Controversies in Stroke: Past and Present
The Willis Lecture

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In homage to Dr. Thomas Willis of Christ-Church in Oxford, as a prologue I would like to share a quote from the "Preface to the Reader," in The Remaining Works of That Famous and Renowned Physician, Dr. Thomas Willis:1

Wherefore all delay being laid aside, I determined with myself seriously to enter presently upon a new course, and to rely on this one thing. Not to pin my faith on the received opinions of others, nor on the suspicions and guesses of my own mind, but for the future to believe nature and ocular demonstrations . . .

These conclusions, written over three centuries ago, were based on Dr Willis' study of philosophy; if followed, they might have prevented many of the controversies we will discuss today.

I am honored to have been asked to give this year's Willis lecture. As I review the high quality of my predecessors, I forgive the selection committee for this year's lapse in judgment. I hope you will, too, after I am finished.

Now join me in a 40-year personal odyssey through some selected controversies in cerebrovascular disease in which I have been an observer and a sometime participant.

Although this begins in 1953, we must first stop in 1955. This was a time that younger members of this audience cannot imagine. Computed tomography, magnetic resonance imaging, and ultrasound were far in the future. Even angiography was in its infancy. It was almost always performed by neurosurgeons, and cutdowns were not infrequent. It was not until 1956 that I would be the first non-neurosurgeon to perform an arteriogram in the state of Indiana. Because it was the perception that there was no treatment for stroke, patients were admitted to the big general hospitals only if they could not handle their secretions or swallow. The therapeutic literature for these patients consisted primarily of anecdotal, retrospective reports.

It was in this environment in 1955 as a resident, late one night after finishing rounds on my very sick patients, that I picked up the latest issue of the Journal of the American Medical Association, at that time the most widely distributed medical journal in the world. I was struck by one of the lead articles. Three New York investigators2 reported that 27 of 35 consecutive stroke patients were dramatically improved after receiving cortisone. In 21, this improvement was seen within the first 24 hours. My patients were lying on the ward having difficulty swallowing and handling their secretions and often dying, and all I could do was support them. In the face of these very impressive statistics in consecutive patients, it seemed unethical not to go back to the wards and start cortisone immediately. But cortisone was and is a dangerous drug.

My first experience with the shortcomings of anecdotal studies had been two years before, in 1953. I had read a similar article describing dramatic improvement of consecutive patients with Huntington's disease treated with procainamide.3 As a senior medical student already converted to the true religion of the supreme organ system, I pleaded with my first-year resident, Dr William DeMyer, and my chief, Dr Alexander Ross, to prescribe it. They, with Dr Ralph Reitan, who at the time was developing the Halstead-Reitan battery which would become the basis for modern neuropsychology, were supportive. Their support was conditional upon my setting up, with their help, a well-designed experiment that would establish the effectiveness or lack of effectiveness of the therapy. I did. The study was completed and published in 1954 and to my disappointment showed no effect at all.4

So again with the support of my staff, Dr Philip White, I designed a prospective, double-blind controlled study.5 Because we had observed many patients who completely recovered within minutes to hours, entry was delayed until 24 hours after the ictus. The results were sobering. Because of a higher mortality in the cortisone group, the study was aborted after entering only 36 patients. We could not prove the drug to be dangerous, but it was extremely unlikely that it would be beneficial. Later studies with less dangerous steroids6-11 followed the same pattern.

If one reviews the major controversies, they seldom are based on difference in science but rather on assumptions made on the basis of different anecdotal experience. Never trust a self-professed "honest man"! They lie to themselves. The investigator who considers the possibility that he might cheat will set up an experimen-
tal design so tight that even if he tries to cheat, it will be impossible. The most reliable results come from the "dishonest" man! I vividly recall Dr. Joseph Foley putting this into his usual picturesque words and completely damming an investigator with a single sentence. "He has never been surprised by any experiment he has ever performed."

