

Report of the Stroke Progress Review Group

April 2002



From the Leadership

We are pleased to submit this Report of the Stroke Progress Review Group (SPRG) to the Director and the National Advisory Neurological Disorders and Stroke Council of the National Institute of Neurological Disorders and Stroke (NINDS).

In their FY2001 Appropriations Committee Report, the House of Representatives and the Senate directed NINDS to develop a national plan for both basic and clinical stroke research. At the beginning of 2001, the SPRG accepted this charge from Dr. Gerald Fischbach, Director of the NINDS, and moved quickly to develop an appropriate plan. The result of the SPRG's efforts is this report, which the SPRG members and the participants at the Roundtable Meeting produced in record time, reflecting the energy and enthusiasm of the clinical, research, industrial, and advocacy communities for identifying effective treatments for stroke.

The Report of the Stroke Progress Review Group highlights the scientific research priorities that represent the next steps toward understanding the biological basis of stroke and developing effective therapies for stroke. We look forward to discussing these priorities with the leadership of the NINDS.

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Foreword

This report represents the collaborative effort of scientists, clinicians, industry representatives, and patient advocates who were charged by the National Institute of Neurological Disorders and Stroke with the task of setting overall priorities for stroke research.

The executive summary of the report outlines those priorities in light of the biological and clinical complexity of stroke and the formidable challenges that have slowed progress toward effective treatments. Many priorities and directions need to be pursued in stroke research, and they are discussed in detail in the breakout session reports. Common themes emerged from those reports, however, and the Stroke Progress Review Group considers the priorities delineated in the executive summary to be the best guide to the future direction of stroke research.

This report and additional related information are available at the Stroke Progress Review Group web page on the National Institute of Neurological Disorders and Stroke web site (www.ninds.nih.gov).

Acknowledgments

The Report of the Stroke Progress Review Group (SPRG) is the product of work carried out over the past several months by the SPRG, the participants at the SPRG Roundtable Meeting, and staff of the National Institute of Neurological Disorders and Stroke (NINDS). The report is based on meetings of the SPRG leadership in Bethesda, Maryland, in October 2000; of the SPRG members in Crystal City, Virginia, in March 2001; of the Roundtable Meeting participants in Denver, Colorado, in July 2001; and of weekly conference calls of the SPRG leadership and NINDS staff throughout 2001.

Special thanks are extended to the NINDS Office of Science Policy and Planning for their extraordinary organization in all phases of the SPRG process. In particular, the guidance of Dr. Paul A. Scott, Dr. Melinda Kelley, and Ms. Patricia Turner has been invaluable. The dedication of Ms. Susie Nelson, of MasiMax, Inc., has been inspiring. The completion of the report was also greatly facilitated by Ms. Catherine Dold, who served as lead science writer, and by the breakout session reports prepared by Ms. Dold and the other expert science writers (Ms. Christie Aschwanden, Ms. Martha Engstrom, Ms. Vonne Sieve, Ms. Elizabeth Staton, and Dr. Linda White) at the Denver Roundtable Meeting.

Particular thanks are also due to the co-chairs of the Roundtable Meeting breakout sessions, who worked diligently with the SPRG members and participants to plan the breakout sessions and prepare the individual breakout session reports.

Finally, the SPRG recognizes the tremendous efforts of the stroke patient advocacy groups in supporting the NINDS in developing the SPRG process, and their invaluable participation in many aspects of the work.

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About the Stroke Progress Review Group

The National Institute of Neurological Disorders and Stroke (NINDS) is the nation's leading supporter of biomedical research on disorders of the brain and nervous system, and supports basic, clinical, and population-based research to identify and study the causes, biology, prevention, early detection, and treatment of stroke. Through years of dedicated study, researchers supported by the NINDS have amassed a significant knowledge base about stroke, and this knowledge, coupled with new technologies, is providing a wealth of new scientific opportunities. At the same time, increasing research needs and scientific opportunities require that the NINDS determine the best uses for its resources. It is necessary to identify clear scientific priorities, both to provide guidance for the scientific community and to create a benchmark against which progress can be measured.

The Stroke Progress Review Group (SPRG) was convened to identify those priorities. It is modeled after the National Cancer Institute's (NCI) planning process, which was originally established to assist the NCI in assessing the state of knowledge and identifying scientific opportunities and needs within its large, site-specific research programs. The SPRG follows on the success of the Brain Tumor Progress Review Group (BT-PRG), which was jointly established in 2000 by NINDS and NCI in recognition of the importance of brain tumor research to both institutes.

CHARGE TO THE STROKE PROGRESS REVIEW GROUP

The Stroke Progress Review Group was charged with assisting the NINDS in addressing the needs of the institute's stroke research program. SPRG members were asked to take a broad view in identifying and prioritizing unmet scientific needs and opportunities that are critical to the advancement of the research field. The SPRG was specifically charged with the following goals:

1. Identify and prioritize scientific research opportunities and needs, and the scientific resources needed to address them, to advance medical progress.
2. Compare and contrast these priorities with an NINDS-prepared analysis of its stroke research portfolio.
3. Develop a research plan of action that addresses unmet opportunities and needs.
4. Prepare a written report describing the SPRG's findings and recommendations, for deliberation by the National Advisory Neurological Disorders and Stroke Council.

This report is the final product of the SPRG's efforts and deliberations, and it describes the group's findings and recommendations for advancing stroke-related research. The following sections detail the process used in producing this report.

THE STROKE PROGRESS REVIEW GROUP PROCESS

The SPRG members include prominent scientists, clinicians, consumer advocates, and industry representatives from the United States and Canada who together represent the full spectrum of scientific expertise needed to make comprehensive recommendations for the NINDS stroke research agenda. Members were selected for their expertise as well as their ability to take a broad view in identifying and prioritizing the scientific needs and opportunities that are critical to advancing the field of stroke research.

In February 2001, the SPRG leadership finalized an agenda and process for the SPRG Planning Meeting. At the Planning Meeting, held in March 2001, additional members of the stroke community were identified and invited to participate in a later Roundtable Meeting. Topics were identified for Roundtable Meeting breakout sessions, and all participants were assigned to attend particular sessions. The SPRG members were assigned to co-chair the breakout sessions.

The SPRG Roundtable Meeting, held in July 2001, brought together approximately 140 leading members of the stroke research and advocacy communities, representing diverse institutions and scientific disciplines. These experts met in an open forum (both as a large group and in smaller breakout sessions) to formulate the key scientific questions and priorities for the next five to ten years of stroke research. The NINDS provided the Roundtable Meeting participants with extensive information about their research programs for use in their review. The research priorities and resource needs that the Roundtable Meeting participants identified in the course of their deliberations are outlined in this report.

DEVELOPMENT OF THE SPRG REPORT

After the Roundtable Meeting, an intermediate draft of this report was prepared, and multiple iterations were reviewed by the SPRG leadership and SPRG members. Upon completion of the final draft, the report was submitted for deliberation and acceptance by the NINDS Advisory Council. The report will be widely disseminated and integrated into the institute's planning activities. The SPRG will meet with the NINDS director to discuss the institute's response to the report. The Stroke Progress Review Group report is available online at the NINDS web site, www.ninds.nih.gov (search for: Stroke PRG).

Executive Summary

INTRODUCTION

The Stroke Progress Review Group (SPRG) occurs at a critical juncture for the field of stroke research. We have enjoyed wonderful progress during the past “Decade of the Brain.” Highlights have included a number of successful large-scale clinical trials that have enabled physicians to make evidence-based decisions regarding stroke prevention and treatment. Even better, these trials have provided us with effective therapies to reduce the risk of stroke, prevent recurrent stroke, and reduce damage in the first minutes after a stroke has occurred. We have developed sophisticated imaging techniques that enable us to diagnose stroke and its pathogenic mechanisms rapidly and precisely. We have made substantial progress in unraveling the complex cascade of hemodynamic, biochemical, and molecular changes that occur in response to ischemic injury. And we have learned about differences in stroke incidence and outcome in various populations, stimulating current research to understand these epidemiologic trends on genetic, behavioral, and lifestyle levels.

Despite this progress, the challenge to make new strides in stroke research is more urgent than ever. From a public health perspective, stroke is the third leading cause of death in the United States, and a leading cause of long-term disability. With the aging of the population, the absolute number of stroke patients in the U.S. is likely to grow substantially. Stroke is also a significant burden on public health

worldwide. Our understanding of the inherited basis of human disease is increasing dramatically, but the energy and focus of such genetic research has yet to be applied fully to stroke. Despite years of laboratory and clinical research, assessing the risk of stroke for individuals remains imprecise. Moreover, stroke is still difficult for non-specialists to diagnose, it is complicated to treat, and there are few effective therapeutic alternatives. Furthermore, too few medical graduates are choosing careers in laboratory or clinical stroke research to carry out the work that is needed to change this situation.

The purpose of the SPRG was to assemble the leaders in various areas of stroke research, as well as representatives of the stroke community, who could identify the current challenges and opportunities in the field. In the end, our goal was to lay out a broad menu of research priorities that might serve to both stimulate and guide stroke research over the next decade.

STRUCTURE AND PROCESS OF THE STROKE PROGRESS REVIEW GROUP

The SPRG identified 15 key areas of research activity in the field of stroke and brought together experts from the basic and clinical sciences, along with representatives from industry and the advocacy community, to discuss future goals for research in each area.

Because stroke research encompasses multiple and wide-ranging disciplines,

experts from diverse backgrounds were invited to take part in the process; the participants included hematologists, vascular biologists, radiologists, clinical trialists, molecular biologists, geneticists, statisticians, vascular physiologists, adult and pediatric neurologists, neurosurgeons, neuroscientists, anesthesiologists, psychiatrists, behavioral scientists, and neuroepidemiologists. Two co-chairs were identified for each of the 15 research areas and asked to lead breakout discussion sessions. The participating experts were invited to take part in as many as three of the sessions.

In July 2001, all the SPRG participants met in Denver. During that meeting, each breakout session group met to identify their top three priorities for research focus and to highlight existing problems in their respective areas, barriers to this research, scientific goals, and the resources necessary to achieve these goals. The co-chairs then prepared documents summarizing each group's findings, along with their priorities. Those documents are found under Scientific Session Reports: Full Reports of the Stroke Progress Review Group Roundtable Meeting Breakout Sessions.

In reviewing the conclusions of the 15 breakout sessions, the members of the SPRG identified five broad Research and Scientific Priorities, as well as seven Resource Priorities needed to implement such research. These priorities have broad implications -- they apply to adult and pediatric patients, to individuals with ischemic or hemorrhagic stroke, and to underserved patient groups within the population. The sections that follow summarize the highlights of the Denver

Roundtable Meeting and formulate the common themes heard in the sessions into a vision for the future of basic and clinical stroke research.

RESEARCH AND SCIENTIFIC PRIORITIES

The five priorities listed below represent a consensus of scientific goals expressed in many of the 15 breakout sessions. In order to effectively address these priorities and to successfully prevent and treat stroke in the future, each priority must be implemented by strong bidirectional interactions between basic and clinical stroke researchers. All of these priorities are considered equally important in accomplishing the goals of the PRG.

RESEARCH AND SCIENTIFIC PRIORITIES

- **Identify genes, mRNA, and proteins for ischemia, hemorrhage, and prevention**
- **Define blood/blood vessel wall/brain integrated function**
- **Understand blood flow regulation and perfusion optimization**
- **Develop combination therapies based on molecular and cellular pathways of injury**
- **Characterize remodeling and recovery after stroke**

1. Identify and isolate the genes, mRNA, and proteins underlying ischemic and hemorrhagic stroke, in order to provide an improved fundamental biologic understanding of stroke epidemiology, prevention, diagnosis, and treatment.

There was universal agreement that the field of stroke is ripe for the genomic revolution that is now creating new and previously unimagined opportunities for diagnosis and treatment of neurological and other diseases.

Advances in mapping the human genome have recently made it feasible to identify and isolate genes that predispose individuals to ischemia and hemorrhage, to understand ways in which the encoded proteins modulate vascular physiology, and to recognize the cellular mechanisms of injury and death that can be initiated by stroke. For example, by identifying stroke-related genes, we can identify populations at risk with greater precision and develop more specific and effective measures for first and recurrent stroke prevention. Knowledge about the genes and proteins expressed during acute injury can help us to better classify and understand the natural history of human stroke subtypes, and to understand the biological basis for these subtypes. Furthermore, the pattern of genes expressed during stroke can be useful to detect the presence, time of onset, and extent of stroke in the emergency setting, thereby aiding physicians in diagnosing ischemia and hemorrhage more quickly and with greater accuracy. In addition, by knowing the patient's genetic profile, therapies can be individualized and tailored to variations in the genome that dictate the optimal

response to specific drugs. Finally, once we identify and isolate the genes and proteins modulating responses to chronic injury and repair and determine how they work together, we may better understand the biological basis for recovery and rehabilitation and expand the limits of brain function after stroke.

2. Study the interface between the brain's vasculature and cellular, matrix, and hemostatic mechanisms, to achieve a better understanding of the events that lead to brain hemorrhage and infarction.

Extensive studies of neurons and glia have resulted in a detailed but still incomplete understanding of ischemic injury. If we are to understand, prevent, and treat stroke effectively, we need to investigate local hemostasis and its relationship to local tissue factors, microglia, endothelium, and the cells of the blood-brain barrier, including astrocytes. At a fundamental level, there is an important need to better define the molecular influences and cell-signaling mechanisms that characterize the interactions between circulating blood elements and the blood vessel wall, extracellular matrix, glia, and neurons (together, the neurovascular unit) during ischemic and hemorrhagic stroke. These interactions critically define events that initiate ischemia, hemorrhage, brain inflammation, blood-brain barrier dysfunction, and white matter changes after stroke. Progress in the prevention, diagnosis, and treatment of stroke will depend upon a critical understanding of these interactions.

To achieve this goal, the SPRG members recommended greater focus on the process of hemostasis, platelet and

leukocyte function, and particularly, aspects of their interactions that are unique to the brain. This knowledge may be useful to identify potential therapeutic targets even more specific for stroke than for thrombotic events in other organs. The SPRG members also emphasized the importance of studying the extracellular matrix proteins that play a role in the development of hemorrhage, inflammation, and blood-brain barrier dysfunction after stroke. In addition to these proteins, the SPRG members highlighted the need to study glial cells and their role in blood-brain barrier integrity, synaptic and trophic functions, inflammation, and angiogenesis. Glia and matrix proteins are fundamental to white matter structure and function, and the white matter lesions that commonly develop after stroke can cause or contribute to vascular dementia. Finally, a study of the blood-vessel wall/matrix/glial interaction would be incomplete without an emphasis on stroke risk factors such as diabetes, hypertension, atherosclerosis, and obesity, and their impact on interactions within component cellular and acellular elements of the neuro-vascular unit. We do not have a full understanding of how these very common diseases modulate hemostasis and vessel wall structure and function to specifically place the brain at high risk for stroke.

