The only safe prediction about stroke in the next three decades is that it will be very different. Progress largely depends on discovery, and discovery cannot be predicted. However, understanding from where we are coming may help guide where we are going. Each of the previous editors of *Stroke* has given his view of stroke and the journal during his tenure, providing a concise and unique chronicle of our field by those who helped shape it. Several trends will likely affect the field and the journal.

**The Field**

**The Growing Burden of Stroke**

Stroke is the second-leading cause of death in the world and rising. In the developed world, the proportion of the population over the age of 65 years is growing. In the developing world, where most strokes occur, the population over 60 will double in the next 2 decades. These trends portend sharp increases in stroke incidence. The shift from traditional, rural ways of life to urbanization and Westernization often means less exercise, more calories, and bad habits, such as smoking. If we are serious about prevention, much can be done to lessen this burden.

**The Changing Pathophysiology of Stroke**

Most attention has been paid to extracranial disease. However, in the developing world and in American minorities, intracranial disease prevails, about which we know little. Moreover, imaging has unveiled the common occurrence of leukoaraiosis and of "silent" infarcts, both of which can be associated with cognitive decline. Increasingly we are becoming aware of not only large strokes that cripple the body, but little strokes that undermine the mind. Cerebral vascular disease and Alzheimer's disease often coincide and may interact in the brains of elderly individuals. New avenues need to be pursued to see whether stroke precipitates Alzheimer's disease, and if so, whether this can be prevented, delayed, or mitigated.

When hypertension is treated, intracerebral hemorrhage declines, but as people survive longer they become more prone to hemorrhages from amyloid angiopathy and cerebral infarcts from atrial fibrillation.

The genetics of atherosclerosis, intracerebral hemorrhage, and small-vessel brain disease are just beginning to be unraveled.

**Imaging**

Some of the most spectacular advances in stroke have been in the application of imaging techniques, such as computerized axial tomography, MRI, and ultrasonography of the extracranial and intracranial vessels. It is likely that imaging will be refined to the point that it can also give physiological information and can replace conventional contrast angiography.
Genetics and Gene Function
Some of the most dramatic advances in diagnosis will come from structural genetics and gene physiology—initially in the identification of individuals who may have adverse reaction to drugs, and eventually in the genetic profiling of individuals in terms of estimating their risk for vascular disease, targeting treatment and assessing prognosis. Studies of the mutants of the low-density lipoprotein receptor have already been highly informative about the genetics of atherosclerosis vascular disease. Comparable research into the functional impact of mutations in the structures of genes affecting vascular tone may likewise be expected to advance the understanding of the pathogenesis diagnosis and treatment of vascular disease.

Gene Imaging
Technology is already being developed to image genes and their impact on cellular function in laboratory animals. Eventually this may also be possible in humans.

One of the paradoxes of advances in diagnostic technology is the neglect of clinical skills. Too often the attitude is to shoot a picture first and ask questions later. Not all that matters can be imaged, and not everything that can be imaged matters—a lesson that some have learned to their patients’ sorrow. Ironically, the more advanced the diagnostic technology, the greater the need for refined clinical skills, since the easy diagnoses will be made by the technological aids, leaving the most difficult cases to be resolved by clinical approaches and judgment.

The Stumbling Steps to Better Treatment

Failed Neuroprotectant Trials
The effectiveness of thrombolysis in acute stroke and of preventive interventions contrast starkly with the long list of failed neuroprotective trials in acute stroke. Many reasons account for this.

Extrapolation From Animal Models to Patients
The problem stems not so much from the animal models but from the failure to pay enough attention to them and to the conditions under which the results were obtained. Most clinical trials comprise patients with strokes of different types, causes, extent, and duration and who have a range of comorbidities. These conditions seldom resemble the standardized animal models and circumstances yielding the promising results.