In the words of Sir Francis Galton,\textsuperscript{12} the introducer of fingerprinting:

General impressions are never to be trusted. Unfortunately when they are of long standing they become fixed rules of life, and assume a prescriptive right not to be questioned. Consequently those who are not accustomed to original inquiry entertain a hatred and a horror of statistics, they cannot endure the idea of submitting their sacred impressions to cold blooded verification. But it is the triumph of \textit{scientific men} to rise superior to such superstitions, to desire tests by which the value of beliefs may be ascertained, and to feel sufficiently masters of themselves to discard contemptuously whatever may be found untrue.

Despite the development of a number of sophisticated design and statistical techniques, all must include the same fundamentals. There must be a testable hypothesis; an experiment designed to exclude bias; and the probability of the results occurring by chance must be so low as to be unacceptable. For clinical trials, this requires that the study is prospective, the treatment determined randomly and double-blinded, and the numbers large enough to avoid type II error. Regardless of how sophisticated the statistical tests are, they must be determined at the onset of the study. By changing statistics and looking at data many times, it is almost certainly possible to obtain any result one would wish.

One of the most important innovations is meta-analysis. Later, when I disagree with some of the conclusions said to be based on meta-analysis, it will not be a criticism of the tool but of the inappropriate extrapolation of conclusions. This is an extremely powerful technique based on pooling data from a large number of similar studies. This large pool of data enables researchers to draw highly significant conclusions because of the increase in numbers and to avoid the systemic bias of drawing conclusions from just a few well-known studies selected from dozens of related studies.\textsuperscript{13} The Antiplatelet Trialists stressed that patients in one trial should never be directly compared with those in another. Not only might the patients have been different but so too might the treatments, duration of treatment, quality of follow-up, and end-point definitions. We should compare only like with like within one trial and not assume that the sizes of any risk reductions in different trials must be similar. The scientific requirements for meta-analysis are the same as for individual studies just described\textsuperscript{14} and at best can answer only the hypothesis proposed in the original studies.

The method of analysis commonly used in stroke studies is that of Mantel-Haenszel-Peto.\textsuperscript{13} Its brilliance is reflected in its simplicity. In summary, O refers to the observed end points in the treatment groups and E to the expected end points. The observed minus the expected end points (O\textminus{}E) is calculated for each study and then these are added together for all studies. In the Antiplatelet Trialists' illustrative example of 500 treated patients and 500 control subjects, they assumed that 65 patients died; of these, 25 (the observed end points) were in the treatment group. The expected end points would be half the total of 65 who died, or 32.5. The observed (O) minus the expected (E) is 7.5, which would represent not 7.5 deaths but 15. Variance is calculated in the usual fashion. This is done for each trial and the results totaled. Obviously, in a true universe if treatment is ineffective, the sum of O\textminus{}E in an infinite number of studies would be zero. If it is effective, the total would be a minus. If it is worse than control, the total would be a plus. Variance of the grand total can be calculated by adding the separate variances of each separate difference, and odds ratios can be estimated.

Despite the power of this technique, it must never be viewed as a substitute for simple, well-designed clinical trials.\textsuperscript{15} It can address only the testable hypotheses posed in the original studies, and the results cannot be extrapolated to test new hypotheses.

Now we are prepared to continue our odyssey, looking at some examples of the many controversies that have occurred to see whether they continue under the cold, hard light of science.

In the 1950s a number of anecdotal reports suggested that patients presenting with transient ischemic attacks (TIAs) and mild stroke were favorably affected by acute treatment with heparin and long-term treatment with warfarin. Although this was one of the first areas in which properly designed studies were initiated, the controversies are still raging. For TIAs, only four studies have been reported\textsuperscript{16-19}; because these were so numerically underpowered (with a total of only 93 treated patients and 85 controls), it is not surprising that, except for a trend toward increased mortality in the treated patients, no statistical differences were noted in any individual study or in aggregate. These numbers are far too low to exclude type II error.

