Management of Ischemic Stroke in the Next Decade: Stroke Centers of Excellence

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Stroke has been increasingly recognized as an important and expensive medical and societal problem during the past 10 years. Currently, organized stroke care is delivered to the American population in only a few cities and hospitals that provide an efficient system for rapid transportation, diagnosis, treatment, and rehabilitation. The Brain Attack Coalition (BAC) has recently proposed the concepts of stroke centers of excellence (akin to trauma level I centers), primary stroke centers, and comprehensive stroke center. The U.S. government, with the Paul Coverdell National Acute Stroke Registry and the Stroke Treatment and Ongoing Prevention Act of 2003, further supports these concepts. Herein, a discussion of the influence that the BAC, the Paul Coverdell National Acute Stroke Registry, and the Stroke Treatment and Ongoing Prevention Acts of 2001 and 2003 will have on the future of stroke therapy in this country during the next 10 years is presented. Also discussed are the elements that are crucial to organized stroke care and the formation of stroke centers of excellence. These include triage and diagnosis in the field, transportation, triage and imaging in the emergency department, prompt transfer to a dedicated stroke unit with focused care, rehabilitation, manpower, prevention and research, reimbursement issues, and politics. The importance of multidisciplinary collaboration on the professional and societal levels and, finally, government- and private sector-sponsored research are also presented.

J Vasc Interv Radiol 2004; 15:S133–S141

Abbreviations: BAC = Brain Attack Coalition, NIH = National Institutes of Health, tPA = tissue-type plasminogen activator

The medical issues associated with the management of ischemic stroke cover all aspects of stroke physiology, diagnosis, and treatment. As of today, however, stroke remains the third leading cause of death and the leading cause of serious, long-term disability in the United States (1). There are more than 750,000 new strokes per year, resulting in more than 250,000 deaths per year in the United States alone (2). Stroke is the leading cause of inpatient Medicare expenditures for long-term care, and the lifetime cost of stroke exceeds $90,000.00 per patient.

The latest estimates are that annual stroke costs exceed $30 billion in direct costs and $20 billion in indirect costs. Between 15% and 30% of stroke survivors are permanently disabled. Approximately 4.7 million Americans and their families live with the disabling effects of stroke (3).

Members of the general public have difficulty recognizing the symptoms of stroke and are unaware that stroke is a medical emergency. The two major causes of delay in treatment are failure on the part of the patient or family to recognize stroke symptoms and failure to access the medical system most efficiently by calling 911 (4). Frequently, stroke patients wait more than 22 hours before presenting to the emergency room. Forty-two percent of individuals over the age of 50 years do not recognize numbness or paralysis in the face, arm, or leg as a sign of stroke, and 17% cannot name a single stroke symptom (3). Recent advances in stroke treatment can substantially improve the outcome for stroke patients, but these therapies must be administered properly and promptly. Only 3% of patients with stroke who are candidates for acute stroke intravenous thrombolytic drug therapy receive the appropriate medication (5–8). New technologies, therapies, and diagnostic approaches are currently being developed that may extend the therapeutic time frame and result in greater treatment efficacy for stroke patients. However, few states and communities have developed and implemented stroke awareness programs, prevention programs, or comprehensive stroke care systems. The degree of disability resulting from stroke can be reduced substantially by educating the general public about stroke and by improving the system for the provision of stroke care in the United States.

During the 107th Congress, the Stroke Treatment and Ongoing Prevention Act of 2001 (STOP Stroke Act) (3) was introduced by Senators Edward Kennedy (D, Mass) and Bill Frist (R, Tenn) and Representatives Lois Capps (D, Calif) and Charles “Chip”
Pickering, Jr (R, Miss). The STOP Stroke Act received strong support in the House and Senate during the 107th Congress. The STOP Stroke Act passed the Senate unanimously by voice vote on February 6, 2002. The House bill received overwhelming support from more than 213 cosponsors. The Stroke Treatment and Organizing Prevention Act of 2003 will soon be introduced to the U.S. Senate; its goals are to improve the provision of stroke care in every state and territory, including the District of Columbia, and to increase public awareness about the prevention, detection, and treatment of stroke.

