Abstract—Advances in stroke are occurring at an unprecedented pace, but often in disciplinary isolation and without optimal mechanisms for systematically translating, integrating and applying the findings.

Knowledge accrues in pieces, but is understood in patterns. To optimize knowledge acquisition and application, infrastructures and systems need to be set up along with appealing incentives. The approach needs to be transdisciplinary, going beyond the bounds of any given discipline, reciprocally translational, and transactional, meaning that the interchanges have to yield previously agreed benefits to the parties (The Triple T Approach). A new breed of leaders needs to be developed and nurtured to catalyze the process.

Opportunities abound. Stroke and most brain diseases share the same pathophysiological fundamental mechanisms. An integrated, systematic approach to these processes could yield not only greater understanding but new, common therapeutic targets for several diseases. Biphasic clinical trials could combine the best features of pragmatic and explanatory, randomized clinical trials. The greatest opportunity of all may be the largely under-explored and under-exploited borderlands between cerebrovascular and Alzheimer disease. One in three of us will have a stroke, become demented, or both. For each person who has a stroke or Alzheimer disease, two have some cognitive impairment short of dementia, often subclinical cerebrovascular disease on a substrate of Alzheimer changes. The fact that cerebrovascular and Alzheimer disease share the same risk factors, provide a great opportunity for prevention, if implemented at the “brain at risk” stage.

Systematically integrating what we know and evaluating what we do could spur progress. Research is not only an activity but an attitude. Making evaluation and incentives to excel part of the funding of all stroke activities would yield far ranging cumulative improvements in all aspects of stroke.

No system can replace the individual initiative, creativity and insights that lead to the great discoveries, but progress is not made by breakthroughs alone. No one’s work is so exalted that it cannot be improved, nor so humble that it has no value. We can all make a difference. (Stroke. 2007;38:1396-1403.)

Key Words: Alzheimer disease ■ clinical trials ■ discovery ■ intervention ■ stroke ■ treatment ■ vascular cognitive impairment

Unprecedented advances in genetics, proteomics, imaging, informatics, diagnostics and therapeutics stem partly from the increasing numbers and sophistication of dedicated researchers. Investigators often push their research to the limits of their discipline but seldom beyond. This tends to happen to the detriment of areas that fall between specialized interests. Probably subclinical vascular disease is the most neglected area of all. Our focus has been on clinical, catastrophic stroke and yet advanced imaging studies suggest that in 1998 in the United States, 770 000 strokes occurred, about 9 040 000 so called “silent infarcts” and 1 940 000 microhemorrhages. These usually inflict subtle cumulative brain damage resulting in cognitive and behavioral changes and confer a heightened risk for both clinical ischemic and hemorrhage stroke. Although the deficits from subclinical events may be smaller compared with obvious stroke, the public health burden may be greater, because of the substantially larger number of individuals.

One in three North Americans will experience a stroke, become demented, or both. For each person over the age of 65 years who has experienced a stroke (8%) or is demented (8%), two have some cognitive impairment short of dementia.
Vascular cognitive impairment is becoming recognized as a highly prevalent and preventable syndrome. Given the rising number of the elderly worldwide, we must accelerate our knowledge acquisition, availability and application, to successfully confront the looming epidemic of cerebrovascular disease and its drastic and subtle manifestations. Stroke and associated vascular cognitive decline and Alzheimer disease share the same risk factors, and both occur commonly in the same patients, but these two conditions tend to be studied at the extremes, ie, clinical stroke and dementia. Probably the most promising time to intervene is before clinical manifestations appear, the “brain at risk stage”. This remains a big, under-explored and under-exploited area for treatment and prevention of stroke and cognitive disorders.

Although great advances have occurred in prevention and acute treatment, such as the use of tissue plasminogen activator in the treatment of acute stroke, we have not always managed to bring all the required knowledge together for optimal results. Witness the long litany of failed acute stroke “neuroprotective” trials. Over a thousand drugs and interventions have proven promising in acute experimental stroke, but only a handful of experimental studies have met minimal standards for clinical relevance.