3. Understand blood flow and perfusion optimization.

The fundamental pathophysiology of stroke is caused by an interruption of blood flow. Building on our existing knowledge of cerebral blood flow and metabolism, we should explore emerging imaging technologies that will

enable us to understand the regulation and restoration of blood flow after both ischemic and hemorrhagic stroke.

We need to better understand how to optimally reestablish flow in the macro- and microcirculation. One important approach will involve the amplification of existing acute ischemic stroke therapy by accelerating the testing of devices and new pharmacologic approaches to achieve reperfusion more quickly, more completely, and safely.

Reperfusion brain quickly can improve recovery, but reperfusion can also promote mal-adaptive responses. We need to understand the consequences of reperfusion at the molecular and cellular level so that tissue survival can be optimized in the reperfused brain.

Many clinical questions must be addressed. Among them:

- What are the effects on the endothelium of intra-arterial cannulation, drug infusion, and various ultrasonic and other energy-producing devices?
- What are the cellular and hemostatic events that cause arteries to bleed and to stop bleeding? Can we improve our efforts to prevent or limit bleeding?
- What determines the formation of thromboemboli in the cerebral circulation?
- Taking the lead from recent data in the coronary circulation, can we identify unstable plaques in the cerebral circulation?
- Can these investigations lead to more selective surgical and endovascular prevention, and more effective post-stroke thrombolysis and less

re-occlusion?

- What determines the return of flow in the microcirculation? How can this be augmented?
- Can mechanisms of stroke recovery in the developing brain help to identify novel repair strategies in adults?
- How does microcirculatory reperfusion increase damage?
- Can answering these questions help us design therapies that may augment those that target large vessel occlusion?

4. Develop combination and sequential therapies based on our understanding of known cell death mechanisms in ischemic neurons and glia.

Despite substantial investigation into the biology of ischemic and hemorrhagic injury over the past two decades, there is still no effective therapy that targets the toxic events that develop within cells and tissues as a consequence of stroke. This type of therapy would fulfill an important need since some patients cannot be treated with clot-lysing compounds, and others could benefit from a strategy that combines neuroprotectants with clot lysis and other strategies to reduce tissue injury.

Combination therapy has been successful in treating other diseases, such as hypertension and diabetes, that have been resistant to treatments that target a single cellular or molecular mechanism. Emphasis should be given to research that promotes a more complete understanding of the natural neural pathways that protect the brain and of the blockade of pathways triggered after stroke that cause cell

death alone and in combination.

Therapeutic strategies based on these mechanisms should be developed, particularly after validating them by in vivo or in vitro studies in human or primate tissues or cells. As an important practical issue, drug treatment could be improved greatly if we had a better understanding of the complexity of drug delivery to the ischemic brain and optimized transport of drugs into injured tissue. This information is essential to interpret complex outcomes from clinical trials and to improve the possibility of identifying more effective treatments.

To develop combination therapy with a high probability of efficacy in humans, members of the SPRG emphasized the need to develop and validate large and small animal models that reflect the complexity and diversity of the human brain and its responses during stroke. To facilitate model development and validation, the genome of large animals (e.g., pigs, sheep, and primates) should be sequenced along with the use of mathematical and statistical methods to improve the efficiency of combination drug therapy. Molecular imaging technologies should also be developed to profile gene expression after stroke, to validate stroke in animal models, and to identify therapeutic targets. Ideally, these technologies will inform us about the molecular, cellular, and synaptic events that predict stroke outcome, response to therapy, and recovery of function in humans.

5. Characterize the mechanisms and time course of remodeling and recovery after stroke, at both the systems and cellular levels.

The SPRG members strongly emphasized the need to develop new therapeutic approaches to restore lost motor and cognitive function after stroke. At the moment, very little is known about the mechanisms that govern stroke recovery, and the natural history of recovery in humans and in animal models is incompletely understood. Evidence from brain injury in the clinic, particularly in children, strongly suggests that the brain does exhibit self-repair mechanisms that involve complex coordination between endogenous and exogenous elements, including blood vessels of the brain, neurons, and glial cells. However, the precise molecular and cellular events are not well understood. Nevertheless, it is becoming increasingly clear that brain recovery and remodeling occurs in response to external influences such as drugs and physical rehabilitation. To understand and perhaps amplify this process, we need to characterize the molecular and cellular mechanisms by which behavioral experience and environmental enrichment modulate the recovery process in brain after stroke. In particular, we need to develop rational pharmacological strategies based on these molecular mechanisms and determine the importance of genetic factors as a predictor of stroke outcome. Finally, we need to explore the potential use of stem cell technology as a tool to augment brain recovery in adult and pediatric stroke patients.

RESOURCE PRIORITIES

There is general agreement that the development of new and emerging technologies, as well as the application of existing ones, will be necessary to implement the research and scientific

priorities and goals discussed above.

There is also general agreement that, more specifically, the seven resource priorities listed below, identified in many of the breakout sessions, will be necessary to meet those goals. These resources will help researchers generate and test hypotheses important to understanding all basic and clinical aspects of stroke, and to advance the prevention, diagnosis, prognosis, treatment, and rehabilitation of stroke patients. All of these priorities were considered equally important in accomplishing the overall goals of the PRG.

RESOURCE PRIORITIES

- **Platform technologies**
- **Translational models**
- **Imaging technologies**
- **Clinical trial technologies**
- **Stroke centers network**
- **National databases**
- **Education and training**

1. Develop and apply emerging array technologies that have an impact on stroke.

Breakthroughs in science and technology have altered immeasurably the practice of neurology and have improved our understanding of basic disease mechanisms. Gene microarrays, in particular, are a recent breakthrough developed from advances in miniaturization, microfabrication, and

high-density chip technologies that provide state-of-the-art platforms for genomics, proteomics, and pharmacogenetics. Microsystems such as these may become useful to generate data reflecting changes in enzyme activity, protein-protein interactions, and receptor-ligand binding plus gene expression. In addition, chip technologies may one day provide an individualized molecular portrait of stroke and its recovery course as well as a blueprint for therapy. Nominating and then testing candidate genes or mechanisms of interest individually will no longer be required, as thousands of different gene candidates can be assessed simultaneously within a single drop of fluid. Used in conjunction with molecular imaging techniques, markers in blood or other body fluids may then be used to profile stroke as it evolves. By applying these techniques, we may learn how molecules compromise cells, as well as parse their individual contributions to stroke pathogenesis.

Whereas gene chips and arrays use micron-based technologies, nanotechnologies focus on even more miniaturized systems and the manipulation, assembly, and targeted delivery of molecules into nanoparticles for applications such as biosensing, drug delivery, and cell repair. At such dimensions, nanoparticles may be particularly useful because the blood-brain barrier becomes less of an obstacle to drug delivery during stroke.

High-throughput initiatives, albeit exciting, are expensive and require centralized resources and high-throughput data analysis (bio-informatics). The sheer weight of the information generated, which is

often non-intuitive and cryptic, can be daunting, and will require advanced data processing capabilities. The SPRG embraces the notion that emerging micro- and nanotechnologies will make it possible to investigate stroke in ways not previously possible.

2. Develop and validate large and small animal models that reflect the complexity and diversity of the human brain and its responses during stroke.

One theme raised in many breakout sessions was the need to reconcile clinical and laboratory disciplines in all areas of stroke research. This includes better models of stroke disease, especially in primates.

Improved animal models are needed to accomplish all five of the SPRG research and scientific priorities; their availability would help to advance drug development as well as our understanding of basic stroke biology. In this task, special emphasis needs to be given to species differences in hemostasis, inflammation, white matter content, and brain size, as well as vascular considerations such as anatomical distribution and regulation. Model validation is deemed essential and will require, at a minimum, the use of microarray and imaging tools and the development of physiologically based behavioral and pharmacological assays that accurately reflect the human condition in both short- and long-term studies.

Potential applications include:

- Use of these models with high-throughput screening strategies (see above) to identify pre- and

post-stroke peripheral markers that are predictive of stroke risk, impending stroke, recovery, and outcome.

- Use of these models and molecular imaging tools to inform us about tissue and cellular responses, within both brain and cerebral blood vessels, that render tissue vulnerable to blood flow compromise. In addition, these models should be used to define the molecular correlates of the therapeutic window during reperfusion.
- Use of animal models to facilitate laboratory and imaging studies of macro- and microcirculatory pathology, hemostasis, and reperfusion in a cerebrovascular bed more closely simulating human stroke.
- Use of animal models to enable investigators to better evaluate the pharmacodynamics of therapies targeting the pathophysiological cascades in neurons and glia after ischemia and hemorrhage.
- Use of animal models for preclinical screening of leading drug candidates and for evaluating pharmacokinetics of the different agents used in combination therapy.
- Use of genetic engineering tools in animal models to examine the impact of specific genes on cerebral vessels and their interaction with tissue matrix, white matter, glial cells, and neurons in small and large animals (e.g., primates).
- Use of models to better understand hemostasis and platelet function and their perturbations before, during, and after stroke treatment with antithrombotic drugs.
- Use of animal models for developing and testing biomedical engineering

devices that augment reperfusion or novel delivery systems of therapeutic drugs.

Models can also be useful in the context of developing a more comprehensive understanding of stroke recovery and developing treatments that enhance stroke rehabilitation and maximize the potential for restoration of function. Accordingly, these models can be used to:

- Study the genomic and proteomic correlates of brain plasticity during recovery of function after stroke.
- Allow behavioral and functional imaging studies of the brain during recovery and determine how they are affected by environmental, biological, and pharmacological interventions.

Because animal models for stroke are technically difficult to develop and often require special facilities for surgery, imaging, and housing (e.g., primates), we need to encourage collaborations between groups dedicated to perfecting these models and laboratories applying these models to complementary research interests. Development of models of both brain ischemia and hemorrhage remains a high priority.

3. Expand brain imaging capabilities.

Brain imaging already has revolutionized the diagnosis and management of stroke. We need to develop new imaging techniques. We also need to better understand the existing modalities, to improve our understanding of stroke pathophysiology and recovery, and to provide a translational link between experimental

advances and clinical applications.

Imaging techniques could be used to:

- Identify neuroimaging markers of “tissue at risk” in order to better link therapy to tissue pathobiology.
- Understand the effects of reperfusing the brain on the underlying vascular pathology, cerebral blood flow, and blood-brain barrier integrity.
- Improve clinical trial design in both patient selection and in assessing drug activity within the brain.
- Improve continuous non-invasive monitoring of patients at the bedside, to better evaluate the evolution of injury, evaluate treatment, and assess risks.
- Inform about the status of the blood-brain barrier.
- Optimize drug delivery by establishing parameters for dose, duration, and time window.
- Provide predictive information about outcomes in both acute and chronic stroke.
- Allow improved mapping of brain plasticity and reorganization.

In addition to the above, there are important unmet needs that require further technology development and validation. The needed technologies include:

- Imaging methods that directly reflect electrophysiological and synaptic activity, rather than blood flow. Such techniques can be used to assess neuronal networks and other neural substrates responsible for good recovery following stroke.
- Cellular- and molecular-based imaging techniques. These can provide new opportunities to

characterize and classify stroke in ways not previously possible (e.g., the choice of acute treatments targeted to specific cellular and molecular events during stroke).

Thus, the SPRG places a high priority on developing and validating new imaging markers and techniques to facilitate the spatio-temporal assessment of stroke at both the tissue and the molecular level.

4. Improve clinical trial technology.

Clinical trials are necessary to define how to best apply basic research advances to the treatment of patients. Building on the conspicuous successes of NINDS-sponsored clinical trials in stroke prevention and treatment during the past decade, new, better designed clinical trials will use innovative approaches to get needed answers efficiently and expeditiously.

Clinical trials in stroke are time consuming and expensive. These constraints may serve to discourage innovative or start-up strategies as well as drain the good will and resources of funding agencies, investigators, clinical resources, and patients.

We need to develop more streamlined clinical trials of prevention strategies and acute stroke therapy by improving trial design, developing and testing new outcome measures, and forming clinical trial consortia/networks. Depending on the questions asked and the population studied, both large simple trials and smaller focused trials with surrogate endpoints should be explored. Proper guidelines for such studies should be developed. We need to develop outcome measures with more relevance to the

patient as well as measures that might be more sensitive to therapeutic effect than those currently used. Treatment trials in certain clinical areas have been relatively ignored and need more attention; these include intracerebral hemorrhage, pediatric stroke, and rehabilitation.

There also needs to be greater collaboration between industry and academia in designing, prioritizing, and funding clinical trials. Networks of collaborating centers and individuals interested in conducting clinical trials should be established to help prioritize resources and expedite trial execution. The establishment of specialized centers pioneering translational research in acute stroke will expand treatment options for acute stroke when prevention fails. Finally, we need to develop better methods for encouraging more physicians, patients, and advocacy organizations to participate in clinical trials. Clinical trials are the front lines in the fight against stroke and will define the next generation of treatments used in clinics throughout the world.

5. Develop stroke center networks.

The SPRG recognizes that existing and future preventive and acute interventional therapies need to be more widely and rapidly adopted by health care workers and patients. This could be accomplished by a better understanding of the existing barriers to health services implementation pertaining to stroke, including the lack of incentives, information, and essential personnel and technologies. We need more accurate and universal information regarding existing practice patterns and we need to understand the administrative

barriers to obtaining medical resources and care.

To promote better implementation we need to develop and test interventions aimed at improving community practice, and partner with payors and other groups in stimulating good practice. We need greater regional collaboration to develop multidisciplinary teams (i.e., stroke center networks) that can better overcome the local barriers that exist to implementing stroke prevention and therapy, including health disparities.

6. Improve databases for stroke.

A national stroke surveillance system would establish a database of stroke that would help characterize the public health burden of stroke and identify those populations that need special emphasis. An effective database would include substantial socioeconomic and ethnicity detail that is often unavailable when doing epidemiologic analyses. A database would also facilitate the study of the many stroke-related conditions that occur too sporadically for randomized comparison studies.

Such a database will also facilitate the application of targeted genetic analyses. The complex variability of the stroke phenotype requires such a database in order to carry out research on stroke genetics. Genetic databases are also needed. These would be particularly important in sharing and sifting through the exploding information in this area. A centralized genomic/proteomic/bioinformatic facility would support the establishment of such a database.

Stroke information that is widely available to clinicians in an electronic

format would help to foster the development of collaborative consortia and standardized methodology for conducting research and for patient management, and might help increase implementation of therapies.