We are at the dawn of stroke therapy organization, and much work remains to be done. Stroke treatment remains very fragmented, with only a few organized areas of excellence dispersed throughout the country. Most hospitals do not have the necessary infrastructure (personnel and equipment) and organization required to triage and treat patients with stroke rapidly and efficiently. In one recent study (9), 66% of hospitals surveyed did not have stroke protocols, and 52% did not have means for rapidly identifying patients experiencing acute stroke. This shortcoming is well demonstrated by the experience with tissue-type plasminogen activator (tPA) for stroke therapy. The approval of intravenous tPA as the first treatment for acute ischemic stroke was a landmark event, yet a recent study in the Cleveland, OH, area (10) found that only 1.8% of patients with ischemic stroke received this agent. Nationally, only 2%-3% of patients with stroke are being treated with tPA (5–8). A few of the many reasons for this low rate include patient presentation beyond the required 3-hour treatment window, clinicians’ concerns about bleeding complications, and the inability of some medical systems to triage and evaluate such patients rapidly.

In 1997, J. F. Mohr, MD, in the Excellence in Clinical Stroke Award Lecture (11), said the following: “None of us in current neurology regret the passage of the ‘diagnose and adios’ era humorously criticized years ago by Dr. Labe Scheinberg in a grand rounds talk. Rapid innovations in imaging, the rush to ever more clinical trials, and the shortening time frame for action are turning many of us into happy interventionalists, rivaling colleagues in cardiology and emergency medicine. The very pace of events is quickly rendering obsolete a more leisurely approach to the analysis of the meaning of symptoms and signs. The practical needs dictated by hyperacute therapy threaten to change our field so thoroughly as to eclipse the once intensely debated clinical issues of how the brain responds to injury, for which stroke has always been the leading model.” Dr. Mohr discussed proposals for areas referable to clinical stroke research: adopting a 1-hour rule for diagnosing stroke, better understanding of time from known occlusion to syndrome, definition of factors affecting outcome, and implications for trials.

James Grotta, MD, in the 1999 Feinberg lecture (Acute Stroke Therapy at the Millennium: Consummating the Marriage between the Laboratory and Bedside) made a few key remarks (12). “First, stroke therapy is difficult. It’s a complex disease and nobody said it would be easy. There are not going to be any magic bullets for stroke patients. Second, the most critical but ignored lesson from the laboratory is the importance of time. Third, it’s critical to change the role of neurologists in taking care of stroke patients, particularly because of the importance of time.”

The development and organization of stroke centers of excellence will improve the treatment of these patients. Issues that relate to stroke centers of excellence include patient education, imaging before hospital transport, rapid and safe transportation, wireless imaging transmission, the importance of stroke units, rehabilitation, manpower issues, reimbursement issues, therapeutic stroke prevention and research (apoptosis, translational research, genetics, neuroplasticity and repair, to mention only a few), and politics. Issues that are of importance to the prompt and efficacious treatment of stroke are summarized in Table 1.

**Table 1**

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**STROKE CENTERS OF EXCELLENCE**

Guidelines for the development of stroke centers of excellence have now been published. These include: (a) “Recommendations for the Establishment of Primary Stroke Centers. Brain Attack Coalition” (7), and (b) “Establishing Data Elements for the Paul Coverdell National Acute Stroke Registry. Part 1: Proceedings of an Expert Panel” (8).

These are currently the models of stroke center organization in this decade.

Stroke centers will mirror the experience of trauma centers, which were organized to provide care for patients with acute trauma. These were established after studies found that many lives were being lost due to the frequent lack of necessary medical infrastructure needed to stabilize and treat patients with severe trauma.

