Abstract—The gap between existing knowledge and the patient care provided in stroke has become more apparent. The translational gap is evidence of our scientific progress, but the sheer magnitude of our implementation gap is astounding. For instance, almost 5 decades ago we recognized the risk factors for stroke, yet in Canada until recently fewer than 20% of cases of hypertension were effectively controlled. We recognize that continued exposure to risk factors will not only lead to clinically evident strokes, but far more frequently to silent strokes resulting in cognitive decline. In addition, the same risk factors cause damage to other organs. This growing gap between existing knowledge and its translational delivery is leading our politicians to demand more practical returns. As scientific and clinical opinion leaders in stroke, we have a huge opportunity now to lead the process of narrowing the translational gap. We need to keep our emphasis on individual research excellence but temper it with a social mission to improve stroke prevention, care and rehabilitation. Toward this end, the Canadian Stroke Network partnered with the Heart and Stroke Foundation of Canada to develop the ‘Canadian Stroke Strategy’, an approach to focus research, increase training of stroke specialists, coordinate the care of patients, and bring ‘systems change’ to respond to the growing gap in all facets of stroke care. Lessons learned from both successes and failures can inform our translational efficiency in the future and facilitate collective progress in stroke care. (Stroke. 2007;38:3296-3301.)

Key Words: dementia ■ stroke ■ systems change ■ vascular disease

It is a special honor to be invited to submit the 2007 Willis Lecture for publication in Stroke. There is a bit of a tradition in Willis lectures to review progress made in stroke highlighting the awardee’s contributions. This will be reviewed quickly as it is largely a matter of record. Then I offer an assessment of the most striking developments in our field to date, outline my personal reflections on the frontiers ahead, and talk about the growing knowledge-action gap in stroke care. After sounding a warning about the dangers lurking ahead for all of us in stroke care, I will propose some models, derived largely from our experience with the Canadian Stroke Network (CSN), on how to improve our approach to stroke.

Summary of Progress in Stroke Research
In the seventies, the saying that we learned our neurology “stroke by stroke” was very apt because of the emphasis we put on lesion localization. It made for very erudite awe-inspiring neurologists, but the patient was simply a conduit to knowledge and there was nothing we could really offer stroke patients. So my research career, in summary, became an exploration of regional blood flow and regional metabolism in the setting of ischemia. Using autoradiography studies, Matt Hogan and I showed that binding to radioactive nimodipine, a signal that the region was destined to die, was in fact reversible if perfusion was reestablished.1 With positron emission tomography (PET) studies we confirmed the hemodynamic and metabolic responses to ischemia and showed that perfusion and metabolic functions in the penumbra region do deteriorate if untreated but can be modified by therapy.2 These and other studies eventually led to the conclusion that irreversible cell death in ischemia was not instantaneous, and this concept eventually led to the development of tissue plasminogen activator (t-PA) for stroke therapy in the acute phase.3 This was a watershed discovery that converted stroke from a chronic degenerative condition to an acute emergency, and this enormous success has had major impacts on our field.

In the last few years we have studied the increase in the brain’s resistance to ischemic damage that can be imparted through preconditioning.4–8 It will be very exciting in the...
next phase of these studies to make the concept clinically relevant.

The New Frontiers Ahead
Where do I think our field is going, and what are the likely new discoveries and applications in stroke?

I believe there will eventually be neuroprotection offered the stroke patient in the acute phase. It is true that we still don’t have a drug to show for all of our improved understanding of cell death and survival, but this is mainly because the field is very complicated, and that translation from animal studies to patients is a science in itself and we have not yet mastered it. In this context, because when faced with 2 patients showing identical deficits we cannot distinguish on clinical grounds alone the one who still has salvageable brain from the one in whom no penumbra remains, we must, I believe, when conducting clinical trials in neuroprotection, increasingly use functional and metabolic imaging in real-time and online in the acute phase of stroke to identify subpopulations of patients who still have a sizeable penumbra zone and may benefit from a neuroprotective agent. That would substantially enhance the statistical power of any neuroprotective trial and allow us to beneficially revisit and perhaps successfully reprofile some of the neuroprotective drugs that have been tried, failed, and shelved.

In terms of recovery after stroke, we now know through the pioneering work of Randy Nudo10–12 and others that the brain injured by stroke can recover because it remaps itself, resulting in recovery of lost or diminished function. Bryan Kolb has stated that nothing is as good a promoter of recovery after stroke in animals as an environment that encourages physical activity and social interactions, particularly with other nonstroked normal rats.13,14 So it is likely that the next research frontier in this field will be understanding the role the patient’s external environment and internal milieu play in influencing recovery, by exploring the proteomic changes in brain and blood during recovery as well as understanding how stem cells and inflammatory processes respond to optimized internal and external environments. In Canada, the Heart and Stroke Foundation Centre Excellence for Stroke Recovery, where I have the pleasure of partnering with Sandra Black and Don Stuss, is exploring many of these issues.