Selection of Drugs and Time Window
Thus far, all trials have been of one drug at a time, often with a single purported mechanism. The ischemic cascade, even if it could be stopped by a single step, would require exquisite interventional timing, which is almost impossible to achieve in the human situation, where timing and duration of the ischemia vary widely. Neuroprotectant trials have typically been with a time window of 6 hours or more; such timing may be beyond the ability of the drug to salvage ischemic brain. Moreover, however powerful a neuroprotectant may be in preserving ischemic tissue, ultimately it will fail, unless blood perfusion is restored, naturally or through treatment.

Selection of Outcomes and Sample Size
Current methods of evaluating outcome are coarse and heavily weighted toward motor function. Coupled with this has been an overoptimism about the degree to which a drug could affect outcome, resulting in inadequate sample sizes.

Self-Preservation of the Clinical Trial Team
Typically, by the time a team is appointed, following expert external advice not to proceed with the trial would mean dissolution of the team and embarrassment for those who led its formation. So the trial goes on, with predictable results.

Patients need to be selected or characterized more carefully, and ideally, imaging the volume of viable tissue at the time of the intervention. Outcome measures need to be refined, expectations diminished, sample sizes amplified, and combination therapies tried, allowing thrombolysis to reestablish perfusion and neuroprotectants to act at multiple steps in the ischemic cascade.

Despite trial shortcomings and exaggerated expectations, a rationale remains for carrying out trials of neuroprotectants in stroke. Stroke is so common and devastating that a little difference in salvaged tissue may make a big difference in the ultimate quality of life.

The Future
Molecular genetics will play a growing role. The unraveling of the human genome will lead to the identification of new proteins and novel therapeutic targets. Genotyping individuals will allow not only earlier but more appropriate interventions. Drugs will be tailored to individual responses and side effects. Along with better drugs will come better delivery systems, including means of breaching the blood brain barrier and improving gene therapy.

Models will include virtual chemistry, where promising molecules will be fitted atom by atom to their therapeutic target, the drug will then be tested on transgenic animals, and treatment responses and side effects will be modeled on virtual patients created from clinical trial databases.

Globalization and the convergence of industry, academia, and government will create more uniform international standards and accelerate drug development and approval. Progress will come at a price. The increasing commercialization of science will skew development toward large-market, large-profit therapeutic agents and will leave little incentive for developing treatments for rare diseases or testing further drugs of great therapeutic power but limited profit potential, such as acetylsalicylic acid.

Individuals will play an increasingly important role in their own treatment. From surfing the Internet to being the subject of direct advertising, more and more individuals will make their own choices, including alternative medicine.

The next 30 years will transform stroke from a field of diagnostic precision and therapeutic impotence of 30 years ago into the most exciting area of treatment opportunities.
proaches need to be reconciled and integrated, because it matters to patients.

It has long been established that organized stroke care as delivered in stroke units has a favorable and lasting effect on outcomes.12 We need to learn which of the many components of diagnosis, evaluation, treatment, avoidance of complications, and rehabilitation contribute to this beneficial effect.

The rehabilitation literature has suffered from lack of interest in the brain. What reliable clinical trials exist have largely focused on global evaluations and not on identifiable pathophysiological mechanisms. Moreover, much of what is done is based on tradition and belief. As recently as 1997, 66% of the recommendations of the guidelines for poststroke management had no basis in research.13,14 However, imaging, genetics, and experimental work in brain reorganization and grafting offer real hope of progress. If neuroscientists, trialists, and clinicians converge their efforts, we will begin to understand why strokes are remarkable, not because of the damage that they inflict but because of the recovery that they allow.

Even before joining forces to advance our understanding of brain injury and repair, a number of relatively simple trials can be carried out. There is now excellent evidence that an enriched environment enhances functional outcome and that the environment interacts with more direct measures such as drugs or neocortical grafting.15 Although much stock is put on stem cells, the 2 fundamental steps toward their clinical application have not yet been taken—to show that embryonic cells can integrate and replace lost function in damaged brain and that stem cells can be engineered to perform as well as embryonic cells.