To establish guidance about the formation and operation of stroke centers, the Brain Attack Coalition (BAC) formed a multidisciplinary working group that includes most major medical organizations involved with stroke care. BAC members determined that two levels of stroke center service should be established: (a) a primary stroke center and (b) a comprehensive stroke center. The primary stroke center would stabilize and provide emergency care for patients with acute stroke. The primary center would then either transfer the patient to a comprehensive stroke center or admit the patient and provide further care, depending on the patients’ needs and the center’s capabilities. The comprehensive stroke center would provide complete care to patients experiencing the most complex strokes that require specialized testing and other interven-
tions. Comprehensive stroke centers would typically include tertiary care medical centers and hospitals with the infrastructure and personnel necessary to perform highly technical procedures and provide all needed levels of care. The BAC recommended that primary stroke centers be organized around 11 major aspects of stroke care, grouped into direct patient care areas and support areas (Table 2). The patient care areas include (a) acute stroke teams, (b) written care protocols, (c) emergency medical services, (d) an emergency department, (e) a stroke unit, and (f) neurosurgical services. Support services include (a) commitment and support of the medical organization and stroke center director, (b) neuroimaging services, (c) laboratory services, (d) outcome and quality improvement activities, and (e) continuing medical education.

The expected outcomes of this infrastructure are as follows: (a) an improvement in the efficiency of patient care, (b) fewer time-related (ie, closely following the stroke) complications and an increase in the use of acute stroke therapies, (c) a reduction in morbidity and mortality, (d) an improvement in long-term outcomes, (e) a reduction in costs to the healthcare system, and (f) an increase in patient satisfaction. What is the proportion of hospitals that currently meet the recommended BAC criteria for primary stroke centers? In a recent study, Kidwell et al (13) surveyed 3,245 U.S. neurologists, neurosurgeons, and emergency physicians regarding the BAC guidelines for the establishment of stroke centers. Seventy-nine percent of respondents believed there was a need for stroke centers. If formal stroke center designations were established, 81% would like their hospital to become a primary stroke center. Although 77% of respondents believed that their hospital currently met recommended criteria for a primary stroke center, only 7% actually met all recommended elements. However, 44% of the hospitals already provide most acute stroke services. The BAC criteria most frequently lacking were continuing medical education for professional stroke center staff, stroke training for emergency department staff, formal establishment of a stroke unit, and designation of a stroke center director. In summary, more than 40% of hospitals already possess substantial existing acute stroke care resources and are poised to function as primary stroke center with modest additional administrative and financial commitment.

In 2001, Congress appropriated $4.5 million to the Centers for Disease Control and Prevention for the development of a national acute stroke registry to track and improve the delivery of care to patients with stroke. Congress further directed that the registry be named after U.S. Senator Paul Coverdell of Georgia, who had a fatal stroke in 2000. The congressional language directed the Centers for Disease Control and Prevention to (a) consult with the panel from the BAC and professional and nonprofit organizations to develop registry data elements and (b) design and test registry prototypes. Data elements recommended by the expert panel included patient information organized in domains that reflect the entire timeframe of the acute stroke episode from onset through treatment to follow-up (Table 3).
These elements were categorized as follows: (a) prehospital, (b) emergency evaluation and treatment, (c) in-hospital evaluation and treatment, and (d) discharge information and postdischarge follow-up.

The prehospital elements involve excessive delays in time, from onset of signs and symptoms to arrival at an emergency department; public education as to recognition of the signs and symptoms of stroke; and delays in transport that signal needed improvements in the way an emergency medical system handles patients with acute stroke.

The emergency evaluation and treatment data elements address patient care activities that occur during the 1st few hours after arrival at the hospital such as triage, diagnostic evaluation/NIH stroke scale score, and the delivery of thrombolytic treatment.

In-hospital evaluation and treatment data elements address aspects of care that occur between the emergency treatment of the patient and hospital discharge, such as stroke units, the use of other diagnostic or surgical procedures, and the use of a physician specialist or allied health consultation during hospitalization.