Crucial pieces of a pattern often lie beyond unbreached disciplinary boundaries. The systematic integration of existing knowledge, the establishment of common standards and a synergistic, targeted approach may accelerate the rate of progress in confronting stroke and related disorders.

**Brain Diseases: Common Mechanisms, Manifold Manifestations**

Although the brain functions with infinite complexity, it fails through common basic pathophysiological mechanisms, such as excitotoxicity, mitochondrial DNA damage, oxidative stress, disturbed neurotransmitter release, and apoptosis. These fundamental mechanisms underlie not only stroke but also Alzheimer disease, Parkinson disease, epilepsy, amyotrophic lateral sclerosis, multiple sclerosis among other neurological disorders (Figure 1).

Although each of these mechanisms has been studied in the context of each of these diseases, little systematic effort has been devoted to understanding their common biology. Similarly, mechanisms such as that of the blood-brain barrier, the microcirculation and the transport and role of different molecules, too often are studied in isolation. When efforts are made to bring specialists together, such as in workshops, participants learn much, return to their disciplinary labors enriched by the experience with some ideas for collaboration but with no true incentives or follow-up. Typically, individuals asked to participate in such workshops are well established in an area and over-committed, so even given willingness would require a considerable sacrifice of a proven approach for the uncertainty of transdisciplinary collaboration. And yet, the greatest promise is in integration, focusing on questions ripe for answers and in synchronizing and leveraging what knowledge we have. To follow through on a systematic approach would need to be planned, funded, and undertaken.

Specialized terminology poses another obstacle to interdisciplinary research because nomenclature varies by discipline. For example, the trauma literature on “carotid dissection” cannot be accessed through PubMed because the term is not used. “Blunt injury” to the artery involved would yield a number of key articles. At the moment, no system exists for accessing some of the relevant knowledge in an equivalent way.

**Broadening Clinical Trials**

Although the return on investment in clinical trials is substantial, not enough are done, nor perhaps optimally. Two major types of randomized clinical trials prevail: the large-scale simple pragmatic trials, and the smaller-scale intensive explanatory trials. Advantages of the large trials include greater ability to generalize, ease of performance, and in
principle are faster. The explanatory trials, with imaging and other investigations, allow for a better characterization of the patients and give better grounds for understanding pathophysiology and subtypes. Moreover, because these trials are often carried out in highly qualified selective centers, the results may be more reliable. On the other hand, trials are increasingly cumbersome and expensive, have limitations on generalizing the findings, and at times lack the statistical power to answer important secondary questions.

Biphasic Clinical Trials (the COMSENS method)
The process of discovery is seldom connected to its application although that is often the ultimate aim. Application of knowledge, on the other hand, often misses the opportunity of contributing to learning. One example is the large disconnect between experimental work in acute stroke and its evaluation in clinical trials.6

Attempts should be made at integrating the best aspects of both approaches. First, the preparatory experimental work can be more extensive and interactive. Typically, experiments are performed on a single strain of rodents, under standardized and optimal conditions, in young animals, and results are then tested in elderly stroke patients with comorbidities under heterogeneous conditions, in strokes of diverse etiologies, causing varying degrees of damage at different times. Drugs should be tested on a variety of animals under different conditions with induced comorbidities, such as hypertension and diabetes, and under the most varying and challenging conditions. If the drug has an effect despite these confounding factors, then it clearly has promise for application in humans. A necessary step between showing efficacy in rodents and applications in humans is to verify the therapeutic effect in animals with gyri, the closer phylogenetically to humans, the better.

The animal experiments could then be modeled for possible effectiveness and tested against a database from the placebo arm of previous trials. In phase I of the clinical trial, there should still be a close interaction between the experimental model and the safety and dosage finding studies in humans. The phase I trial should not be limited to young, healthy volunteers, but also to individuals of an age comparable to the ultimate test population. The phase II trial would initially take place in highly experienced and sophisticated centers to study inpatients extensively, to include all measurable effects, including the neurological status, cognition, imaging, pharmacokinetics, pharmacogenetics, dynamic imaging and other relevant measures, while maintaining close touch with those who performed the experiments and those responsible for phase I. Once the protocol has been refined and safety monitoring measures implemented, then a simplified protocol could be developed for the use of a large number of centers that, in addition to regular monitoring, would have statistically valid audits to ensure both adherence to the protocol and that the patients entered in the larger centers are comparable to those being studied at the smaller centers. The simplified protocol would facilitate entering more patients of diverse ethnicity, socioeconomic status and settings. Patients would continue to be entered in both types of centers. When an end point is reached, conditional approval would be sought and a further simplified version of the protocol would continue, focusing on the efficacy and safety findings of the main study. This obligatory registry would have its quality assessed systematically by statistically valid audits (Figure 2).