Prevention: The Hope and the Disappointment
The hope is that up to 75% of cardiac and cerebrovascular disease can be prevented by the successful management of the known risk factors.16 The disappointment is that only about 25% of those with known risk factors have them controlled.17,18

The fact that this gap between knowledge and application has been observed in different countries and in different health care systems suggests that the problem goes beyond accessibility and economics. Almost certainly ignorance, different risk perceptions, and attitudes to their management play a role.

An intervention can be not only underused but also overused and misused, as exemplified by carotid endarterectomy, the most effective surgical procedure for stroke prevention.19

Open surgery is increasingly being replaced by less invasive procedures, such as angioplasty, stenting, infusion, ballooning, and coiling. We trust that the pioneers of innovation will work closely with trialists seeking proof for effectiveness of these procedures.

Between the Ideal and the Affordable
The price of improvements often exceeds their value. Better methods of diagnosis, treatment, prevention, and rehabilitation will become available, but at increasing cost. We need to develop a common currency of evaluation or a Relative Return Ratio (RRR) (my term). Such a common unit would allow ranking of treatments according to their effectiveness and return for investment in comparison with some health outcome measures such as a quality-adjusted life year (QALY) or another measure depending on the purpose. Knowing what it costs to attain a QALY by treatment A would give a direct comparison with what it would cost to attain a QALY by treatment B. Choices could then be made by the individual and/or society in comparison with other health measures or in comparison with competing demands, such as education. The price of implementing an intervention will vary from country to country, eg, staffing a stroke unit, but the value per measure or the RRR will be similar.

The RRR can be calculated, the costs computed, and informed decisions made regarding yield per effort and what that is worth to an individual or a health care system. Sophisticated consumers of the future may ask their doctors not only about the latest drug that they see advertised in the media but also about its RRR.

The Journal
In 30 years, Stroke may not be a paper journal. There are strong trends toward electronic publishing, linking and creating a customized learning environment. However, the demand for wisely selected and evaluated new, valid, and important information will remain. While the Internet has made every author into a potential editor and publisher,20 the need for quality assurance has not diminished. If the peer review system were to be abolished, it would have to be reinvented.21

The magnitude of the problem of stroke along with the increasing ability to do something about it have created an unprecedented demand for stroke experts. Special training programs need to be devised, the door opened to a wider range of individuals to train and retrain, and the great potential of online education should be fully exploited. Stroke can play a role as a major source of relevant and reliable information.

In addition to publishing results of original research, journals can provide systematic reviews, meta-analyses, and guidelines that can make knowledge more tractable, accessible, and relevant. However, systematizing information cannot provide guidance in areas where the state of the art is ignorance, nor where knowledge is meager but the physician has to act. Moreover, by their nature, the results from clinical trials are averages, while the real need is for individual profiles of risk, response to treatment, and rehabilitation. The individual phenotype, genotype, and personotype need to be understood and considered in diagnosis, treatment, and rehabilitation. Perhaps a new discipline of integrated approaches will emerge from the proliferating fragments of subspecialization.

Stroke could play an increasing role in setting standards, providing the means for education of professionals, the public, and policy makers, and become a forum for the advocacy of measures that may advance the field, and a clearing house and synergerizer of new ideas.

Conclusion
Seldom has a field in medicine been transformed so radically from pessimism to the beginnings of hope as stroke. However, many challenges remain, particularly in the developing world, where stroke numbers continue to mount. Genetics, proteomics imaging, and informatics offer unlimited possibilities of progress but pose unprecedented issues in ethics,
funding, ownership, and accessibility. We need not only to make further discoveries but to ensure that what we learn is applied for the benefit of humankind. Stroke can play a role by publishing, facilitating, and highlighting the best work to address these challenges. The journal itself will be challenged by contemporary trends, including speed. Everything is accelerating so much that speed is threatening to overtake quality. We believe with Augustus in festina lente (make haste slowly). We will aim to be comprehensive, succinct, credible, accessible, and attractive but will focus on the one irreplaceable quality: quality.

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Vladimir Hachinski

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