Discharge information and postdischarge follow-up data elements include a summary of the patient's medical and functional status at discharge as well as summary elements of the patient's overall treatment while in the hospital, such as an assessment at 90 days after discharge with regard to the patient's function, medications being used, and setting of the patient's residence.

In addition to the previously described elements, the panel recommended a number of hospital-level measures pertaining to stroke center guidelines to augment the patient-level data. Domains pertinent to basic hospital level included characteristics about the hospital and availability of a hospital diagnostic laboratory. Domains relevant to stroke center guidelines included availability of current head imaging technology and rapid interpretation, an acute stroke team, treatment protocols, monitoring capabilities, a stroke unit, and essential diagnostic equipment for stroke evaluation. Other important hospital-level elements that could affect the quality of care for patients with stroke included the presence of neurosurgical capabilities and the availability of rehabilitation therapy, an extant research program in stroke prevention and treatment, and stroke education and training programs. The final conclusion was that optimal improvements in stroke care would require a synthesis of improvements in (a) community education programs about the early recognition of stroke symptoms and the importance of treating stroke as a medical emergency, (b) emergency medical service evaluation of patients suspected of having stroke and prehospital notification, (c) effective triage for the most appropriate emergency care, (d) establishment of a systematic national program for monitoring the quality of medical stroke care, and (e) national and local collaborative efforts to guide continuous improvements in the delivery of stroke care and stroke prevention.

PATIENT POPULATION
EDUCATION/STROKE CAMPAIGNS

The Temple Foundation stroke project (14) was organized to determine whether an aggressive, scientifically based behavioral intervention could increase the proportion of patients with stroke who are treated with a U.S. Food and Drug Administration-approved acute stroke therapy within a representative community. This study effectively showed that an aggressive, multilevel stroke educational intervention program could increase the delivery of acute stroke therapy. In this study, treatment with intravenous tPA increased from 1.38% to 5.75% in all patients with a cerebrovascular event in the intervention community \((P = .01)\) compared with a change from 0.49% to 0.55% in the comparison community \((P = 1.00)\). Among the patients with ischemic stroke, an increase from 2.21% to 8.65% was noted in the intervention community \((P = .02)\). Of patients who were eligible to receive intravenous tPA, treatment increased in the intervention community from 14% to 52% \((P = .003)\) and was unchanged in the comparison community. This study provides evidence that aggressive professional and community education may increase the utilization of therapy for acute stroke (14).

IN-FIELD IMAGING

Advances in transcranial sonography have now made it possible to image the brain parenchyma through the bony skull with conventional low-frequency probes (15–18). Several brain disorders can be depicted with this technique (eg, bleeding, brain tumors, or enlargement of the ventricular system). Midline shift can reliably be detected.

In a study of 151 patients, Maurer et al (17) compared computed tomography (CT) and transcranial color-coded duplex sonography and found that transcranial color-coded duplex sonography enabled ischemic stroke to be correctly differentiated from intracerebral hemorrhage in 95% of patients. Stroke complications depicted with CT (disturbance of cerebrospinal fluid circulation, hemorrhagic transformation, midline shift, ventricular bleeding) were correctly shown with transcranial color-coded duplex sonography in 83% of patients (17).

In the future, a patient with ischemic stroke could be diagnosed and imaged in the field (possibly with the help of wireless imaging transmission) and be given a systemic medication that could either prolong the therapeutic window for therapy or treat the underlying thrombus.

TRANSPORTATION

Availability of efficient and rapid transportation is an integral part of a modern stroke center of excellence. The most important barrier to delivery of medical or interventional stroke therapy is the delay between the onset of symptoms and transportation to an appropriate stroke center before the current window of opportunity of 3 to 6 hours.