In my opinion, the biggest frontier ahead was one recognized by that great scientist after whom this lecture is named. In 1672, Thomas Willis said “Foolishness may also result from great strokes.” We now realize that dementia is a frequent consequence of stroke,15 and we have been forced to widen the definition of stroke to include not only the classic strokes that are evident to the patient and the therapist but also those that are silent. Vladimir Hachinski16,17 and Phil Gorelick18 and others19 have taught us that silent strokes become evident largely through cognitive decline. These arise from the same risk factors, predominantly high blood pressure,20 that cause the evident strokes. Elevated blood pressure in middle age results in poor cognitive function in later life,20 and the shocking conclusion is that each 1-mm mercury rise in blood pressure over time increases the risk of poor late-life cognitive function by 1%.21 The incidence of silent strokes may be as high as 9-fold that of evident strokes,22 and they clearly exacerbate the preexisting tendency for dementia due to Alzheimer changes.23 In addition, we now know that the same risk factors that lead to both evident and silent strokes also lead to macular degeneration.24,25 “This is a condition our specialty doesn’t spend a lot of time thinking about, but the incidence of macular degeneration is approximately the same as evident strokes: there are currently 3.5 million Americans who are blind or have low vision, and among whites, 54% of these have macular degeneration.26 In addition, evidence of small vessel disease in the retina increases the likelihood of finding it in the brain,27 and people with macular degeneration develop cognitive deficits more frequently28 and have a higher incidence of strokes29 than patients with other causes of low vision.

So in summary: (1) The footprint that vascular risk factors leave on the brain is much, much bigger than we thought even 5 years ago, and we haven’t even included the effect of the very same risk factors on the induction of diseases of the retina, heart and kidney. (2) It should be evident, therefore, that the benefits of controlling the risk factors are commensurately much bigger than previously anticipated. It is estimated that lowering blood pressure by 5 mm Hg from any pretreatment level reduces the risk of stroke by an estimated 34%, and ischemic heart disease by 21%.30 It is often said that doing primary prevention of risk factors for stroke is not economically advantageous because you have to treat so many in the population to avoid one stroke, but if you include evident strokes, silent strokes with cognitive impairment including dementia, macular degeneration, kidney disease and heart disease, and you follow the patients long enough to show the anticipated benefits, the number needed to treat to show benefit should become quite small. (3) The link between vascular diseases of the brain and dementia opens a whole new field of study in my opinion, one we have not sufficiently exploited. It was my colleague Don Stuss who put it best: “Stroke is the most appropriate model to study, understand, and improve behavior resulting from brain-environment interactions, and doing so will elucidate broader issues in mental health.”

The Growing Knowledge-Action Gap
If the burden of illness on the brain due to vascular risk factors is several-fold what we believed to be the case just a few years ago, then one can understand why some colleagues have referred to vascular disease in general, and stroke in particular, as the tsunami of health care.31 In the series of articles published recently by Lancet Neurology, Ruth Bonita and her colleagues32 make an eloquent plea for improved stroke prevention measures around the world, but particularly in low- and middle-income countries where most strokes occur. In North America >60 million people experience hypertension, and the problem is compounded by our increasing longevity and by the obesity epidemic, which is at least in part due to the fact that we have engineered physical activity out of our daily lives. Still, a lot of knowledge exists on how to prevent stroke, but we seem challenged to convert a lot of what we know into action despite wishing to do the best for our citizens. For example, despite the overwhelming evidence
that hypertension is very prevalent and increases the likelihood of damage to many organs, and in particular the brain, hypertension control in our first-world societies, the United States and Canada, has been unsatisfactory. In the United States, hypertension control in 2003 was about 36.8%, and has been below 30% for the past 20 years or so.\textsuperscript{33} Approximately, the same is true for control of hyperlipidemia.\textsuperscript{34} Until recently in Canada only 16% of hypertensive individuals had their hypertension under control, with 42% of the hypertensive population unaware that they experience this condition, 19% aware but not treated, and 23% treated but not controlled.\textsuperscript{35}

So let me drive a major point home. How long has the healthcare community known about the harmful effect of hypertension on the brain? In the 1950s it was a widely held belief that noninfectious conditions, such as stroke, were not preventable. Then in 1965, >40 years ago, Kannel and colleagues wrote their article “Vascular disease of the brain—epidemiologic aspects: The Framingham Study.”\textsuperscript{36} They concluded their article with this statement: “A preventive approach to the control of vascular disease of the brain seems imperative.” None of us would argue with this statement, but we still have not been able to take full advantage of a solid finding from 40 years ago, confirmed since many times, and we need to. Even though we cannot prevent all strokes, this condition sets itself apart from other major conditions that can affect brain function by the fact that it is very significantly preventable.