As recently as a month ago, I was shocked to hear an internationally known investigator state that as long as randomization is successful, blinding is not necessary. As an example of how bias might affect even a randomized, well-designed study that is not blinded, I would like to share an anecdote with you. In the 1960s we were interviewing a non-neurologist for a position at Indiana University who came from one of the centers participating in one of the controlled studies of anticoagulation. I asked why he thought this center had excellent results in its randomized pilot study and such poor results when it entered a multicenter blinded study. The answer was not surprising. The patients in the pilot studies who were assigned to the warfarin group were monitored very closely, seen immediately for any complaint, and followed up frequently with all risk factors treated vigorously. Those assigned to the placebo group were asked to call or return if they had any events and were sent back to their referring physicians. Obviously, the study was biased not by the differences in the use of anticoagulation but by the better general treatment of risk factors.
The entire subject of anticoagulation in stroke prevention must be reopened. In this country the dose of warfarin has been based on a prothrombin time of 2.0 to 3.0 INR units, but the North American thromboplastin used is not equivalent to that used internationally. We may have been poisoning a large number of patients. A prothrombin time of 2 to 3 times normal would exceed 4.0 INR.

The good news is that at long last several studies are in progress that are expected to give definitive answers within the next few years. Acute therapy with heparinoids is being investigated in a multicenter trial under the leadership of Dr Harold Adams. Another, headed by Dr J.P. Mohr, is investigating the value of long-term, low-dose warfarin in patients with stroke.

Another bright spot is the use of anticoagulants in chronic atrial fibrillation. Four studies (Copenhagen, Boston, Stroke Prevention in Atrial Fibrillation [SPAF], and Veterans Affairs) have reported a marked reduction in outcome events in patients on low-intensity anticoagulation with warfarin. Unfortunately, they were not double-blind; however, as the design is rigid and all are going the same way, we would hope that they are valid. The participants in each of these studies agree on the warfarin results but disagree whether aspirin is effective.

In the SPAF Study, 325 mg/d aspirin was associated with significant relative risk reduction. The Copenhagen and Boston trials reported no aspirin effect. In the Boston study, aspirin was not randomly assigned but taken at the discretion of the patient; in the Copenhagen study, the dose was only 75 mg/d and the patients were much older than those in SPAF. Therefore, these studies are not comparable. The SPAF study is continuing with the aspirin and warfarin arms, and this controversy should be settled soon. The study has been concluded and the final results will soon be available.

In 1985, the entire medical and surgical community and the investigators were stunned by the results of the Extracranial-Intracranial Arterial Bypass Study. This was an exquisite procedure that technically could successfully bypass arterial blood from extracranial arteries to intracranial arteries. It had to work, but it didn’t. No subgroup benefited from the procedure. Surgically treated patients did worse in two groups: those with (1) internal carotid artery occlusion with symptoms and (2) middle cerebral artery stenosis. Many of us had been sure that the surgery would be effective for these patients. Immediately there was a great furor, but ultimately this was neurosurgery’s shining hour. By 1987, Walker reported that only a fraction of the number of procedures expected (565 of an expected 2225) were still being performed. Obviously, the clinical community accepted the results of this well-designed scientific study over their prejudices and, to paraphrase the words of Galton, rose superior to superstitions and discarded contemptuously what they found to be untrue.

In the early 1980s, a culmination of events led to a general expression of concern regarding the possible overuse and excessive complications associated with carotid endarterectomy. The procedure was commonly used with increasing frequency in the United States despite appreciable complication rates and the absence of properly designed controlled studies supporting its efficacy. The only large multicenter study was inconclusive, with complication rates that were far too high. Robert Pokras and reported data from the National Hospital Discharge Survey showing that the number of carotid endarterectomies had increased from 15,000 in 1971 to 107,000 in 1985, with just under 3% discharged dead. Based on these data, it was estimated that the combined stroke and death rate was somewhere between 5.6% and 16.8% for the nation. A number of retrospective studies of a total community or hospital experience supported this. As early as 1977, Easton and Sherman called attention to a stroke and death complication rate of 21%. The surgical community considered the complications to be too high, but to establish a risk-benefit ratio, properly designed prospective studies were needed.