7. Expand education and training.

It is clear that prevention, diagnosis, and treatment of stroke is a public health problem that is too large to be managed only by stroke specialists. Yet training of other medical personnel in modern stroke management is currently inadequate. Non-neurologists and neurologists alike need more exposure to the advances made in the field of stroke. Even more important, the next generation of medical personnel should receive an educational curriculum, starting early in professional school, that ensures they will be more knowledgeable about stroke.

We also need to improve the training of neurologists in the emerging disciplines that will be critical for researching and applying new stroke therapies, including genomics, endovascular therapy, imaging, and rehabilitation. Existing barriers to such cross-training should be identified and eliminated.

As we focus our research on the interface between circulation and the brain, the lack of neuropathological information about and expertise needed to effectively study stroke is recognized as a major deficiency.

CONCLUSION

Stroke is the third leading cause of death and a major disabler of the American people. Although many challenges lie ahead, we are currently experiencing an extraordinary and unprecedented time of scientific growth and technological breakthroughs. Our greatest advances in stroke research have been made in the prevention of stroke through surgical and drug therapies. Early stroke treatment with t-PA (tissue plasminogen activator) has reinforced the belief that stroke is a treatable disease. However, now we are in great need of new treatments that reduce damage and promote recovery once a stroke has occurred. To attain these reachable goals, we will require new initiatives and new applications of technologies that can advance the field of stroke in the laboratory and at the bedside.

The research and scientific priorities and resource priorities identified by the SPRG provide an outline for academia, industry, government, and patient advocates to guide progress in stroke research. Commitment and joint sponsorship among these vested communities to address these priorities will facilitate the development of creative solutions to prevent, diagnose, and treat stroke in the current decade and beyond.

Cerebrovascular Biology

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STATEMENT OF THE PROBLEM

Research on basic vascular biology has now provided us with the underpinnings needed to understand vascular diseases in specific organs. This critical information includes an understanding of how vessels develop, as well as the molecular and functional differences between the endothelial and smooth muscle cells making up arteries, veins, and capillaries.

It is likely that extension of this basic biology to the neurovasculature will lead to fundamental new directions in cerebral vascular biology (as it already has in the biology and pathology of other organ systems). Major advances in the understanding of causes and treatment of stroke (especially cerebral hemorrhage) are likely to be delayed until this improved understanding of neurovascular biology is achieved. As a precedent, lessons learned from vascular biology were critical for recent advances in treatment of myocardial infarction.

Obvious areas of interest include characterization of physiological responses to acute stimuli and to major risk factors, especially hypertension and diabetes, as well as inflammatory diseases involving the nervous system. The availability of comprehensive human and mouse genetic data, as well as newly developed technologies

including arrays, genetically altered mice, and proteomics, should move the field of cerebrovascular biology very rapidly.

CHALLENGES AND QUESTIONS

The neurovasculature has many properties that are not found in other organ systems. These properties likely account for a great deal of neurovascular pathology, including not only obvious targets such as neurovascular spasm and stroke, but also less obvious targets as diverse as brain metastases, developmental anomalies, and inflammatory diseases.

We already know that brain endothelium is distinctive, as manifested by the blood-brain barrier, for example. The role of smooth muscle cells in the distinctive characteristics of cerebral vessels is not well understood, and the likely role of smooth muscle in determining the unique phenotype of cerebral endothelium has not been explored. Adventitia, which has emerged as an important tissue in regulation of blood vessels, is less prominent in cerebral vessels than in extracranial vessels. The functional implications of this structural difference are not clear.

A number of opportunities for study already exist based on current knowledge of vascular biology. For

example, although we have some knowledge of the effects of risk factors on cerebral blood vessels, other important risk factors (including atherosclerosis, diabetes, smoking, and aging) have received little attention. Newly recognized risk factors, including hyperhomocystinemia and chronic inflammation, may be fertile areas for study.

Although inflammation and infection may play an important role in cerebral vascular disease, new classes of anti-inflammatories directed at vascular adhesion molecules, chemotactic factors, and the death receptor family have received little attention in the neurovascular system.

The role of oxidative and antioxidant mechanisms in cerebral vessels is an especially promising area of research. Recent studies suggest that oxidant injury may be an underlying mechanism in vascular injury in response to a variety of stimuli.

BARRIERS

- It is likely that the relatively small size of intracranial vessels and the difficulty of anatomical access to them have led most vascular biologists to focus on the aorta and peripheral blood vessels, rather than the cerebrovasculature.
- Basic research of neurologists, neurobiologists, and neurosurgeons usually focuses primarily on neurons and glia rather than blood vessels. Consequently, research in cerebral vascular biology lags behind that in other organs, and representation on grant review committees in NINDS is limited.

- There may be some reluctance to apply basic approaches of vascular biology to neurovascular vessels, to avoid simple replication of findings. Yet there are many fundamental differences from extracranial vessels that make studies of intracranial vessels of great interest.

RESEARCH AND SCIENTIFIC PRIORITIES

Current and future research should focus on building the basic knowledge of vascular biology needed to proceed with more broadly based efforts with a disease focus. The obvious challenge is to leverage current knowledge of vascular biology with the opportunities offered by new methods to accelerate research. Applications of arrays, genetically altered mice, and proteomics, combined with our existing, finite knowledge of the entire set of transcribed genes, should greatly accelerate research in this area.

- One approach to expanding our knowledge is from vascular development. Today, at a systemic level and in certain specific tissues, we know a great deal about growth factors and receptors involved in the primary differentiation of endothelium, the role of endothelium in recruiting smooth muscle, and the role of smooth muscle in determining endothelial behavior. Developmental biology of cerebral vasculature, however, has received little attention.
- We know enough about fruitful approaches from the peripheral vasculature to suggest areas of focus in the brain and vasculature. For example, it is very likely that

specific vasculatures have very specific sets of genes that control cell function. These sets of genes might be called “molecular phenotypes,” and are obvious targets for analysis by new methods of transcription and proteomic systematic analysis. It would be of great value to know the extent of endothelial and smooth muscle phenotypic specificity in different cerebrovascular beds, as well as the modulation of these phenotypes in the face of risk factors known to affect cerebrovascular disease.

- Another useful tool comes from murine genetics. Genetically altered mice have altered functions in areas ranging from the formation of the layers of the vessel wall to inflammation and angiogenesis. These mice can be used to address critical questions in neurovascular biology by combining the mouse models with advanced physiological methods for determining murine neurovascular function. Processes of specific interest may include the relative roles of growth and proliferation versus cell death as determinants of vascular responses to several stimuli.

Priority 1:

Understand developmental and basic aspects of cerebral vascular biology.

The basic discoveries of developmental vascular biology have identified mechanisms underlying not only the formation of blood vessels, but also the mechanisms of vascular response to injury in general. Brain-specific vascular biology is needed to identify the precise mechanisms underlying neurovascular

disease. Specific questions to address include:

- Embryonic origins and development of neurovascular endothelium and smooth muscle.
- Phenotypic differences between the endothelium, smooth muscle cells, and adventitia of the neurovasculature, as compared to other vasculatures, using arrays and other contemporary systematic analysis.
- Development of suitable in vitro and transgenic models to understand the interactions of endothelium and smooth muscle with glia and neurons.
- The unique properties of the cerebrovascular endothelium, including the BBB, transport properties, cell trafficking, and metabolism, applying findings from the genome project and the systematic tools of molecular biology.

Priority 2:

Understand mechanisms of response to injury.

Reactive oxygen species are products of metabolism in ischemia, and are produced by specific enzymes. Oxidative mechanisms may regulate vasomotor responses of cerebral vessels to ischemia, the inflammation accompanying brain ischemia, remodeling associated with cerebral vasospasm, and chronic effects of risk factors on cerebral vascular structure and function. Specific areas to be explored include:

- Genetic regulation of responses to injury.

- Regulation of cerebral vascular growth and apoptosis by oxidant or other mechanisms.
- Adherence and expression of adhesion molecules.
- How mechanisms associated with risk factors affect cerebral blood vessels.
- Clotting and anticoagulant mechanisms in neurovascular vs. peripheral blood vessels.
- Angiogenesis, in relation to injury and to age (with implications for germinal matrix hemorrhage).
- Inflammatory responses and mechanisms.
- The molecular changes in the vasculature underlying hemorrhage in premature infants, neonates, and adults.

Priority 3:

The application of developmental and basic aspects of cerebral vascular biology and mechanisms of response to injury can provide a deeper understanding of vascular pathophysiology of great importance to stroke. The approaches outlined above can address the consequent effects of recognized risk factors for stroke and may help to elucidate new stroke risk factors. Research priorities include:

- Animal models.
 - * Development and/or refinement of animal models that reflect pathophysiologies of cerebrovascular risk factors such as atherosclerosis, diabetes mellitus, hypertension, and intracerebral hemorrhage.
 - * Development of models that accurately reflect and allow us to understand germinal matrix hemorrhage, berry aneurysm,

and perinatal stroke.

- Cerebrovascular neuropathy.
 - * Application of advanced molecular biological approaches.
 - * Integration of molecular and functional studies with neuroimaging techniques.
 - * Studies to distinguish large-vessel pathophysiology from microvascular pathophysiology.
 - * Determinants of cerebral vascular aging.
 - * Identification of preclinical markers.

RESOURCES NEEDED

A large number of resources now exist that may enhance the study of the neurovasculature, but they have not been fully evaluated. Resources that should be evaluated include:

- Genetically modified mouse models targeted to specific problems of vascular biology, including selected expression systems and genes known to be critical to the formation and pathology of blood vessels. For example, there are numerous murine models of atherosclerosis, but the neurovascular physiology and pathophysiology of these animals has not been evaluated.
- A stroke-prone mouse.
- Animal genetics, including congenic animals generated to target heritable diseases of the vasculature, such as hypertension, atherosclerosis, and diabetes.
- Genetically and phenotypically defined human populations at risk for vascular diseases, including stroke.
- Newly developed resources such as single nucleotide polymorphism

(SNP) maps, expression profiling, and proteomic analysis, which should greatly accelerate the usefulness of such populations.

Training and research needs include:

- The training of individuals in neurovascular pathology and cerebral vascular biology.
- The development of interdisciplinary programs promoting interactions among neurologists, interventional radiologists, pathologists, neurosurgeons, and vascular biologists.
- Forums of intellectual interchange, such as workshops among individuals who share common interests. These could be co-sponsored by organizations such as the North American Vascular Biology Organization, the American Heart Association, the American Physiological Society, and NINDS.
- Increasing the number of investigators with expertise in general vascular biology and cerebrovascular biology on relevant grant review committees.

Neuro/Cerebrovascular Degeneration

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STATEMENT OF THE PROBLEM

The cause of neuronal death in stroke is deceptively simple. When blood flow to any part of the brain is stopped for only a minute, neuronal function is impaired. A complex cascade of events is set in motion that irreversibly damages the brain over the next few hours. When blood flow can be restored within three hours of the onset of stroke, a substantial fraction of brain function can be rescued. However, much of the injury is irreversible after six hours. Any combination of therapeutic approaches that could somehow expand this narrow window would have significant health benefits.

Over the past few decades, remarkable progress has been made in unraveling the mechanisms that cause neurons and glial cells to die after stroke. By the early 1980s, a variety of clever methods had been developed to induce focal strokes in small-animal models, which enabled large numbers of therapeutic and transgenic approaches to be tested rapidly and inexpensively. Hundreds of studies have demonstrated that cooling the brain, blocking the actions of excitatory neurotransmitters and inhibiting free radicals, nitric oxide, proteases, and caspases, can reduce infarction by as much as 70 percent in these animals. This rich literature has demonstrated that the complex cascade

leading to permanent brain injury can be stopped at many points if initiated in the proper time window.

The problem remains that no individual approach, with the exception of thrombolytic agents given within three hours, has translated into a clinically useful treatment for stroke. We need to understand why animal stroke models fail to predict clinical trial results. We need to better characterize the complex interactions between different components in the cascade initiated by ischemia in animal models, and we need to understand how they relate to human disease. Recent progress in other degenerative diseases, as well as advances in genomics and proteomics, can be better applied to provide insight into cellular mechanisms of injury and death activated in stroke.

CHALLENGES AND QUESTIONS

The brain is more susceptible to ischemic injury than is any other organ. Failure of energy production causes a flood of neurotransmitters to be released from neurons, which further amplifies the damage. A major contributor in this regard is the release of the excitatory amino acid glutamate, which activates several different types of channels to allow toxic concentrations of calcium and zinc to enter neurons. A large research effort has involved the

development of antagonists of these glutamate channels, but clinical trials in acute stroke have been disappointing. The toxic effects of glutamate may occur too rapidly to be prevented in treating stroke patients. However, prophylaxis may be possible, and protection from brain ischemia resulting from surgery can potentially aid 400,000 Americans a year.

In the past decade, significant progress has been made in understanding the intracellular signaling cascades involved in the cell death process. Many genes have been identified that are involved in Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis, and other forms of neurodegeneration, and the functional consequences of these mutations are gradually becoming known. A variety of approaches may help rescue these damaged neurons, to restore their function. Understanding these molecular mechanisms is helping to broaden our understanding of neuronal injury and death in stroke.

When stroke occurs, many neurons die by a process called apoptosis, where a series of "suicide" enzymes become activated and internally digest neurons. Drawing from progress in cancer and other fields, many strategies have been developed to block apoptotic death and these same treatments have been shown to protect the ischemic brain. This type of cell death takes time and so might be successfully treated hours after a stroke has occurred.

Mitochondria, small organelles in cells that produce energy in the form of adenosine triphosphate, have a central role in initiating the apoptotic cascade. Additionally, for many years,

mitochondria have been viewed as no more than small engines that stall in response to a lack of oxygen and fuel during ischemia, but are ready to restart immediately if blood flow is restored. However, prolonged ischemia can cause mitochondrial damage, which leads to further injury. A variety of metabolic interventions may help preserve mitochondrial function and improve stroke outcome.

Many cells in the damaged brain die by less well-understood necrotic mechanisms. For example, at the edge of an ischemic region there is marginally perfused tissue that can potentially be salvaged; this tissue is known as the ischemic penumbra. Furthermore, it is not known which factors determine whether a brain region suffers a diffuse loss of neurons or frank infarction. Still, even in forms of cell death that are less well understood, certain pathways can be pharmacologically inhibited. For example, DNA repair by PARS may be such a mechanism that can be potentially reversible with appropriate therapy.

In the days following a stroke, damaged regions of brain undergo a broad-scale necrosis, which causes the death of all types of cells, including astrocytes, Schwann cells, oligodendrocytes, supporting microvessels, and neurons. Identifying the interactions between the different cell types in brain that lead to the development of this necrosis is a crucial need. For example, the responses of supporting cells, like astrocytes and microglia, in the brain during a stroke are critical determinants of injury and an area that needs further investigation. Microglia are important for defending the brain from infection, and activation of these cells can produce a wide range

of proinflammatory and toxic molecules that will further damage the brain. Advances in understanding neuroinflammation from diseases like multiple sclerosis and infections may be useful in understanding reactions of the brain to ischemia. Additionally, swelling of the brain, or edema, is a major complication of stroke that occurs days after the initial injury. The basis for swelling in the brain parenchyma needs to be better understood.