In 1999, Harbison et al (19) established a rapid ambulance protocol for acute stroke in Newcastle, England. After the protocol was established, patients with acute stroke were successfully diverted to an acute stroke unit. Feedback to ambulance staff of initial results with the protocol prompted a substantial increase in admissions owing to the protocol. With the protocol, admissions of patients with acute...
stroke increased during the 1st year, from three to 13 per month, and diagnostic accuracy was maintained at a rate higher than 80%. Training in stroke recognition may increase the proportion of acute stroke cases recognized by paramedics; acute stroke assessment by paramedics may be sufficiently accurate to permit redirection of patients to centers with acute stroke units. Patients with acute stroke who contact paramedical services are more likely to present to secondary care units within a time window facilitating administration of acute stroke therapies.

An ambulance and paramedic system is effective in an urban environment, but what about rural environments? Stillman et al (20) evaluated the efficacy of the Shands-Jacksonville Acute Stroke Transport Program, a field-to-stroke center helicopter transport program that serves rural counties in the northeastern Florida/southeastern Georgia region. The average field-to-hospital distance for all patients was 29.4 miles (range, 11–90 miles). Most patients (n = 65) arrived within 135 minutes from symptom onset. It was concluded that a helicopter-based transport system could link a rural region to a stroke center and promote access to thrombolytic therapy.

Early notification by the emergency medical services about patients with stroke would enable stroke teams to be present at admission, thus improving the likelihood of a better outcome for patients (21).

STROKE UNITS

Sulter and Keyser (22) stated that the goal of a stroke care unit is early detection and rapid correction of extracranial factors that may aggravate cerebral damage in ischemic brain, including hypoxia, hyperglycemia, hypotension, cardiac arrhythmias, and elevated body temperature. Indredavik et al (23) showed that stroke unit care improves long-term survival and functional state and increases the proportion of patients able to live at home 5 years after the stroke.

A meta-analysis of available randomized controlled trials (24) has shown that care of patients with stroke in a stroke unit is superior to that in conventional general medical, neurologic, or geriatric wards, with reductions in early case fatality, functional outcome, and the need for long-term institutionalization. The Stroke Unit Trialists’ Collaboration (25,26) has shown convincing evidence for improved survival and functional outcome in patients with an acute stroke treated in stroke units compared with those cared for in general wards. This study showed an odds reduction of 19% in case fatality and a 25% odds reduction in combined outcomes of death or need for institutionalized care after the stroke. Furthermore, a 29% odds reduction in death or dependency on others for activities of daily living has been reported.

Indredavik et al (27) also identified the differences in treatment between the stroke unit and the general ward and assessed which aspects of the stroke unit care were most responsible for the better outcome. Characteristic features of the stroke unit were teamwork, staff education, functional training, and integrated physiotherapy and nursing. Other treatment factors that were substantially different in the stroke unit compared with the general ward were shorter time to start of the systemic mobilization/training and increased use of oxygen, heparin, intravenous saline solutions, and antipyretics. Consequences of the treatment seemed to be less variation in diastolic and systolic blood pressure, avoidance of the lowest diastolic blood pressure, and a decrease in the levels of glucose and temperature in the stroke unit group compared with the general ward group. Results of univariate analyses showed that all these factors except the level of glucose were significantly associated with discharge to home within 6 weeks. In the final multivariate Cox regression model, a shorter time to start of the mobilization/training and stabilized diastolic blood pressure were independent factors significantly associated with discharge to home within 6 weeks. The effects of characteristic features of a stroke unit, such as specially trained staff, teamwork, and involvement of relatives, were not possible to measure.

Steegmayr et al (28) demonstrated that the improvement in outcomes after stroke care in stroke units compared with that in general wards could be reproduced in the routine clinical setting, but that the magnitude of the benefit appeared smaller than that reported from meta-analyses.

REHABILITATION

In a recent review of 32 studies about the effect of stroke rehabilitation (of which 18 were randomized controlled trials), the efficacy of comprehensive occupational therapy was found to have a small but significant effect on primary activities of daily living, extended activities of daily living, and social participation (29). Clearly, a comprehensive rehabilitation service should be part of any stroke center of excellence.

