A Glimpse of Canaan, 40 Years On

The Johann Jacob Wepfer Award 2009

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THE JOHANN JACOB WEPFER AWARD

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OF THE
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2009

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NEW YORK, USA

FOR OUTSTANDING WORK IN
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FOR STROKE TREATMENT AND
PREVENTION

STOCKHOLM, MAY 27TH, 2009

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Key Words

Aspirin • Brain arteriovenous malformations • Broca's aphasia • Clinical trials • Compensatory mechanisms • Functional reorganization • Functional magnetic resonance imaging • NIH Stroke Scale • Stroke data bank • TOAST stroke diagnoses • Transient ischemic attack • Reversible ischemic neurological deficit • Warfarin

Abstract

During the last few decades an explosion in definitions has occurred covering brief to permanent focal syndromes, diagnostic categories for stroke and subtypes, scoring systems characterizing clinical syndromes as well as imaging, and fostered the ascendancy of biostatistics and meta-analyses. These advances have led to the clinical trials which have changed the management, hyperacute therapy and prevention of recurrent stroke. Stroke trial design is now so well codified that its form is expected by the funding agencies, especially companies supporting trials. Despite criticism, transient ischemic attacks remain >24 h, uncommon diagnoses now fit into 'stroke of other determined mechanism', hyperacute treatment within 3, maybe 6 h is standard, as are outcomes at 30 days and 3 months. Unsettling to some, the randomized clinical trial may have reached a plateau in development. Clinical trials have also passed the point where outcomes can be measured in easily described events. The current problems find their focus in smaller cohorts, requiring multicenter efforts, nowadays spanning continents. They have also crossed into areas formerly considered the exclusive purview of sibling specialties, some members not predictably as concerned with the same research questions. Threats to the randomized clinical trial are also emerging in outcomes research. This approach is popular with agencies hoping to apply the widely accepted definitions to readily available clinical databases and will see only more use in times of limited budgets. One effect has been the unintentional restriction into the algorithms of new subtypes of ischemic and hemorrhagic stroke. Similarly, there has been insufficient focus on the effect of functional reorganization on poststroke clinical changes. It was long neglected when the clinical effects of lesions were inferred more or less permanent and explained as inferred ambidexterity, reversible tissue deactivation from edema and diaschisis. It was even explained that embolism was a transient process, leaving little brain injury in its wake. Long awaited, modern technologies are at last providing a means to study functional reorganization and compensatory mechanisms. Current results predict a radical change in our understanding of the course of syndromes from focal lesions, hopefully opening a new era for

clinical neurology, maybe even a resurrection of semiology. Studies can be pursued in advance of lesions, during the poststroke course of living patients and for those planned for brain interventions, which could perturbate pretreatment functions and pathways. Those long dead would have envied us our current opportunity. Uncertain to be among those who reap the eventual harvest, this author is grateful for a glimpse of Canaan.

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Since the first of the Johann Jakob Wepfer awardees, many now know he described the initial report of hemorrhagic stroke [1]. He was also 6 years ahead of Thomas Willis in his description of the vascular polygon at the base of the brain. Why, then, is Willis given the credit? Rather than just a 'Rule Britannia' effect, it may well have had as much to do with the quality engravings by his artist collaborator Christopher Wren. Georgia's Crawford Long, who administered anesthesia before that done in Boston [2], was also neglected in favor of the greater fame and team effort at the Massachusetts General Hospital. These examples help explain the gratitude I feel as the latest Wepfer awardee. The happy synergism of institutional location and exposure to dynamic colleagues allowed most of the work leading to this award, which must be widely shared. Considering the list of future professors, future departmental chairs and coworkers from 13 countries, it is a disappointment that this manuscript cannot cover all of their contributions. However, I hope all of them, including those not cited directly, see this dwarf's thanks for their ideas and efforts and the privilege to stand on the shoulders of giants. Further, I, not they, bear responsibility for the incompleteness of much of the work described in this article.

