

Platelets, aspirin, and cardiovascular disease

Peter C Elwood, Ceri Hughes, John R O'Brien

Summary

Aspirin was first synthesised 100 years ago and its preparation and marketing is generally reckoned to have been the foundation of the pharmaceutical industry. For most of the time since then it has been used for the relief of pain and fever. The modern phase of aspirin use commenced with the reporting in 1974 of a randomised controlled trial in the secondary prevention of death by low-dose aspirin given to patients who had suffered a myocardial infarct. Reports of other trials followed and an overview of the first six trials was presented to the inaugural meeting of the Society for Clinical Trials in Philadelphia in 1980. There have been two further major overviews and the most recent, based on 145 trials, established that low-dose aspirin reduces vascular events by around one third.

It has been estimated that, used appropriately, aspirin could prevent 100 000 premature deaths each year worldwide, at a cost of about £250 (\$400) per life saved, and about £80 (\$130) per cardiovascular event prevented. The evidence indicates that it is seriously underused at present. The aspirin story continues and trials are in progress to test other possible uses of aspirin, in vascular dementia, colorectal cancer, and cataract.

Aspirin, given after myocardial infarction or stroke, is probably the best established prophylactic available in clinical practice. A recent overview of 145 randomised controlled trials has given convincing evidence of a reduction in vascular events of 25–30%.¹ It has further been estimated that as many as 100 000 deaths could be prevented each year in developed countries, including about 9000 in the UK, by the appropriate use of aspirin, and at least this number of non-fatal infarctions and strokes, at a cost of about £250 (\$400) per life saved (MRC Press release: Life-Saving Aspirin. 7 January 1994). This is equivalent to about £80 (\$130) per cardiovascular event prevented, making aspirin the most cost-effective drug available today. Concern has, however, been expressed that aspirin taking after infarction, and knowledge amongst doctors of the possible benefits of aspirin, is very much less than optimal.^{2,3} Use of the drug has probably been limited by the fact that, outside Germany, it carries no patent, it is commonly available, inexpensive and makes no profit.¹

Early work on platelets

Donné, writing in 1842, was probably the first to describe platelets.⁴ He called them lymph particles ('globulins du chyle') and described them as precursors of white cells. Others believed them to be derived from disintegrated white cells (Reiss L, quoted in⁵) or precursors of red cells (Zimmerman R, quoted in⁶), while yet others dismissed them as organisms, cell debris, or artefacts.⁷ Hayem,⁸ in 1878, seems to have been the first to use the name 'plaquettes' and this was translated as 'platelets' by Osler in 1883,⁹ but as late as 1931 there was some doubt as to whether they were functional elements in the circulation.⁷

Despite these uncertainties, a few early writers showed considerable insight into platelet function. In 1874, Osler gave a dramatic description of platelet pseudopods as 'fine projections and oval swellings', and he described their aggregation and adhesion to fibrin.⁵ Bizzozero, in 1882, described a white platelet thrombus but thought that it consisted of white cells.¹⁰ He and a number of early writers used the phrase 'viscous metamorphosis' to describe the aggregation of platelets and this term continued in use into the 1960s.¹²

Several strands of work on platelets seem to have developed. Clinical concern focused largely on purpura. The paucity of platelets in affected patients was reported in 1887¹³ and the long coagulation time in 1912.¹⁴ Others sought to elucidate the origin and nature of platelets, and the megakaryocyte was discovered and named by Wright in 1906.¹⁵ In retrospect, however, it would seem that the most fruitful research focused on the involvement of platelets in thrombosis and to some extent this seems to have arisen out of the encrustation theory of atherosclerosis proposed by Rockitansky in 1854, which he termed 'mummification'.¹⁶

Platelet adhesion and aggregation

A bleeding time test was first described by Duke in 1910¹⁷ and this stimulated the development of techniques for studying the adhesion of platelets on various surfaces.¹⁸ Tests of both bleeding time and adhesiveness were, however, greatly limited by poor reproducibility.

