should limit the scope of subject matter that can be patented and provide extensive safeguards to ensure that patent rights are not exploited inappropriately. The agreement signed on 30 August 2003 falls far short of this recommendation.

Lastly the UK commission, again, has drawn attention to the complexity of the legal and administrative architecture of the WTO and the way in which developing countries are disadvantaged in the negotiations and by the absence of civic dialogue and public debate.[7] Until these issues are put at the top of the WTO agenda the real effect of this and any future trade rounds will continue to be the entrenchment of the interests of western countries and their industries.

Allyson M Pollock *professor*
(allyson.pollock@ucl.ac.uk)

David Price *senior research fellow*

Public Health Policy Unit, School of Public Policy, University College London, London WC1H 9QU

Competing interest: None declared.

1 WTO. *Declaration on the TRIPS agreement and public health.* Geneva: WTO, 20 November 2001 (WT/MIN(01)/DEC/2).
2 Raghavan C. Medicines won't be cheaper under TRIPS and public health decision. Geneva: Third World Network, 31 Aug 2003. www.twnside.org.sg/title/5409b.htm (accessed 7 Sep 2003).
3 Koivusalo M, Rowson M. Who will inherit the earth? *Health Matters* 2000;41. www.healthmatters.org.uk/stories/rowson2.html (accessed 8 Sep 2003).
4 Braithwaite J, Drahos P. *Global business regulation.* Cambridge: University Press 2000:39-87.
5 WTO takes first step. *Lancet* 2003;362:753.
6 WTO. *Implementation of paragraph 6 of the Doha declaration on TRIPS and public health.* Geneva: WTO, August 2003 (W/TL/540).
7 Commission on Intellectual Property Rights. *Integrating property rights and development policy.* London: CIPR, 2002. www.iprcommission.org/graphic/documents/final_report.htm (accessed 8 Sep 2003.)
8 Drahos P. Biotechnology patents, markets and morality. *European Intellectual Property Review* 1999;21:441-9.
9 Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and public health policy failure. *Lancet* 2002;359:2188-94.

What are all the things that aspirin does?

This fascinating but simple and cheap drug has an assured future

Ask any medical student and he or she will tell you that aspirin reduces fever, pain, and inflammation but may cause ulcers. Students may also recollect that it prolongs bleeding, and may prevent strokes and heart attacks, but would be unlikely to know of its use in cancer or Alzheimer's disease.

A defining point in the history of aspirin was the discovery that it inhibited the prostaglandin forming cyclo-oxygenase.[1] Prostaglandins cause inflammation, fever, and pain; have gastric cytoprotective actions; and are implicated in platelet aggregation, so this discovery provided a unified explanation for the effects of aspirin (and most other non-steroidal anti-inflammatory drugs). However, events took an even more interesting turn when a further isoform of cyclo-oxygenase, cyclo-oxygenase-2, was discovered.[2] While similar in many ways to the original enzyme (COX 1) there were important differences, including the fact that COX 2 was induced in cells by inflammatory insults. COX 2 therefore seemed to be the most relevant target in inflammation, which led to the notion that the constitutive COX 1 generated prostaglandins required to maintain physiological functions (such as protection of the gastric mucosa, platelet aggregation) whereas COX 2 generated pro-inflammatory mediators.[3] Aspirin inhibited both isoforms, as did most non-steroidal anti-inflammatory drugs, perhaps explaining why these compounds were not only effective therapeutically but also had characteristic side effects.

The ensuing search by the pharmaceutical industry for selective COX 2 inhibitors culminated in the recent introduction of new, safer anti-inflammatory drugs as well as the rediscovery of older drugs that had COX 2 selective actions. But, as aspirin inhibits both isoforms, why does it continue to be used and why is there continuing interest in its pharmacology?

The answer to the first part of this question is partly down to aspirin's unique mechanism of action that inhibits both COX 1 and COX 2 irreversibly. The effects of this are evident in platelets where cyclo-oxygenase cannot be replaced, explaining why a single aspirin can depress platelet aggregation for many days. The half life of aspirin in plasma is short; esterases remove the acetyl group leaving free salicylate, which may have a secondary pharmacological effect through cyclo-oxygenase inhibition or other mechanism, adding to the complexity of aspirin's action.

The current interest in aspirin stems from the fact that many animal experiments and human epidemiological studies now link aspirin (and other non-steroidal anti-inflammatory drugs) with beneficial effects in various cancers, including breast, ovarian, oesophageal, and colorectal cancer. Recent meta-analyses supported the idea that the overall relative risk of colorectal cancer is reduced in people taking long term aspirin.[4] Another meta-analysis of observational data confirmed a protective effect in oesophageal cancer and provided evidence of a relation with dose and duration of treatment, and other studies showed a beneficial effect in ovarian cancer.[4 5] How aspirin or other non-steroidal anti-inflammatory drugs produce this effect is not entirely clear, but the synthesis or activity of COX 2 is increased in many tumours, and inhibition could activate apoptotic mechanisms or suppress angiogenesis.[6] It has even been suggested that the link between diet and the prevention of colorectal cancer is attributable to the presence of salicylic acid in plant and vegetable foodstuffs.[7]

Evidence from longitudinal studies of long term users of non-steroidal anti-inflammatory drugs originally pointed to a reduced risk of Alzheimer's disease,[8] and these findings are supported by other, more recent data,[9] where an inverse relation was found between taking aspirin (and other non-steroidal anti-inflammatory drugs) and Alzheimer's disease, but not other forms of dementia. The mechanism is uncertain—Alzheimer's has an inflammatory component and therefore COX 2 may be the target, although other mechanisms have been suggested.[10]

BMJ 2003;327:572–3

Two questions bedevil what is otherwise an exciting therapeutic prospect. What is the minimum dose required to achieve these effects, and how can we assess the relative risk and benefit of a preventive treatment that will entail treating healthy people for many years with a drug known to have gastric and other side effects? It is here that aspirin's grandchildren may have a role. COX 2 seems to be the main culprit in both cancer and Alzheimer's, so the selective COX 2 inhibitors, which have reduced gastric side effects, are natural choices for such long term prophylactic treatment.