Half a century ago, lacking much therapy, neurologists were thought limited to 'diagnose and adios'. Imaging was in a primitive stage, forcing much dependency on clinical judgment and limited use of remarkably invasive studies such as direct-puncture carotid angiography and pneumoencephalography. Brain function was widely understood to lack compensatory mechanisms: focal lesions in places like Broca's area produced the full and permanent syndrome of Broca's aphasia. Transient ischemic attacks (TIAs) were dismissed as unimportant because they were said to occur in only 10% of all types of stroke. Although true for stroke in general, its importance for the subset of carotid stenosis was overlooked. Where awareness of stroke subtype existed, thrombosis was assumed to be the cause of 70% of the strokes; embolism as a pro-

cess was deemed rare. A relationship with atrial fibrillation was widely doubted. One future famous clinician, C.M. Fisher, expressing interest in stroke for his career on return from World War II, was told to go into something where there was something new to learn.

With this background, imagine the personal wonder at witnessing the onset of a stroke in a right-handed patient, not that she was struck mute and with right-sided faciobrachial plegia, but amazed that she began speaking within hours, and steadily improved over the days before death from fatal cardiac cause. Pending autopsy findings, the clinical observation was assumed to be the usual effect of an embolus (often assumed to break up and pass on, leaving no lesion) or that the patient was actually left-handed. However, sympathetic mentors, alert to the then novel finding, encouraged a literature review both to seek precedents for her aphasia syndrome and also for any relationship to her patent cardiac foramen ovale. As they did for a generation of residents, this trainee was started on a career journey still incomplete [3].

Two subsequent examples of autopsy-documented Broca area infarction, also seen clinically within hours of onset, had a similar brief course [4]. Lacking PubMed to bypass long hours in the library, a painful lengthy literature review uncovered many such examples, starting with Scotland's Byron Bramwell's first case [5]. Once summarized in detail to include the timeline, the syndrome appeared to be related more to lesion extent, not highly focal site [6]. The requirements for autopsy correlation clearly seem to have limited the number of cases available, and prevented ready documentation of the clinical course after onset. Broca's contribution was the unilateral nature of the lesion, and his reliance on his professors led to his emphasis on only a small and circumscribed portion of the large sylvian location. The dogma for Broca's aphasia from Broca's area infarction looked more like veneer than solid wood blocks. It was exciting.

Aphasia proved a lifetime interest as a field for research [7] but proved a disappointment for funding. Another interest, *Stroke by Cause*, offered a further path that might allow both. Harvard 4th-year student R.J. Goldstein approached Lou Caplan, then at the Beth Israel, and me, shortly after my return from the Army, for estimates of clinical features which might separate hemorrhage from infarction. Hoping for honors, his visit was prompted by his internist-biostatistician and database mentor Howard Bleich, whose work was supported by an NIH grant for the development of statistical programming innovations for clinical medicine. Chances existed to create something called a database, a great improvement over a collection

of loose-leaf clinical notes. The project quickly morphed into the Harvard Cooperative Registry [8]. Primitive phone cradle computer painful slow BAUD rates made for exasperating links between the 2 institutions, but during frequent meetings testable definitions emerged for infarction and hemorrhage, infarct subtypes, quantifiable characterizations of syndromes, and systems for scoring angiography, autopsy and the new CT technology.

By focusing on the main features of each stroke subtype, we innocently and unintentionally cut across categories of clinical syndrome, risk factors, anatomic location, lesion size and vascular (and later anatomic CT) imaging. Then recent evidence clearly linking atrial fibrillation to embolism [9], and the steady stream of autopsies showing branch occlusion without any intramural pathology, justified search for other causes of embolism, and gave it a prominent place in the frequency as an ischemic stroke subtype. Lacunar syndromes, many also recently defined, seemed justified for inclusion in hopes their delineation may avoid the then risky direct-puncture carotid arteriography. MR and MRA were not even on the horizon, but the project was construed to encourage expansion in scope.

Subsequent NINDS contract funding expanded the effort into the Stroke Data Bank project [10]. We were brought into contact with a number of NIH operatives, with a dominating interest in biostatistics. An early test of interobserver reliability for the diagnosis of infarct subtype demonstrated the unsurprising observation that clinicians did not uniformly agree when confronted with a series of live patients [11]. High levels of agreement for infarct versus hemorrhage were obtained by interpretation of the new CT scan technology, less so for convexity infarct location and least for the presence of small, deep infarcts [12]. These difficulties left unsettled how much and what weight was given by individual clinicians in arriving at each diagnosis subtype. Instead of forcing assessment of the role of each element for each subtype diagnosis, it led to decisions for disappointing and severe trimming of the details of clinical examination dear to some of us in favor of less controversial application of diagnostic algorithms. (Some 30 years on, the problems for infarct subtype diagnosis have yet to be resolved to the satisfaction of all, regularly posing considerable burdens on adjudicators of therapeutic trials for ischemic strokes.)

