Aspirin — Effective in Males Threatened with Stroke

A CLINICAL TRIAL on 2 drugs which inhibit platelet function has been concluded after 5½ years of cooperative effort. The results indicate that male patients threatened with stroke will benefit by the daily use of the commonest and one of the oldest pharmaceutical agents — aspirin. Females will not benefit and neither men nor women will benefit from the use of sulfinpyrazone.

This claim may be said to demand the attention of all who are engaged in clinical practice, since vascular stroke has been identified as the likely cause of death of 1 in every 5 persons by 1980. An expected 225,000 people will die each year in the United States and Canada, and, of a slightly larger number who will survive, half will be disabled, continuing as a burden to themselves, their families and the community. To those who frequent the wards of neurological departments and institutions these chilling figures require no elaboration. They are the "raison d’être" of this journal and the compelling argument behind the apportionment of a significant part of the annual budget of the U.S. National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) to the pursuit of stroke-oriented research. It is imperative and appropriate that many American and Canadian neurologists and neurosurgeons occupy much of their time with problems of stroke.

Progress in stroke research has been slow but measurable over the past 3 decades. The adoption of angiography focussed attention on the importance of the extracranial arteries and led in turn to the realization that atheromatous lesions in these extracranial sites were associated with some of the phenomena of the "transient ischemic attack." These transient events came to be recognized as the forerunners of thrombo-embolic stroke, with a prognosis for stroke approximating 5–6% per year, and a similarly high annual threat of vascular death. It became possible to identify, in advance, a significant proportion of patients who were going on to have a stroke and to initiate such imperfect measures of investigation and therapy as were known. Anticoagulants were tested in studies wherein the entry criteria were not screened with sufficient scrupulousness to satisfy modern critical methodology. Their final role in TIA and in patients afflicted with partial non-progressing stroke (PNS) remains unsettled.1 Extracranial vascular surgery was introduced. In some hands, but decidedly not in others,2 it has found a limited but definite place in stroke prevention.

Concomitantly came an increased understanding of the important role of platelets in initiating arterial thrombosis. Whitish material passing through retinal arterioles in patients experiencing amaurosis fugax was observed and identified as aggregates of platelets with fibrin. The ulcerated plaque in the extracranial arteries was recognized as a potential source for these aggregates. In addition, embolic material containing cholesterol and other elements of atheromatous debris have been seen in retinal arterioles ("bright plaques") and it was determined that these fragments were conducive to extending platelet-induced thrombus formation.3 Thus, the 2 varieties of artery-to-artery retinal or cerebral emboli were known to have a significant dependency on platelet reaction.

Beginning in Mustard’s laboratory in 1965,4 and continuing with the work of Weiss and Aledont,5 of Zucker and Peterson,6 and of Emmons et al,7 it was discovered that platelet function could be altered in a significant way by sulfinpyrazone, acetylsalicylic acid and by pyrimido-pyrimidine compounds. Experimental evidence from a variety of sources, a few clinical trials on cardiovascular and systemic vascular disease, and a few clinical fragments, largely of anecdotal variety, in cerebral vascular disease made it appear that the time had come to submit the platelet-inhibiting drugs to a full-scale clinical study. It was apparent that a trial would require a population of patients sufficiently large to settle the question of the drugs’ efficacy in altering the prognosis in patients with TIA and PNS, and it was calculated that a minimum of 540 patients should be entered into the program. This demanded a collaborative effort among many neurological centers. It was recognized that the trial would utilize drugs whose mode of action, for the most part, was unknown.