A considerable stimulus was given to platelet research by the simultaneous development by O'Brien¹⁹ and Born²⁰ in 1962 of methods to examine platelet aggregation *in vitro*. The reproducibility of these methods was better than that of any earlier test, but it would appear that their chief value lay in the fact that they focused attention on thrombosis, rather than on bleeding as had been the case with tests of adhesion. Writing whilst aggregometry was being developed, O'Brien commented that these new techniques should facilitate the identification of platelet-active drugs.²¹

MRC Epidemiology Unit, Llandough Hospital, Penarth, South Glamorgan CF64 2XW, UK
P C Elwood
C Hughes
J R O'Brien

Accepted 13 May 1998

Platelets and drugs

An interest in the effects of drugs on platelets appears to have arisen first because of the occurrence of haematemesis as a complication of high or prolonged salicylate therapy. Some attributed this to increased capillary fragility,²² although the irritant action of aspirin on the gastric mucosa had been known since at least 1938.²³

The effects of drugs on platelet function was studied by many workers. For example, in 1961 it was reported that adhesion to glass and to damaged cells was reduced by antimalarial and antihistamine compounds, and by 'a strong solution of sodium salicylate',²⁴ but the doses likely to be required to reduce the risk of thrombosis were so high that they were judged 'incompatible with life'.²⁵ By 1963 many workers seem to have been searching for an antiplatelet drug which might prevent thrombosis,²⁸ although it was recognised that it would be difficult to find a therapeutically acceptable inhibitor.

In 1966, Quick²⁸ and Wjinja *et al*²⁹ described a prolongation of the bleeding time after aspirin ingestion and Morris³⁰ in 1967 suggested that the interference by aspirin of the 'plasma platelet-aggregating factor' and depression of platelet stickiness might also influence thrombus formation and therefore that aspirin might 'play a therapeutic role in the management of pathological thrombosis'.

During the late 1960s, a number of important developments were reported. Weiss and Aledort³¹ showed that aspirin inhibits the release of platelet ADP and prolongs bleeding time, and they suggested that the drug might have antithrombotic properties. Mustard and colleagues³² attributed bruising in rabbits and dogs given aspirin to an inhibition of the platelet response to collagen and the production of a haemostatic plug. Zucker and Peterson³³ observed that one of their study volunteers, whose blood constantly yielded abnormal clotting and aggregation results, had been taking aspirin regularly.

Interest then centred on the dose of aspirin required to affect platelet function. O'Brien showed that the effect on aggregation was the same at doses of 2.4 g and 6 g.³⁴ In 1968, when the same effects were shown after a dose of only 150 mg, a therapeutic trial of aspirin and thrombosis was recommended.³⁵ Later in that same year, it was shown that prolongation of the bleeding time and other effects on platelet behaviour were detectable for up to 7 days after a single dose of aspirin.^{36 37} Subsequently, the action of aspirin was shown to be permanent, the effect on aggregation and bleeding being lost only when platelets are replaced.³⁸ Each of these findings enhanced hopes of the possibility of prophylaxis of arterial thrombosis by aspirin.^{35 36}

Clinical trials of aspirin

The first report of aspirin as a prophylactic in cardiovascular disease came from Lawrence Craven, a family practitioner in Glendale, California. In the first of three communications Craven commented that the lower incidence of coronary thrombosis in women might be due to their more frequent use of aspirin for minor discomforts, while men hesitate to resort to such 'effeminate' methods.³⁹ Craven therefore suggested that the drug might be of value as a preventive of vascular thrombotic conditions, such as coronary thrombosis. In his final publication, Craven reported that "having urged friends and patients to adopt the practice of taking aspirin, one or two 5 grain tablets daily... Approximately 8000 men and women adopted the regime ...not a single case of detectable coronary or cerebral thrombosis occurred among patients who faithfully adhered to this regime during a period of eight years".⁴⁰ Craven himself died shortly after this from a coronary thrombosis.

The first randomised controlled trial was set up by the MRC in 1969 in response to O'Brien's urgings.⁴¹ This assessed the effect on postoperative venous thrombosis of 600 mg/day of aspirin given before surgery and for 5 days postoperatively. Although the results were totally negative (95% CI of the reduction in venous thrombosis -12.3% to 1.3%), the final paragraph of the report of this trial urged that prophylaxis in arterial thrombotic conditions be tested.