Disappointments aside, with federal funding the project's scope expanded in different directions for more reliably measured variables, and included population-based studies [13], risk factors for first and recurrent stroke [14], use of a database for computer diagnosis expert systems

[15], issues of race and gender [16], later to be pursued in a clinical trial, identification of 'silent stroke' [17], circadian rhythms affecting stroke onset [18], eventually setting the stage for their use in large clinical trials [19]. Through it all, efforts continued to refine the elements for ischemic stroke subtype [20, 21].

For any such system of categorization of stroke subtype to survive, it needs flexibility to incorporate new means of proof of the diagnosis. These issues remain [22]. The emphasis on proof of diagnosis caused initial surprise in how few were explained by the once-ubiquitous thrombosis. It also proved worrisome that so many ischemic strokes remained unexplained despite strenuous use of diagnostic modalities. Hoping to isolate this problem, a category of 'infarct of undetermined cause' was created. However, its introduction reduced even further the percentage attributable to large-artery thrombosis, this latter category having become more easily documented with the then emerging Doppler techniques. Although retained in a validated, now popular classification scheme [23], this term soon lost favor for many outside the project who often assumed this diagnosis was a default for little effort to establish a cause. Thinking a medical-sounding diagnostic name might point up these uncertainties and force more investigation, the term 'cryptogenic stroke' was coined [24]. Apart from 'rounding up the usual suspects', this category has already seen its fair share of potential causes, some fading under the spotlight of case-control series [25], others failing to show an impact on recurrence [26], or emerging with reanalysis of earlier data [27] and some simply too infrequent. It can be hoped this category will slowly be ground down by new discoveries [28], eventually joining other terms like 'ministroke' deserving oblivion.

Although satisfying to see these diagnostic and scoring schemes gain traction, it is disappointing they have now been silted in place to a degree not easily modified, maybe not even despite a recent, elegant efforts [29]. A radical reshaking of these foundations is needed to provide more room for newer structures. Some of them are not mere expansions in scope and do not easily fit in the traditional categories: CADASIL, reversible cerebral vasoconstriction syndrome, intracranial dissection or aortic arch embolism, just to name a few.

Other workers world-wide independently contributed to this growing field, including different classification schemes, also now in wide use [30]. However, even here few of these attempts have modified the elements for the subtype diagnosis nor their rank ordering as to importance [31]. More efforts have been made at clinical syn-

drome quantification. So many such schemes emerged that space exists only to cite a few [32–36], (apologies to those not referenced) but most have yielded to the NIH Stroke Scale [37]. For some of us, the low scores for aphasia and the large emphasis on motor function remains a source of disappointment, especially considering how much of the cerebrum is devoted to behavior, but there is no arguing the NIHSS enjoys wide acceptance.

Despite its focus on taxonomy, biostatistics and epidemiology, the Stroke Data Bank allowed some 'flying below the radar' for *structure-function correlations*. Through the laborious effort to map the convexity lesions by hand using the primitive computer technology of the time, considerable variability was documented for hemiparesis profiles in cerebral infarction, not shown clearly related to size for Rolandic infarction [38]. They reflected some of the striking variation in the shape of the homunculus notes in the original works of Penfield and Boldrey [39]. Lesions associated with depression were demonstrated [40]. Moreover, an unexpected large range of nondominant hemisphere syndromes was found from localized perisylvian infarct [41]. Sadly, aphasia and other features of higher cerebral function were deemed too arcane to pursue. The current emphasis on biostatistics, now in its ascendancy, has dwarfed former emphasis on the unusual case report in favor of the confidence intervals as the focus in manuscripts. No criticism intended, but case reports are being declined in principle by most journals, including some cases that prove exceptions to the rule. How many conditions like CADASIL, reversible cerebral vasoconstriction syndrome and the like have failed to pass the confidence interval threshold? Broca may have been fortunate to live when he did.