Cognition as an Outcome Measure
Cognitive impairment may be the earliest, commonest and subtlest manifestation of cerebrovascular disease. Elias et al found an inverse correlation between the Framingham stroke risk score and the presence of abnormalities in executive function.8 Consequently, selective cognitive tests could be a more sensitive primary outcome measure than stroke, myocardial infarction and vascular death for prevention studies and the Rankin Score for acute trials. One sixth of patients have cognitive impairment before9 and one third after an acute stroke.10

Cognitive competence contributes to quality of life and cognitive impairment represents the most important factor in determining institutionalization three years after a stroke.
Cognitive impairment is a more powerful predictor than age and physical impairment.\textsuperscript{11}

One previous obstacle to the use of cognitive measures has been the time it takes to administer the tests. Recently, a 5-minute screening battery has been recommended. If positive, a standard 30- or 60-minute battery can be used to define more precisely the nature and extent of the cognitive impairment.\textsuperscript{4} Cognitive impairment can be quantitated. “Dementia” is a coarse, end stage, “yes” or “no” measure that requires a large sample size and obscures the different types and degrees of cognitive impairment that correlates with quality of life and self-sufficiency measures.

Patients with cognitive impairment are either excluded or not identified in clinical trials. Hence, we do not know the relative response of these patients to our common treatment modalities such as antihypertensive agents, antiplatelets, agents, statins, oral anticoagulants, carotid endarterectomy and tissue plasminogen activator. The answer may not be the same for each modality nor the directional effect of the treatment obvious. Patients with cognitive impairment could benefit less because of lesser or deleterious effects, or more because being at higher risk could reap greater benefits from the treatments. This represents another area of opportunity for further research.

**Clinical Trials: Challenges and Opportunities**

Clinical trials in uncommon conditions pose a special challenge. One way to evaluate unproven interventions in less common types of strokes is to link reimbursement to participation in a study: for example, the use of intra-arterial tissue plasminogen activator for the treatment of basilar artery occlusion. A convergent stepwise approach\textsuperscript{12} has been suggested. Each center would define “a priori” which patients they would be willing and unwilling to treat and abide by their criteria. Data and outcomes on all the patients would be documented. An external blinded monitoring committee would determine which categories of patients have such a bad outcome that treatment cannot be justified and which have such good outcome that intervention becomes unnecessary.

The process would be iterative, whereby the categories of patients where treatment is demonstrably useless, harmful or unnecessary would be reduced in a stepwise convergent fashion. A randomized clinical trial could then be justified in patients in whom the results of treatment remained uncertain.

A similar approach could be used for purported treatments of carotid and vertebral artery dissection, moyamoya, central nervous system vasculitis, in stroke prevention and rehabilitation trials as well as in other fields.

Clinical trials contribute important answers because they either show an intervention to work or do not, in the latter case saving money and potential injury to patients. Clinical trials in stroke sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) have repaid the investment handsomely.\textsuperscript{7,13}

The increasing merger of drug and devices companies creates the opportunity for doing factorial design studies because the portfolio of the merged company may contain several potentially complementary interventions. The factorial design allows for the evaluation of two treatments simultaneously and of their potential interaction. Another possibility lies in a drug or device company sponsoring a randomized clinical trial to test one of their products and a governmental, volunteer or other nonprofit organization paying for the additional cost of a factorial design to test a generic treatment, such as the best dose of acetylsalicylic acid.

Networks of excellence in all aspects of stroke, such as the Canadian Stroke Network (CSN; http://www.canadianstroke.network.ca) and the consortia of academic and community clinical trials investigators such as the Canadian Stroke Consortium (http://www.strokeconsortium.ca/) and the National Institute of Health Sciences specialized program in Translational Research in Acute Stroke (SPOTRIAS; http://www.spotrias.com/) are steps in the right direction toward integrating research and its application.