The pleas for the investigation of aspirin prophylaxis^{35 36} had already led Elwood and Cochrane to commence a randomised controlled trial in post-myocardial infarction patients in 1970. Over 1000 post-infarction male patients were put on a daily dose of 330 mg aspirin, or matching placebo. Considerable difficulties were experienced at that time in persuading colleagues that this was a serious study, and in persuading some of the patients that the capsules contained only aspirin! Many physicians and others judged the dose of aspirin likely to be inadequate, and most of the trials which were set up later reflected the persuasiveness of clinical opinion, rather than evidence from platelet aggregation studies.

Uses of aspirin

Use mandatory unless there are contraindications

- post-myocardial infarction
- post stroke
- stable or unstable angina
- transient ischaemic attacks
- peripheral vascular disease
- patients at 'high-risk' of a cardiovascular event

Clinical judgement required

- patients judged to be at 'high-risk' to be advised to carry soluble aspirin

Further research required

- cognitive decline
- colorectal cancer
- cataract
- pre-eclampsia
- retarded foetal growth

The results of this first trial were reported in 1974.⁴² They show a reduction in all-cause mortality by aspirin of 24% which was not statistically significant at conventional levels of probability (95% CI -42.4% to 5.3%). Interest was, however, stimulated widely and by 1983 the results of five other trials had been reported, the results of all of which were non-significant at conventional levels of probability.⁴³⁻⁴⁷ However, the combined results of the six trials indicated a highly significant reduction in total mortality by aspirin (overall reduction: 23%: 95% CI 21.7-24.3). An overview of these six trials was presented to the inaugural meeting of the Society for Clinical Trials in Philadelphia.⁴⁸

The development of 'overviews'

The report to the Society for Clinical Trials was the first of a series of overviews reported by Peto and his colleagues in the Clinical Trials Service Unit in Oxford,⁴⁹⁻⁵⁰ and these have pioneered the use of overviews as a basis for clinical action. The most recent⁵⁰ is based on 145 randomised controlled trials and establishes that aspirin reduces non-fatal myocardial infarction by 34% and all-cause mortality by about 16% with no evidence of any important differences in the effect of aspirin after a variety of previous clinical events (unstable angina, myocardial infarction, stroke and transient ischaemic attacks, coronary artery by-pass grafting, percutaneous transluminal angioplasty, valve replacement and peripheral vascular disease), nor any evidence of significant heterogeneity in the reduction achieved within different groups of patients (males/females, diabetic/non-diabetic, hypertensives/non-hypertensives, older and younger). With this evidence, the current under-use of prophylactic aspirin^{2,3} is inexcusable.

Unanswered questions

Aspirin is of uncertain value in primary prevention. The difficulty is that, although the relative reduction by aspirin is probably the same as in subjects who are at high risk of a thrombotic event, the absolute risk of an event in low-risk men is low, and therefore the actual number of events that will be prevented by aspirin given to healthy men is likely to be close to the number who will experience a serious undesirable side-effect from the drug. Two major trials have been completed in healthy men and while these suggest relative reductions by aspirin of 33% in non-fatal infarction and 10% in vascular events,^{1,51} the absolute numbers of events prevented in such men is only about two or three per thousand, that is, close to the incidence of serious bleeding from aspirin.

It is now recommended that general practitioners and ambulance men give aspirin on first contact with a patient with chest pain who may have suffered a coronary thrombosis.^{52,53} While this would appear to be a most reasonable measure, it does represent an extrapolation from the available evidence which is as yet inadequately tested. A further use of aspirin, which would also appear to be most reasonable, but is untested, is for patients who are judged to be at high risk of a thrombotic event, to be advised to carry a few tablets of soluble aspirin and to take one or two immediately if they experience severe chest pain.

Other uses of aspirin

The aspirin story is not over. Benefit from its use in further conditions with a thrombotic basis would not be surprising. Thus there may be benefit in pre-eclampsia and in retarded foetal growth, although this is controversial.⁵⁴ Aspirin is also of possible value in vascular dementia. There have been calls for randomised controlled trials in the reduction of cognitive decline⁵⁵ and intervention studies have already given evidence suggestive of benefit.^{56,57}

Some of the other possible uses of aspirin, however, do not seem to arise from its antiplatelet action. Thus, it has been observed in a number of cohort studies and case-control comparisons that habitual aspirin takers have a markedly reduced incidence of and mortality from colon cancer.⁵⁸⁻⁶¹ The relevance of aspirin in this condition may be related to an inhibition by aspirin of the proliferation of colon adenocarcinoma cells which is observed *in vitro* and an arresting of the cell mitotic cycle. Another observation, which may be relevant in cancer and which opens up a new field for investigation, is that in certain plants, and therefore possibly in man, aspirin promotes cellular apoptosis, or cell suicide.⁶¹