Interest in stroke subtype was also based on a separate assumption that there would be *therapy specific to cause*, like that for infectious disease. This was the hope that drove a large multicenter trial comparing 2 classes of antithrombotic therapy [42]. The theorized major difference in recurrent stroke rates for the 2 therapies failed to be shown. More unsettling were similar results for the parallel studies, where even the entities themselves showed little impact on recurrence rates [43–46]. Perhaps it was these disappointments that made for considerable delays before many of the prespecified hypotheses finally saw publication [47]. Using a comparable research plan, the main findings survived challenge in a subsequent trial of intracranial atherosclerosis [48]. Similar efforts for lacunar syndromes awaits a current clinical trial [49]. Undeterred, and hoping it would be a new high in clinical stroke research, a recent huge international effort sought

to determine if the effects of multiple therapies would prove synergistic, additive or merely duplicative. The latter turned out to be the case [50]. Might one invoke an Icarus effect?

The failure of subtype-specific therapy was sobering. Some could claim the results argue against the efforts at detailed workup, given no expected modification of therapy. Hoping not to awaken a sleeping regulatory giant, I mention this point only in passing. These disappointments for neurologists notwithstanding, colleagues in cardiology continue the *search for monotherapy*. Many noted that our Warfarin-Aspirin Recurrent Stroke Study and its parallel efforts did not show warfarin inferior, merely more demanding for its use. Aware that the prevalence of atrial fibrillation rises with each decade in the elderly population, they continue to seek an alternative to warfarin that could accomplish both the anticoagulant and antiplatelet effects in 1 compound. Such studies have quietly set aside concern for the niceties of infarct subtype diagnosis [51].

Even should the infectious disease simile not prove sustainable, there is a certain irony that the concept may still be applicable but for a different reason: *some antiplatelet agent effects appear subject to decline over time*, like those of antibiotics in infections, adding a new dimension to search for a stable response to therapy [52, 53]. We may be facing a far more fundamental reassessment for therapy. It could well emerge that, like our original ECIC (extracranial-intracranial bypass surgery) study [54, 55], our insights into pathophysiology and therapy were not wrongly conceived but lacked current techniques to assess their importance.

Also subject to major revision are the ancient concepts of *TIA and reversible ischemic neurological deficit*. Despite evidence to the contrary, like diagnosis subtype, TIA also hardened to the <24-hour duration, preserved mainly in company-sponsored trials. Modern imaging has justified revision of the prognosis for TIA, prompted the suppression of reversible ischemic neurological deficit and even allowed insights into cerebral compensatory mechanisms to explain the short-duration clinical syndrome with fixed imaged infarct [56]. Thanks to these efforts, C.M. Fisher, alive, well, and mentally clear, can take some comfort in the resurrection of the initial, prescient observations of half a century ago that TIA is a typically very brief event, usually 10–15 min, not prolonged [57]. The expansion to the <24-hour time frame was the proposal of others, mainly making it a diagnosis by default [58]. Had modern clinicians been unwilling to consider an infarct unless 24 h had passed, tissue plas-

minogen activator would never have achieved much traction. With some luck, perhaps the proposed 1-hour rule will eventually prevail [59].

These challenges to traditional concepts opened the path to testing ischemic effects not producing abnormal imaging. The results offer hypotheses of a *clinical ischemic spectrum*: at 1 end, a brief clinical syndrome with normal imaging, commonly called TIA, its clinical features capable of being relapsed by an intravenous benzodiazepine (midazolam – Versed®) [60]; next, a brief event with DWI+ imaging, some cases showing clinical and DWI reversibility [61]; further, a clinical short-duration syndrome with DWI+ and emerging T₂ focus, and finally ischemic stroke syndromes with long-standing parenchyma abnormalities, the fate of the initial syndrome arguably related as much to lesion size as to location [62]. This spectrum poses a burden to try and determine the temporal relationship between the onset of the offending occlusion and that of symptoms. They need not be tightly linked in time. Many clinicians having witnessed iatrogenic embolism can testify to a delay of minutes, sometimes hours, from the documented occurrence of occlusion and subsequent syndrome onset.

