk with a wider range of coxibs.^{58 62 63} A study of parecoxib in patients undergoing coronary artery bypass surgery previously suggested an increase in myocardial infarction. A contemporaneous study showing the same effect is now published.⁶³
 - **7 April 2005** FDA request withdrawal of parecoxib.⁶⁴
 - **July 2005** Long overdue system of clinical trial protocol registration to be introduced.
- ...story to be continued

2005 AND ALL THAT

When I was 15 history became more complex and I read Herbert Butterfield’s *Whig Interpretation of History*⁶⁵ in which

the author criticised historians who took the view that history's arrow traced a straight line of constant improvement to the present day. When current controversies about selective COX-2 inhibitors and the colourful claims and counterclaims are examined, one would have to conclude that we have in a general sense been here before, and more than once! While the controversies surrounding aspirin, non-selective non-aspirin NSAIDs, and selective COX-2 inhibitors have been different, the mixture of bias, politics, mischief, and science has been very similar. This is probably inevitable when potentially large profits are on offer, as was the case in the early 1900s, the 1960/70s, and the 1990/2000s.

Much attention has focused on accusations that pharmaceutical companies have concealed data and in some cases this has been literally true.⁴⁰⁻⁴¹ Mostly, such criticism seems naïve. Pharmaceutical companies certainly influence research output. However, this is seldom by distortion or concealment of data so much as constraining the questions to those of (ultimately economic) interest to the company. This is a far more challenging issue to academics who subscribe to evidence based medicine because only industry can afford to conduct the kind of studies that are most highly rated. In this context the broad position taken by academics (and the associated processes of cognitive distance) arguably leads to just as much bias. Thus it is difficult to understand the point of a sequential analysis that finds out that the VIGOR study was published in the year 2000 and manages to draw conspiratorial conclusions. Equally, the Kaiser Permanente study of NSAIDs use⁶¹ and myocardial infarction is a well done scholarly work that is undermined by the reluctance of the author and accompanying editorial comment to deal with an association that appeared to exist between myocardial infarction and non-selective NSAIDs as well as that which exists with selective COX-2 inhibitors on which the discussion of the paper focuses exclusively.

QUESTIONS

The questions now to be addressed are:

- (1) Do COX-2 inhibitors increase the risk of myocardial infarction? Of this there can be no doubt, given the placebo controlled nature of much of the data and evidence for dose dependence.⁵⁸⁻⁶²⁻⁶³
- (2) Have these placebo controlled data emerged despite efforts of the pharmaceutical industry to conceal them? This accusation seems largely misplaced. It would be difficult to see why, if companies knew of or suspected a true relationship they would embark upon such a clinically self destructive programme of placebo controlled trials as has been the case here.
- (3) Do non-selective NSAIDs cause myocardial infarction? Rapidly emerging data suggest they do.⁶¹⁻⁶⁶⁻⁶⁸ These data seem likely to be valid although it is strange that earlier studies failed to show such an association.⁶⁹
- (4) Is the effect of NSAIDs on myocardial infarction as large as that of COX-2 inhibitors? This question cannot be clearly answered, particularly because an association between NSAIDs and myocardial infarction has not yet been unequivocally established. On pharmacological grounds one might predict that inhibition of COX-1 would modulate the harmful effects of COX-2 inhibitors to an extent that varies with different drugs. The best established example of this proposition is naproxen which, despite some data to the contrary, seems to have an aspirin-like effect and to be associated with an approximate 15% reduction in infarct rates.⁷⁰ I would predict that non-naproxen NSAIDs will emerge as associated with some increase in risk of myocardial infarction but to a lesser extent than selective COX-2

inhibitors. If this increase in risk is very small, it could be tolerable for those with sufficient pain and relief from NSAIDs/COX-2 inhibitors to justify. However, that is not necessarily so because a small effect in a large number of users could amount to a problem as big as the issue of ulcer complications which originally stimulated the development of COX-2 inhibitors. Certainly the recently rediscovered dictum for drugs of "using the least amount for the shortest possible time" is apposite. It may be possible to select NSAIDs with a particularly favourable cardiovascular profile where appropriate.

