Personal Reflections From a Front-Row Seat at the Greatest Show on Earth (Life)
Part II (Stroke Research Commentary)

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Part I of this discussion of my 65 years since graduating from medical school covered my reasons for being in medicine at all, my explanation for the theatrical terms in the earlier para-scientific document, and finally the effect of World War II on my career.1

Part II will attempt to touch on the privileged life I led in the field of stroke prevention research. In its entirety it is designed as a story or tale about my 50 years in medical practice and does not follow the standard format of a scientific paper.

Previously I alluded to the ongoing prejudicial custom of critical attempts to resist new ideas in scientific endeavor. I gave as examples the discordant behavior in Toronto that greeted the discovery of insulin and of less far-reaching consequence my own attempts to convince Canadian and American colleagues that there were 5 distinct causal mechanisms leading to syringomyelia. Surgeons in Cleveland and Boston were adamant that there was but one. Postmortem studies and now routine MR studies prove them wrong.

New Insights Into Previously Unrecognized Causes of Stroke

My next contribution of a controversial nature was a description of a group of young patients with stroke whose causes we defined in a study with age and gender-matched controls as being due to emboli associated with mitral valve prolapse and to suggest that this was a clinically overlooked cause of cerebral ischemic events.2 Denials of variable vehemence appeared but the accumulating pathological and surgical data were quite incontrovertible. Ultimately in an Olmstead County prevalence study its occurrence as a cause of stroke was validated.3 Its prevalence is probably less than we suggested in our first report. The difference is probably explained by improvement in the conduct, interpretation and the delineation of newer stroke causes revealed by echocardiography. At times more than one potential cause of stroke is revealed by careful study of the heart and great vessels including the aorta. A major contributing factor to the dispute about mitral valve prolapse as a cause of stroke was that mitral valve prolapse is quite common, usually causes no symptoms, and many cardiologists did not encounter or attend to cerebral ischemic events in their patient populations. By contrast, at the time of writing our first paper my referral practice consisted almost exclusively of patients with unusual cerebral ischemia, including those who were younger than most stroke and transient ischemic attack (TIA) patients so that I was dealing with a totally different population than that being seen by cardiologists. From this biased population sample our early reports emerged. As this product of echocardiography was coming into focus so too was annulus calcification found commonly in the mitral and aortic valves of the very elderly. It can be claimed definitively that both underlying conditions are of common asymptomatic occurrence but are rare causes of stroke. In both instances pathologists at postmortem have detected the breaking off of atheromatous fragments or attached thrombi, or there has been clinically associated atrial fibrillation in the absence of other flagrantly recognizable causes for cerebral ischemia. Both must be sought because they are surgically treatable.

More immediately acceptable was our report from the aspirin study data bank that it was incorrect to postulate that there could not be focal ischemic events beyond a carotid occlusion.4 We reaffirmed what Thomas Willis had described in 1664 that when the internal carotid artery becomes occluded the external carotid artery will supply anastomoses to become the alternate source of hemisphere and ocular blood supply. Among causes of such events we identified the “Stump Syndrome.”5

In regard to embolism from the stump of the occluded internal carotid artery a possibly important unpublished observation came out of our Extracranial/Intracranial Bypass Study. One of the participants analyzed the angiograms of all patients whose postoperative images revealed a satisfactory surgical anastomosis to become the alternate source of hemisphere and ocular blood supply. Despite this, in some there was a later return of ischemic events that were usually submitted to further imaging. In five of these instances the second repeat angiogram detected a stump of the occluded internal carotid artery that had dark material outlined within the white contrast in the stump. The previously good circulation beyond the bypass was no longer visible. The external carotid artery...
had no visible evidence of atheromatous irregularity but instead within what had been the bypass site was the round-edged obstruction suggestive of an embolus. We were tempted to invite resection or ligature of the stump but in time learned that this carries an unacceptably high risk of ischemic stroke. A brief period on anticoagulants may be empirically indicated until the thrombus in the stump dissipates. This speculative therapy is unproven and so it will likely remain.

**Early Attitudes to Stroke Victims**

During my medical student days, I learned that patients with stroke were not welcomed in general medical units. They “tied up beds.” At Toronto General Hospital if severe enough, incontinent and difficult to keep clean, noisy and restless, while awaiting transfer to a scarce chronic institutional bed, they would be assigned to the infamous basement-located “Observation Ward.” Here with shouting schizophrenics, alcoholics hallucinating with delirium tremens or demented with Wernicke’s encephalopathy, syphilis with the confusion of syphilitic General Paresis of the Insane or tabetic screaming with lightning pains and gastric crises: the Ward was a Bedlam. To this auditory overload was added the offensive odor of paraldehyde mixed with the stench of urine, feces and vomit. New knowledge was coming and in time each of these hopeless entities would respond to preventive and therapeutic measures and the “Observation Ward” would be closed forever. For me stroke became my paramount challenge. I watched while over the next decades several great changes converged to add meaning to my own increasing enthusiasm to pursue the prevention and treatment of stroke.

**Major Breakthroughs**

Egaz Moniz in Portugal developed cerebral angiography⁶ using the contrast radioactive thorotrast. I met his surgical colleague and coauthor Lima lecturing at Queen Square on the identification of carotid occlusion as a cause of stroke. James Bull at the same hospital tolerant coached me in the technique of percutaneous carotid angiography. This capability I took back to Toronto, where the radiologists were willing only to make the images, not to insert the needle or inject the contrast. I can recall being invited to the Hospital for Sick Children to perform a carotid arteriogram on a 3-month old infant by this primitive direct-puncture method. Through a tiny carotid artery, using a hypodermic needle and with trepidation we successfully demonstrated a large but curable aneurysmal dilatation of the vein of Galen.

Postmortem dissections of the neck portion of the carotid arteries (previously left for the convenience of the embalmers) were made by Hultquist⁷ in Sweden and a decade later by Fisher⁸ in Montreal. Both concluded that occluding lesions in the neck were commoner causes of stroke than the traditional blame attached to the middle cerebral artery.

The demanding science of Epidemiology, Trial Methodology & Biostatistics began to emerge, and evidence-based decision-making began its steady march to change medical and surgical practice for the better. Double-blind randomized trials were key in perfecting this advance. The risk profile of stroke began to unravel with major contributions from the Framingham Study under Phil Wolf’s guidance and the work of many others including Doll, Bamford and Peto in Oxford. Cigarettes emerged eventually as more lethal for addicts than modern highways and battlefields and second-hand tobacco smoke as a killer of innocent nonsmokers. The tobacco barons stopped their blatant lying, but because tobacco was not illegal none of them went to jail to keep marijuana growers company.