Following this, guidelines were suggested for maximum complications, and several prospective studies began. A blue ribbon committee of the American Heart Association issued a policy statement. They recommended an ongoing prospective audit of the occurrence of death and stroke within 30 days of endarterectomy. They considered complication rates above 5% for TIAs and 3% for asymptomatic stenosis. Changes occurred very early. By 1986 the number of endarterectomies had dropped from an expected 127,000 to 83,000.

In 1991 (much earlier than expected), two large prospective randomized studies, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), almost simultaneously reported the same electrifying results. In both studies, symptomatic patients who underwent endarterectomy for severe (70% to 99%) stenosis as determined by linear measurements of the arteriograms had markedly fewer strokes in the territory of the symptomatic artery. In NASCET, as in ECST, the 18-month event rate was conclusively in favor of surgery. The ECST study also conclusively demonstrated that endarterectomy on arteries with less than 30% stenosis was not beneficial. In each study, operative morbidity and mortality was acceptably low. A third well-designed prospective study, a Veterans Affairs multicenter study, was terminated early because of these results. Despite this, for stroke and “crescendo” TIAs, final analysis revealed a statistical difference in outcome similar to that of the NASCET study. For the first time, scientific evidence supported the benefit of endarterectomy for a defined group of patients. If the surgeon has a low complication rate and the patient has 70% to 99% stenosis of a carotid artery that is symptomatic, endarterectomy is effective. It is of no benefit when stenosis is 30% or less.

The value of the operation for asymptomatic patients with 30% to 70% stenosis and all asymptomatic patients should be determined by ongoing studies now in process. Unfortunately, many physicians may have naively extrapolated the results of these studies to all patients. Barnett et al. have pointed out that the absolute decrease is greatest at 90% to 99% and progressively decreases as the degree of stenosis lessens. Patient accrual in the NASCET study initially decreased rather than increased. We expect that the medical commu-
nity will continue to respond to calls for concern and this trend will rapidly reverse.47-49

Asymptomatic stenosis is a separate issue. The Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA),49 a multicenter randomized trial, involved 410 patients with asymptomatic stenosis (50% to 90%) of the internal carotid artery. There were no significant differences in the number of neurological deficits and deaths between patients who received medical therapy and those who underwent operation. Despite the large numbers, this study does not settle the controversy. All patients with greater than 90% stenosis received surgery. If the stenosis progressed to greater than 90% during the study, surgery was performed.

Recently, the Mayo Asymptomatic Carotid Endarterectomy Study Group51 terminated their study after only 71 patients had been randomized because of a significantly higher number of primary and secondary end points in the surgical group. This also does not establish the lack of effectiveness. In this study, only the medical group received aspirin. The trialists concluded that the results were likely related to the absence of aspirin in the surgical group.

A Veterans Administration Cooperative Study reported in the New England Journal of Medicine recently52 a significantly decreased number of ipsilateral events in patients who underwent operation. Unfortunately, in a study in which the treatment cannot be blinded, these were primarily transient events and quite likely could have been influenced by bias. The primary, hard, nonsurgical end points of stroke and death were not significantly different.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) has now randomized more than 1200 of its planned 1500 patients.49 When this study is completed, the value of endarterectomy for asymptomatic patients may be known.