In some instances, the brain tissue does not die shortly after the onset of ischemia. Brief periods of ischemia can produce long-lasting changes in the brain that substantially increase its resistance to subsequent longer ischemic challenges. This suggests that the brain initially responds to stroke by inducing protective mechanisms, which can be overwhelmed with sustained ischemia. Some changes, such as acidification of the brain, were first viewed as exclusively damaging, but later found to also be protective. For example, it is possible that acidification can protect neurons by diminishing the activation of glutamate channels to prevent subsequent damage.

There is also growing recognition that mechanisms that protect the brain from some types of insults can have negative consequences in other circumstances. Pathways that are protective early in stroke may amplify injury as the stroke evolves.

A crucial next step is to examine how different brain components interact during a stroke to produce injury. How does the cell death cascade initiated by stroke evolve over time and how do the various biochemical steps interact?

If one part of the cascade is prevented, what factors decide whether the remaining tissue will die? It will be necessary to revisit many previous results using recent technological advances, to take into account the multiple actions contributing to brain injury.

BARRIERS

- Reviewers of grant applications often expect a narrow focus on one particular aspect of the ischemic cascade, which discourages the investigation of interactions. If several treatments are given simultaneously, such as thrombolysis plus neuroprotection (which will soon become a standard clinical practice), one may not be able to address simple “data-driven hypotheses.” Study sections, consisting predominantly of basic scientists, often view complex investigations as being difficult to interpret mechanistically and frequently do not assign them fundable priorities.
- Pharmaceutical companies resist testing their products in combination with treatments from other sources. Enforcement of proprietary rights has blocked many studies. It can be nearly impossible to get permission from one drug company to test their compounds in the same animal with a compound from a second company.
- Clinical study designs may need to be modified based upon preclinical data. The need for early treatment of patients has contributed to the failure of many recent trials.
- Large animal models are very expensive and their use is becoming a lost art.

- The development of animal models is a full-time and technically challenging pursuit in itself. It is nearly impossible for an investigator new to the stroke field with a novel approach derived from some other area of research to investigate a hypothesis in an animal stroke model.
- A primary goal of testing for pharmacological protection in animal models is to suggest possible therapeutics in stroke patients. So far, these models have failed to predict clinical efficacy and safety in most instances. Preclinical trial designs still rely on inefficient, brute-force methods.
- Endpoints that can be used to predict clinical efficacy need to be defined.
- Preclinical protocols have not been designed well enough to simulate a feasible clinical protocol. In some cases, the animal models have not been sufficiently relevant to the clinical condition.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Improve animal models and endpoints to more closely reproduce the complexity and diversity of human disease.

- Many clinical studies have failed and the reasons for these failures need to be reinvestigated in animal models. We need to understand our past mistakes before we can learn from them.
- Human studies should be performed in collaboration with animal studies to help in the translation of research findings.
- New tools to describe the pathology of human stroke should be used to guide the evaluation of animal models. The effects of risk factors identified in human stroke and cardiovascular disease should be modeled in animal studies.
- Improved animal models are needed that reproduce the multiple aspects of human disease. These would include preclinical studies in both older and very young animals.
- Quantifiable biomarkers that link therapeutic efficacy to disease mechanisms or progression should be developed. These biomarkers should facilitate comparisons of healthy tissue to ischemic tissue from the same animal.
- Embolic, thrombotic, hemorrhagic, and global ischemia models of stroke in several species should be developed. Models that use clots to produce occlusion should be further developed to clarify questions regarding the type of clot and its complex interactions with the vessel wall and the parenchyma.
- Better methods for hypothesis testing in transgenic knockout and overexpression mouse stroke models should be developed. This includes standardization of outcome measures and long-term survival.
- New methods of drug delivery are needed in experimental animal models. Intravenous therapy often fails to deliver putative neuroprotective drugs to ischemic brain.
- Models of white-matter injury and other types of stroke should be more thoroughly investigated.
- Outcome measures, including surrogate markers, behavioral

endpoints, and global functional recovery indexes should be developed.

Priority 2:

Better define the interactions between components of the ischemic cascade in multiple animal species and in relation to human cerebral dysfunction and recovery.

An enormous effort has focused on investigating individual mechanisms that lead to infarction. These studies are appropriately funded as hypothesis-driven projects. However, there is a great need to understand how these different processes interact. For example, energy failure induces the necrotic death of neurons. If necrotic death is prevented, will the same neurons die a short time later of apoptosis?

Areas that should be investigated include:

- The network of positive and negative interactions and their relationship to one another after injury (rather than individual mechanisms).
- New methods to identify novel markers of irreversible injury in ischemic brain versus recovering brain tissue, including computerized histology, gene arrays, proteomic approaches, and phage display of antibodies.
- Glial interactions with neurons, which differ widely between animals and may be an important source of the variability between animal models and humans.
- The potential of rehabilitation, enriched environments, and long-

term recovery.

- Natural neuroprotective pathways that could be reinforced to further protect the brain.
- The heterogeneity of different cell types and brain regions, using genomic and proteomic approaches.
- The entire range of ischemic injury.
- The role of metabolic homeostasis, given the recent appreciation of the central role of mitochondria in many forms of necrotic and apoptotic types of cell degeneration.
- Standards for comparing experimental endpoints from a variety of animal models, rather than relying on one standard.

Priority 3:

Develop methods to investigate how simultaneously altering several components of ischemic injury modulates the evolution and final outcome of stroke.

Combination therapies will almost certainly be used to treat stroke patients, but few combinations have been adequately tested in preclinical models. Thrombolysis is currently the only approved method for treatment of acute stroke. All patients who meet the treatment criteria receive this therapy, but it is ineffective in the majority of these patients. For the large majority of patients who do not meet the rather stringent guidelines for thrombolytic therapy, this intervention can be ineffective and even harmful. Combinations of thrombolytics plus neuroprotectives or various classes of neuroprotectives may be synergistic.

- Studies of the safety and efficacy of thrombolytics combined with

neuroprotective and hemostasis-altering agents should be encouraged because they will simulate near-term clinical investigations.

- Studies of combinations of various classes of neuroprotective drugs should be conducted. Attempts to achieve mechanistic understanding in these studies are desirable but not an immediate priority.
- Better preclinical trial designs and methods of data analysis and interpretation need to be developed.

RESOURCES NEEDED

Priority 1:

- Development of new animal models that can be used to conduct preclinical pharmacology studies.
- Continued support for the study of stroke in large animal models (pigs, sheep, rabbits, primates). Their brains more closely approximate human brain anatomy than do smaller species.
- Gene sequences for large animal species. A limitation of large-animal research is that their genomes have not yet been sequenced and there are few species-validated reagents. However, these models are of immense value to other NIH institutes and agricultural agencies and it would be worth seeking to have several of these organisms sequenced soon and to validate other research reagents in these species.
- Human brain banks for acute stroke tissue, so researchers can obtain primary cells, including astrocytes and microglia, and use them to parse data from complex proteomic and gene array approaches.

Priority 2:

- Funding for resources for core facilities and capital equipment, to enable better analysis of the heterogeneity of brain injury and to enable evaluation of multiple endpoints of brain injury.
- Advanced imaging and immunohistochemical methods, for evaluating the heterogeneity of brain injury. Better statistical models are needed to evaluate this information
- Advanced methods for analysis of single cells from ischemic animal and human brain.
- Correlative studies between rodents, large-animal models, and human diseases.
- An administrative mechanism to encourage collaboration among investigators to maximize the value of expensive and well-controlled animal models and expensive methodologies.

Priority 3:

Funding is needed to support preclinical investigations. Resources should also be devoted to developing mathematical models and statistical methods that can improve the efficiency of combination studies. Other resources needed are:

- New models of stroke in which delayed thrombolytic therapy can no longer rescue the brain, as a way to evaluate neuroprotective therapies.
- New analytical methodologies to evaluate the pharmacokinetics of the different agents used in combination therapy, and to develop biomarkers to facilitate clinical studies of these combination therapies.

Healing Process of Stroke

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STATEMENT OF THE PROBLEM

It is known that limited functional recovery can occur during the weeks and months after stroke. The current challenge to the scientific and clinical community is to develop new therapeutic approaches to restore lost function.

Over the past decade, potential mechanisms that underlie recovery of motor and cognitive function after stroke have begun to emerge. In addition to the resolution of acute pathophysiologic events associated with ischemia, several long-lasting processes have been identified that may play a role in recovery. Animal models recently have provided detailed information regarding neuroanatomical and neurophysiological plasticity in the undamaged cortical tissue during recovery. However, the degree to which each of the long-term alterations in neural, glial, and vascular systems contribute to behavioral recovery is still not known. Also, while modern neuroimaging techniques have advanced our understanding of the long-term changes in brain function after stroke, these techniques have yet to address changes at the cellular and molecular level during the recovery process.

These new insights into the mechanisms underlying brain remodeling and the role

of motor experience after stroke in modulating those mechanisms have already resulted in promising novel therapeutic approaches in chronic stroke. Once these processes are better understood, it should be possible to identify patients who could benefit from a particular intervention, and to devise therapeutic interventions to maximize functional recovery. The goal of restorative neurology and neuro-rehabilitation over the next decade should be to design successful clinical trials based on the underlying mechanisms of recovery. Such information is potentially of critical value in defining molecular targets for restorative therapies.

CHALLENGES AND QUESTIONS

Mechanisms

Self-Repair Mechanisms

“Self-repair” mechanisms are constitutively triggered during the acute and subacute phases following stroke. The cellular basis of some of this plasticity is programmed into neural networks and progenitor/stem cells. What are the signals that trigger this response? What are the signals that terminate this response once the acute/subacute phase has passed? Can the expression of repair signals be prolonged such that the window

for repair is left open longer? Can the window be re-opened in the chronic phase? What other signals might trigger or enhance repair, such as cytokines, chemokines, transcription factors, or signaling molecules?

The roles of neurogenesis, angiogenesis, and other proliferative responses (e.g., glial proliferation) in the recovery process following ischemia are still unclear. The molecular mechanisms that lead to these processes, as well as the role played by the new cells in behavioral recovery, need to be uncovered. The precursor cells that proliferate following ischemic injury need to be characterized and the molecules that control their growth and differentiation delineated. Is there a coupling between angiogenesis and neurogenesis? Further insight into the role of these processes in recovery will likely lead to novel targets for therapy.

Endogenous and Exogenous Factors

While it may be possible to enhance the effects of endogenous substances (growth factors, neurotransmitters, receptors, and others) as therapeutic approaches, there is still a need to identify which substances improve recovery and which impede recovery in experimental models. In addition, we need to characterize the effects of endogenous inflammatory cells (i.e., within to the central nervous system) and exogenous inflammatory cells on the recovery following stroke and how the role of each can be manipulated. Though the inflammatory response to ischemia has been studied, many issues related to the role of nonneuronal elements (microglia, macrophages, leukocytes, lymphocytes, etc.) after ischemia are still unresolved.

Increasingly, restorative approaches utilizing exogenous substances (e.g., growth factors, other small molecules, d-amphetamine) are being investigated. However, the mechanisms of action of these substances are only partially understood. In addition, behavioral experience after stroke (physiotherapy, environmental enrichment, etc.) is now known to play a substantial role in recovery. Again, the underlying mechanisms are still unclear. Finally, increasing evidence points to an interaction of behavioral experience and pharmacotherapy. What are the mechanisms by which experience can modulate the effects of drugs such as amphetamine?

Pre-Existing Factors Related to Recovery

Cellular, molecular, and network changes during recovery should be characterized as functions of degree and location of injury, degree of recovery, age, gender, race, stress, and environmental enrichment. The molecular processes that underlie such interactions consider other disciplines also exploring those issues.

Developmental Models

It is known that the plasticity of the newborn and neonatal brain is much greater than the adult brain. What is the molecular basis for limitations for recovery in adults? Understanding the factors that support plasticity in the developing brain may lead to the potential to activate or augment this process for therapeutic purposes. Is the process of development literally recapitulated at the molecular level, much as early 20th Century neurologists believed that recovery of the organism's

behavior mimicked the development and loss of reflexive behavior? In other words, what lessons can developmental biology lend to recovery?

Network Processes

The likelihood that focal lesions of brain produced by focal ischemia, or isolated loss of neurons following global ischemia, lead to network disturbances and compensatory changes in excitatory and inhibitory connections needs to be explored at the molecular, cellular, electrophysiological, systems, and behavioral levels. Though individual cells are often studied in isolation, the changes in networks have only recently been approached. The roles of dividing cells, synaptic pruning and synaptogenesis, and changes in excitatory and inhibitory circuits need to be better defined in order to better delineate points at which therapies might be useful.

Definition of Functional Recovery

The differences between brain recovery and behavioral compensation have not been adequately defined or studied. There is a need to define these differences using clinical, imaging, and other parameters, as the two may arise on the basis of different brain events. This may aid in designing clinical trials, by more precisely defining the behavioral outcomes measures of interest.

Pre-Clinical and Clinical Models

Pre-Clinical Models

Animal models can provide information regarding the complex interactions of

large numbers of neurons in central nervous system circuits. New ways to record and process the large sets of multidimensional data that can result from such models are needed; that might best be accomplished by incorporating scientists from fields such as mathematical modeling and statistics into the field of stroke recovery. There is also a need to develop animal models of sensory and cognitive deficits that can be used for performing better preclinical studies of functional recovery after stroke.

Clinical Models

Validated methods are needed to define and characterize stroke impairment and disability. Models need to consider clinically significant covariates such as the nature of disability, the location of injury, and the type of injury. Defining sources of population heterogeneity will be critical to designing and interpreting studies of new therapeutics. Criteria must be developed for adequate testing of drugs, cells, and other therapies in animal models before proceeding to human trials (e.g., time window, dose-response, lesion type/size/location, etc.).

Integration of Basic and Clinical Research

How can appropriate patient candidates be identified for eventual treatment based on animal studies? Markers are needed for in vivo observation and monitoring of key processes related to stroke recovery and the effects of drugs or endogenous/exogenous neural progenitors in animal and human studies.

Monitoring and Measuring Recovery

The natural history of recovery in humans and in animal models is incompletely understood; paradigms often cannot be compared between laboratories, and there is considerable evidence that the process of recovery differs depending on the location of injury and the functions that are affected. Advances in imaging technology will play a large role in better characterizing these events.