MANPOWER ISSUES

Cloft and colleagues (30) assessed the current and future supply of interventional neuroradiologists in the United States in relation to the potential pool of neurologic disease that can be treated with endovascular approaches. They noted that, according to the American Hospital Association, 174 trauma level I centers exist. The number of acute stroke centers in the United States might be expected to someday be similar to the number of such regional centers. As of July 2002, almost 300 centers claimed to be able to treat aneurysms with coils; the same centers would certainly have the endovascular capability for treating stroke. Therefore, we may already have enough neuroendovascular manpower to manage stroke. The future demand for intrararterial reperfusion techniques remains unclear because the management of stroke in the future will certainly continue to evolve and we do not know the fraction of patients with acute ischemic stroke for whom intraarterial thrombolysis or other techniques are best. A problem certainly arises with 24-hour coverage. In many of the 300 neuroendovascular centers, there is only one interventional neuroradiologist, which makes it difficult to provide stroke care coverage 24 hours a day, 365 days a year. Higashida and Connors (2), in a statement from the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology, stated that additional manpower may have to be trained and brought in from the Society of Interventional Radiology as well as from the American Society of Neuroradiology to provide adequate stroke coverage. Specific standards of training in neuroendovascular surgery/interventional neuro-
radiology have also been developed and published (31). This will improve training issues and guidelines related to endovascular therapy of stroke. Finally, more than 9,000 interventional cardiologists are also beginning to take an interest in stroke therapy and may contribute to the manpower pool.

REIMBURSEMENT

Reimbursement is a very important issue in the future of stroke therapy. Currently, neurologists and emergency physicians do not get reimbursed for intravenous tPA stroke therapy. No more than a standard consultation fee can be charged for intravenous therapy, which is time consuming and risky. Most neurologists in the United States have not expressed an avid interest in the treatment of acute stroke patients. We cannot expect neurologists in private practice or elsewhere to be doing this without adequate reimbursement. For intrarterial therapy, there is a code that reimburses at a very low rate, and most of the revenue is derived from billing for diagnostic angiography performed along with the intrarterial therapy. It is the responsibility of our professional organizations to ensure that all medical participants get reimbursed properly for reorganizing their lives to carry out effective ischemic stroke therapy.

PREVENTION

All stroke programs should incorporate patient education and preventive measures. Modification of lifestyle habits such as cessation of smoking and control of hypertension and obesity can take place in public information programs (32–34).

A new area of research for stroke prevention is concerned with statins. Recent publications have suggested that statins probably reduce stroke by a variety of mechanisms, including modulation of precerebral atherosclerosis in the aorta and the carotid artery, thus preventing plaque disruption and artery-to-artery thromboembolism (35,36). Statins also improve endothelial homeostasis by increasing the bioavailability of nitric oxide, which orchestrates the paracrine anti-atherosclerotic functions of the endothelium. Putative anti-inflammatory actions of statins may also contribute to neuroprotection and stroke prevention. These pleiotropic effects extend far beyond cholesterol reduction and involve non-lipid–related mechanisms that modify endothelial functions, immunoinflammatory responses, smooth muscle cell activation, proliferation and migration, atherosclerotic plaque stability, and thrombus formation. In addition to reducing stroke risk, emerging data suggest that statins may also reduce dementia.

RESEARCH

An important component of the future stroke center of excellence must incorporate research. It should span basic and clinical issues related to stroke and should involve all the departments involved in stroke care.