Many more physicians in practice may become involved in clinical trials. In 2005 the NINDS launched a Clinical Research Collaboration (CRC) project whereby hundreds of practice-based and academic-based neurologists will become part of an investigators network linked through a web-based CRC coordinating center (https://secure.emmes.com/crc/home.htm).

In the future, clinical trials probably will be larger with simpler designs and include measures of cognitive outcomes, disability scales and quality of life outcomes.\textsuperscript{13} Trials in the future may also use a greater variety of designs. An adaptive design trial allows for early stopping of the study if the criteria predicting success fails to be met.\textsuperscript{14}

Probably, therapy will become individually tailored\textsuperscript{15} and patients will play a greater role in setting outcomes. A goal attainment scale instrument has been proposed. Through it, individuals set their own goals according to their needs and state improvement or worsening in their own worlds.\textsuperscript{16} Whatever shape clinical trials will take, they will likely remain mainstays of progress.

**A Transdisciplinary, Translational, Transactional (Triple T) Approach**

Individually initiated and driven research is being complemented by large-scale collaborations. The Genome Project represents a massive and successful example of integration of knowledge, as is the ongoing International HapMap Project.\textsuperscript{17,18} The Road Map of the National Health Institutes\textsuperscript{19,20} also marks an innovative step, but the translational research budget may not exceed 1% to 2% of the $29 billion total budget.\textsuperscript{21}

The American Stroke Association’s Bugher Foundation competition to fund three interactive centers in stroke prevention may be an auspicious beginning to integrate and apply knowledge in stroke (http://www.americanheart.org/presenter.jhtml?identifier=2530). The subspecialized, reductionistic approach has been highly successful and needs to be continued but as part of a larger, interactive, synergistic system.

Undeniably, experimental, longitudinal, clinical and outcomes studies continue to make major contributions to understanding stroke. Each approach has its advantages and limitations. Longitudinal epidemiological studies provide invaluable data on the natural history on a number of vascular risk factors and their relationship to stroke, Alzheimer disease and vascular cognitive impairment. However, they seldom
address mechanisms, and without an understanding of pathophysiology, the results can be misleading. Hypertension has emerged as the single most powerful predictor of stroke and its relationship to salt intake has been raised. Physiological studies show that for some individuals, high salt consumption contributes to their high blood pressure, and in others, high salt consumption reflects the need to maintain their blood pressure. In a population with both types of individuals, in equal proportions, an epidemiological study would find no association between salt consumption and blood pressure.22 Similarly, for many years, the epidemiological studies showed a strong relationship between high cholesterol and cardiac embolism and the discovery that stroke itself can temporarily decrease the blood levels of lipids24 from recumbence,25 to show a relationship between high lipid levels and the risk of stroke,26 despite atherosclerosis being a leading cause of stroke. It took studies that subdivided stroke into those attributable to atherosclerosis from those arising from hypertensive small vessel disease, and cardiac embolism and the discovery that stroke itself can temporarily decrease the blood levels of lipids from recumbence,25 to show a relationship between high lipid levels and stroke, now widely accepted.26

These observations imply that epidemiological data can best be interpreted in close relationship to clinical and experimental work, and that considerable knowledge can be gained by systemically evaluating, applying and interpreting knowledge in the different disciplines as it grows. Clinical trials often provide valuable data about the natural history of diseases and conditions and can also yield useful information regarding their mechanisms.

Administrative databases that document stroke, and other conditions in hospitals, clinics and offices give a glimpse of the condition in the real world and paint a more realistic picture of what happens to stroke patients outside of clinical trials. Several provinces in Canada keep extensive databases27 on all users of the medical care system including admissions, procedures, prescriptions and outcomes. For patients participating in studies, it is possible, with their permission, to continue to follow them for major outcomes indefinitely.