Molecular Neuroimaging

What can be learned from molecular neuroimaging studies of the pharmacokinetics of drugs and bioactive molecules (e.g., growth factors) used to enhance the restorative capacity of brain tissue? Can treatment effects on molecular mechanisms and synaptic/enzymatic activity be demonstrated by functional imaging methods? Also, new imaging technology is needed to monitor neuronal plasticity and treatment effects at cellular and network levels of analysis. There is a need for high-throughput screening tools for evaluating therapies.

Analogous neurophysiological tools are needed in animal models. More animal models and studies, especially primate models and studies, are needed that can correlate functional MRI and other imaging parameters with electrophysiological and cellular and molecular outcomes following stroke.

Monitoring Network Processes

It will be important to identify the essential neuronal networks responsible for good recovery following stroke and

to define, image, and monitor these networks using established and new imaging techniques (e.g., PET, SPECT, fMRI, MRS, TMS, MEG, EEG, etc.). The ability to monitor these networks and other image parameters with adequate spatial and temporal resolution will provide independent outcome measures of stroke recovery in clinical trials. How does the process of recovery differ in various regions and lesions? Why is there adequate redundancy for some functions and not others? What role do inter- and intrahemispheric interactions play in promoting, inhibiting, or supplementing specific functions and how can positive effects be encouraged? Such studies will require new approaches that include functional and molecular imaging and interventions that directly address causality. Such information may be critical to predicting and understanding treatment responses in this setting.

Treatment and Enhancing Recovery

There is a current lack of knowledge on patient selection for specific treatment protocols. Treatment approaches using growth factors, as well as progenitor/stem cells and engineered cells hold promise, but require further study. There is increasing support for the independent and interactive effects of physiotherapy/environmental enrichment and pharmacotherapy, but important gaps must be filled by further animal studies and controlled clinical trials. A viable mechanism for delivery of pharmacotherapeutic treatments is still a problem. We need the ability to manipulate molecular events underlying the potential mechanisms. Appropriate preclinical models that systematically address lesion size, location, and

recovery period are needed to help reduce the possibility of poor design in future clinical trials.

Interactive Effects of Physical Rehabilitation and Other Therapies

How does physical therapy (and other behavioral experiences, such as environmental enrichment) interact with new therapies such as trophic factors, promoting neurogenesis, and cellular transplantation? What effect, if any, does rehabilitation have on molecular events (e.g., distribution kinetics of labeled cells and molecules) that potentially influence behavioral outcome?

Clinical Trial Design

Treatment paradigms need to be evidence-based and hypothesis-driven and supplemented as much as possible by mechanistic experimentation, so that even failures will yield important new knowledge. A variety of potentially therapeutic treatment options to stimulate recovery already exist, such as enriched environment or performance of specific physical tasks, adrenergic stimulation, growth factors, stem cells, and engineered transplants. However, in the absence of a better understanding of the process of recovery, it is possible that trials addressing these approaches may fail as a result of improper timing, inadequate models, or inadequate outcome measurements in human trials.

Clinical trial design for stroke recovery treatments remains a conundrum that needs to be resolved. How can we predict outcomes in order to properly identify patients appropriate for a new therapeutic intervention? How do we identify patients with comparable

prognosis? How do we separately evaluate sensorimotor and cognitive recovery after stroke? What can be learned from controlled clinical trials of the efficacy of various physiotherapeutic and drug-supported treatments in the rehabilitation of stroke?

How can we manipulate molecular events underlying angiogenesis, neurogenesis, and neuronal remodeling? Are there pharmacological methods (e.g., ephrin and notch proteins) to induce neurogenesis, angiogenesis, or neuronal remodeling? Can cellular therapies such as endogenous inflammatory cells and exogenous cells (e.g., marrow stromal cell, stem cell, cord blood) act as growth factor “factories” that respond to the neurotrophic needs of the tissue?

Timing of recovery interventions may be critical. Many models equate acceleration of short-term recovery (the first few days after infarct) with long-term processes that are likely to be fundamentally different events. This may be a critical error if applied to patients for whom the experimental paradigms are not appropriate. Lesion size and location may be important factors that will restrict the range of applications. An approach that may be beneficial in one model (e.g., cortical infarct) may fail or even be detrimental in another model (e.g., white matter lacunar infarct).

New approaches for transport of large molecules across the blood-brain barrier are needed to deliver therapeutic agents (viral vectors, opening barrier, etc.). Approaches that are most promising for the development of pharmacotherapeutic tools for stroke recovery are still unclear.

Modulators of neurotransmission and growth factors appear to be the leading candidates at present.

There is evidence that physiotherapy modulates the effects of pharmacological treatment for stroke recovery (e.g., amphetamine). Are there other methods that can enhance or target the effects of pharmacotherapy, such as electrical stimulation, psychological state, or environment?

Can cellular and gene therapies be combined with tissue engineering, including the use of biomaterials (e.g., biodegradable synthetic scaffolds that provide templates for exogenous or endogenous cell growth and/or secrete various molecules that might promote repair, neuroprotection, angiogenesis, or neurogenesis)? Can cellular therapies be used to create natural pumps or factories of therapeutic proteins beyond or in addition to replacement of degenerated cells? Cellular replacement approaches should recognize the importance of nonneuronal elements (e.g., astrocytes). Recovery of function may require reconstitution of the entire milieu.

Efforts to integrate and orchestrate multifaceted, multidisciplinary approaches over time should be encouraged (e.g., neuroprotection, cell replacement, molecular therapies, tissue engineering, neurite-outgrowth promotion, and remyelination).

BARRIERS

- There are no accepted long-term imaging or behavioral measures that can serve as reliable, quantitative outcome measures for assessing the effects of a therapy that targets

the process of stroke recovery.

- There are no validated surrogate imaging or other short-term markers for good or poor long-term outcome following stroke in animal models or in humans.
- It is not known what clinical assessment measures would identify those patients most likely to benefit from therapeutic interventions to improve outcome from stroke.
- There are no established ways to relate outcomes in animal stroke models to outcomes in humans.
- There is a lack of knowledge concerning basic underlying mechanisms of recovery.
- There are few neuroimaging methods that are readily and widely available to image at the molecular, cellular, and behavioral level in stroke.
- Few centers currently have all of the tools required to evaluate stroke recovery in using multiple imaging modalities.
- Understanding the clinical problem of stroke is not the most urgent priority of basic scientists.
- The cost and availability of primates could become insurmountable financial barriers in the future.
- Paradigms for clinical trial design for therapies to improve stroke recovery currently are not adequate.

RESEARCH AND SCIENTIFIC PRIORITIES

Although the following three priorities will likely be advanced in concert, they represent a logical progression from (1) basic science insights into the underlying mechanisms of recovery, to (2) new neuroimaging techniques for monitoring these mechanisms in humans, to (3) new

clinical interventions based on mechanistic targets. This strategy should yield improved therapies quickly utilizing approaches already identified as promising. More importantly, basing the development of both monitoring and treatment strategies on a solid foundation of basic science should result in new interventions that have yet to be proposed.

Priority 1:

Understand the molecular, cellular, and network changes in the brain that lead to good versus poor behavioral recovery following stroke.

- A host of neuronal and nonneuronal processes must be characterized more fully after stroke (e.g., neurogenesis, angiogenesis, synaptogenesis, and other “self-repair” mechanisms). There is an urgent need to define which mechanisms associated with structural and functional alterations after stroke are adaptive, maladaptive, or epiphenomenal. These events will have to be examined at cellular and molecular levels as well as at network, systems, and behavioral levels. There must also be more extensive work done in primates to determine if these mechanisms can be generalized across species.
- Several exogenous factors (e.g., growth factors, neurotransmitters, other pharmacotherapeutic agents) have been identified that putatively can modulate recovery. It is necessary to understand their mechanisms of action at the molecular and cellular level.
- Behavioral experience after stroke

is now known to be an important modulator of recovery. We must define the mechanisms of how environmental enrichment and physiotherapy improve outcome from stroke and modulate drug effects. An understanding of the specific cellular and molecular events associated with behavioral therapy and pharmacotherapy, and their possible interactions, should lead to the identification of potential therapeutic targets for improving recovery from stroke as well as other neurological diseases.

- We must examine more closely the relationship between development and stroke in order to understand factors that lead to good versus poor recovery in children and in adults following stroke. To what degree are genes expressed during the self-repair process a re-expression of developmentally relevant genes “awakened” in the mature brain?

Priority 2:

Develop neuroimaging and other methods for detecting molecular, cellular, synaptic, and circuit mechanisms of recovery following stroke that can predict outcome.

- There is a need for new techniques for molecular neuroimaging (e.g., gene expression, enzymatic activity, altered synaptic transmission, receptor state, etc.). Current techniques (e.g., fMRI, PET, MEG, etc.) are limited in their ability to monitor neuronal plasticity at the mechanistic level. Development of this proposed technology will allow the monitoring of recovery mechanisms and eventually allow

the tracking of treatment effects.

- In addition to molecular neuro-imaging, enhanced techniques for monitoring recovery mechanisms at the cellular, synaptic, and circuit levels could provide a means to use imaging data as surrogate markers of therapeutic efficacy. These new techniques should eventually allow us to define patient populations most likely to respond to treatment. There is a growing need to develop high-throughput screening tools for assessing stroke recovery.
- There is a great need to develop markers of recovery in animal models that can also be applied to assessing outcome following stroke in human trials. To accomplish this goal, animal models with more complex brains, especially primates, need further development.
- Methods for assessing the degree of recovery following stroke should include the development of means to transiently perturb putative recovery events (e.g., with drugs, transcranial magnetic stimulation, etc.) and also ways to assess the behavioral and imaging effects of these interventions. This powerful approach would allow the testing of hypotheses regarding causal relationships.

Priority 3:

Develop new clinical interventions based on mechanistic models of recovery.

- The use of progenitor/stem cells and engineered cells holds great promise for functional restitution. The development of treatment

approaches based on these cells must be a top priority.

- The introduction of other exogenous substances, such as growth factors and small molecules, continues to provide important avenues to improve recovery following stroke. This will necessitate the development of improved methods for the delivery of drugs, molecules, and cells across the blood-brain barrier.
- Interdisciplinary teams of basic and clinical scientists must be formed to maximize translational research. Interaction between these groups should lead to improved animal models of stroke recovery that are more likely to reflect recovery in the complex human brain. It should also encourage the development of animal models to assess cognitive deficits and the effects of white matter injury. The most promising therapies must be tested first in these models.
- Integrated, multifaceted approaches to repair should be developed, possibly including combinations of environmental, pharmacological, and cellular interventions.
- The natural history of stroke must be better understood before treatments can be optimally applied to individual patients. Important subject parameters are likely to include age, gender, race, stroke location and volume, initial clinical deficits, stress, and psychological states. These may help researchers to predict outcome, to identify patients most likely to benefit from therapy, and to identify therapeutic targets.

RESOURCES NEEDED

We propose the establishment of multicenter networks for collaborative studies in animals and humans focused on single issues, including imaging. Centers require not only imaging and other tools, but also teams of scientists to address mechanisms of recovery and methods of measuring recovery, and to develop treatments to enhance recovery. The focus of these networks must be on translational approaches to stroke recovery, because of the strategy outlined in the priorities. Novel interventions will be based on underlying mechanisms of recovery. Specific therapeutic agents will likely have effects on specific targets that are involved in brain plasticity mechanisms. These interventions will then be tested in animal models, including primate models, to verify their specific effects and efficacy. Recovery progression in human stroke survivors will be closely monitored at molecular, cellular, and network levels using new neuroimaging techniques.

In addition, significant support is needed for the training of basic and clinical

scientists in several areas: studying the mechanisms of recovery from stroke and brain injury, developing outcome measures, developing neuroimaging tools, and assessing therapies for improving stroke recovery. It has been difficult to recruit basic neuroscientists into the field of stroke, especially in the development of preclinical models. Other fields (engineering, computational modeling, etc.) have not been drawn to this area. A major effort must be made to lure bright, young scientists from these areas into an increasingly interdisciplinary field.

The scientific stroke community also recognizes the importance of maintaining a variety of animal models for preclinical assessment, including animals with complex brains. If we are to continue supporting non-human primate studies for stroke recovery, primate centers need to be responsive to the needs of researchers to obtain animals with required characteristics (e.g., B virus-free, particular age, sex) at a reasonable cost. Regional primate centers are no longer reliable resources, except for a host institution's investigators.

Neurovascular Protective Mechanisms

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STATEMENT OF THE PROBLEM

Acute and chronic dysfunction of the neurovascular (NV) unit leads to cerebrovascular disease such as stroke and other cerebrovascular disorders.

- The functional NV unit is composed of interacting cellular and acellular elements. Most prominent of the cellular elements are the endothelium, astrocytes, and pericytes. The acellular elements are proteins and enzymes that regulate the composition of the matrix. These elements are structurally and functionally integrated and interdependent. It is to be emphasized that both neuronal and endovascular elements are critical. However, the NV unit is defined as such in order to emphasize the most under-studied elements of its function and dysfunction.
- The functional NV unit is recognized as subject to protective and damaging events, which lead to a continuum of transformation from health to disease, and to recovery or death. In this respect, systemic, endocrine, and neural factors can transform all or part of the NV unit. Examples of known risk factors for stroke include age, hypertension, dyslipidemia, and gender, as well as environmental (stress, toxins) and behavioral (smoking, alcohol, drug abuse) factors.
- Disorders of the NV unit contribute to initial stroke pathology and to development of cerebral injury after stroke. Chronic injury of small penetrating arteries is the leading cause of lacunar stroke (about 20 percent of all stroke), vascular dementia, and intracerebral hemorrhage (about 10 percent of all stroke). Low microvascular density or microvascular dysregulation is likely a major factor contributing to ultimate brain injury after large vessel stroke. In the setting of acute stroke from large artery embolism or thrombosis, dysfunction of the NV unit is also responsible in part for brain edema (the major cause of neurological death immediately after stroke) and may determine the progression of injury into the ischemic penumbra. The role of cerebral microcirculation in stroke recovery remains to be established.
- Understanding disease of the NV unit provides opportunities for therapeutic intervention in stroke prevention and acute stroke. In addition, disruption of the NV unit impacts other acute therapeutic approaches. Ischemic injury of the cerebral microvessels leads to hemorrhagic transformation, the single limitation that prevents widespread implementation of thrombolytic therapies. Furthermore,

the intact or injured blood-brain barrier (BBB) determines brain delivery of potential therapeutic approaches, including neuroprotective agents.

- Analysis of the NV unit biology and pathology will be focused on the major components of the NV unit. These include: endothelium, glial, matrix, smooth muscle cells, and other cell types. Each of these elements will be reviewed in view of identification of the key challenges and questions, research priorities, and resources needed.