Many clinical improvements have long been known to begin before any cytotoxic edema can be expected to have faded. In some paradigms, the brain response is activated almost immediately [63]. Recent work with fMRI in human hyperacute ischemic stroke indicates that *some areas of brain response are an independent predictor of more complete syndrome improvement* than the usual 70% from baseline toward normal [64]. If ever questioned before, modern imaging has brought the patient into the position as the ideal animal model. For me, data like these are the look into Canaan after 40 years from the first observation of the original cases, when ignorance of cerebral mechanisms prompted the title of rapid amelioration of motor aphasia.

These observations add further to the demand we *revisit and revise the current simple clinical scoring systems* for estimation of stroke syndrome and severity. These important insights into compensatory mechanisms could well resurrect interest in reintroducing detailed characterization of higher cerebral function in clinical scales [65]. To make these observations, modern stroke researchers will have to join other emergency clinicians in the management of hyperacute stroke, efforts that can only encourage diffusion of these concepts in the medical (and surgical) fields.

One final subject is the revered *randomized clinical trial (RCT)*. The time has long passed when we could ask, 'Is

it a stroke or not?’ and put a checkmark in a data box. The time has also passed for the large trials featuring simple dichotomous outcomes [66]. RCTs now face smaller cohorts of eligible patients and requirements to refine the definition for endpoints that formerly sufficed merely to be given a name, an obvious example being hemorrhage.

Unbled brain arteriovenous malformations are a good model for the problems in modern RCT design: here is an uncommon condition, one increasingly being detected incidental to brain imaging. The risk of hemorrhage, the true natural history of the feared event, remains unknown but seems infrequent in the subset deemed suitable for attempted eradication. The spontaneous hemorrhage event, should it occur, usually causes a syndrome far less severe than that from brain hemorrhage of other cause. Interventions to eradicate the lesion may occasion unwelcome complications at rates that may exceed the natural history. No standard treatment plan has been demonstrated [67]. It has been asked which is worse, the disease or the cure [68]. These widely published uncertainties led to an RCT application and, after 2 NIH/NINDS study section reviews, approval by council of the accepted community equipoise and an award for the trial using US tax dollars. For the neurologists, apart from the final results, the trial also provides a unique opportunity to test the ipsihemispherical and transcallosal pathway theories of brain function through the clinically-indicated schizencephalies occasioned by eradication of arteriovenous malformation. Much can be gained for insights into improvements following ischemic stroke. Some arteriovenous malformations also occur in sites usual for naturally-occurring infarction.

Despite such justification, our efforts have been widely seen as simply challenging clinical judgment, the trial a program designed to halt such interventions, prompting resistance from some in our sibling specialties. Much can be said for the strengths of beliefs and their persistence [69]. Might we be asking more questions than those

in other specialties see a need to be answered? Even if so, the mere existence of a trial, especially one funded by NIH, has an impact on practice, as some former enthusiasts of a given treatment quietly make for the exits before the results are known. Instead of resistance or premature abandonment, the RCTs brought to a credible conclusion have set the positive treatment on a long-term course [70]. It is unreasonable to assume there will not then be future challenges, given further modifications for therapy [71]. For unbled arteriovenous malformations, we hope we will demonstrate the intervention does little long-term disturbance to basic brain function, but such hopes hinge on the outcome of the trial.

Have we reached some *limits in the applicability of the RCT*? Brain arteriovenous malformations are a small subset of available cases, requiring the participation of centers worldwide. The same has proved true even for carotid stenosis [72], let alone carotid occlusion, cardiac low ejection fraction embolism, arterial dissection or arteritis, to name but a few. Further, in such small clinical fields, might scientific justification alone fail to arouse interest in powerful interest groups? After all, RCTs usually question clinical judgment and could threaten established practice. However, in so doing, their goal is to foster inter-specialty cooperation and improve the outcome for patients. We have no need to see a repeat of the outcome for *Karl von Müller*, captain of *Wilhelmina* Germany’s World War I light cruiser, the SMS Emden. His exploits against the Royal Navy exposed the basic weaknesses of his well-entrenched adversaries, after which they never recovered their former position of unchallenged authority. His ethical standards during the conflict also won him wide admiration, even if grudgingly so from some among his enemies, and made it difficult for them to take much pride in his finally being sunk. Times have changed. Absent any war, the 2 navies could have worked together to monitor and improve the safety for travelers on the high seas. We should do the same for our patients.

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