Systolic blood pressure of “100 plus your age” became an unacceptable platitudine; the fractionation of cholesterol fragments was accomplished with a sharp division between harmful and essential elements. Labeled details of food content were demanded of the food industry. The importance of these advances was recognized by the Stroke Council of the American Heart Association (AHA) and guiding statements and risk profiles began to appear.⁹

Denny-Brown and Fisher in Boston and Millikan at the Mayo Clinic played important roles in putting the phenomenon of TIA into convincing manuscripts popularizing the revolutionary concept of stroke-threatening symptoms. (TIAs in the hemisphere or the eye.) Sixty years later the significance of these clinical occurrences are as well known as harbingers of stroke events to the “person-on-the-street” as is the significance of a crushing chest pain suggesting to the general public an impending heart attack. TIAs and even Ischemic strokes are occasionally homodynamic; most often they are of thrombo-embolic origin, commonly with lesions in stenosed or occluded cerebral arteries.¹⁰ Traditionally and until the late 40’s, platelets were the most overlooked of the three cellular blood elements, a neglect that 60 years later seems incredible. In time aggregates of platelets were identified in the retinal arterioles during episodes of amaurosis fugax,¹¹ in the cerebral arteries at postmortem,¹² in the cortical branches of the middle cerebral artery (MCA) during EC/IC bypass surgery,¹³ and in the intramyocardial branches of the coronary arteries in patients dying with unstable angina. Pomerance’ postmortem studies demonstrated that this location of aggregated platelets was characteristic and usual in patients dying from myocardial infarction heralded by unstable angina.

The anticoagulants heparin and warfarin were discovered and were introduced in cerebral vascular conditions in the decades before the demanding imperative of adequate clinical trials. Great quantities of them were exhibited in a great variety of vascular conditions. Fortunately, it can now be stated that they are of proven value in definite but clearly defined entities in the cerebral vascular area. These will not be covered extensively but include especially patients with atrial fibrillation, patients with presumed red thrombi in the great vessels, heart chambers, or cerebral arteries and in cerebral venous thrombosis but not in situations where large-artery cerebral arterial infarcts are present or threatening. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) and the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trials wrote finis to much of this traditional overuse.

Following Fisher’s descriptions of lacunar (small-vessel) disease and the introduction of xenon blood-flow studies, Hachinski began his research on vascular dementia; Mohr
and Caplan identified stroke by cause in the Harvard Stroke Registry, focusing attention on a surprising number of “unknown cause.” Work remains to be done and many “unknowns” can now be recognized. Readers must watch with continuing interest the Framingham project under Wolfe, The Manhattan Stroke Project (Sacco), and The Oxfordshire Community studies (Bamford).

**More on Newly Recognized Causes of Stroke**

The list of newly-recognized causes of stroke continues to grow. Unusual vascular, genetic and cardiac mechanisms have been uncovered by technology. The commonest of these was probably spontaneous (and traumatic) dissections of the extracranial carotid and vertebral arteries as well as intracranial basilar and middle cerebral arteries. Chiropractic manipulations, vigorous yoga exercises and rear-end collisions, especially when the patient has his head turned sharply at the time of the blow are among the commoner associated circumstances. Twice Andrew Kertesz presented patients at our weekly rounds with the locked-in syndrome resulting from bilateral vertebral artery dissections. In each instance there were minor symptoms from the first dissection after a manipulation so that (mirabile dictu) another manipulation was suggested and the second vertebral artery dissected with major brain stem damage. Unusual vascular genetic and cardiac mechanisms have been uncovered by technology. Parisian neurologists are responsible for describing or at least popularizing three vascular conditions. Bousser and her associates described the genetically based Cadacil. With improvements in transthoracic and esophageal echocardiography, patent foramen ovale was extensively studied in cerebral ischemic events by Gauthier. Fatty atheromatous potential embolic debris or thrombi were identified with the same technology by Amarenco, coming from ulcerations in aortic plaques.

**Departing Toronto: the Organization of a Combined Department and a New Research Institute**

I moved from my academic position in Toronto to the University of Western Ontario in 1969. Here the plan conceived with Charles Drake was to bring together specialized teams of full-time faculty (neurologists, neurosurgeons, neuropathologists and neuroradiologists) with residents and research fellows who had primary dedication to stroke patients and stroke research or other neurological areas needing research. A unique team for Canada would be the first group of neuro-oncologists, led by Greg Cairncross. All members of this team were trained at the Sloan Kettering in New York by Jerry Posner, the pioneer in this field. Montreal and the Mayo Clinic contributed an epilepsy group, an immunology/transplant team assembled under the lateral-thinking Stiller. A team of twelve imaging experts under Fenster from Toronto grew to have 250 scientists and support staff at work. Evidence of their intention to succeed was heralded by the group of 12 having 6 or 7 sleeping bags among their laboratory equipment. Important to my personal endeavors came a still growing force in the Clinical Trials Group with special ability to pursue randomized, double-blind studies of drugs and surgery. Hegele with a cardiovascular team has been adding to knowledge about the impact of genetic factors in his focused vascular area. Growth in molecular biology has obscured the lines between many of the original groups and helped accomplish our goal of interdisciplinary research activity particularly impressive in the study of neurodegenerative disorders. With the help of colleagues, provincial government and a philanthropic community, we added and later expanded a large independent research facility (The Robarts Institute) adjacent to the new University Hospital and the Medical School. In both of these adjacent institutions research space had become cramped. Its founding and funding were made easier because of the aura created in this community by Charles Drake’s special skill in the posterior fossa and his worldwide following of referrals, Calvin Stiller’s ideas and his reputation and work that had made feasible organ transplantation by his visionary introduction to North America and the world of the primary antirejection drug Cyclosporine. Transplantation became commonplace and durable immediately. Luckily the newly created University Hospital had a caring, charismatic, visionary and supportive giant in its new CEO, Patrick Blewitt. He helped make the Robarts Institute possible. The juxtaposition of a research-oriented clinical staff at University Hospital and the ever-growing Robarts Research Institute across the road from the Medical school has been magic.