CHALLENGES AND QUESTIONS

Brain Microvascular Endothelium

- The endothelium of brain vessels (including capillaries) integrates and responds to myriad intravascular, vascular, and extravascular signals. The endothelium is viewed as a key regulator of blood flow, transport, BBB function, and immune surveillance of normal brain tissue.
- The endothelium has ongoing direct interaction with extravascular (astrocytes, microglia, neurons), vascular (pericytes, smooth muscle), and intravascular (leukocytes, platelets, red blood) cells. In addition, the endothelium integrates and responds to neuronal, humoral, and matrix-derived factors as well as autocrine and paracrine mediators that normally maintain a physiological state with the following phenotype: (1) adequate blood flow to brain tissue, (2) anti-adhesive, (3) anti-inflammatory, (4) antithrombotic, and (5) an intact blood-brain barrier.
- The endothelium may revert under

certain conditions to a cellular phenotype incompatible with maintenance of its critical role in blood flow and BBB function. Such conditions include: (1) the presence of inflammatory mediators (e.g., cytokines, chemokines, lipid mediators), (2) activation of coagulation factors and platelets, (3) presence of abnormal shear rates and flow pattern, (4) a failure to maintain autocrine (nitric oxide) and paracrine (growth factors) protective factors, (5) redox imbalances (oxidative stress), (6) aberrant matrix signaling and support, and (7) neurohormonal factors (estrogen, vasoactive neurohormonal factors).

- The endothelium under pathophysiological conditions (vide supra) may assume a prothrombotic, proinflammatory phenotype that leads to thrombosis or neurovascular damage with hemorrhage. Furthermore, under such conditions, necrosis, apoptosis, and other degenerative changes in the endothelium degrade function of the vascular unit and lead ultimately to brain injury.

Glial Cells

- Glial cells, particularly astrocytes, are an integral part of the BBB, contributing to both barrier and transport functions. Astrocytes also influence endothelial function and contribute to formation and degradation of the intercellular matrix.
- Astrocytes maintain intercellular communication with each other and with endothelial cells via gap junctions. These may be important in transmitting calcium waves,

spreading depression, and possibly triggering vasospasm.

- Microglia and astrocytes serve as inflammatory cells in the brain. These cells are responsible for disposal of blood products after blood crosses the BBB. However, activated astrocytes and microglia also release nitric oxide and other substances that may play an active role in microvascular dysfunction.

Matrix and Matrix-Modulating Proteases

- The extra-cellular matrix (ECM) is a critical element in organ development, remodeling, angiogenesis, and cell survival and death.
- Physiological matrix milieu is dependent on several cellular contributors (astrocytes, microglia, endothelium) and regulatory enzymes, including the matrix metalloproteases (MMPs) and a disintegrin and metalloproteinase (ADAM) family of proteases.
- The endothelium basement membrane is a specialized matrix milieu that structurally and functionally supports the vascular unit function.
- Active, regulated, and genomically imprinted processes secure “evergreen” matrix milieu and provide signaling input to both the endothelium and glial cells that compose the BBB.
- Pathological changes in matrix compositions and MMPs (gelatinases and stromelysins) disrupt endothelium function as well as glial cells. Such aberrations lead to disruption of the BBB.
- The ECM may play a role in

initiation of stroke, vasculopathic conditions, and BBB malfunctions. The role of specific MMPs in this respect, as elucidated by pharmacological investigational tools and genetic models, carries the promise of preventive and therapeutic opportunities for stroke and neurodegenerative disorders in the near future.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Cerebrovascular endothelium: in order to understand the role of endothelial cells in the NV unit under both normal and disease conditions, elucidate the mechanism of endothelium signaling pathways that regulate survival or death as well as the factors that support an antiinflammatory/antithrombotic phenotype.

- While a large database of information regarding the stimuli and mediators that affect endothelium phenotype exists, there are limited or no data on the signaling pathways that govern endothelial cell survival or death. The cytosolic and nuclear pathways that translate such external signals should be elucidated.
- While extensive research has emphasized the relevance of blood-borne, neurohormonal, oxidative stress, and inflammatory/immune factors in endothelial cell phenotype “switch,” their relative contributions and the use of an integrated mechanism for preservation and repair are unclear. The role of matrix

proteins and endothelial-matrix adhesion molecules in regulating endothelium phenotype is unknown.

- The role of factors derived from glia and neurons in the regulation of endothelium and BBB is poorly understood.
- Survival factors and mechanisms that lead to tolerance of the endothelium to injury have not been clearly defined.
- Technology that allows investigation of integrated functions of the brain microvessels in the context of all relevant cells (glia, pericytes, neurons, etc.) and matrix proteins has not yet been developed. Likewise, it is currently impossible to study the function of brain microvessels in humans (normal, individuals at risk for stroke, and those who have had a stroke).
- Transgenic and knockout mutant rodents for studying endothelial survival/death signaling, BBB function, and repair are not available.
- Strategies for endothelium cell therapy, angiogenesis, and replacement (stem cells) have not been developed.
- The molecular mechanisms through which stroke risk factors interact with endothelium to increase stroke likelihood are unclear.

Priority 2:

The role of glial cells in neurovascular function: in order to understand the role of glial cells in the operation of the NV unit in both normal and abnormal conditions, elucidate the mechanism of astrocyte and microglial growth and differentiation as well as interaction with the endothelium and matrix milieu.

- There is a clear paucity of knowledge on the cell biology, biochemistry, and molecular biology that underlie the activation, proliferation, and release of mediators from glial cells. In particular, the releases of growth and differentiating factors need to be investigated.
- The intercellular connections and pathways that govern glial regulation of the BBB are poorly understood.
- The specific functions of astrocytes and microglia in the formation and degradation of the intercellular matrix are not known.
- Genomics and proteomics information on glial cells is not available. Stimuli, signaling pathways, and “molecular switch” mechanisms that secure physiological phenotype of astrocyte and microglia need to be understood.

Priority 3:

Matrix proteins and matrix-regulating proteases: in order to understand the role of the matrix in normal and disease conditions of the NV unit, elucidate the proteins and enzymes (MMPs, ADAMs) that compose and regulate the structure and function of the matrix.

- A vast number of novel MMPs and ADAM proteases have been discovered over the past few years, yet little is known about their role in brain matrix and BBB function. There is an urgent need to identify the relevant and important MMPs and ADAMs that could be risk factors for stroke and other neurodegenerative disorders.

- The specific associations of matrix proteins with cell (glia, endothelium) adhesion molecules and the signaling pathways that regulate vascular cell biology are poorly understood.
- Pharmacological tools that provide for selective and potent inhibition of specific MMPs and ADAMs need to be developed to allow better understanding of their function in normal and disease conditions. Likewise, genetic models need to be developed to address these issues.
- Genetic information on matrix proteins and MMPs and ADAMs need to be generated to gain insights on possible polymorphism in matrix and regulating elements as risk factors for stroke.
- Genomic examination of the complete set of matrix proteins and the regulatory elements (proteases and protease inhibitors) needs to be completed.
- The role of the ECM in healing processes and angiogenesis in brain disorders is largely unknown.
- The availability of transgenic and knockout rodents in MMP is limited.

RESOURCES NEEDED

- Establish animal models that simulate stroke risks identified in clinical studies. Age, hypertension, pro-coagulant states, and dyslipidemia, are some of the risk factors that should be addressed.
- Develop genetic models that enable studies of discrete elements of the NV unit. In particular, genetic models that allow for conditional regulated and targeted gene manipulation in tissue and cell levels should be developed.
- Develop imaging technology for experimental animal studies that help visualize structural and functional conditions of the NV unit as representing human cerebrovascular diseases.
- Establish resource centers for a large-scale database of genetics, genomics, and proteomics of the NV unit in health and well-defined NV diseases.

CNS Thrombosis and Hemorrhage

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STATEMENT OF THE PROBLEM

Stroke is a vascular disorder with neurological consequences. Vascular thrombosis is responsible for the majority of ischemic strokes. But loss of vascular integrity during focal cerebral ischemia is responsible for ischemia-related hemorrhagic transformation and contributes to spontaneous hemorrhage in the non-ischemic brain.

Successful treatments for ischemic stroke are limited to a few anti-thrombotic approaches, but unfortunately, these treatments carry a significant risk of hemorrhage. Such hemorrhage imparts significant injury, but there is no effective treatment or management strategy. Hemorrhage-related injury erodes benefit and has a negative impact on the outcome of stroke trials.

Downstream effects of the reduced blood flow that occurs during ischemic stroke target the microvasculature. The integrity of cerebral microvessels (which contain the endothelium, matrix, and astrocyte end-feet, as well as smooth muscle cells and pericytes) is important for normal vascular hemostasis and for preventing hemorrhage. Hemostatic factors and other enzymes are compartmentalized in the central nervous system (CNS). The increased

incidence of intracerebral hemorrhage during thrombocytopenia suggests that normal platelet function is necessary for cerebrovascular integrity.

Although vascular hemostasis primarily involves the blood and the luminal aspect of the endothelium, it also involves the vascular compartment and the neuronal tissues. The cerebral blood vessel is the interface between the blood and neuronal cells. Very little is known about the interactions of the microvascular compartment and the neuronal/glial compartment under normal conditions and during ischemia; it is known, though, that vascular interventions very early in thrombotic stroke can limit the extent of ischemic injury. It is expected that increased understanding of these interactions can be applied to new therapies for ischemic stroke and hemorrhage.

Furthermore, little is known about the particular contributions of the brain microvasculature to normal hemostasis and their relation to abnormal neuron function. This includes a significant lack of information about how the endothelium and the glial compartments interact with each other and regulate vascular responses to ischemia. Families of proteases are generated from both the vascular and the nonvascular compartments during ischemia, which

participate in tissue injury. These include hemostatic factors and thrombin, plasminogen activators, matrix proteases, and other enzymes. Selective protease activation in the microvasculature is essential for maintaining hemostasis, but also accompanies brain ischemia. The balance of these processes in the CNS is unknown. Antithrombotic agents (antiplatelet agents, anticoagulants, and plasminogen activators) significantly increase the risk of intracerebral hemorrhage, while limiting vascular thrombosis. Developing and properly testing protease inhibitors and anti-thrombotics that reduce the potential for hemorrhage are likely to improve patient outcome for acute interventions.

CHALLENGES AND QUESTIONS

A major challenge that needs to be addressed is our poor understanding of several factors: (1) the interaction between cerebral microvessels and the neuronal tissues they serve, (2) the role that vascular integrity plays in spontaneous hemorrhage and in hemorrhagic conversion of the cerebral infarct, and (3) the impact that inhibitors of thrombosis and of protease generation have on these processes. This requires an understanding of the relationships between normal cerebral endothelial cells and astrocytes in capillaries, their contributions to normal hemostasis, and their responses to ischemia and parenchymal hemorrhage.

These issues can be addressed by increasing our knowledge about hemostasis in the normal brain and under pathophysiologic conditions, with a focus on intravascular, vascular, and perivascular targets. Here, the

relationship of hemostasis within the microvessel (which necessarily involves the vessel wall) to astrocytes and to brain cell functions must be considered. (Although not a focus of these considerations, it is understood that activation of inflammation also involves activation of coagulation and of platelets. Platelets and other cellular elements provide surfaces upon which proteases are generated.)

Current and future research priorities should take advantage of advances in parallel areas of cardiovascular research, particularly with regard to mechanisms of injury, tools for understanding those mechanisms, and therapeutic approaches. Smooth translation from in vitro work to animal models and human stroke is required. New specific targeted inhibitors of coagulation factors, their receptors, and platelets can be used as probes to examine their roles in microvascular integrity and hemorrhage. Overall, we need a significantly better understanding of the roles that the microvasculature plays in cerebral hemostasis and its responses to ischemia and hemorrhage.

BARRIERS

Interdisciplinary Barriers

Poor communication exists between researchers in vascular biology, hemostasis, and neurobiology. For instance, while more sophisticated antithrombotic agents are being used in clinical trials of ischemic stroke, there is little understanding of their effects on neuronal tissues and how to limit their contributions to hemorrhage. A multi-disciplinary approach to understanding hemostasis in the CNS is likely to

significantly increase the possibility of positive outcomes in clinical trials of stroke.

Translation of Animal Model Studies to Clinical Trials

Significant differences exist between rodents and primates/humans in terms of hemostasis; there are also significant differences in the results of interventions in rodent models of focal ischemia and human ischemic stroke. Furthermore, there are major differences between rodents and humans in important receptor-ligand interactions in hemostasis. These factors also raise the concern that vascular-tissue interactions in the rodent brain may not translate to human brain. Although rodents account for the bulk of preclinical testing, beneficial outcomes observed in other animal models of human stroke also have failed to translate into clinical success thus far. Attention to the role of white matter injury is necessary. Furthermore, modeling of spontaneous intracerebral hemorrhage and of hemorrhagic transformation has been curtailed by a lack of understanding of the causes. This has limited approaches to the clinical treatment of these conditions. Finally, there are significant limitations in the availability of primates and novel rodent strains for experimental studies.

Technological Barriers

There is a discordance between experimental work on cerebral vessels at the molecular level and the ability to image only large cerebral vessels. The rational development of biochemical and molecular imaging tools for translation from model systems to human

application has been largely ignored. Clinical imaging has focused on changes in anatomy and physiology. Significant advances in functional imaging (including fMRI, PET, and SPECT) now allow collection of data about damaged brain at the physiologic/organ level. However, fundamental knowledge of ischemic and hemorrhagic cerebral pathology is now being collected at the cellular and molecular level. Molecular imaging tools that span the range from model systems to human brain are needed.

Clinical Trial Design

Despite the apparent success of antithrombotics in the treatment of ischemic stroke, most clinical trials are negative or too small. Furthermore, preclinical testing and exploration of mechanisms in animal models is often inadequate. Proper use of antithrombotics and appropriate clinical trial designs are required to efficiently examine more novel agents in ischemic stroke. Specific antithrombotic agents can be used as probes. Strikingly, there have been similar limitations placed on our understanding of the mechanisms of antithrombotic-related hemorrhage, spontaneous hemorrhage, and hemorrhagic transformation. As most of the trials involving antithrombotics are sponsored by industry, early communication between scientists and the clinical trial designers in the development of the projects is required. The absence of information regarding brain penetration of antithrombotics, related side effects, matching drug action to stroke subtype, and efforts to design preclinical and clinical trials with similar principles are of concern.

RESEARCH AND SCIENTIFIC PRIORITIES

These three research priorities are closely related in that each seeks to extend molecular studies to clinical application.

Priority 1:

Understand the normal biology of cerebral microvessels, as well as the interactions of cerebral microvascular endothelial cells, matrix, astrocytes, and other related cells in response to focal ischemia and parenchymal hemorrhage.