The conclusion is evident that there is a huge gulf between what we know and what we are able to do, and the poor control of hypertension is the prime evidence that we need to do better in translating our knowledge into action. We need to change the system, because after all, measuring blood pressure is a snap, and treating it is relatively easy. And hypertension is not the only example where it is clear that the system needs to change to become more responsive to solid research findings. Take the example of t-PA. Millions of dollars were spent to discover this drug and to prove its efficacy. We owe John Marler and his colleagues a great debt of gratitude. Yet in the United States, t-PA is administered at a “distressingly low rate.”\textsuperscript{37} So I will suggest later that if we the experts do not get hold of this issue of the ever-widening gap between existing knowledge and our ability to translate it into health care, and do not significantly change our approach and our level of involvement, we too will be swept up by the tsunami.

Proposed Solutions: CSN and CSS as Prototypes

It was on this background that the CSN was created in 1999. The Networks of Centres of Excellence is this typically Canadian institution where successful applicants are expected to work together to make the whole more than the sum of the parts. The CSN has just been approved for its second 7-year cycle, with a 36% increase in its budget, an almost unheard of stamp of approval. We must be doing something right!

The 5 essential responsibilities of every Canadian network of Centres of Excellence are: (1) Research Excellence, (2) Training and Retention, (3) Networking and Partnerships, (4) Knowledge Exploitation, and (5) Effective Management. In the first 7-year cycle which ended in 2006, the CSN coordinated stroke research across the country within the themes of prevention, acute care, cell death and survival, and stroke recovery and rehabilitation. In each theme, several scientists, sometimes as many as 30, worked together to coordinate their research and share their data. By this process unique contributions were made including setting up a Registry to collect data on stroke patients in the acute phase in real-time at >20 sites in the country, which allowed identification of the impediments to bringing the patient to the appropriate emergency room rapidly.\textsuperscript{38} We also established a program of support for fellowship training in the field of stroke from which hundreds of young investigators benefited.

For our renewal application in 2005, our ambition was that our activities should have strong healthcare, social and economic impacts, so we proposed that new discoveries had to walk hand-in-hand with better methods to bring what we knew to application. To satisfy that higher standard, we created the Canadian Stroke Strategy (CSS) as the kingpin project in our reapplication. This proposed that the CSN, in partnership with the Heart and Stroke Foundation, would undertake to lead a society-wide effort to decrease stroke incidence and improve stroke outcomes by developing and sustaining 5 foundational platforms to support provincial stroke strategies (Figure 1). We learned a lot from the pioneering initiatives that had started in Ontario, supported by that government and led by Mary Lewis and others in the Heart and Stroke Foundation of Ontario, which resulted in that province moving its stroke patients rapidly from a preidentified community network of hospitals to district stroke centers and to regional stroke centers, in order to maximize the number of patients accessing t-PA therapy.\textsuperscript{39} We also hired and established in every Canadian province a coordinator to work with local stroke champions, who are usually but not always clinicians, and with local politicians and regional health authorities to improve the quality of stroke care being delivered in their jurisdiction and offer the support of the CSN. And all of this has begun to pay off. Here are some examples:

1. There are now 23 stroke prevention clinics in Ontario, and we are copying this organizational model in other parts of Canada. In addition to the physician, these stroke-prevention clinics are staffed with nurses who educate patients and follow-up with them whenever it is necessary.\textsuperscript{40,41} Those who have worked with guidelines know that the rate of adherence to them is poor unless the physician is motivated, the patient is made a partner in the therapeutic steps taken, and ideally there is follow-up, hence the importance of working in a team in these clinics.

2. The second example is improved hypertension control. As stated above, when we started out in 1999, only 16% of hypertension was controlled in Canada. With the institution of the Canadian Hypertension Education Program and the launch of the CSN, there has been significant improvement in antihypertensive prescribing trends.\textsuperscript{42} Since the start of the Ontario and the Canadian Stroke Strategy, there has been a phenomenal rise in the rate of t-PA administration. In 1999, 2% to 3% of stroke patients got t-PA.
Today, some of the Regional Stroke Centres in Ontario give t-PA to more than 25% of eligible patients.43

These are examples of what can be done when people of good will decide to work together to achieve what isolated individuals cannot achieve. Although these are examples from Canada, the principles apply broadly. Canada faces, as in other jurisdictions, limited healthcare dollars, fragmentation of care, and decreased access to specialized care. The methods used in Canada to alleviate the burden of vascular disease transcend the specific healthcare delivery system and can be largely implemented in the United States, and indeed anywhere. The proof is that one can point to many notable United States successes in the field of stroke, especially the speed with which Stroke Centres are being established. After all, the consensus statement from the Brain Attack Coalition, which included recommendations for the establishment of Comprehensive Stroke Centres, was published in 2005,44 and today hundreds of stroke centers are certified across the country.