The Stroke Therapy Academic Industry Roundtable published their recommendations for advancing the development of acute stroke therapies (37). They reported that novel approaches must be considered and used in future clinical trials. The focus of the meeting was to explore new concepts for expanding the therapeutic time window and consider strategies for developing combination acute stroke drug treatments and new paradigms for stroke trial design and organization. Several strategies might be considered to increase the proportion of treatable acute stroke patients. These strategies were divided into four broad categories, as follows: (a) reduction in delays between the onset of a patient’s symptoms and presentation for treatment; (b) use of imaging or other laboratory measures to help identify patients who might benefit from delayed interventions; (c) evaluation of novel treatments that have a mechanism of action permitting delayed intervention, and (d) administration of early temporizing treatments that can potentially prolong the time window for definitive interventions.

The following important points about the potential benefits of imaging in acute stroke trials were also made: Imaging can help (a) confirm that the patient is experiencing ischemic stroke and exclude symptoms that may mimic stroke, (b) identify contraindications to treatment (eg, presence of hemorrhage in a trial of fibrinolytics), (c) determine that the lesion affects tissue responsive to the drug under trial and that there is an appropriate tissue target of therapy (eg, large, persisting penumbral zone), (d) provide a more homogeneous patient population (eg, inclusion of middle cerebral artery territory lesions only, or exclusion of brain stem lesions), (e) determine whether there is an appropriate large vessel occlusion target for reperfusion therapy, (f) potentially identify tissue markers at increased risk of therapy (eg, a large necrotic core increasing the likelihood of hemorrhagic transformation with fibrinolytic or antithrombotic molecules), and (g) serve as a possible surrogate marker for clinical outcome (in addition, findings can be correlated with traditional clinical end points).

The potential benefits of organized consortia for performing stroke trials are as follows: It provides a scientific forum for reviewing trial proposals and generating feedback on feasibility and trial performance; establishes better and more direct links with industry sponsors; initiates a system to help develop and endorse standards of design, safety, and reporting of trials; provides a mechanism to help streamline the administrative infrastructure of trials; identifies in a timely manner high-quality centers capable of delivering the needed number of patients in a timely manner; and provides an efficient means to maintain quality standards and certification of investigators.

It was recommended that future stroke trials (a) incorporate advances in trial design methodology, including sequential designs, factorial designs, and appropriate application of simple and complex designs; (b) optimize stroke trial target populations and expand to larger, more heterogeneous populations where appropriate and account for changing stroke profiles (older, race-ethnicity, coexistent morbidity, stroke subtypes); (c) incorporate measures of bioactivity and innovative diagnostic modalities (ie, imaging, serum markers) in the design of trials; (d) include collaborations with prehospital and emergency room systems to enhance entry and reduce randomization delays; (e) refine stroke outcome assessments, including the judicious use of continuous outcomes and the development of more sensitive scales, and encourage the use of adjusted outcomes (eg, by adjusting
for baseline stroke severity; (f) incorporate lessons from cardiology and oncology trials and form cost-efficient regional, national, and international trial consortia consisting of academic and community sites; (g) reduce delays between data collection and analysis with use of electronic records, internet systems with standard platforms, and audit trails; (h) improve Institutional Review Board efficiency, including wider acceptance of centralized decisions, waiver of consent and use of next-of-kin consent, and streamlining the system of updating internal review boards about serious adverse events; (i) strongly encourage early academic-industrial collaborations at all levels, from design to execution to reporting of trials; (j) improve funding for clinical trials by increasing NIH support for trials, reducing time delays in funding, and encouraging NIH-industrial collaborations; and (k) support the establishment of a centralized stroke trial data base. This group also discussed various aspects of the design of clinical trials for promising new acute stroke drugs and focused on the design of both initial and pivotal clinical trials of single and combination therapies for acute ischemic stroke (38). They concluded that the design, implementation, and conduct of clinical trials for acute ischemic stroke are challenging, time-consuming, and expensive tasks. They require close cooperation between the sponsor (typically, industry or government agency), academic advisors, and the investigators who actually carry out the study. It is important that each part of this triumvirate be involved at every stage of the organization of the clinical drug development process and that good cooperation be established to ensure the design and performance of optimal trials with the greatest possibility to safely and fairly evaluate the drug being tested. In addition, regulatory agencies should be consulted at various stages of the drug development process to ensure that existing regulatory guidelines are met. An agreement should be reached between an industrial sponsor and the academic/investigator participants that the trial results will be presented at an appropriate public meeting and submitted for publication, even if the results are negative (38). Gladstone et al (39), in a recent article titled “Toward Wisdom from Failure: Lessons from Neuroprotective Stroke Trials and New Therapeutic Directions,” noted that neuroprotective drugs for acute stroke have appeared to work in animals, only to fail when tested in humans, and that, with the failure of so many clinical trials, the future of neuroprotective drug development is in jeopardy. By recognizing the strengths and limitations of animal models of stroke and the shortcomings of previous clinical trials, they hoped to move translational research forward for the development of new therapies for the acute and subacute stages after stroke. DeGraba and Pettigrew (40) noted that many neuroprotective agents that seemed promising in animal studies of ischemic brain injury proved to have no effect when tested in clinical trials, suggesting that fundamental elements of translational research required better definition. They examined preclinical modeling and its translation to prospective studies of acute stroke therapy and focused on some potential solutions directed at clinical trial design.