Clinicians and trialists most often work from established, well-equipped and experienced centers on a selective population focusing on individual patients. Although trialists often will stratify for center size and other known parameters, typically, they do not measure the impact of medical infrastructures and systems of care, which can have as much influence on outcomes as the medical interventions themselves. For example, in Canada an inverse relationship emerged between the size of the centers looking after stroke patients and mortality and quality of care.27

A systematic integration of experimental, longitudinal studies, clinical trials and administrative databases, would yield an amplified database suitable for generating hypotheses and allowing modeling. The hypotheses and models could then be tested by the most appropriate experimental studies, longitudinal studies, clinical trials and health outcomes research or combinations of the above (Figure 3).

Such an IdeA center would call for a team of complementary talents working from diversity and fragmentation toward convergence and integration. The team would use not only the methodologies of their own disciplines but contract other necessary ones, and if they do not exist, invent them.

The Marketplace of Knowledge and Transactional Research

The free enterprise system has probably been the most successful in developing technologies such as imaging, therapies such as drugs and devices, and in marketing their products. The profit motive is a great incentive, but it does not always serve the common good. A large number of drugs reaching the market offer little additional benefit and much additional cost compared with available products.28

We should become more aware of the existence of a medical-industrial complex of mutually self-interested relationships among researchers, providers and users of medical knowledge and products, and the extent of its influence. Much of the research and educational agendas are sponsored and hence influenced by industry.29 One consequence is that the emphasis is on drugs, devices and diagnostic technology, and while welcome in themselves, they probably play a much larger role than they deserve if cost-effectiveness were the main criterion.

The industry, regulatory agencies and consumers should assure a focus on developing and evaluating new therapies and applying optimally and effectively the existing ones.

Although we must define clear boundaries between commonality and conflicts of interest, we have much to learn from the free enterprise approach. If the identification and application of new knowledge in a commercial area would be undertaken, it would not simply rely on researchers to do their investigations as they wished, but it would begin with a survey of available knowledge, its quality and promise. The ideas would be evaluated and tested and mechanisms put into place to bring the product to market.

In the field of stroke, an orderly, in-depth evaluation of what is known should be undertaken, interpreting the knowl-
edge from the viewpoint of the multiple, relevant disciplines, but expressed in common, accessible terms, perhaps in the language of systems biology (www.sysbiosociety.ca) with the establishment of a semantic web that can access facts, mnemonics, and concepts from behind jargon jungles. This knowledge could be enhanced by taking several long-term perspectives: How does this knowledge fit in the broader context of evolution and similar mechanisms in other species? What is the natural history of this phenomenon from conception to maturation and demise? What modulating effect does age play on mechanisms? Do the mechanisms that lead to the development of the nervous system go in reverse during degeneration? Promising areas could be identified and parties interested in investing in the answers could be made aware of the opportunities and the individuals and centers willing to tackle parts.

The work would need to begin modestly, with dedicated centers to address a specific question, in all its aspects, with a strong interactive network with other centers that may provide parts of the answer, and also with an adequate budget to allow for contractual work to be performed as part of seeking an answer. The nature of the exchange and interaction of knowledge could be termed transactional. The relationship needs to be interactive and bi-directional or multi-directional, as required and of mutual benefit. The contracts need not be only monetary, but could be exchanges of knowledge, scientific credit and other reciprocal advantages. Relationships must remain voluntary, lest they breed an oppressive bureaucracy.

Although physicians and scientists are buffeted by external forces affecting their productivity, they can also become obstacles to progress by favoring a particular approach. John Dick, the recent discoverer of cancer stem-cells, recalls how difficult it was to get funding for his investigations from 1975 to 1995 because the research world was captivated by the wonder of genes and molecular biology. “Cell biology had fallen by the wayside and stem-cell research was carried on by a fairly small club of people . . . laboring in the shadows”. Stem-cell research itself may become the new hot windows.32

Enhancing the Availability of Knowledge

The technology for linking and integrating data proceeds apace. Soon we will have a semantic web. However, data integration still requires common data formats and identifiable vocabularies.33 That remains the task of those who know the most about the subject matter. The study of cognition as a manifestation of cerebrovascular disease has been hampered by the lack of common standards of assessment. Now that these have been recommended, existing technology could allow access of the results and integrate all studies using the agreed methodologies, accelerating the search for answers.