Aspirin also has effects on the eye which have led to the suggestion that it may reduce cataract formation. Aldose reductase, an enzyme which seems to play a part in cataract formation, is inhibited by aspirin,⁶² as is intra-ocular fibroblast proliferation.⁶³

A future for aspirin

Aspirin is rapidly becoming the victim of its own success and further controlled trials are proving to be increasingly difficult. There is often a 'window of opportunity' for intervention studies and in the case of aspirin it would appear that this window is closing. An ever-increasing proportion of older people are taking the drug and are therefore unsuitable for inclusion in a placebo-controlled trial. Recent evidence from the Caerphilly Cohort Study⁶⁴ indicates that around 30% of men aged 70 years of age and over, who have no clinical reason for prophylaxis, are taking aspirin regularly. Although it reduces rates of myocardial infarction, stroke and vascular death by 25%, aspirin should not be seen as the ultimate antiplatelet drug. It only partially inhibits platelet aggregation to certain agonists, and leaves the responses to thrombin and serotonin virtually unaffected.⁶⁵ Due to these limitations, more potent platelet-specific drugs are being sought. These are sometimes somewhat optimistically being referred to as 'super-aspirins', and already claims are being made for one drug that might be marginally more effective, but vastly more expensive, than aspirin.⁶⁶

Conclusion

Salicylates appear to have been first used therapeutically around 400 BC.⁶⁷ Aspirin was the first drug to have been synthesised and its formulation is regarded as the foundation of the modern pharmaceutical industry.⁶⁸ The benefit of aspirin as a prophylactic after a thrombotic event was first reported in 1974 and its use after coronary or cerebral thrombosis is now virtually mandatory, unless there are signs of intolerance. The current phase of the aspirin story is not over, and its possible use in new conditions seem likely to ensure that it will long continue to play a remarkable part in clinical practice.

Ceri Hughes is grateful for a grant from the Office of Research & Development for Health and Social Care, Wales.