What of the future of aspirin itself? Because of its profound effects on platelets it is unlikely to be supplanted as a cheap and effective prophylactic treatment for those patients at risk from excessive platelet aggregation, but in view of its venerable history, it is surprising that aspirin is still the subject of ongoing medicinal chemistry effort. Attaching a nitric oxide donor to the molecule seems to ameliorate the side effects of the drug while boosting its therapeutic effects.[11] The discovery of a third form of cyclooxygenase,[12] mainly confined to the central nervous system and heart, which is also inhibited by aspirin, will no doubt provide yet another twist to the continuing story of this fascinating but simple drug.

Rod Flower *professor of biochemical pharmacology*
William Harvey Research Institute, London EC1M 6BQ

Competing interests: RF is on the scientific advisory board of Nicox Spa and has received consulting fees and research support from this company. He has appeared as an expert witness for Searle-Monsanto, manufacturer of Celebrex.

1 Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971;231:232-5.
2 Xie WL, Chipman JG, Robertson DL, Erikson RL, Simmons DL. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc Natl Acad Sci U S A* 1991;88:2692-6.
3 Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci U S A* 1993; 90:11693-7.
4 Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an update to 2001. *Eur J Cancer Prev* 2002;11:535-42.
5 Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 2003;124:47-56.
6 Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst* 2002;94:252-66.
7 Paterson JR, Lawrence JR. Salicylic acid: a link between aspirin, diet and the prevention of colorectal cancer. *QJM* 2001;94:445-8.
8 Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997;48:626-32.
9 Broe GA, Grayson DA, Creasey HM, Waite LM, Casey BJ, Bennett HP, et al. Anti-inflammatory drugs protect against Alzheimer disease at low doses. *Arch Neurol* 2000;57:1586-91.
10 Gao F, Bales KR, Dodel RC, Liu J, Chen X, Hample H, et al. NF-kappaB mediates IL-1beta-induced synthesis/release of alpha2-macroglobulin in a human glial cell line. *Brain Res Mol Brain Res* 2002;105:108-14.
11 Burgaud JL, Ongini E, Del Soldato P. Nitric oxide-releasing drugs: a novel class of effective and safe therapeutic agents. *Ann N Y Acad Sci* 2002; 962:360-71.
12 Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci U S A* 2002;99:13926-31.

The Wanless report and public health

Wanless's fully engaged scenario means a bigger role for public health

Poor levels of health in the population will put considerable pressure on the NHS that risks swamping the government's efforts to meet targets and achieve solid gains through its sizeable injection of money. Not surprising, then, that former banker Derek Wanless's report on long term funding challenges for the NHS, which was published last year, struck a chord with ministers and advisers.[1] In his 2003 budget the chancellor invited Wanless to provide an update of the long term challenges in implementing the fully engaged scenario.[2] This scenario was the most ambitious and optimistic of the three scenarios described in Wanless's first report and has been endorsed by the government. It contains heroic assumptions about the ability of people to take greater responsibility for their health, and services to transform themselves through efficient use of resources and a high rate of uptake of technology. A dramatic improvement in health status is anticipated with life expectancy going beyond current forecasts. But the real appeal of the scenario for the government lies in an estimated saving to the NHS of some £30bn ($47bn; €43bn) if it succeeds.

The plea of the former health secretary Alan Milburn for a better balance between prevention and treatment in health policy seems to have gone unheeded.[3] The government remains preoccupied with downstream acute care. The call for a "sea change in attitudes" has not happened. Public health remains marginalised and lacks capacity, especially in primary care trusts, to challenge effectively the prevailing orthodoxy. Yet the outpouring of policy statements testifying to the grim picture of the nation's health continues. The latest is an action plan designed to promote "often minor changes in the way … services are provided," in the hope of "making today's inequalities a thing of the past."[4]

The action plan concedes that "health inequalities are stubborn, persistent and difficult to change." But they are also widening "and will continue to do so unless we do things differently." The health gap between rich and poor is growing in line with the income gap, and a generation of overweight and underexercised individuals is maturing.

The scenario will be unpicked and developed in the progress report on which Wanless is engaged, to identify cost effective public health interventions. But the review contains two further key features. Firstly, it will be concerned with assessing how public health policy is formed. Secondly, it will examine national and local governmental arrangements for delivering the public health agenda set out in the *NHS Plan* (chapter 13) and in subsequent guidance and targets.[5] This means Wanless's reach will go well beyond the NHS and embrace local government, regional bodies, and others engaged in health improvement and tackling health inequalities.

With his private sector background, Wanless is regarded as someone the government can trust. He is respected and listened to. His progress report, to be completed by late February, will be presented not just to the chancellor but also to the prime minister and the

BMJ 2003;327:573–4