**Platelet Inhibitors**

In October 1969 Fraser Mustard whose earliest platelet laboratory was down the hall from me in Toronto and was now Dean of Medicine and one of the dynamic founders of McMaster Medical School, drove to London expressly to urge me to launch a randomized clinical trial to determine whether his laboratory observations about the alteration of platelet function by 2 drugs (aspirin and sulfinpyrazone), coupled with our maturing knowledge that platelets were involved with TIA and stroke, might be capable of preventing stroke. Aspirin was known as an analgesic and antiinflammatory agent and sulfinpyrazone an antigout remedy. Mustard had studied the phenomenon of platelet aggregation in response to injured endothelium. The trial we designed with Mustard, Sackett, Taylor, Hirsh and Gent was to be double-blind and factorial so that each patient received one or other of the drugs with placebo, both active agents or double placebo. Candidates fitting our protocol entered from the 10 Canadian teaching centers (Newfoundland to British Columbia) and without any remuneration for randomizing the patients. The Canadian Medical Research Council grant purchased the drugs. We were able to state after 2 1/2 years of follow-up and with a mere 585 randomized patients that the aspirin-containing arms were surviving with fewer strokes than in the arm taking only placebo and that sulfinpyrazone alone was ineffective5 (Figure 1). Neither then nor subsequently has it been shown that there is synergism between the two trial drugs. Nobody at the time of our trial launch knew of the greater risk facing stroke-threatened men than women, but in exploring the results by gender post hoc the aspirin arms in men were significantly superior to the arms without aspirin. There was only a trend to aspirin benefit in women.
In retrospect had we known of this disparity we should have randomized twice as many of the lower-risk women. We were sharply criticized after publication for this post hoc analysis, and later when the mechanism of action of aspirin had been detected we were criticized for choosing as high as 1300 mg of aspirin daily in divided dosage. Knowledge of the chemical pathways of this antiplatelet activity lay in the immediate future and our choice of dose not based on later disclosures. With interest I reflect that throughout a trial that touched two oceans we kept it alive with no Fax, cell-phone or emails. Office phones, regular mail and airplanes were our means of communication. Later when we were doing the 3-continent Bypass Study and had overseas calls to make, London was still awaiting its satellite connections. I grew impatient with “all overseas lines are busy, please call back.” The Bell manager for London, Ontario suggested that if I told their monthly staff meeting of my activities in trying to prevent strokes that I might provoke them to a shorter wait-time. I gave 30 to 40 women telephone operators an illustrated talk and never again was my overseas call cancelled or delayed. Circuits were opened more quickly. I was recognized in a book-shop 6 years later by a young lady who shook my hand and told me that as a late but direct result of this staff luncheon she had just come from signing her lease for a medical office, having been induced to leave her switchboard and go to medical school to seek a more active seat closer to the front row in the great show on earth: “life.”

In spite of criticisms and some understandable skepticism, the era of antiplatelet therapy had now been launched for patients with recent ischemic events and as prophylaxis for individuals with a risk profile putting them at greater likelihood than others for stroke or by later research from heart attack.

Universal acceptance of aspirin in stroke prevention properly awaited the positive results of about a dozen more trials, including first the Bousser trial in Paris and then the UK trial under Warlow. As then Editor-in-Chief of Stroke, I had flown to Paris to meet Bousser at Charles de Gaulle airport to ensure that her report reached English-speaking-only readers for what I strongly suspected to be a turning point in this development. The UK TIA trial eventually was confirmatory but curiously did not cite the Canadian or the Bousser Trials. Instead an accompanying paper introduced the concept of meta-analyses. As a confirmed believer in scrupulous trials, I was wary of this; first of all it can and did use not just scrupulous but also more casual pragmatic trials some known to be flawed (eg, a Hamilton trial of sulfinpyrazone run by a vascular surgeon, who from his own service admitted more patients in a few months with amaurosis than did all of the 10 Canadian academic centers combined). The results were positive for anturan but he admitted to me that he consulted neither neurologist nor ophthalmologist to confirm the diagnosis.

The Ciba-Geigy Company used his results to advertise the benefit of Anturan in patients with a TIA. After a struggle I was able to put a stop to this madness.

This whole scenario confirmed my belief that scrupulous studies, taking longer and costing more will carry an advantage in credibility over trials of imperfect design. Pragmatic trials with little data and scrutiny are in serious danger of diluting the stroke benefit. Another example of this dilution was the comparison between the results of the first 4 larger trials against placebo already referred to Table 38-3). In the UK it took longer for potential candidates to get through to scarce stroke neurologists for randomization and their benefit results in terms of relative risk reduction were half those of the other 3 trials. The patients in the UK trial faced half the risk in the placebo arm as they did in the other 3 early placebo-containing studies. Unless the populations at entry and the outcome events are truly similar (as will be further discussed in the ACAS/ACST comparisons) and the internal monitoring is known to be properly conducted, meta-analyses make me uncomfortable in seeking evidence-based data to guide therapy, particularly dosage. My final cautionary example of the need to be wary of the extra care required in adding any and all manuscripts to a meta-analysis came when a well-known neurologist emerged from the first Antiplatelet Trialists Meeting and stated that he now favored sulfinpyrazone as the first choice for TIA patients. This opinion changed when he was apprised of the flaws in the amaurosis trial. Cautionary comments about undisciplined use of meta-analyses are beginning to appear from serious investigators.

Scrupulous trials are more expensive but so are sloppy results leading to weak claims of benefit.

