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 of 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 thromboembolic 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. Extracranial vascular surgery was introduced. In some hands, but decidedly not in others, 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. 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, and continuing with the work of Weiss and Aledont, of Zucker and Peterson, and of Emmons et al., 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 end-point, 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. Sulfin-
pyrazone, on the other hand, is a competitive reversi-
ble inhibitor. Its effects are overcome by strong
aggregating stimuli which generate high concen-
trations 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 cyclooxy-
genase activity.

A sex difference in arachidonate-induced platelet
aggregation has not been demonstrated in human sub-
jects, but Uzunova’s observations on arachidonate-in-
duced thrombosis in rodents are of considerable in-
terest in this respect. The thrombosis induced by
arachidonate infusion in rabbits has been shown to be
accompanied by prostaglandin and thromboxane syn-
thesis. It is possible that the lack of effect of aspirin
in female patients may be due to less complete inhibi-
tion 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 throm-
boxanes, 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 exer-
ting an undesirable effect by inhibiting PGI-2
synthesis. A greater sensitivity of vascular cyclooxy-
genase 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 con-
siderations 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 ac-
tivity. 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 sulfin-
pyrazone. 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 throm-
boxanes.

Presumably, the future will see considerable
research directed towards finding a cyclooxygenase in-
hibitor which has maximum effect against prostaglan-
din 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 syn-
ergetic with aspirin requires further scrutiny in males
and females.

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