Funded by the Canadian Medical Research Council, 12 university centers involving 31 neurologists, contributed 585 cases with TIA and PNS into a randomized double-blind trial. The study enrolled the first patients in November 1971, the final entrant in June 1976, and followed the patients until June 30, 1977. Despite the fact that the patients were scattered between the Atlantic fishing-fleets of Newfoundland and the logging camps of Vancouver Island, modern jet travel by the methodological and neurological coordinators, and a long-distance telephone switchboard made it possible to achieve a 99.3% follow up of the patients. It was also possible to recall them to the centers for 3-monthly check-ups on their
neurological status and compliance to therapy, to maintain therapy for an average of 717 days and to obtain an average follow up of 1,002 days. Patients were divided into 4 treatment categories and received a daily dose of either 1,300 mgs of aspirin and a placebo appearing like sulfinpyrazone, or 800 mgs of sulfinpyrazone and a placebo, appearing like aspirin, or both active treatment programs, or else 2 placebos, 4 times daily. Three-quarters of the patients had symptoms suggesting brain ischemia in the area supplied by the carotid artery and one-quarter in the vertebral-basilar arterial territory. Patients were excluded if the threatening ischemic events appeared to be explained by hemodynamic or cardiac causes, if they had serious co-morbid conditions, if they were likely to be unwilling or unable to tolerate the therapeutic program, or if they could not provide informed consent. Angiography was encouraged, not demanded, and was done in 75% of the patients entered.

The disappointing results of the major collaborative randomized trial on extracranial vascular surgery were available to the designers of this drug study. As summarized by Kurtzke, these results did "not mean that one should operate, but rather that one is not obliged to operate for TIA's." Accepting the equivocal evidence from this, the only major randomized attempt to assess the value of extracranial vascular surgery, the Canadian trial discouraged surgery and excluded those submitted to this procedure. Thus, an unoperated "surgical lesion" was present in a high percentage of the cases entered into the carotid group.

It is reasonable to assume that the patients included in this study were as representative of the problem of threatened stroke, from presumed arterial embolic sources, as could be achieved. Withdrawals, when they occurred, were followed up and end-points occurring in these patients were charged against the corresponding study regimen. Failure to pursue this course might have biased the results in favor of their particular regimen, as a tendency to precipitate withdrawal due to deteriorating neurological status might have been overlooked in the subsequent analysis.

The analysis, reported in detail elsewhere, indicates that a remarkably high degree of compliance and follow up are possible in a collaborative study. Although intolerance of the trial drugs occasioned 57 of the 585 patients to discontinue their use, it is striking that a total of 289 patients persisted with a treatment program demanding the ingestion of 4 aspirin tablets a day for an average of approximately 2 years. Heartburn, nausea, vomiting, and upper abdominal discomfort occurred as the commonest side-effects. They were commonest in the aspirin-only regimen, but if both active treatment drugs were employed there was a significant addition in these side-effects. Hematemesis or melena, the only important side-effects encountered in the trial, occurred in 2.1%. Surprisingly, it involved none of the patients on aspirin alone, but involved 2.5% of those on sulfinpyrazone alone, 4.1% of those taking both drugs and 1.5% of those on double placebo. All of these patients responded without serious result to therapy, including cessation of the study drugs.

Utilizing the end-points of continuation of any TIA activity, stroke or death, the results indicate a clear and statistically significant risk reduction (19%, $P < 0.05$) from aspirin. Since continuing TIAs are more difficult to assess with certainty than are stroke and death, a second analysis, omitting the TIA endpoint, indicated a 31% risk reduction in stroke or death from aspirin ($P < 0.05$). Sulfinpyrazone did not produce a statistically significant risk reduction for either group of events, nor was there significant synergism with, nor antagonism to, aspirin therapy.

A 48% risk reduction ($P < 0.005$) in stroke or death was found for male patients on aspirin but females did not appear to benefit. Although quite unexpected, this benefit of platelet inhibition in males only, is not unique. In a randomized trial on dialysis patients subject to thrombus formation in the surgically-produced arteriovenous shunts, the administration of sulfinpyrazone produced a statistically significant reduction in the number of thrombi in males, but not in females. Recently, evidence has been published indicating a reduction of venous thrombosis in male patients but not in females given aspirin after hip replacement surgery. A similar sex difference has been reported in the incidence of experimental thrombosis, with an increase in both sexes from testosterone administration, but a reduction in male animals only with the addition of oestradiol.

In both sexes, a reduced thrombotic tendency followed the administration of an anti-androgen. In another recent study, thrombosis was significantly reduced in male rabbits only with small doses of aspirin. Larger doses affected both sexes equally. Altogether these various experiments utilized mice, rats and rabbits and involved mechanical injury as well as biochemical means to induce the thrombi.

