

thinks gastric ulcer, gastric carcinoma, and pancreatic carcinoma equally likely. The normal barium meal at once advances pancreatic carcinoma as the leading diagnosis. A barium-meal request made with such critical expectations of a normal result is clearly proper and appropriate. Note that this patient would have been covered by the Californian rule on grounds of age.

A third objection: is there no value in diagnostic certainty? Patients and doctors like to know, even if the answers change nothing in the objective terms of treatment and outcome. "We'll just do an X-ray and check" can be a nice piece of magic for both parties, attested by the growth of private institutions devoted to routine overhaul of the healthy. In 1980 we have to ask whether we can afford this sort of irrational motive, however human. If we choose to, we have to leave something else undone, in all likelihood by default rather than reasoned selection.

It is difficult to resist the Californian conclusion that the barium meal is overused. MARTON and co-workers suggest that their empirical rule, taken together with clinical judgment, may improve matters, "decreasing the cost of care without significantly affecting its quality". If we were all experienced clinicians with good judgment, there would be no difficulty at all. Meanwhile, the Californian four-point rule deserves serious consideration for teaching ourselves and our students how to cut barium-meal requests safely by 20%. We might even enjoy the exercise; medicine lean and to the point can hardly be bad.

Aspirin after Myocardial Infarction

It is not surprising that the newborn Society for Clinical Trials chose to devote the final plenary session of its May meeting in Philadelphia to independent reviews of the randomised trials of aspirin after myocardial infarction (MI). After all, everything that the Society for Clinical Trials stands for has been done; in six trials,¹⁻⁶ a total of over 10 000 MI patients have been strictly randomised between aspirin and double-blind placebo control and over 1000 have died, so surely no confusion should remain?

What was perhaps more surprising, in view of the arguments that these six trials have previously generated, was that a reasonably clear consensus did emerge between the several speakers and the 500-strong audience. Aspirin, it was agreed, does reduce the risk of death, but the reduction is small, only about a sixth of the deaths being prevented (a benefit very similar to that achievable with anti-coagulants⁷), and it is only the smallness of the benefit that has led to the previous apparent difficulties of interpretation. Even in quite a large trial, in which so many MI patients are randomised that about 60 would be expected to die in each treatment group, prevention by aspirin of about 10 deaths in one group would produce the sort of difference which can perfectly well arise by chance (60 versus 50, $p > 0.1$), and so even if exactly correct results emerge from one such trial they may not be believed. Conversely, chance fluctuations could easily make the results of one particular such trial misleadingly indicate either no benefit from aspirin⁵ or double the true benefit from aspirin.⁴

Reliable information, therefore, can be expected only when the results of all six trials are viewed together, especially since there is no statistically significant heterogeneity in the magnitudes of the benefits reported in the six separate trials. Of course, patients in one trial must never be compared *directly* with patients in other trials. However, within one single trial it is possible to compare the number of deaths observed (O) among the aspirin-takers with the number that would have been expected (E) if, among each prognostic category of patients entered into that trial, the probability of death was unaffected by aspirin. For example, if in each prognostic category the numbers of aspirin and control patients happened to be similar then in the foregoing example with 50 aspirin deaths and 60 control deaths the expected number of deaths, E, in the aspirin group would be about 55.0, and O-E would be 5.0. Alternatively if, as happened in one trial,⁵ the initial allocation happened to put substantially more poor-prognosis patients onto aspirin, E would be greater than the average of the numbers of deaths in the two groups, and might perhaps be as much as 58.0 (in which case the expected number of deaths in the control group would necessarily be correspondingly smaller, i.e., 52.0). If aspirin were of no material benefit then for each trial O-E would differ only randomly from zero, and the sum of the six O-E values, one from each trial, would likewise differ only randomly from zero.

This, however, was not the case. In aggregate, there were 35.5 fewer deaths than expected among the aspirin patients, and correspondingly therefore 35.5 more deaths than expected among the controls, suggesting that aspirin had prevented 70-odd

1. Elwood PC, Cochrane AL, Burr ML, Sweetnam PM, Williams G, Welsby E, Hughes SJ, Renton R. A randomised controlled trial of acetylsalicylic acid in the secondary prevention of mortality from myocardial infarction. *Br Med J* 1974; **i**: 436-40.
2. Coronary Drug Project Research Group. Aspirin in coronary heart disease. *J Chron Dis* 1976; **29**: 625-42.
3. Breddin K, Loew D, Lechner K, Uberla K, Walter E. Secondary prevention of myocardial infarction: A comparison of acetylsalicylic acid, phenprocoumon and placebo. *Hæmostasis* (in press).
4. Elwood PC, Sweetnam PM. Aspirin and secondary mortality after myocardial infarction. *Lancet* 1979; **ii**: 1313-15.
5. Aspirin Myocardial Infarction Study Research Group. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980; **243**: 661-69.
6. Persantine-Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. *Circulation* (in press).