Extrapolating results from all subsequent antiplatelet trials randomized with symptoms in other target organs and performing meta-analyses the advice from the Antiplatelet Trialists Consortium was that aspirin was an effective antiplatelet agent and opined that the lowest dose (81 mg) is adequate. There is a necessary leap of faith here: all vascular bed arteries and target organs have an equal likelihood of responding to the same dose of platelet inhibitory drugs. My contention remains that in considering the striking physical differences between the carotid and coronary arteries and their own unique linings of particular endothelium plus the fact that the alternate-day aspirin used in the Physicians’ Health Study reduced myocardial infarction (MI) but not
stroke, it would have been preferable to have obtained knowledge of optimum dose based on a study of direct dose comparison confined to TIA and stroke patients. Such a trial was planned but never materialized. We had purchased the drugs for the Canadian Trial and should have done so for this sequel that never came about. The Bayer Company favored the 81 mg, pill charging twice as much in my local pharmacy as for 325 mg enteric-coated aspirin. The 81 mg pill cannot be purchased across the counter. A company representative advised me that they estimate that 1 billion people take a prophylactic aspirin daily. Their interest in a comparative dose-trial from the point of view of the share-holders’ bottom line is understandably limited. How nice it would be if we were unequivocally certain of these facts about optimal dose. Were a trial to be revived today it would have to take note of the recently and repeatedly proven fact that the first week and 10 days after the very first cerebral ischemic event represents the time when such individuals are at the highest risk of a recurrent event and would be the appropriate patients to randomize in any new study of risk reduction.20,21 Unhappily the academic community and industry have grown tired of trying to fine-tune such things as the absolutely optimum dose of aspirin for particular target organs. Certainly low-dose is enough for patients threatening a heart attack. It remains unknown that just because the Swedish SALT trial proved that 75 mg was effective against placebo that a higher dose might have been somewhat better.22 The Dutch trial compared their results against historical controls with two arms of variable amounts of low-dose but failed to administer higher doses to two other arms.23 Pity! It became a trial without an answer to the burning question.

At first it seemed incongruous to many that a common headache pill had serious ability to prevent threatening disabling and even fatal diseases. A former Deputy Minister of Health in Ontario once asked me: “is this whole aspirin business in stroke merely a ruse and just a way of giving something because we do not have anything else to give?” I have watched from the sidelines while two other platelet-inhibitors have been tried. The data for the trials have been held secret by industry or their paid functionaries. The promotion, some of which has been grossly misleading, has been of an extravagance unlike anything seen in neurologically recommended drugs up to now. Their considerable cost is surely adding to strained health-care budgets, and their superiority in stroke prevention not convincing to me. The first trial, ESPS I,24 of what became Aggrenox was badly inferior in stroke prevention not convincing to me. The firm data of aspirin’s ability to prevent stroke was well established when this trial was launched. It was unacceptable to have a placebo arm. 250 strokes were counted in the placebo group. All those involved in designing and conducting this trial should have been aware of the Bousser trial (AICLA) in which 990 mg aspirin was compared to placebo with a relative risk reduction of 44.3% favoring aspirin and of ESPS I with 990 mg aspirin plus dipyridamole with a significant relative risk reduction of 37.7% favoring the active treatment group.25 In ESPS II had the patients been given aspirin instead of the placebo, it has been estimated that the 250 strokes in the placebo group would have only been 44. (Statistical calculations courtesy Prof Michael Eliasziw.) Absolutely scrupulous data gathering, ethical conduct and total transparency about the data are the sine qua non for the credibility and acceptance of any therapeutic trial.

The makers of the other drug (Plavix or Clopidogrel) were publicly warned several times by the FDA with copies disseminated on the internet that they were advertising for benefit that was outside the limits of the FDA-accepted usefulness.27,28 It was sold at a very profitable rate, compared to the few pennies needed for what is probably an equally efficacious dose of aspirin. When all outcomes and data about complications are the secret property of the manufacturer, the public and the profession are entitled to be skeptical of claims of efficacy and of marginal differences separating new preparations from more cheaper and conventional treatments.

The manufacturers of Aggrenox and particularly those of Clopidogrel (Plavix) must be disappointed in the recent presentation of the results of the much-advertised PROFESS trial of patients with cerebral ischemic events in which the two treatment arms revealed no superiority of one preparation to the other. Both are very expensive compared to the aspirin that they did not compare against in PROFESS. There was of course 50 mg ASA in the Aggrenox used.

Recently a trial (ESPRIT) conducted by a stroke neurologist/epidemiologist from Holland, Ale Algra, with no commercial sponsorship, tested the differences in compound outcome vascular events when receiving either aspirin (75 mg) versus dipyridamole with aspirin and found 20% reduction for the composite events of vascular death, nonfatal stroke, nonfatal MI or major bleeding. When the cerebral ischemic events were separately analyzed there was no trend for reduction of stroke. This analysis involved too few outcome events for robust conclusions. For obscure reasons this drug trial was not blinded. As in other trials of dipyridamole headaches dogged the subjects causing a substantial number of patients to leave the trial. Unhappily these results do not justify switching TIA patients to Aggrenox, nor can Aggrenox be used as a 2nd level of therapy in cases of aspirin intolerance.

Because clopidogrel in the CAPRIE study gave no result of benefit for stroke patients, it cannot be given a recommendation either. What is needed is a new antiplatelet preparation that for stroke-threatened patients has been proven to prevent...
stroke with more benefit than aspirin in a direct trial of one against the other. The trial should be sufficiently large that in the end the company and its hired investigators cannot hide failure behind the spurious nostrum that “the trial was not designed to analyze a subgroup,” a claim that was repeated for the 6000 plus patients who entered the CAPRIE Study after a stroke. I disagree with this rigidity, especially if all outcome events are carefully and independently monitored. We knew in detail the risk of stroke and death for patients in the placebo groups when aspirin was evaluated in the patients in the first 4 large randomized trials as set out in Table 38-3 of reference.13 Quickly there was acceptance of aspirin as an effective agent in stroke prevention by the world of stroke neurologists and by regulating agencies who accepted the beneficial results. If this was possible with a total of 6120 patients why did the CAPRIE investigators not regard >6000 as an adequate number to allow them to give out more details on the stroke arm of their study?

The ultimate dose study should be conducted without input in design, execution or data management and analysis by anybody receiving money from any platelet-inhibiting manufacturer. Until it is done the Health Protection Branch in Canada and the FDA should continue to monitor closely the sale and promotion of all preparations advertised for stroke prevention. Neurologists should carefully study the outcomes table in the CAPRIE report. There they will observe that those who entered with an MI were at greatest risk of an outcome of MI, patients entering after a stroke were at greatest risk of recurrent stroke and the same tendency to peripheral vascular disease complications for the patients entering with peripheral vascular disease. The notion that prescription should be given for Plavix for anyone with any vascular disorder is not acceptable to this writer. Supporting evidence is weak and conversely promotion is strong and forms part of the expense of the drug.

Placebo-controlled trials with double-blinding of patients and investigators have by now passed through review by thousands of ethics committees and very importantly family physicians have come to accept and even embrace them. They were not always so well understood and received. Early in the Canadian Aspirin trial I was invited to speak at the noon-hour staff meeting at a local hospital to about 30 physicians and explained the design of a randomized placebo-containing factorial trial and asked their help. The first question after I finished: “Do you mean that you are asking us to let you use our patients as guinea-pigs?” My explanation of the raison d’etre for the design of the double-blind trial was too novel and as yet too nontraditional for older doctors. There were no more questions as they got up in a body and left the room!