While technology will facilitate research, it also can enhance accessibility. Information should be available in usable form, preferably integrated, graded and ranked, where and when it is needed. This is far from the usual situation. Information grows with profligate ease, knowledge slowly and wisdom painfully.

Sometimes we suffer not from a scarcity of information but from a surfeit. For the busy clinician, recommendations may come packaged in a glut of guidelines more suitable for specialized centers than the vast majority of settings where it would take major motivation and considerable incentives to have successful researchers in one area venture beyond their expertise, grant and publication success. A legitimate debate between how much funding agencies should invest in large-scale, integrated projects, compared with individually generated research, needs to continue. The potential advantages of a Triple T approach is that it is voluntary. Industry and other users or investors would see faster and better results from their investments. They may fuel the system with the most powerful of motives: self-interest. Much knowledge already exists behind the conceptual and semantic barriers of subspecialties that seldom talk to each other, and when they try, often do so from different premises, concepts and vocabularies. Complementary knowledge is held in thought-tight compartments within the same subspecialty. If we only knew what we already know!

A structure for transactional research needs to be set up, availing itself of the latest information technology and expertise from other fields where some integration has been successful. The focus should not be so much on acquiring new bits of information, but integrating what is known, across disciplines, across methodologies, and formulated in dynamic and logically sound concepts, with specific formulation of questions that then can be addressed systematically. “The mere formulation of a problem is far more often essential than its solution, which may be merely a matter of mathematical or experimental skill. To raise new questions, new possibilities, to regard old problems from a new angle requires creative imagination and marks real advances in science”, Albert Einstein (1879–1955). This may apply most obviously to the physical sciences, but the principle of formulating a specific, feasible goal and then finding the best means to attain applies universally. “If you do not know to which port you are sailing, no wind is favorable” Lucius Annaeus Seneca (5 BC–65 AD).
stroke patients are seen. Recommendations need to be prioritized and their cost effectiveness evaluated.

The knowledge that we do have needs to be ranked much more pragmatically and its application evaluated much more systematically.

The Role of Journals

Medicine is not the only field bedeviled by too much specialized information and not enough creative synthesis. Over a decade ago, the American Historical Review was seeking articles that were “new in content and interpretation and make a fresh contribution to historical knowledge . . . . that reach beyond the specialties that have enlivened yet also fragmented the discipline in recent years”.

Peer-reviewed journals play pivotal roles in evaluating, publishing and publicizing knowledge. They may also encourage integration and interaction among different disciplines. An annual feature of the journal Stroke, “Advances in Stroke” often carries articles coauthored by a clinician and a basic scientist. Likewise, this was a noteworthy feature introduced at the last Princeton Conference on Cerebrovascular Diseases, where sessions were cochaired by a clinician and a basic scientist and the relevant disciplines were presented and had their article discussed in the same session. The proceedings of that conference were subsequently published in Stroke.

Stroke offered a symposium on “Cerebrovascular Disorders: Opportunities for Transdisciplinary Progress” at the 2007 International Stroke Conference, a theme likely to continue in future conferences. The journal Stroke encourages not only the acquisition, integration and application of knowledge, but the evaluation of how this translates into the real world.

Stroke is the leading publication of articles in outcomes research in the field and is appointing two section editors to further promote this aspect.

Application of Knowledge

The more knowledge grows, the greater the gap between the known and its application. Several factors contribute to this.

The emphasis of our research is on producing knowledge, not in applying it. Many of the factors that influence patient’s adherence to treatment regimes are beyond the scope of the most sophisticated laboratories and in the most modest of stroke-care settings. Many people making small improvements can have as much impact as a few people making big advances. We need both.

Conclusion

Scientific and technological advances generate knowledge at accelerating rates. The more knowledge grows, the greater the gap between the known and its application.

We probably can improve both knowledge acquisition and application by systematically integrating what we know and evaluating what we do. This would apply to all aspects of stroke and to all concerned.

“There is no comparison between that which is lost by not succeeding and that which is lost by not trying.” Sir Francis Bacon (1561–1626).

References


Stroke and Vascular Cognitive Impairment: A Transdisciplinary, Translational and Transactional Approach
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