- 1 Editorial. The aspirin papers. *BMJ* 1994;308:71-2.
- 2 Vogel RA. Aspirin and coronary disease. *N Engl J Med* 1996;335:1161-2.
- 3 McCallum AK, Whincup PH, Morris RW, Thompson A, Walker M, Ebrahim S. Aspirin use in middle-aged men with cardiovascular disease: are opportunities being missed? *Br J Gen Pract* 1997;47:417-21.
- 4 Donné A. De l'origine des globules du sang, de leur mode de formation et de leur fin. *Compt Rend Acad Sci* 1842;14:366-8.
- 5 Tocantins LM. Historical notes on blood platelets. *Blood* 1948;3:1073-82.
- 6 Tocantins LM. The blood platelets - past, present and future. In: *Henry Ford Hospital International Symposium Blood Platelets*. London: Churchill Ltd, 1960; pp 3-6.
- 7 Hayem G. Recherches sur l'évolution des hématies dans le sang de l'homme et des vertébrés. *Arch Phys Norm Pathol* 1878;5:692-734.
- 8 Osler W. Editorial. *Med News* 1883;43:703.
- 9 Osler W. An account of certain organisms occurring in the liquor sanguinis. *Proc R Soc Lond* 1874;22:391-462.
- 10 Bizzozero G. Über einen neuen frombes tandeil des blutes und dessen rolle bei der thrombose und der blutgerinnung. *Virchows Arch Pathol Anat* 1882;90:261-332.
- 11 Eberth JC, Schimmelbusch C. Experimentelle untersuchungen über thrombose. *Virchows Arch Pathol Anat* 1886;103:39-87.
- 12 Zucker MB, Borelli J. Change in platelet adenosine triphosphate concentration and distribution during viscous metamorphosis and clot retraction. In: *Henry Ford Hospital International Symposium Blood Platelets*. London: Churchill Ltd, 1960; pp 3-6.
- 13 Denys J. Blutbefund und culterversuche in einem fall von purpura hamorrhagica. *Zentralbl Pathol Anat* 1893;iv:174-81.
- 14 Duke WW. The pathogenesis of purpura hemorrhagica with especial reference to the part played by blood-platelets. *Arch Intern Med* 1912;10:445-69.
- 15 Wright T. The origin and nature of blood plates. *Bost Med Surg J* 1906;154:643-5.
- 16 Rockitansky C. *Pathological anatomy*, Vols i-iv. London: Sydenham Soc, 1854.
- 17 Duke WW. The relation of blood platelets to hemorrhagic disease. Description of a method for determining the bleeding time and coagulation time and report of three cases of hemorrhagic disease relieved by transfusion. *JAMA* 1910;55:1185-92.
- 18 Wright HP. The adhesiveness of blood platelets in normal subjects with varying concentrations of anticoagulants. *J Pathol Bacteriol* 1941;54:161-8.
- 19 O'Brien JR. Platelet aggregation. Part II Some results from a new method of study. *J Clin Pathol* 1962;15:452-5.
- 20 Born GVR. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 1962;194:927-9.
- 21 O'Brien JR. Annotation. *Lancet* 1961;2:91.
- 22 Frick PG. Hemorrhagic diathesis with increased capillary fragility caused by salicylate therapy. *Am J Med Sci* 1956;April:402-6.
- 23 Douthwaite AH, Lintott GAM. Gastric observation of the effect of aspirin and certain other substances on the stomach. *Lancet* 1938;ii:1222-5.
- 24 O'Brien JR. The adhesiveness of native platelets and its prevention. *J Clin Pathol* 1961;14:140-9.
- 25 O'Brien JR. The adhesiveness of native platelets: some anti-adhesive drugs and their mode of action. *Proc VIII Congress Eur Soc Haematol* 1961; pp 51-6.
- 26 O'Brien JR. An *in vivo* trial of an anti-adhesive drug. *Thromb Diath Haemost* 1963;9:120-5.
- 27 O'Brien JR. The mechanisms and preventions of platelet adhesion and aggregation considered in relation to arterial thrombosis. *Blood* 1964;24:309-14.
- 28 Quick AJ. Acetylsalicylic acid and haemorrhage. *Lancet* 1966;ii:1134-5.
- 29 Wijnja L, Snijder JAM, Nieweg HO. Acetylsalicylic acid as a cause of pancytopenia from bone marrow damage. *Lancet* 1966;ii:768-9.
- 30 Morris CDW. Acetylsalicylic acid and platelet stickiness. *Lancet* 1967;1:279-80.
- 31 Weiss HJ, Aledort LM. Impaired platelet/connective tissue reaction in man after aspirin ingestion. *Lancet* 1967;2:495-7.
- 32 Evans G, Mustard JF, Packham M. Spontaneous bruising. *Lancet* 1967;ii:724-5.
- 33 Zucker MB, Peterson J. Inhibition of adenosine diphosphate-induced secondary aggregation and other platelet functions by acetylsalicylic acid ingestion. *Proc Soc Exp Biol Med* 1968;127:547-51.
- 34 O'Brien JR. Two *in vivo* studies comparing high and low aspirin dosage. *Lancet* 1971;i:399-400.
- 35 O'Brien JR. Effects of salicylates on human platelets. *Lancet* 1968;ii:779-83.
- 36 Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. *J Clin Invest* 1968;47:2169-80.
- 37 O'Brien JR. Aspirin and platelet aggregation. *Lancet* 1968;ii:204-5.
- 38 Stuart RK. Platelet function studies in human being receiving 300 mg of aspirin per day. *J Lab Clin Med* 1970;75:463-71.
- 39 Craven LL. Acetylsalicylic acid; possible preventive of coronary thrombosis. *Ann West Med Surg* 1950;4:95-9.
- 40 Craven LL. Prevention of coronary and cerebral thrombosis. *Miss Val Med J* 1956;78:213-5.
- 41 Anon. Report of the steering committee of a trial sponsored by the MRC Effect of aspirin on postoperative venous thrombosis. *Lancet* 1972;ii:441-5.
- 42 Elwood PC, Cochrane AL, Burr ML, et al. A randomised controlled trial of acetylsalicylic acid in the secondary prevention of mortality from myocardial infarction. *BMJ* 1974;1:436-40.
- 43 Coronary Drug Project Research Group. Aspirin in coronary heart disease. *J Chron Dis* 1976;29:625-42.
- 44 Breddin K, Loew D, Lechner K, et al. Secondary prevention of myocardial infarction: a comparison of acetylsalicylic acid, placebo and phenprocoumon. *Haemostasis* 1980;9:325-44.
- 45 Elwood PC, Sweetnam PM. Aspirin and secondary mortality after myocardial infarction. *Lancet* 1979;ii:1313-5.
- 46 Persantine-Aspirin Reinfarction Study (PARIS) Research Group. Persantine and aspirin in coronary heart disease. *Circulation* 1980;62:449-61.
- 47 Aspirin Myocardial Infarction Study Research Group. A randomised controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;243:661-9.
- 48 Anon. Aspirin after myocardial infarction (Editorial). *Lancet* 1980;ii:1172-3.
- 49 Antiplatelet Trialists Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet therapy. *BMJ* 1988;296:320-31.
- 50 Antiplatelet Trialists Collaboration. Collaborative overview of random trials of antiplatelet therapy I: prevention of death, myocardial infarction and stroke by prolonged anti-therapy in various categories of patients. *BMJ* 1994;308:81-100.
- 51 Steering Committee of the Physicians' Health Research Group. Final report on the aspirin component of the ongoing physicians' health study. *N Engl J Med* 1989;321:129-35.
- 52 NHS Executive. *The health of the nation: assessing the options: CHD/Stroke. Target effectiveness and cost-effectiveness of interventions to reduce coronary*