So let me suggest how we may additionally improve our approach to stroke care using some of the tools we already have on hand. First, perhaps everyone who applies to NIH or the Canadian equivalent CIHR for support to do research in the field of stroke, regardless of whether the applicant is a basic scientist or a clinician investigator, should be asked what plans they have for advocacy for better stroke care. The plans can be any verifiable activity that contributes to more coordinated care, the formation of multidisciplinary teams, or political commitment and action. Second, The Canadian Stroke Network is increasing its partnership activity with NINDS. Collectively, US and Canadian scientists will make a coordinated effort to reenergize the science of neuroprotection. As well, the CSN and NIH cosponsored 2 consensus conferences.45 The one on vascular cognitive impairment has set standards that will be very useful for clinical and epidemiological research.46 So an additional way we can improve stroke care is to open a broad front of partnerships not only between Canada and the United States, but also with other nations interested in exploring innovative methods to improve stroke care. Third, NIH has instituted the Clinical and Translational Science Awards with the goal of linking together in the next 5 years >60 institutions to energize the discipline of clinical and translational science.47 Let’s engage in this vehicle and focus on solutions to the growing translational gap in stroke.

**The Dangers Lurking Ahead**

Why do I think so strongly that it is important for all of us to get involved in changing our healthcare system to be more responsive to the challenge of vascular disease? Because I sense that there is a broader society debate swirling around us, and this debate on healthcare issues is gradually turning into questions directed at our attitudes and approaches as experts in the field. Congress a year ago was tempted to ask NIH: We doubled your budget in the last 10 years, have you doubled the cure? And in Canada, the current mantra is that funding for health research must be linked to outcomes. It is an investment that needs to pay back to society in tangible ways. So I believe that if we do not wholeheartedly embrace the mission of closing the gap between what we know and what we do, we will not long maintain our exalted standing in society as clinicians, researchers and healthcare administrators.

We must resolve to change the healthcare delivery system, and the system must allow us to do so. A recent article48 crystallized what it takes to change any organized healthcare system, and the ingredients are listed in descending order of importance in Figure 2. You can see that the first ingredient in any stroke strategy has to be leadership. Without champions and vocal opinion leaders, no strategy has a chance. And leadership is all of us. Whether we are clinicians or scientists, we are smart and we are opportunists who see a big problem and focus on its solution. By nature, we are also optimists: whether we are looking down a microscope or participating in a clinical trial, we believe there are solutions to problems. So while no one has all the answers, in stroke, business as usual will no longer work for us and can no longer be tolerated.

“Fund me for my favorite gene or protein, and the rest is not
What you Need to Change the Healthcare System

1. Leadership commitment and support
2. Key stakeholder involvement
3. Simple changes in practice should be introduced first.
4. Regular communication must convey the evidence
5. It takes money… and patience.
6. Data gathering, evaluation, and monitoring of outcomes.
7. Educate, educate, educate.

Figure 2. The essential ingredients in any attempt at increasing practitioners’ adoption of research evidence in clinical practice.48

my problem” is tenable any more. We have no choice but to get involved in the wider issues facing our societies in stroke prevention and care. Excellence must be at the very core of everything we do, but the emphasis must increasingly shift away from immediate outputs such as the number of grants funded, the manuscripts published, and the number of students trained, to the more downstream impacts of stroke research, such as improvements in prevention and treatment, and very much in that order, prevention and treatment. This is what the public is interested in and will increasingly demand. All of us—students, postdoctoral fellows, research assistants, faculty and Willis awardees—have a tremendous opportunity to demonstrate to the public and to our political leaders the value of health research, and the best way to bring that message is to endeavor to close the knowledge-action gap. The question is not how can we do something about this. The question is how can we afford not to. Goethe had it right: “Knowing is not enough; we must apply. Willing is not enough; we must do.”

Sources of Funding
Support was provided by The Canadian Stroke Network and the Heart and Stroke Foundation Centre for Stroke Recovery.

Disclosures
None.

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Vascular Disease: The Tsunami of Health Care
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Stroke. 2007;38:3296-3301; originally published online October 25, 2007;
doi: 10.1161/STROKEAHA.107.492793
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/38/12/3296

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