**EC/IC Bypass to Prevent Stroke**

After bloody battles in the US war over slavery in the South and in World War I some front-line hospitals were almost entirely devoted to amputations. In World War II protected by antibiotics many limbs could be salvaged. One of the requirements was to develop ability to repair torn arteries. Vascular surgery emerged as a specialty. After the stress of war was over, operating microscopes introduced microvascular surgery, another great step forward. Yasargil in Switzerland and Donaghey in Vermont perfected skills to anastomose the superficial temporal artery from the scalp through a burr-hole to a cortical branch of the middle cerebral artery. The suture used was no larger than a human hair and small-animal practice was required of the surgeon. The Japanese in particular had attempted earlier to revascularize the brain by a cortical overlay of omentum in patients afflicted with thirsty brains because single or multiple arteries were occluded as in carotid occlusion or in Moyamoya Disease. The results were not promising.

By contrast enthusiasm for superficial temporal artery/MCA anastomosis spread quickly and before long hundreds had been performed in North America, Europe and Asia. The procedure was performed when ischemic events recurred despite internal carotid occlusion or when the symptomatic stenosis was beyond the neck. One European enthusiast for regional xenon cerebral blood flow studies and for the bypass procedure reported at an international meeting on revascularization that he had done by-pass surgery in three patients with reduced regional flow but without any symptoms. I was asked to comment and had to struggle to be firm but gracious.

Worried that enthusiasm exceeded our knowledge of its benefits in reducing stroke, the NINDS put out a request for a grant to submit the procedure to a randomized trial. Submissions had imperfections in their designs so that the frustrated Director of NINDS (Don Tower) knowing of our interdisciplinary team in the Canadian Aspirin Trial from its presentation at the Princeton Conference29 asked us to put a trial together and to conceive of a strategy to preserve the double-blind nature of a trial where half of the patients had an obvious craniotomy. This was an attractive challenge. We asked, “When is the deadline?,” “well it was three months ago but we might extend it for 3 weeks, no more!” On the morning of the absolute deadline one of my office staff took the morning plane to Washington and the application got to the Council Meeting the next day. Nine years and nine million dollars (US) later without loss to follow-up 1377 patients were randomized from USA, Canada, UK, Italy, Holland, France, Germany, Finland, Hungary, Yugoslavia, Taiwan and Japan. We paid modest sums for the completion of each of the entry, outcome and follow-up documents. To frustrate seizure of any of this hard currency by Soviet-occupied countries we opened New York accounts and sent airline tickets to facilitate attendance of these politically oppressed participants at the annual meetings of other European collaborators.

To the surprise of the investigators, stroke (or death within 30 days) was less with medical care alone.30 The response to our negative report was tumultuous. I was reminded of the outburst in years gone by when Lord Macaulay described the public anger directed at the unpopular support given by Lord Clive to some contemporary parliamentary discussion as “a tempest of execution and derision (occurred) alike to the outbreak of public feeling against the (hated) Puritans in the time of the Restoration”(of the monarchy).31 Surgeons who had learned the procedure, many of whom had published their own observational series, for some of whom it was to have been their route to fame and fortune, in addition to hundreds who were training in preparation for the final word, were
deeply disappointed with our results. So too were many physicians including me who believed it was helpful.

Disappointment turned to anger when it was learned that Medicare, Blue Cross and other insuring agencies were contemplating disallowing payment for EC/IC procedures. One of America’s leading neurosurgeons and one of the most experienced proponents of the procedure, who had declined requests to randomize his patients, telephoned some of our trials’ surgeon collaborators and learned that several had violated their signed agreements with us to randomize all eligible patients. They admitted to operating on some patients who they truly believed would benefit. (This “choice” by participants is standard practice in trials run by the Oxford Trials group.) I have failed to understand how participants agreeing to seek facts to replace belief built on conventional wisdom would be able to select patients who in their faith-based opinion should immediately be submitted to the innovative treatment. The belief was that they would “know” enough to leave out of the trial their selected “best subjects” deserving of the unproven therapy. Nevertheless the disappointed in several centers volubly claimed that our trial was flawed. How would the late Kenneth Galbraith speculate on this medical tendency to “belief” rather than proven fact?32 I mused on this several years ago in an Editorial.33

A “Blue Ribbon Committee” was appointed with representation from NINDS and four senior neurosurgeons. No independent methodologist was asked to join the Committee but it did include the complainant. On the appointed day for their visit we made accessible all correspondence between us and our centers, all EC/IC study files plus two tables covered with the documents relating to communications between us and all centers which included signed agreements to randomize all suitable candidates. None of the committee looked at them. The meeting was one that the likes of Margaret Wente of the Toronto Globe and Mail and many a cynical, critical and caustic investigative reporter would have relished as would have the late Lewis Carroll who loved dream-like and unreal scenarios. The Chairman came two hours late, one of the Committee members nodded, caught up on his sleep needs soon after we convened without our Chairman. He asked no questions. Because we could not admit to the possibility of other participants breaking their promises to us (how could we possibly know without a mole in each center?) the meeting concluded by the Blue Ribboners agreeing that “internal validity” was intact but there was reason to believe that the last word on the value of EC/IC was not yet written. Failure to include all eligible patients put a “cloud over the trial,” as one editorialist wrote.34 Contrary remonstrations by Sackett were made but ignored: “what is important is that there be internal validity and a representative mix of patients essential to the trial,” and that it was “of little consequence that some good candidates were not recognized or were deliberately not randomized because their attending physicians and surgeons wished to believe that bypass surgery for them would be best.”35,36 Quoting Julius Caesar: “men willingly believe what they wish.”37

Our Blue Ribbon colleagues would proceed to submit the criticism, already written in the name of the main complainant and in their brief-cases when they arrived.38 In due course a variety of government agencies accepted our results, and all the insuring agencies, Prudential, Blue Cross etc, followed the lead of Medicare. It has been estimated that this virtual ban on the procedure has annually saved billions of dollars to healthcare systems in most parts of the world. No payments were to be made for a procedure of uncertain merit.