The value of the widespread awareness of controversy may be favorable even before studies are completed. Recently, several reports suggest that favorable changes are occurring and low morbidity and mortality are becoming more commonplace. Robert Pokras has expedited analysis of the 1990 and 1991 data from the National Hospital Discharge Survey so that I would have new data to present to you. In 1986, the annual number of endarterectomies performed dropped from an expected 127 000 to 83 000 and continued to decrease to 67 000 in 1991, the year of the NASCET and ECST reports (81 000 in 1987, 70 000 in 1988 and 1989, and 68 000 in 1990). Between 1987 and 1988, a new hospital population was used for sampling, which probably accounted for the slight break in the curve. We had hoped that reliable numbers to estimate the death rate might be obtained by combining figures from several years. Unfortunately, the numbers are still too small for reliable estimates. Before 1987, it is estimated that around 3% were discharged dead and after 1987 around 0.9%, but the figures are unreliable.

Because these data are so critical to the impact of the procedure, I contacted David Hsia, who had published the actual data from Medicare.53 He and his colleagues had published these data, which are calculated from all patients and are very reliable, up to 1989. Although he was no longer with the Inspector General’s office, he contacted a colleague, W. Mark Krushat, who ran a special analysis for 1990 and 1991 (W. Mark Krushat, personal communication). Because it is possible that these figures could change slightly with final payment of Medicare bills, I have rounded them off to the nearest thousand. The results are most interesting. Endarterectomies paid for by Medicare fell from around 63 000 in 1985 to 48 000 in 1990 (53 000 in 1986 and 1987 and 50 000 in 1988). In 1991, the year of the NASCET and ECST reports, they increased by about 9000, to a total of 57 000. Regardless, and most reassuring, the 30-day death rate continued to fall from a little over 3% in 1985 to 2.3% in 1991. The Medicare death rates would be expected to be higher than those of the National Hospital Discharge Survey because they are based on 30-day mortality, whereas the National rates are based on deaths that occur in the hospital. The decrease in mortality rate appears to be across the board in all groups. The decrease was uniformly present in hospitals large and small, urban and rural, teaching and nonteaching, and for profit and not for profit. Although the trend is good, the death rate of 2.3% is still far too high, and the combined mortality and stroke rate still must range from 5% to 11% for all Medicare patients. This must be corrected, as the benefit reported in the NASCET and ECST studies depended on a much lower complication rate from the participating surgeons. These studies establish that lower rates are possible in the hands of selected surgeons.

Aspirin has been known to be effective in stroke prevention for some time. At least nine studies of aspirin for patients with TIAs or minor stroke were reported before 1990.54-65 In all but two, a statistical benefit was established.51,62 The value of aspirin should no longer be a controversy, but several issues are still debated, including gender differences, benefit of adding dipyridamole, proper dose, and the risk-to-benefit ratio compared with that of ticlopidine.

Women did not appear to benefit from aspirin in the Canadian study56 and the United Kingdom Study.64 In 1980, I reviewed the controls in prospective studies in which events were related to gender.66 In the studies of aspirin, the event rate in treated men only approached that of untreated women. It was postulated that the lack of an observed effect on women was probably because the event rates are comparatively low in women; thus, an effect might not become apparent during a few years of follow-up of a small number of women who were at relatively low risk. Aspirin was effective in women with TIA and mild stroke in the European Stroke Prevention Study63 and the French AICLA Study.58,60 I cannot resist commenting on the European study results because they so closely reflected what was predicted. The life-table analysis indicated that results in treated men were quite similar to those in untreated women, but both do better on aspirin.

Aspirin doses as low as 30 mg/d will block cyclooxygenase and the release of thromboxane A2 in platelets and have very little or no effect on the prostacyclin system in the endothelium. Therefore, low dose might induce a desirable combination effect. Also, in theory, if the prostacyclin function in the endothelium could be
enhanced by a drug like dipyridamole, the patient might additionally benefit.

Dipyridamole combined with aspirin has been compared with aspirin alone in three studies, two French studies58-60 and the American-Canadian Co-Operative Study Group.61 In none was an additional benefit shown by adding dipyridamole to aspirin. Although the controversy is said to continue, these studies should have settled the issue.