The temporal responses of endothelial cells and astrocytes to ischemia occur together, and in relation to neuron injury. Several factors imply a high level of interaction between these cells that may be extended to the neurons they serve. These factors include the interaction of endothelial cells and astrocytes to generate matrix during development, their use of the same signaling molecules (e.g., Ca^{++}), and pores that allow entry of small molecules into the astrocyte compartment. These factors imply that the endothelial cell-astrocyte relationships may act as a unit. Subclinical ischemia may involve perturbations of these relationships. To better understand these interactions, we need to:

- Define the normal molecular (i.e., ligand/receptor) relationships of endothelial cells and astrocytes to extracellular matrix within microvessels, their responses to ischemia, and their contributions to hemorrhage.
- Determine the nature of endothelial

cell and astrocyte cross-talk in culture and in vivo with well-defined animal models.

- Determine the genesis of the blood-brain barrier.
- Define the role of angiogenic factors in vascular neogenesis and their relation to hemorrhage and tissue recovery following ischemia.
- Determine the roles of proteases generated during focal ischemia and their effects on vascular integrity, blood-brain barrier function, tissue injury, and hemorrhage.
- Determine the effects of specific antithrombotic agents on endothelial cells, astrocytes, and perivascular cells.
- Determine whether specific molecular features of antithrombotic agents can disrupt normal cerebral microvessel cell relationships and functions.

Priority 2:

Understand the requirements for hemostasis and platelet function within the normal CNS, and how they are perturbed by ischemia, parenchymal hemorrhage, mechanical interventional approaches, and antithrombotic agents.

Activated platelets and products of coagulation accumulate in ischemic microvessels, implying changes in normal endothelial cell function and loss of vascular integrity. Little is known about the processes that underlie normal hemostasis in the brain, their responses to ischemia, or their effects on astrocyte and neuron viability. Ischemia initiates the appearance of serine proteases, metalloproteinases, and other proteases within the vasculature and brain tissue.

To understand this area better, we need to:

- Define the nature of brain-specific hemostatic mechanisms.
- Define the roles that parenchymal cells (astrocytes, microglia, pericytes, and neurons) play in maintaining normal hemostasis and in the microvessel pathology of cerebral ischemia.
- Determine the effects of flow and cessation of flow on the endothelial cell and astrocyte contributions to hemostasis.
- Determine the effects of thrombin on microvessel integrity and on perivascular cells.
- Determine the nonhemostatic functions of hemostatic molecules (e.g., coagulation factors and plasminogen activators) in the normal CNS, and their contributions to post-ischemic injury and spontaneous hemorrhage.
- Determine the effects of instrumentation (e.g., catheter delivery systems) on normal vascular function and local hemostasis.
- Determine what activities of antithrombotic agents contribute to hemorrhagic risk.
- Develop and test, in proper model systems, novel agents that alter hemostasis without altering vascular wall or neuronal function.
- Develop well-designed, high-quality experimental studies of the ability of acute interventions with novel antithrombotic agents to reduce ischemic injury in appropriate models, as the basis for developing high-quality, well-conceived clinical trials.
- Extend studies to models with pre-existing vasculopathy.

- Define prothrombotic states that can contribute to cerebral ischemia in neonatal and pediatric stroke patients.

Priority 3:

Develop fundamentally new strategies to limit the impact of hemorrhage on brain function in the setting of focal cerebral ischemia and spontaneous hemorrhage.

Present treatment strategies for spontaneous hemorrhage and hemorrhagic conversion have had limited utility because of a poor understanding of (1) the pathobiology of the events, (2) the effects of hemorrhage on the brain parenchyma, and (3) the potential targets. Inadequate modeling has also contributed to this issue. Furthermore, while outcomes for modeling of ischemic stroke are reasonably well-defined, outcomes for the injury caused by hemorrhage are uncertain or diffuse. We need to:

- Develop a strategy to identify those individuals at risk for spontaneous hemorrhage. Identify the genotypes of those who have suffered spontaneous hemorrhage or significant hemorrhagic transformation.
- Determine which clotting factors and platelet receptor genotypes are specific for intracerebral hemorrhage or hemorrhagic transformation. Alterations in vascular structure and matrix integrity or composition are included.
- Define the nature of the vascular injury mechanisms and the effects on brain cells of hemorrhage into the ventricles or brain tissue, in appropriate animal models.

- Determine the factors that limit hemorrhage extension in the CNS, and the regional differences.
- Develop firm measurable and standardized outcomes to quantify hemorrhage (model systems and clinical trials).
- Develop strategies that limit the impact on normal brain tissue and microvessel function of proteases generated during ischemia and hemorrhage, to limit ischemia-related injury and the impact of hemorrhage on neuronal tissues.
- Develop strategies for the acute preservation of vascular integrity during ischemic stroke.
- Develop high-quality clinical trials of acceptable treatment strategies for removal of intraventricular and parenchymal hemorrhage.
- New technologies, including detection systems such as real-time photon/ion detection confocal microscopy systems, to follow signaling between intravascular cells (platelets) and vascular components (endothelial cells and astrocytes).
- Imaging technologies for real-time evaluation of vascular responses (both gray matter and white).

Priority 2:

Appropriate in vitro and in vivo studies are required to evaluate the roles that the hemostatic (and vascular) systems play in the normal CNS and during ischemic and hemorrhagic injury. Resources needed include:

RESOURCES NEEDED

Priority 1:

Understanding the complex biology of cerebral microvessels will require multidisciplinary efforts and the availability of high-quality reagents and models. Resources needed include:

- Integrated multidisciplinary efforts involving researchers in vascular biology, neurobiology, and hemostasis, through dedicated meetings and grant mechanisms for collaborations.
- The availability of human-relevant species and novel rodent strains (rodent knockouts and transgenic constructs) for modeling of focal ischemia and hemorrhage, and reliable probes for identification of relevant cell receptors.
- Integrated multidisciplinary efforts involving researchers in vascular biology, neurobiology, and hemostasis, through dedicated meetings and grant mechanisms for collaborations.
- High-quality, novel antithrombotic agents with selective activities to use as molecular probes for mechanistic studies.
- Single-cell PCR capability, to identify the cellular compartments for expression of hemostatic factors.
- Genomics and proteomics approaches to identify responses of hemostatic factors within the CNS to ischemia.
- Specific and general inhibitors of thrombin, metalloproteinases, inflammatory mediators, hemostatic factors, and new classes of proteases.
- Targeted funding for select mouse and rat knockout/transgenic constructs and for adequate availability of primate species.

- Expert translation of animal model work to high-quality, relevant clinical trials.

Priority 3:

The causes of brain hemorrhage are inadequately understood and there are no standard therapeutic approaches for spontaneous hemorrhage. Resources needed to address this issue include:

- Integrated multidisciplinary efforts involving researchers in vascular biology, neurobiology, and hemostasis, through dedicated meetings and grant mechanisms for collaborations.
- Consortia to screen populations with spontaneous cerebral hemorrhage for genotypic characteristics of vessels and hemostasis.

- Molecular and vascular imaging tools to continuously evaluate vascular responses to hemorrhage in models and patients.
- Adequate availability of primate species (with adequate white matter) for model work.
- Expert and early translation of animal model work to high-quality, relevant clinical trials.
- High-quality clinical trials of well-conceived surgical and medical treatments of spontaneous hemorrhage and hemorrhagic transformation.

The co-chairs of this session thank Drs. Robert Rosenberg, Maiken Nedergaard Sidney Strickland, and Charles Esmon for additional contributions to this report.

Vascular Dementia

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STATEMENT OF THE PROBLEM

Vascular causes of cognitive impairment are common, especially in the elderly. It is estimated that as many as one-third of those who have a stroke have post-stroke dementia. Vascular disease is considered to be a major contributor to slowly progressive dementia. Among persons at high risk of stroke, such as Asians, vascular dementia may be more common than Alzheimer's Disease (AD).

As stroke and AD are both common in the elderly, many stroke patients may have concomitant clinical and neuropathologic changes of AD. In these cases it may be difficult to decide which changes caused or contributed to the dementia. Vascular brain disease, often clinically silent, may also be important for the clinical manifestations of dementia in individuals with mild Alzheimer encephalopathy. Differentiation of pure vascular cognitive impairment (VCI) from AD, or from mixed VCI/AD, is therefore problematic. In contrast to AD, the definition, clinical picture, course, risk factors, markers, preventatives, treatments, and vascular biology of VCI and mixed VCI/AD are not well established.

In this text we denote VCI as a heterogeneous group of syndromes in which there is cognitive impairment with

cerebrovascular disease (CVD). Some forms of CVD lead to cerebrovascular brain injury (CVBI) sufficient to be associated with cognitive impairment, whereas other forms of CVD and CVBI do not lead to cognitive impairment. Descriptive information is needed about the pathophysiology of VCI to establish a causal link between CVD and cognitive impairment.

VCI is a heterogeneous condition that can result in a wide range of clinical deficits and manifestations. VCI may manifest structurally as large- or small-vessel territory infarction, rarefaction of the white matter, A β peptide deposition, brain hemorrhage, or a combination of these states. The spectrum of cognitive impairment may vary from isolated dysfunction in one or two cognitive domains to dysfunction in many domains. When research diagnostic criteria for vascular dementia are compared, there is substantial variation in prevalence, sensitivity, specificity, and inter-examiner reliability across the criteria. Isolation of a homogeneous, definable vascular dementia syndrome has proven difficult. Definition of VCI subtypes may be a more promising approach. Similarly, the heterogeneity of VCI provides conceptual and operational challenges in measuring the effectiveness of treatment.

Risk factors for vascular forms of cognitive impairment seem to be similar to those for cerebrovascular diseases (e.g., hypertension, diabetes mellitus, lipid disorders, atrial fibrillation), and now have also been linked to AD. Furthermore, the AD susceptibility gene, Apolipoprotein E (ApoE), may also be important in VCI, as this gene has also been linked to an increased risk for atherosclerosis and myocardial infarction. However, it is not known whether such similarity in risk factors and susceptibility genes reflects the difficulty in differentiating AD from mixed VCI/AD syndromes. Cerebral amyloid angiopathy (CAA) may lead to brain dysfunction and injury in both VCI and AD, by shared or by different mechanisms. The apparent overlap of the risk factors for vascular dementia with those for stroke and AD has important implications for preventive strategies, but has not been studied in sufficient depth.

The cellular and molecular pathology of VCI has not been defined. An understanding of these factors is needed to provide insight into the mechanisms of these conditions. Such knowledge will heighten our ability to identify risk factors and biological markers, and to develop rationally based prevention and treatment strategies, which are non-existent to date. The study of the molecular pathogenesis of VCI is complicated by the heterogeneity of these conditions, their multifactorial pathogenesis, the complexity of the reaction of the brain tissue to vascular and neuronal injury, and the interaction between genetic and epigenetic factors in the resulting tissue damage. While considerable emphasis has been placed on the mechanisms of the damage

produced by acute severe ischemia and static cognitive impairment, very little is known about the effects of chronic moderate ischemia on neurons and white matter, from the standpoint of molecular, cellular, network, and cognitive changes.

CHALLENGES AND QUESTIONS

- VCI syndromes reflect a wide spectrum of heterogeneous disorders. Valid and reliable neuroimaging, and clinical/neuropsychological and neuropathological diagnostic criteria for VCI subtypes are lacking.
- Similarly, valid and reliable diagnostic criteria to categorize the contributions of CVBI and AD to mixed vascular and degenerative dementia, as distinguished from the pure forms of these disorders, need to be developed. The interactions between CVBI, stroke, Alzheimer-like pathology, and cognitive impairment remain unclear. Furthermore, the causative mechanisms of slowly progressive cognitive decline in patients with CVBI remain to be explored.
- Some of the clinical risk factors for VCI appear to be the same as those for cerebrovascular disease and AD. Can we validate this for VCI subtypes?
- Can we develop predictors or markers of CVBI, VCI, CAA, and AD using advanced neuroimaging technologies (quantitative MRI, fMRI, diffusion tensor imaging, MR spectroscopy, and PET) or molecular-biochemical analysis of blood, cerebrospinal fluid, or other accessible tissues?
- Which susceptibility genes (e.g., ApoE) or causative genes play a role

in the pathogenesis of VCI subtypes? What are the molecular pathways by which these genes act? Are there important gene-vascular risk factor interactions? Are there genetic and epigenetic changes common to different VCI subtypes?

- What are the basic mechanisms by which parenchymal and vascular amyloid, as well as prefibrillary A β peptides, influence the onset and progression of VCI and AD?
- Do alterations in cerebrovascular reactivity, endothelial function, blood-brain barrier exchange, and extracellular matrix influence the initiation and progression of VCI and AD? Do factors such as oxidative stress and the activation of molecular programs leading to cell dysfunction or death play a role in these alterations?
- What role do cardiovascular disease risk factors such as hypertension, the renin-angiotensin system, diabetes mellitus, insulin, the pituitary-hypothalamic-adrenal axis, and plasma lipids play in cerebrovascular biology? How do these risk factors interact with each other and with the process of aging?
- How do we cope with VCI's heterogeneity when trying to measure the effectiveness of treatment?

BARRIERS

Interdisciplinary Barriers

There is poor communication among clinical researchers and between clinical researchers and basic scientists. Although substantial expertise exists in these scientific realms, there is a paucity of cross-communication. Furthermore,

most clinical and epidemiologic studies are being carried out in relative isolation, with disparate study methodologies and study populations. A large-scale, systematic and integrated approach including both clinical and basic arms for the study of vascular dementia is lacking.

Nosology Barriers

There are several major limitations in current nosology. First, current definitions and classifications of vascular dementia direct attention to the relatively late stages of cerebrovascular disease and vascular-related brain injury, and may not address the early or “brain-at-risk” stages of the disorder. Second, there is no fundamental agreement on the neuropsychologic parameters that best characterize VCI. Current diagnostic criteria, when compared, differ substantially in parameters such as sensitivity, specificity, and inter-examiner reliability. Furthermore, the criteria may be difficult for a general practitioner to apply in the community at-large. Third, when there is substantial overlap between two conditions, such as between AD and CVD, categorical approaches to nosology have limited utility. Alternative approaches to classification should be sought.

Technology Barriers

Suitable quantitative structural and functional neuroimaging tools are undergoing technology assessment to determine their role in the diagnosis and staging of VCI. However, their value in the study of vascular dementia has not been established, and they are not yet ready for use in the community at large. In the basic science community,

techniques for studying cerebrovascular function in transgenic mouse models are not as widely available as those for investigations in larger mammals. This is an obstacle to the study of the alterations in cerebrovascular function in mouse models relevant to VCI.