The personal and more widespread fallout from this report were both disturbing and interesting. “Disturbing” for several reasons:

1. After attempting to conduct a scrupulous trial on three continents, it was unpleasant to be confronted by a wall of hostility erected by previously collaborative colleagues.
2. The principal investigator of the trial was to blame for the negative result that was “due to mistakes in managing the centers properly.” No allusion was made to the fact that the participating centers had all promised to randomize all of their patients and the offenders had broken their written agreements.
3. The Japanese senior surgical coordinator who doubled as our recruiter and translator was denied the prestigious promotion that was in his grasp until the trial “failed” in the eyes of his associates.
4. It was a huge disappointment also to the enthusiasts interested in evaluating cerebral blood flow. Speculatively this testing would have demonstrated correctable pathophysiology. It lost its worth as a surrogate outcome or even as a means of further investigation.

“Interesting” for a variety of reasons:

1. An interdisciplinary team proved that it could combine expertise and evaluate the efficacy of a surgical procedure.
2. Some human strengths and frailties were unmasked.
3. Some innocence of the nature of disciplined trials and evidence-based decision-making were uncovered: (a) one participant wrote a letter of complaint to the Editor of the NEJM, stating that if it had been known in their center that we were conducting a negative trial patients from that center would not have been randomized; (b) after the final analyses all centers were provided with their own results. Plainly none of them were large enough to permit robust analysis. As expected there was a reasonably thin line that could be drawn between centers conferring benefit and those causing harm; a few centers were above and slightly more just below the benefit/harm line. This difference was the 5-year accumulations of stroke and 30-day death outcomes. Most centers recognized this reality. Some expressed dismay and suggested that in their centers the procedure should be allowed to continue. In the long run, most centers stopped doing the procedure, including many with long experience.
4. Currently in St. Louis, William Powers and colleagues have detected a subgroup at highest risk of stroke. They have launched a randomized trial confined to this group of patients: all have carotid occlusion but with continuing ischemic events after the detection of the occlusion. All had hemodynamic insufficiency determined by PET scans. This is a worthy trial despite the fact that this subgroup minus PET-scan studies was identified at the
onset of our NIH-sponsored trial. They were separately analyzed without evidence of benefit, but with larger numbers this trial may validate the hypothesis.

Performing superficial temporal artery/MCA bypass to prevent stroke outside a trial such as being conducted by Powers is on very uncertain ground and should be discouraged. Posterior fossa bypass procedures are not safe. In Holland, attempts are being made to perform anastomoses using MCA major branches instead of scalp arteries. To date this work must be regarded as experimental.

**Carotid Endarterectomy-NASCET**

Among the surgeons suturing torn arteries and saving limbs, guts and brains on the battlefields of Europe was a young man (Felix Eastcott) from St. Mary’s Hospital. He put this guts and brains on the battlefields of Europe was a young man aged. Posterior fossa bypass procedures are not safe. In

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By the late 1970’s several things had happened of which my front-row seat in this theater afforded me a good view. About one million CEs had been done worldwide; as Editor-in-Chief of the journal *Stroke* I was receiving an increasing number of manuscripts questioning the unaccept-

ably high stroke and death complications based on commu-

nity surveys; the Rand Corporation devised a method of evaluating the need for CE and concluded that too many were being done inappropriately. Warlow at Oxford had initiated a randomized trial in the United Kingdom to test CE against best current medical care; Plum and Walton had joined me in an Editorial in *Stroke* expressing concern common to our three countries.

Murray Goldstein, the indefatigable and wise Director of NINDS, bespoke of our experienced team a competitive grant submission to be given for independent review. Hachinski with Sackett, Haynes and Taylor at McMaster helped us put together a trial whose goals were to: (1) define the indications for CE in symptomatic patients; (2) determine which patients were not candidates; (3) determine the acceptable limits to the complications of post-CE stroke and death.

The NASCET study was funded, lasted 11 years, cost $45 million, and at its peak had 128 full- and part-time paid employees, in the Central Office and eventually in 107 participating centers in North America, Europe, Australia, South Africa and the Middle East (Israel). The “raison d’etre” for such a large staff was to ensure timely recruitment, to eliminate prerandomization any proffered noneligible pa-

patients, to allow the Central Office to have a scrupulous data-bank with all requested data intact at entry and on each 3-monthly follow-up visit and to forward complete data expeditiously about all confirmed or suspected outcomes to the Central Office for early external review, and to ensure submission of all arteriograms to the Central Office for rereading of lesion type and stenotic degree. We knew that failure of a center to report promptly suggested laxity in patient contacts and this would be the surest way to have drop-outs. Our goal was few or none. All patients had ultrasound images but we resisted all requests, especially pushed by one member of our Monitoring Committee who conducted a big Doppler operation, that Doppler images would suffice in lieu of conventional angiograms. Central Office comparisons of ultrasound and angiograms consistently showed over-reading of the degree of stenosis by approximately one third when ultrasound was compared to conventional angiography.

All Central Office staff met for a minimum of 2 hours once a week to discuss any problems in randomization, to advise of
strategies to hasten recruitment and to discuss every end point. Two stroke neurologists, 2 vascular neurosurgeons, 2 neuroradiologists, an ultrasonographer, 1or 2 biostatisticians, 2 dedicated stroke research fellows (supervised by Hachinski), a study manager and 5 to 6 data clerks (mostly nurse practitioners)and secretaries agonized over every entrant and all outcome data. In regard to the cause of every stroke or death we followed the principal taught to me by my early-life mentor in field biology: “Never give me guess-work. Go back if need be and stay with it until you are absolutely sure.” In the case of some unusual problems we had fairly thick correspondence files. The treatment arm was carefully kept secret during all of our deliberations, known only to the research fellow and the senior management staff. We kept the faith in our “double-blinding.” Our study goal was to ensure sufficient data that centers would ascertain the cause of each stroke by predetermined defined criteria (large artery, lacunar, cardioembolic or “other”) and that the effect of predetermined but important subgroups could eventually be analyzed (age, gender, collateral arterial supply, vascular risk profile, cause of stroke outcome, contralateral occlusion, degree of stenosis). The primary analyses for any stroke ipsilateral to the CE or 30-day death after CE or randomization were published, twice for those with severe stenosis (70% or more)44,45 and once for those with moderate stenosis (50% to 69%) (Figure 2).45 A separate manuscript on surgical complications was published.46 Several summarizing and cautioning papers have been published.47–53 Separate analyses have been published for the predetermined subgroups planned in advance.54–57