The widespread acceptance of low-dose aspirin may have been enhanced by conclusions drawn from meta-analysis.13 The Antiplatelet Trialists performed a meta-analysis of clinical trials of TIA, stroke, surgical trials, myocardial infarction, and unstable angina. They also used a heterogeneous group of end points (definite stroke, probable or definite nonfatal myocardial infarction, and all deaths that might have been vascular or hemorrhagic). Therefore, the hypothesis could not have been the same for each study. In this mixed group, 900 to 1500 mg/d was associated with a 23% reduction in end points and 300 to 325 mg/d with a 24% reduction. But none of the lower dose studies were of cerebrovascular disease. In this report the studies of cerebrovascular disease all used 975 mg/d or more.

In the only direct comparison of 300 versus 1200 mg/d, the United Kingdom Study, 2435 patients were entered with TIA or minor stroke.54,55 They were randomized to 300 or 1200 mg/d aspirin or to placebo. Neither aspirin dose alone was significantly better than placebo. Data reported in the paper indicated a slight trend for a better response to 1200 mg than to 300 mg. The percentage differences were not significant but were as high as 8.9%. For the combined aspirin group there was only an 18% (interim report)64 or 15% (final report)65 reduction in risk of myocardial infarction, stroke, or death; a 7% reduction in disabling stroke or death; and 3% in disabling stroke and vascular death.

Since then the Swedish Aspirin Low-Dose Trial (SALT)66 has reported that 75 mg/d aspirin results in a statistically significant 18% reduction in stroke and death. This result suggests that low-dose aspirin is effective but gives no information concerning whether it is as effective as doses of 975 mg/d or higher.

A Dutch study69 has reported no significant differences in the primary end points between low-dose (283 mg/d) and very-low-dose aspirin (30 mg/d). As the probability of seeing a 33% risk reduction was greater than 0.80, it is likely that at these very low levels 30 mg/d and 283 mg/d are equivalent.

Because the reductions in end points in the UK-TIA Study and the SALT study are modest (15%, 18%, or less), Dr Barnett and I performed independent analyses comparing these results to those of studies of TIA and mild stroke that showed a benefit using higher doses of aspirin.70 The same calculations were performed for each study using the actual numbers published in the original papers. In only one study was this figure different from that published by the authors (13% versus 15%), which may reflect a slightly different type of analysis.

The reduction in stroke and death ranged from only 3% to 18% in the SALT and UK-TIA studies compared with 25% to 42% in the others. Only three studies reported stroke, myocardial infarction, or vascular death as end points. In the SALT66 and UK-TIA studies, reductions were 17% and 13%, respectively, compared with 40% in the Parisian study58-60. This is not the way science should be conducted, but this mini-meta-analysis raises the possibility that 325 mg or less may not be as effective as 975 mg or more.

After carotid endarterectomy, Boysen et al71 compared 50 to 100 mg/d to placebo. Despite dose titration to the point of a platelet effect, stroke and death were not reduced. Studies using higher doses have shown an effect. Kretschmer et al72 observed in a retrospective study a marked reduction in mortality in patients receiving 1500 mg/d aspirin. Following this, their prospective study73 reported a statistically significant decrease in death in only 68 patients. In the surgical arm of the United States aspirin study by Fields et al,55 those who received 1300 mg/d aspirin had significantly fewer strokes and stroke deaths at 24 months of follow-up than those on placebo.

In the NASCET study, Barnett observed that at 18 months, ipsilateral stroke had occurred in 11% of those taking 325 mg/d aspirin, in 10% of those taking 650 mg/d, and in only 4% of those taking 1300 mg/d.70 These data must be interpreted with caution because the study was not designed to test the effect of aspirin. Nevertheless, if the dose of aspirin had been a primary end point, the numbers were high enough and the differences great enough for this to be statistically significant.