During the past 5 decades, accelerating trends in acute stroke controlled trials include growth in number, sample size, and quality and reduction in entry time window. These changes reflect increased understanding of the pathophysiology of acute stroke, the imperative for treatment initiation within a crucial time window, and a more sophisticated trial design (41).

There is increasing evidence that neuronal death after brain ischemia is mediated by the action of cysteine-requiring or aspartate-directed proteases (caspasases)—the proteins responsible for apoptosis in mammals—although this form of neuronal death is not always accompanied by the morphologic changes that are typical of apoptosis and other tissues (42–44). Focal cerebral ischemia results in necrosis at the infarct core and activation of complex signal pathways for cell death and cell survival in the periphery. Deletion of the proapoptotic and pro-survival genes in the penumbra may not only increase understanding of the process but also help rationalize strategies geared to reducing brain damage targeted at the periphery of the infarct core. A host of processes are involved in the activation of caspasases after brain ischemia and must be better understood.

Recently, there has been convincing in vivo and in vitro evidence that melatonin protects against ischemia/reperfusion injury; melatonin is a potent free radical scavenger and an indirect antioxidant (45).

GENETICS

Rapid advances in understanding and mapping of the human genome will undoubtedly contribute to the better understanding, screening, treatment, and prevention of stroke.

In 2001, Mark J. Alberts, MD, in an editorial (46), discussed the effect of the Human Genome Project and the identification of a stroke gene. He pointed out that sequencing the human genome and the mapping and characterization of thousands of genes is a dramatic step toward unraveling the many genetic disorders that cause familial cerebral vascular disease. The cloning of a putative stroke gene responsible for cerebral infarction is another major advance in this area. These developments could make it possible to provide genetic counseling for at-risk individuals.

To summarize, basic science research will continue to be a pillar of stroke therapy and should be an integral part of any stroke center of excellence.

POLITICS

The future development of stroke centers of excellence will be intimately intertwined with professional societal organizations and government. The Stroke Treatment and Ongoing Prevention Act of 2003, the Coverdell National Acute Stroke Registry, and the BAC will all have pivotal roles in this process. It will be the responsibility of all professional societies involved in the treatment of stroke to join forces and interact with these agencies and government groups. The National Institute for Neurological Disorders and Stroke and private industry should have an important role in the future of stroke therapy research.

CONCLUSIONS

The timely and efficient management of ischemic stroke in the next decade will without doubt occur within the structure of stroke centers
of excellence. We are at the beginning of an era of organization that will bring together the multiple elements required for the formation and sustenance of stroke centers of excellence, better understanding of stroke as a disease and societal problem, research, and funding. Collaboration between government, professional societies, and medical industry should enable a system that is equal to or better than level I trauma centers to evolve in the near future.

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