Three entities were not anticipated in advance but plainly warranted posthoc analyses: (1) mild to moderate intracranial stenosis tandem to the symptomatic artery58; (2) widespread leukoaraiosis59; (3) near-occlusion of the symptomatic carotid artery.60

Early in NASCET days Charles Warlow, the principal investigator of the European study (ECST)61 and I decided to rationalize any differences that might exist in our protocols, analyze together the totality of our primary results which in the end proved to involve over 6000 symptomatic patients followed for an average of 5 years. When adequate data had been gathered we planned to analyze for our predetermined subgroups. Fox reread the ECST angiograms by the NASCET method. The European trial, less solidly funded than NASCET, demanded abbreviated data in comparison to NASCET. At joint meetings, with some jocularity, Warlow would drop a single sheet from the lectern and compare this with a thick bundle representing the work of our collaborators. We knew that the extra data were needed to justify the subgroup analyses essential to our study aims. Peter Rothwell was invited to perform the rationalizing and combining of all pertinent data from the two studies and spent many months in our data center.62 It was observed that the primary analyses gave very similar beneficial results favoring CE over medical care in patients with severe stenosis. In the 50% to 69% range (what we called “moderate stenosis”) the ECST surgeons had a 9% perioperative risk rate and failed to find benefit. The NASCET and the combined analyses both gave definite but muted benefit in this range. It was reassuring that the majority of NASCET’s predetermined, previously published subgroup analyses were validated in the combined analyses. Lack of images of the brain and intracranial vasculature and lack of funding for some repeat studies and lack of detailed cardiac surveys demanded in NASCET, particularly in stroke outcomes, was a disadvantage in the ECST and precluded analyses for example of the risks facing patients with tandem carotid lesions and widespread white-matter lesions (designated as “severe leukoaraisis”) and stroke outcomes by cause. The only major difference in our subgroup analyses, and admittedly it was post hoc as the condition was unknown prior to the NASCET descriptions, was in the patients who had the radiological phenomenon of near-occlusion of the carotid artery. This phenomenon, a subgroup of severe stenosis, was first identified in NASCET material by Morsten.63 An equal number were noted in the two trials and the benefit from CE was significant in the NASCET patients, but failed to yield benefit in the ECST. It was shown in both that the risk of stroke with medical treatment was more like moderate disease than for patients with severe stenosis (70% to 95%). They benefited less from CE than the bulk of the “severe” patients.

The primary goals of NASCET were reached. Now we know with reasonable certainty who will and who will not benefit and who will have only moderate benefit from CE. We know the minimally allowable postoperative stroke and death complications. We should be critically intolerant of departments and institutions who are not meeting these standards. They will be doing more harm than good, and in these institutions and in those circumstances CE should be added to the risk profile for stroke. Stroke neurologists and other physicians must be cautious in their referral of patients for CE. They must remain aware that a high standard of excellence must have been independently achieved and verified by their surgical colleagues. If this cannot be ascertained they must refer to an institution and surgeon with validated excellence. Several additional caveats have emerged from the NASCET’s meticulously constructed data-base:
1. If individual patients have experienced only ocular symptoms, and have a specifically identified low risk profile, the evidence does not support benefit from CE.66
2. Women with no more than 50% to 70% stenosis and again a specifically identified low risk profile will not benefit from CE.55
3. Patients with very severe stenosis and the other criteria identifying a near-occlusion of the carotid artery may expect no more benefit from CE than if they had only a moderate stenosis, and carry no greater a risk than other "moderate" patients if treated medically.66 They should be approached with caution and the CE should be in exceptionally skilled hands.
4. For symptomatic patients with <50% stenosis, the benefit of CE is too small to suggest this procedure. Harm may be the result.
5. Old age by itself, in patients who are not having symptoms suggestive of other organ failure, is not a contraindication to CE. The elderly as a group are at highest risk with only medical care, but have extra benefit when given CE by expert hands. In the total group of severe patients in NASCET, the number needed to treat to prevent a stroke in 2 years was 6; in the "otherwise well" elderly (65+) the number needed to treat reduced to 2 patients.54 The rule is that if the complication rate of the new treatment is not increased and there is a high-risk element in the risk profile, the greatest benefit will ensue by applying the effective treatment. Conversely, low-risk patients will benefit least from the treatment.

Aspirin and CE
NASCET’s protocol required that all patients remain on the recommended dose of 1300 mg daily, enteric-coated, and that this be continued during the perioperative period. When it was apparent that the randomized patients and the surgeons were not in major difficulty with bleeding either at the CE site, or in other areas, independent of the dose (the average patient took 650 mg/d) a parallel trial (ACE)64 was launched that tested 2 low (81 and 325 mg) versus two high doses (950 and 1300 mg). It included all patients that the surgeons at the center were going to operate outside the NASCET protocol. We concluded that the perioperative strokes at 90 days favored the lower dose. Some have erroneously used this 90-day study as an argument in concluding that it proved the correct dose for long-term use in TIA and stroke patients. This is a false presumption. Of the 4 dose groups, 325 mg had a trend toward the best in stroke and stroke death, but the numbers were too small in each cell for robust individual-dose analysis. The only death due to the drug was a fatal gastrointestinal bleed in an individual on 325 mg daily, incidentally the dose I recommend as the standard, for stroke prevention. Hemorrhage related to dose of aspirin is one of our unfinished NASCET analyses. It will get done but meanwhile I am able to state that the highest dose was only minimally more provoking of hemorrhage than the lower doses. NASCET used and provided an enteric-coated formula to all entrants and kept track of its usage by pill-count.

Carotid Endarterectomy-Asymptomatic Subjects
Neither NASCET nor ECST randomized subjects with asymptomatic stenosis. Because we had asked for bilateral angiographic studies and followed all patients for an average of 5 years with regular visits to a stroke neurologist, we were able to document the risk of stroke on the asymptomatic and stenosed “other side.” Our protocol allowed us to determine the cause of each stroke. In conjunction with a senior cardiologist who shared the data on all suspect cardiogenic strokes (Prof R. Gunton), we determined that at 5 years the risk of “contralateral” strokes was low but that in those with stenosis of 60% to 95% forty-five percent did not come from the large artery but were of cardioembolic or lacunar in origin.65,66 This information should sound a note of caution to those enthusiastic about performing CE on asymptomatic subjects. The procedure leaves the patient at risk of a stroke from causes unrelated to the carotid stenosis and indicates that a good cardiac workup must precede the decision to perform CE in the absence of cerebral symptoms.