- (5) So what is the alternative to a COX-2 inhibitor? As discussed elsewhere,⁷¹ overall use of a non-selective NSAID under PPI protection is at least as good as use of a COX-2 inhibitor for patients at high risk. However, PPIs and use of COX-2 inhibitors result in reduced gastroduodenal risk by different mechanisms and it is possible that some patients have predominantly prostaglandin dependent and other have predominantly acid dependent ulcers. Recent data showing that PPIs can further reduce ulcer risk in patients taking COX-2 inhibitors indirectly support this concept.⁷² Personally, I find recommendations for NSAID plus PPI to avoid COX-2 inhibitor cardiovascular risk lacks caution because it does not take account of uncertainty about the possible cardiovascular hazards of NSAIDs. On current evidence the precautionary principle would lead one specifically to recommend naproxen plus PPI except where there is a very high risk of bleeding. Moreover, there is no doubt that non-selective NSAIDs as well as selective COX-2 inhibitors substantially enhance the risk of blood pressure and heart failure⁷³ and at the very least recent events should make checking the blood pressure mandatory in patients taking non-selective NSAIDs and COX-2 inhibitors.
- (6) Is there any place for selective COX-2 inhibitors? It has become clear that if you take enough of it, even the poorly absorbed celecoxib can enhance the risk of cardiovascular thrombosis. Use of parsimonious doses is therefore appropriate both for selective and non-selective NSAIDs.

Several of the ironies in this area surround the drug lumiracoxib. A study that was widely regarded as well done showed⁵³⁻⁵⁴ a very clear gastrointestinal safety advantage but the drug has almost been forgotten in the welter of claim and counterclaims surrounding the VIOXX withdrawal. Another irony is that TARGET was too small to settle clearly the cardiovascular safety or otherwise of lumiracoxib. However, several features of this drug (a short half life and an apparent lack of effect on blood pressure) make it reasonable cautiously to anticipate that when used at 100 mg a day (a quarter of the dose in TARGET) it may have no significant effect on vascular thromboses. Only time will tell, and my history date chart suggests that another controversy might be on us by then!

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Conflict of interest: declared (the declaration can be viewed on the Gut website at <http://www.gutjnl.com/supplemental>).

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EDITOR'S QUIZ: GI SNAPSHOT

Late complications of an ileal pouch

Robin Spiller, *editor*

Clinical presentation

A 39 year old woman with a stapled J pouch following proctocolectomy for ulcerative colitis in 1998 presented with abdominal pain and diarrhoea during her pregnancy in 2003. She continued to be symptomatic with incomplete pouch evacuation and pelvic discomfort following her caesarean delivery. An abdominal radiograph (fig 1) showed a calcified smooth mass in the pelvis. Endoscopy confirmed a mass adherent to the proximal end of her pouch. She underwent a rectal examination under anaesthesia but the mass was not amenable to removal by the transanal route. She later underwent a laparotomy at which the pouch was found to be capacious and the ileum just proximal to the pouch being dilated. The pouch was opened at its proximal end and the mass delivered from the pouch. The patient made an uneventful recovery. Figure 2 shows the complete and cross sectional views of the mass.

Question

What is the diagnosis of this lump?

See page 1526 for answer

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Figure 1 Abdominal radiograph showing a calcified mass in the pelvis.

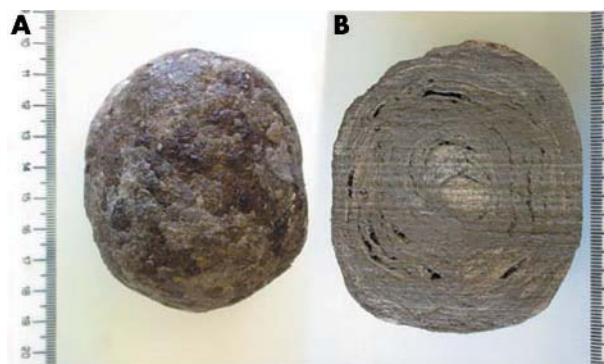


Figure 2 Complete (A) and cross sectional (B) views of the mass.