The Physicians’ Health Study24,25 may give some insight into the appropriateness of extrapolating mixed end points for heart and brain and drawing conclusions concerning a subgroup with cerebrovascular disease. This is in itself a megastudy. In it, 22,071 male physicians received 325 mg aspirin or placebo every other day for 5 years. If the mechanisms and the effects are the same, one would expect that if enough events occurred, the same trends should have been seen for both heart and brain. Because of a very significant decrease in myocardial infarction in the aspirin group, this study was terminated early. Of the 378 who had myocardial infarctions, only 139 (37%) were receiving aspirin (P=0.0002). Yet there was no difference in the occurrence of stroke. This was not because of the rarity of events. A total of 217 strokes occurred, 119 in those receiving aspirin and 98 in those receiving placebo. This trend is opposite to that of myocardial infarction. The same was true for the total of 173 who had ischemic strokes. These numbers are high enough that a significant effect would have been expected if the mechanisms are the same.

Ackerman and associates (Reference 76 and R. Ackerman, personal communication) studied the inhibition of platelet aggregation induced in vitro by adenosine diphosphate and arachidonic acid in patients taking various daily doses of aspirin. An incomplete antiplatelet effect was the failure of aspirin to inhibit secondary aggregation at 10 μM adenosine diphosphate and/or 1500 μM arachidonic acid. There was a progressive increase in the number of nonresponders as the dose decreased below 975 mg/d. About 16% of those who received less than 650 mg/d were nonresponders, but all who were taking over 975 mg/d experienced a full effect.

Helgason and associates77 also evaluated clinic patients taking various doses of aspirin. Of 107 patients
taking 325 mg/d aspirin or less, 22 (21%) had incomplete aggregation. When the dose was increased to 650 mg/d in 9 patients, 4 (44%) did not respond. Three still did not respond at 975 or 1300 mg/d.

Evidence is mounting that brain circulation and systemic circulation are not identical, and some of the effects of aspirin may be more than simply the antiplatelet aggregant effect. A number of responses may be different at higher doses than at lower doses. These include variable strength of the agonist collagen,78 variable aspirin hydrolysis,79 hyperreactivity to shear stress in patients with vascular disease,80 disaggregation response,81 variability of response to aspirin,82,83 decreased platelet membrane fluidity,84 and generation of thrombin.85 For all these reasons, many clinical scientists still consider the proper dose of aspirin an area of active controversy.

Ticlopidine has been established as the first platelet antiaggregant since aspirin to effectively reduce further stroke and death for patients with TIA, mild stroke, and moderate stroke. The Ticlopidine Aspirin Stroke Study (TASS),86 a study of 3069 patients with TIA and mild stroke, compared ticlopidine (500 mg/day) with aspirin (1300 mg/day). The ticlopidine group had a 21% decrease in all types of stroke at 3 years and a 47% risk reduction at 1 year. The Canadian American Ticlopidine Study (CATS)87 demonstrated superiority over placebo in patients with moderate-to-severe stroke.

There should be no controversy over the benefit of ticlopidine. The controversy here is not concerning effectiveness but rather the interpretation of risk-benefit ratio. Almost 1% of patients experienced a serious neutropenia within 90 days. Some interpret this as a contraindication of its use except in special circumstances. Others use it with little reservation because in every case the neutropenia occurs within 3 months, and recovery occurs rapidly when the drug is stopped.

This review of current and past controversies was not meant to be comprehensive. I hope it has been of some value in making the point that we must never vary from our rigid scientific principles. We must draw conclusions only about the hypotheses tested and not extrapolate and make assumptions that are not warranted by the data. If we don’t, we will continue to have more and more unsolvable controversies.

Unfortunately, many good studies have been and are going to be negative and not turn out the way we wish. As I am thinking about this as we approach the end of this 40-year journey and wondering if it is all worth it, a paraphrase of the words of Edna St. Vincent Millay88 keeps echoing through my mind:

My candle burns at both ends. It will not last the night. But, ah, my foes and, oh, my friends It gives a lovely light.

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