These positive results for aspirin confirm a trend noted in an American trial of shorter duration and fewer patients. To explain this beneficial action of aspirin, the failure to benefit females, the failure of sulfinpyrazone to benefit either sex, and the concern about gastrointestinal side effects, requires close scrutiny of the evolving knowledge of the physiology of the platelet and the gastric mucosa.

A variety of agents aggregate platelets in vitro and in vivo by the generation of free arachidonic acid from platelet phospholipid. Catalyzed by the enzyme cyclooxygenase this fatty acid is converted to prostaglandins G-2 and H-2 (PGG-2 and PGH-2). PGH-2 causes platelets to release their granule contents and to aggregate. PGH-2 is then converted to thromboxane A-2 (TXA-2), a highly unstable compound which is an even more potent platelet aggregator. As well as effecting the platelet, TXA-2 acts to produce vasoconstriction. The nonsteroidal anti-inflammatory drugs, including both acetylsalicylic acid and sulfinpyrazone, block release and aggregation by inhibiting cyclooxygenase activity. In
the case of acetylsalicylic acid this inhibition involves the irreversible acetylation of the enzyme. Sulfinpyrazone, on the other hand, is a competitive reversible inhibitor. Its effects are overcome by strong aggregating stimuli which generate high concentrations of arachidonic acid. Differences in both the degree and possibly the kinetic nature of the inhibitory effect of these compounds may account for differences in efficacy observed in the clinical studies. Although it is possible that other mechanisms are operative, it is reasonable to assume that the ability of acetylsalicylic acid to prevent stroke is due to inhibition of cyclooxygenase activity.

A sex difference in arachidonate-induced platelet aggregation has not been demonstrated in human subjects, but Uzunova's observations on arachidonate-induced thrombosis in rodents are of considerable interest in this respect. The thrombosis induced by arachidonate infusion in rabbits has been shown to be accompanied by prostaglandin and thromboxane synthesis. It is possible that the lack of effect of aspirin in female patients may be due to less complete inhibition of cyclooxygenase activity, an hypothesis not yet adequately tested. An alternative explanation recognizes that blood and vascular factors, in addition to platelet activation by prostaglandins and thromboxanes, contribute to the development of a stroke. Such factors not affected by acetylsalicylic acid may be of paramount importance in women. A third possibility relates to the recent demonstration that vascular tissues synthesize PGI-2 (prostacyclin) which in contrast to PGH-2 and thromboxane A2, strongly inhibits platelet aggregation and causes vasodilatation. It has been postulated that this material may account for the resistance to thrombosis of normal vascular endothelium. Since the synthesis of PGI-2 is inhibited by the nonsteroidal anti-inflammatory drugs, acetylsalicylic acid may be exerting an undesirable effect by inhibiting PGI-2 synthesis. A greater sensitivity of vascular cyclooxygenase in female patients, to this effect of acetylsalicylic acid, conceivably could account for the sex difference observed. What effect testosterone and estrogen levels play in these hypothetical considerations is not known at this stage, and deserves study.

There is evidence from animal experiments that the ulcerogenic action of nonsteroidal anti-inflammatory drugs may be due to inhibition of cyclooxygenase activity. It has recently been demonstrated that gastric mucosa, like platelets, preferentially synthesizes thromboxanes from arachidonic acid. This synthesis is inhibited by both acetylsalicylic acid and sulfinpyrazone. Therefore, both the gastrointestinal side-effects and the desired clinical effect of nonsteroidal anti-inflammatory drugs on platelets may be due to inhibition of synthesis of prostaglandins and thromboxanes.

Presumably, the future will see considerable research directed towards finding a cyclooxygenase inhibitor which has maximum effect against prostaglandin and thromboxane synthesis in the platelet mem-

brane, minimum effect on prostacyclin suppression and minimal inhibition of thromboxane synthesis by the gastric mucosa. In the meantime, it is not possible to advise administration of aspirin or sulfinpyrazone to women with symptoms of threatened stroke. Their effectiveness is not established in women and their side effects may be disturbing. Men, on the other hand, will benefit from aspirin in terms of the serious sequelae of threatened stroke and yet must be followed with care for gastrointestinal complications, including bleeding. On the basis of the Canadian Cooperative Trial they need not be given sulfinpyrazone, but the role of the pyrimido-pyrimidine compounds alone and synergistic with aspirin requires further scrutiny in males and females.

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