7. Peto R. Clinical trial methodology. *Biomedicine* 1978; **28**: 24-36.

deaths overall ($p < 0.03$). This overall difference was the sum of a non-significant ($p > 0.3$) difference against aspirin in non-cardiovascular mortality, plus a more significant ($p < 0.01$) difference in favour of aspirin in cardiovascular mortality. Some speakers were inclined to attribute the small excess of non-cardiovascular deaths to chance, but no-one seemed to doubt that the larger shortfall in cardiovascular deaths was real, because it was supported by an even more significant ($p < 0.0001$) reduction in cardiovascular morbidity. Overall, there were fewer strokes in the aspirin than in the control groups, while in each trial fewer reinfarctions than expected were recorded in the aspirin group, and the overall reduction in the odds of reinfarction was 21% with standard error $\pm 5\%$.

However, although aspirin is of definite prophylactic value it is by no means a harmless prophylactic. The doses of about 1000 mg/day employed in most trials caused dyspepsia, nausea, or even vomiting in 10–20% of patients, caused constipation, gout, and melæna each in about 1%/year, and caused hæmatemesis in about 0.1%/year. These side-effects can usually be dealt with by stopping treatment, but they are not trivial. They may perhaps be reduced by the use of buffered⁸ or, still better,⁹ enteric-coated aspirin, which both seem to reduce damage to the œsophagus and the stomach,^{8,9} and by the use of lower doses of aspirin: the antiplatelet effect of only 300 mg aspirin is paradoxically about the same as that of higher doses, which may explain why the apparent benefits in the six trials have not been dose related, even though the doses tested ranged from 300 to 1500 mg/day. Moreover if, as may well be the case, the therapeutic effects of aspirin derive in large part from its ability to prevent the aggregation of platelets then pharmacological studies¹⁰ suggest that treatment only once every two or three days with only 300 mg aspirin may be at least as effective as daily treatment, although such intermittent regimens have not yet been tested in large trials. There are many possibilities to explore, and now that we know that aspirin can reduce to a worthwhile extent the risk of death in MI patients we need to discover which dose schedules have fewest side-effects while retaining, or perhaps improving, the therapeutic effect; to discover which other categories of patient can derive worthwhile benefit; and to discover what the balance of benefit and risk will be in really long-term use of aspirin. Finally, the pharmaceutical companies should now make aspirin available in some practical form of packaging, such as a day-

marked calendar pack, which will help patients to remember to take one tablet a day if it is so prescribed.

Other antiplatelet agents include dipyridamole ('Persantine') and sulphinpyrazone ('Anturane') (both of which have to be taken three times a day and are more expensive than aspirin), but none has been shown^{6,11,12} to be more effective than aspirin in preventing death. It may be that the small benefit indicated thus far by both the antiplatelet and the anticoagulant randomised trials realistically represents all that can be achieved by any form of interference with hæmostasis in the months or years after MI.

Dengue, Ross River, or What?

THE name dengue fever used to have a rather legendary quality. Uncles returning from the tropics used to tell of an unpleasant and debilitating but otherwise harmless acute disease which had laid them low. That legend is now being replaced by hard won and sometimes alarming facts. The virus was recovered, at first with great difficulty, by inoculation of blood from febrile patients into suckling mice. There were four serotypes. In the children of South-East Asia these cause considerable mortality from hæmorrhagic disease, and the explanation seems to lie in the number of serotypes circulating in those parts. One type does not give immunity to the others, and in children reinfection may result in severe disease with hæmorrhage and shock. The theory is that pre-existing antibody combines with the new serotype but does not neutralise it. Antibody from various sources can enhance virus growth—it apparently helps the virus to enter host cells probably by an interaction between the antibody and Fc receptors on the cells. Thus the antibody response that gives immunity to one virus may greatly enhance the multiplication of another closely related to it.¹

An understanding of the epidemiology depends on ready recovery of the pathogens, and new techniques for this purpose are based on the multiplication of these versatile viruses in the arthropod hosts which transmit them to man. Thus workers in Indonesia have inoculated serum into female *Aedes* mosquitoes and then, after incubation at 32°C, detected the presence of virus by immunofluorescence.² With this technique they have studied cases of hæmorrhagic dengue fever in Jakarta and have recovered virus of all four serotypes, though type 3

8. Leonards JR, Levy G. Effect of pharmaceutical formulation on gastrointestinal bleeding from aspirin tablets. *Arch Intern Med* 1972; **129**: 457–60.
 9. Mielants H, Veys EM, Verbruggen G, Schelstraete K. Salicylate-induced gastrointestinal bleeding: comparison between soluble buffered, enteric coated and intravenous administration. *J Rheumatol* 1979; **6**: 210–18.
 10. Masotti G, Galanti G, Poggesi L, Abbate R, Neri Seneri GG. Differential inhibition of prostacyclin production and platelet aggregation by aspirin. *Lancet* 1979; **ii**: 1213–16.

11. Canadian Co-operative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med* 1978; **299**: 53–59.

12. Anturane Reinfarction Trial Research Group. Sulfinpyrazone in the prevention of sudden death after myocardial infarction. *N Engl J Med* 1980; **302**: 250–56.

1. Halstead SG, O'Rourke EJ. Dengue virus and mononuclear phagocytes. 1. Infection enhancement by non-neutralizing antibody. *J Exp Med* 1973; **146**: 210–17.

2. Rosen L, Gubler DJ. The use of mosquitoes to detect and propagate dengue virus. *Am J Trop Med Hyg* 1974; **23**: 1153–60.