Asymptomatic carotid disease and its prophylaxis have been studied in two large but dissimilar multicenter trials.67,68 The absolute risk reduction and the number needed to treat to prevent ensuing strokes is sufficiently marginal (for ACAS the number needed to treat is ~65 to prevent one stroke in 2 years) as to discourage many neurologists but not so many vascular surgeons from pursuing this course of prophylaxis. Recent Medicare data have revealed that the majority of American surgeons are experiencing more strokes after CE in asymptomatic subjects than are required to benefit these individuals.69,70 Postoperative stroke and death rates frequently exceeded the upper tolerable limit of 3% in two administrative data reviews (including Medicare). Tabulation (Table 39/1) of risk of stroke and death facing these subjects is available.71 In 6 of 10 states in which the complication rate was carefully studied from the hospital and office records of ~10 000 Medicare patients, more harm than benefit faced these individuals. The trials have revealed that the annual risk of stroke in asymptomatic subjects is one-sixth to one-eighth that in symptomatic patients with severe stenosis. In subjects of average age of 70, it seems undesirable to offer a treatment with up to a 3% immediate risk of stroke and death when the prospect of annual ipsilateral strokes hovers around 2% in the best-studied series. Furthermore, these subjects face an even higher annual risk of a cardiac death. The absolute annual risk reduction of stroke and death in the two trials was 1%. This contrasts sharply with the absolute risk reduction in symptomatic patients with severe stenosis in NASCET of 17%.

There has been a sharp difference of opinion in regard to the desirability of community screening by ultrasound for these low-risk lesions that have no symptoms and will then face in most places a minimum of 3% risk of stroke and death. An Editorial in the BMJ strongly urges this population screening.72 A previous guideline produced by the AHA and most recently by the American College of Physicians73 recommended that this screening not be done. Some speak blandly about recommending CE if there is an increased stroke risk beyond expected “for those at higher risk.” This subgroup has yet to be identified with any certainty.
A common and serious mistake has been made of equating the low rate of complications in the ACAS and the European ACST, and to take note of the same slim benefit favoring CE in both. They are not equivalent protocols and do not confirm each other’s conclusions. The European trial allowed participant-discretion, and if the surgeon “felt” it best to operate that was allowed. An even greater difference separating the two trials was the fact that in all previous carotid trials including ACAS, the primary outcome and analysis concerned strokes ipsilateral to the randomized lesion. In the recent European study strokes in any cerebral vascular territory were counted as outcomes. This is based on a previous presumption, never proven, that removing one stenotic lesion might reduce the risk of ischemic events in another arterial territory. The British trialists have yet to publish survival curves for the outcomes of ipsilateral stroke, or of curves that focus on benefits or otherwise when the strokes of cardioembolic cause are removed. They have advised that they will not present data on the number needed to have CE to prevent stroke in the future until they extend their follow-up for a sufficient number of years to allow of a projection to 10 years. With a population in the trial which has a life-expectancy of no more than 10 years this is a curious goal indeed. This writer is not in favor of CE for asymptomatic lesions or subjects, and this opinion will persist until a highest-risk profile has been convincingly demonstrated. In conclusion it is this writer’s opinion that care must be taken to guard against allowing CE, especially for asymptomatic subjects, to join the roster of conditions on the risk profile for stroke.

I vacated my front-row seat at the conclusion of the NASCET trial. Exciting acts in this great show went on without me. The dedicated use of thrombolysins has changed the practice of stroke neurology in a convulsive manner never previously witnessed.

We still await the final answer as to the superiority of stenting compared to CE. Published studies have been less than convincing. Simultaneously we need learn of the value, if any, of the added technique of protective devices claimed to reduce intra procedural embolization. From where I sit and watch there appears to be a wish to get this technology introduced quickly, and sacrifices in strict methodological principals are being built into protocols and reports. The Yadav trial used a compound end point including MI, and because of this felt able to claim a benefit of stenting over CE, one that was arrived at and was overwhelmed by the excess of MI. In my opinion this claim of benefit is distorted by the use of the compound analysis.

CREST appears to be our best hope for an answer to this problem, but for reasons that I fail to comprehend (except to increase their numbers to satisfy their Monitoring Committee) they have changed their protocol and now allow the randomization of twice as many asymptomatic subjects as in the substantially higher risk group with symptoms related to severe stenosis. The concern is that we may end up seeing this technology widely used based only on anecdotal and historically based evidence, an unfortunate backwards step!

As the Curtain Falls and a New Cast Assembles for the Next Big Show

This has been one of the most exciting periods in all medical history. I have touched in any detail only on conditions and changes where my observation post has been pretty close to the floodlights. In other theaters nearby very dramatic things have been happening: peptic ulcer is a treatable bacterial infection and gastrectomy has been drastically reduced; psychotropic drugs have emptied many mental facilities; intracranial aneurysm clipping was no sooner perfected than coils became available as a common noninvasive alternative; fibrinolysins have reduced major disability from stroke if given in a timely fashion; anticoagulants have lost their prime position in cerebral ischemia except there be NVAF or thrombi have been identified in heart chambers or major arteries; MR and CT angiography have been identified as essential and transforming in most brain studies to say nothing of the role of functional MR in understanding neurodegenerative disorders; organ transplantation has become common and safe because of the introduction of tolerable antirejection drugs that can be used for decades; imaging of the heart and its blood supply have been revolutionary; most of us in older age groups are still here because we have had useful years added to life from coronary revascularization or valve-replacement surgery; the chemical defect of Parkinson disease was identified and substitute therapy introduced; burn units and plastic surgery came unto prominence when burning airplanes and their crews fell from the skies in World War II; laser surgery converted cataract removal to an outpatient procedure; hormone adjustments and chemotherapy reduced cancer’s toll and cured some lymphatic, prostatic and bone-marrow varieties; fiber-optics and flexible endoscopes are enhancing diagnostic and therapeutic capabilities in many organ systems. Last and far from least is the tremendous boon of the contraceptive pill and other measures unpopular in too many religions because they are designed to control the greatest scourge threatening our earth and its future: population explosion.

What a 65-year period it truly was! With genomics, stem cells and DNA/chromosome studies in their relative infancy, it is impossible not to wish to be in the position of modern medical students who will just be starting to make their 65-year lists of front-row sightings!

References


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