- heart disease and stroke mortality. London: Department of Health, 1995.
- 53 British Heart Foundation Working Group. Role of the general practitioner in managing patients with myocardial infarction. *BMJ* 1989;555-7.
- 54 CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy) Collaborative Group. A randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet* 1994;i:619-29.
- 55 Hachinsky V. Preventible senility: a call for action against the vascular dementias. *Lancet* 1992;340:645-7.
- 56 Meyer JS, Rogers RL, McClintic K, Mortel KF, Lotfi J. A randomised clinical trial of daily aspirin therapy in multi-infarct dementia. A pilot study. *J Am Geriatr Soc* 1989;37:549-55.
- 57 Richards M, Meade TW, Peart S, Brennan PJ, Mann AH. Is there any evidence for a protective effect of anti-thrombotic medication on cognitive function in men at risk of cardiovascular disease? Some preliminary findings. *BMJ* 1997; 62:269-72.
- 58 Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991;325:1593-6.
- 59 Greenberg ER, Baron JA, Freeman DH Jr. Reduced risk of large-bowel adenomas among aspirin users. The polyp prevention study group. *Natl Cancer Inst* 1993;85:912-6.
- 60 Giovannucci E, Egan KM, Hunter D, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995;333:655-7.
- 61 Shiff SJ, Koutsos MI, Qiao L, Rigas B. Nonsteroidal anti-inflammatory drugs inhibit the proliferation of colon adenocarcinoma cells: effect of cell cycle and apoptosis. *Exp Cell Res* 1996;222: 179-88.
- 62 Gupta SK, Joshi S. Relationship between aldose reductase inhibiting activity and anticataract action of various non-steroidal anti-inflammatory drugs. In: Sasaki K, Hockwin O, eds, *Distribution of cataracts in the population and influencing factors developments in ophthalmology*. Basle: Karger, 1991; pp151-6.
- 63 Kahler CM, Kieselbach GF, Reinisch N, Troger J, Gottinger W, Weidermann CJ. Fibroblast growth-promoting activity in proliferation vitrouinopathy: antagonism by acetylsalicylic acid. *Eur J Pharm* 1994;262:261-9.
- 64 The Caerphilly and Speedwell Collaborative Group. Caerphilly and Speedwell Collaborative Heart Disease Studies. *J Epidemiol Comm Health* 1984;38:259-62.
- 65 Anon. Conference report of XVIIIth Congress of the European Society of Cardiology. *Br J Cardiol* 1996;3:154-5.
- 66 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;438:1329-36.
- 67 Fryers G. In: *New perspectives on aspirin therapy 1982*. New Orleans: Aspirin Foundation Symposium, April 1982.
- 68 Hecht G. Entstehungsgeschichte bekannter Heilmittel. Das Aspirin. *Munch Med Wochenschr* 1935;538.