Disease Model Barriers

There is a lack of appropriate in vivo and in vitro models with which to study chronic ischemia and VCI. Rodents have relatively little white matter and may not be suitable models for the white matter rarefaction frequently seen in humans. Therefore, primate models may be needed for investigations involving white matter. Transgenic mouse models of AD and CADASIL are promising, but they do not address the heterogeneity and complexity of vascular dementias. Interaction with genetic and epigenetic factors, species differences, and difficulties with modeling human cognitive deficits in lower animals are also barriers.

Tissue Resources Barriers

There is a general lack of brain tissue from affected individuals for rigorous clinical-pathological correlation, for correlation with ante-mortem imaging, and for genetic and molecular investigations. There are no central resources for tissue collection, storage, and distribution to the scientific community. Modalities for tissue processing, preservation, and analysis most appropriate for vascular dementia syndromes have not been defined, and are likely to differ from those used for AD. Animal models relevant to vascular dementia and related risk factors are not always readily available, presenting

another obstacle to extensive study by the scientific community.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Develop diagnostic criteria or alternative classification schemes for CVBI and VCI subtypes, define stroke and cardiovascular disease risk factors and markers, and identify novel risk factors and markers for these conditions.

- Define VCI subtypes with particular attention to the heterogeneity of the condition. Consideration should be given to the CVD/CVBI type, time course of illness (static, progressive, etc.), levels of diagnostic certainty, and neuroimaging and neuropathologic criteria.
- Identify stroke and cardiovascular disease risk factors and markers, and the pathways involved in the initiation and progression of VCI subtypes.
- Identify genetic, neuroimaging, blood, cerebrospinal fluid, and other accessible tissue markers and the pathways involved in the initiation and progression of VCI subtypes.
- Define the role of vascular and parenchymal β -amyloid, as well as prefibrillary A β peptides, in the initiation and progression of VCI subtypes.
- Develop diagnostic criteria or alternative continuous classification approaches for mixed vascular and AD dementia, determine the frequency and role of AD in VCI subtypes, and identify shared risk

factors and the mechanisms of initiation and progression of these conditions. Study how vascular risk factors may be involved in the pathogenesis of AD.

Priority 2:

Investigate the molecular pathology of VCI subtypes and mixed dementias, and develop preclinical treatment strategies.

- Establish animal models of VCI subtypes, choosing the species most suitable for such studies based on the specific aspect of the disease to be investigated. Apply molecular, cellular, and system approaches to investigate these models with respect to gene and protein expression, cerebrovascular regulation, blood-brain barrier exchange, and neuronal function.
- Use these models in conjunction with existing models of AD, hypertension, ApoE, diabetes, hyperlipidemia, aging, etc., to study the interaction with specific risk factors and other epigenetic factors.
- Investigate the effects of A β peptides on the structure and function of cerebral blood vessels, and study their interactions with risk factors such as aging, hypertension, diabetes, ApoE, and lipids.
- Investigate the effects of chronic ischemia at the molecular, cellular, network, and behavioral levels. Investigate the interaction between known risk factors and the effects of chronic ischemia.
- Validate in patients with VCI subtypes the mechanistic insights obtained from animal models,

through studies of cerebrospinal fluid and available tissues, vascular regulation, blood-brain barrier exchange, and neuronal function. Determine the usefulness of these alterations as diagnostic tools and markers of disease progression.

- Develop preclinical treatment strategies based on counteracting specific pathogenic pathways. Define clear endpoints and outcomes for these treatment strategies.

Priority 3:

Develop and test prevention and treatment modalities in patients with VCI subtypes.

- Identify modifiable standard and novel stroke and cardiovascular disease risk factors with a high population-attributable risk in persons who are at risk of VCI or have early signs of VCI; develop appropriate clinical trial methodology to test prevention strategies.
- Identify modifiable standard and novel stroke and cardiovascular disease risk factors involved in the progression of VCI subtypes, and develop appropriate clinical trial methodology to test interventions to prevent progression of VCI subtypes.
- Identify interventions for symptomatic treatment of VCI subtypes and develop clinical trial methodology for testing symptomatic treatment of VCI subtypes.
- Identify shared vascular risk factors for VCI and AD with a high population attributable risk, target the factors for prevention, and

develop appropriate clinical trial methodology to determine if the prevention strategies reduce the burden of VCI and AD.

- Develop outcome measures that address the heterogeneity of deficits in VCI and incorporate patient preferences.

RESOURCES NEEDED

- National and international research colloquia for scientific exchange on VCI. At the start, emphasis should be placed on developing diagnostic criteria or classification approaches as outlined in Priority 1.
- Comprehensive VCI research centers that would address basic science, as well as clinical, epidemiologic, genetic, neuroimaging, and neuropathologic research questions. Research may include investigations of risk factors and identification of novel genes, pathogenic processes of risk factors, and markers for these conditions. Comprehensive VCI research centers encompassing all these aspects could be modeled after AD research centers. Such centers could incorporate longitudinal studies to better understand the definition, classification, natural history, and neuropathological aspects of VCI.
- Tissue banks for storing and processing relevant brain and other specimens from VCI patients, CVD

patients without dementias, and normal subjects. Brain autopsy rates in vascular dementia are low, and incentives to facilitate donation of brain and other relevant specimens, especially at the time of death, will help increase tissue banking. To take advantage of brain banks, modalities for tissue processing, preservation, and analysis appropriate for the study of VCI syndromes need to be developed.

- Incentives to encourage basic and clinical scientists working in relevant fields (e.g., epidemiology, genetics, AD, vascular biology, transgenic technologies, and advanced imaging) to study chronic mechanisms of ischemia and brain injury, interactions with AD, and VCI. Discoveries deriving from these efforts, including animal models, should be made widely available to the scientific community. Support for costly crossbreeding experiments could be made available to specific centers, which would then supply animals or tissues to investigators.
- National and international clinical trial consortia to test preventive and treatment strategies in patients with VCI, as these strategies become available.

The co-chairs of this session thank Dr. Gustavo Roman for additional contributions to this session's report.

Genetics

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STATEMENT OF THE PROBLEM

The identification of the genetic underpinnings of stroke has lagged substantially behind progress made in other common neurologic disorders such as Alzheimer's and Parkinson's diseases. Only a few genes have been linked to stroke, and these are found only in rare families. These include stroke phenotypes that involve primarily the cerebrovascular system and brain, such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Notch 3 gene), familial cavernous hemangiomas, and hereditary intracerebral hemorrhage (ICH) secondary to amyloid angiopathy (e.g., Icelandic variant). In addition, other systemic diseases due to genetic mutations -- such as sickle-cell disease, polycystic kidney disease, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes), Fabry's disease, Factor V Leiden deficiency, and other inherited coagulation disorders -- have been associated with ischemic and hemorrhagic stroke in some patients. For the overwhelming majority of patients with stroke, however, the genetic risk factors are unknown.

A few small linkage studies in Finnish and Japanese populations have identified chromosomal regions associated with

intracranial aneurysms. One specific gene in the Icelandic population has been identified as a potential stroke candidate gene (unpublished data). Several candidate gene polymorphisms have also been investigated in case-control type studies. The most convincing evidence thus far for any candidate gene is the association between Apo E4 and E2 genotypes and lobar intracerebral hemorrhage.

Despite the limited current knowledge regarding the genetics of stroke, identification of stroke genes still represents the clearest path to a better understanding of the mechanisms underlying stroke. Once the genes have been identified, their effects can be examined in animal models. Identification of the relevant genes, the proteins that they code, and the function of these proteins will lead to new, innovative strategies for primary and secondary prevention of stroke. Eventually, preventive or acute therapy may be chosen based upon genetic makeup.

CHALLENGES AND QUESTIONS/ BARRIERS

The identification of stroke genes is more complicated than is the identification of genes for other neurologic diseases. Stroke has a very high short-term mortality rate that makes

recruitment of living relative pairs much more difficult than in the case of diseases with long survival times, such as Parkinson's and Alzheimer's. Because most strokes occur in the elderly, affected relatives are also more likely to have died from other co-morbid conditions.

Stroke and stroke subtypes have many known environmental risk factors, whereas diseases such as Parkinson's and Alzheimer's have only a few, inconsistently identified environmental risk factors at present. The many environmental factors associated with stroke may confound linkage analyses if they are not accounted for, and may complicate the analysis in general.

There are many mechanisms by which stroke occurs and definition of phenotypes is crucial to identification of susceptibility genes. Phenotypes include:

- Subarachnoid hemorrhage due to rupture of intracranial aneurysm. This is a well-defined phenotype and mechanism. It is also reasonable to include unruptured as well as ruptured intracranial aneurysms within this phenotype.
- Intracerebral hemorrhage. This phenotype includes only a few identified major mechanisms.
- Ischemic stroke. This is the most challenging phenotype; there are many mechanisms by which blood clots can form and cause ischemic stroke.

This phenotypic variability likely will be reflected in genetic heterogeneity as well; there is probably more than one gene underlying stroke. Thus, at the very least, genetic studies of stroke should be

initially designed to address each of the major stroke subtypes separately: subarachnoid hemorrhage due to ruptured intracranial aneurysms (with inclusions of unruptured intracranial aneurysm), intracerebral hemorrhage, and ischemic stroke. A recent report from the company deCODE genetics on the Icelandic population, concerning the identification of a stroke gene related primarily to ischemic stroke and transient ischemic attacks, provides optimism about identifying susceptibility genes, even without further subtyping of ischemic stroke.

Because of the high mortality, late age of onset, and likely genetic heterogeneity of stroke patients, recruitment of sufficient numbers of affected relative pairs is critical to successful identification of susceptibility genes. Genetic studies of complex diseases such as stroke require particularly large numbers of affected individuals and need to be performed in genetically isolated populations as well as in more diverse populations. Other common diseases, such as hypertension and diabetes, have required sampling and genotyping of thousands of affected relatives, and the requirements for stroke are likely to be similar.

Once genes are identified in families where there is aggregation of stroke, the attributable risk (impact of the genetic mutation as a cause of stroke) within the population as a whole and within the population of stroke patients will need to be determined. This determination will require population-based samples of stroke patients and matched controls.

How specific genotypes may modify acute and preventative pharmacologic therapies for stroke will be an important

future issue. The only reported relationship thus far is the association between an Apo E2 genotype and response to t-PA in acute ischemic stroke. While other gene-therapy interactions have yet to be identified, it will be critical to collect genetic samples in clinical trials to begin to address this issue.

Genotype is likely to be related not only to the mechanism of stroke but also to recovery following stroke. The collection of genetic samples in ongoing and future clinical trials will provide a central resource that will help address this issue in the future, even though current hypotheses about genotype and recovery are lacking.

RESEARCH AND SCIENTIFIC PRIORITIES

Our overall long-term goal is to identify genetic polymorphisms that are related to mechanisms of stroke occurrence, response to therapy, and recovery following stroke. To accomplish this goal, we recommend the following research priorities.

Priority 1:

Perform genetic studies of families in which stroke aggregates.

Individual studies are needed for each of the primary phenotypes of intracranial aneurysms (ruptured and unruptured), intracerebral hemorrhage, and ischemic stroke, since these major stroke subtypes are likely to have different susceptibility genes. Large sample sizes will be needed to adequately power these studies, regardless of study design. Ongoing and future case-control studies, and other

study designs, will be critical complementary approaches to identification of susceptibility genes and their impact in the population at large.

Priority 2:

Standardize the methodology for genetic studies of stroke.

Clear and consistently used definitions of stroke phenotypes, standardized collection of environmental risk factor data for inclusion in data analysis, standardized methods of consent for participation in genetic studies of stroke, and standardized methods of obtaining and storing genetic samples from ongoing and future stroke studies are needed. Such standardization will provide the essential data to allow future combinations of data from several studies for meta-analysis of the effect of possible stroke genes.

Priority 3:

Use information from existing clinical/genetic databases for related diseases (e.g., studies of hypertension and diabetes) and from ongoing clinical stroke trials for genetic studies of stroke, to increase the power to identify, test, and characterize susceptibility genes contributing to the risk for stroke.

There are very large, ongoing cohort and epidemiologic/genetic studies of conditions (such as hypertension and diabetes) that are known risk factors for stroke. Stroke as an endpoint has been poorly explored in these databases and new studies and study designs would need to be designed to identify stroke

within these populations. An easily accessible listing of such databases and information on how to gain access to the principal investigators of these studies will be critical for clinical/genetic researchers who wish to explore genes relevant to stroke occurrence in these populations.

Clinical trials of stroke should be encouraged to include collection of genetic samples. These samples can be used to explore the pharmacogenetics of response to therapy and adverse events.

RESOURCES NEEDED

- Large genetic studies of all three major stroke subtypes. Stroke is a complex disease and identification of relevant stroke genes will require substantial levels of financial support, personnel resources, and time. Issues pertinent to these clinical genetic studies are very similar to those of clinical stroke trials: recruitment of a large number of subjects who meet study criteria, adequate power, and the need for efficiency. These studies are most likely to be accomplished quickly and cost-effectively if the centers that are already participating in ongoing clinical stroke trials or epidemiologic studies also function as centers for these clinical genetic studies. Funding mechanisms could include traditional investigator-initiated awards, special grant solicitations, or contracts, if proposals are not forthcoming in the near future.
- A mechanism for maintenance and standardization of the collection and storage of genetic materials from stroke patients in currently ongoing epidemiologic studies and clinical stroke trials. These studies can provide databases critical to evaluating the impact of identified candidate stroke genes in the population overall. A task force could be formed by NINDS to help standardize a basic informed consent for collection of genetic materials, definitions of phenotypes, and standardization of the key environmental risk factors and demographic variables that need to be collected with the genetic samples.
- Consolidation of efforts of other research groups studying the genetic basis of related conditions (such as hypertension, atherosclerosis, and diabetes). This should include an online database of ongoing studies and funding from the National Heart, Lung, and Blood Institute, NINDS, and other institutes, as well as how to access these investigators and how to collaborate.
- Training of clinical neurologic physicians who are stroke-geneticists. There are currently very few clinical stroke researchers with substantial training in genetics (for example, in population or statistical genetics). Such individuals are best suited to combine the basic knowledge of clinical and basic cerebrovascular disease with the accelerating knowledge and tools provided by the field of genetics.

Defining Disease I (Genomics/Proteomics)

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STATEMENT OF THE PROBLEM

Technological advances in genomics, proteomics, pharmacogenomics, and bioinformatics have the potential to advance research on the biology of stroke and to contribute to diagnosis and treatment. The best ways to apply these emerging fields to stroke are still uncertain, however.

Because the techniques involved are new, the cross-disciplinary expertise, collaboration, and training programs that will be required for them to benefit patients with stroke do not yet exist. To derive maximum clinical benefit from these new advances, it will be essential that:

- Clinical knowledge informs the design of experiments.
- Funding agencies show flexibility in defining what is hypothesis-driven research, to accommodate the less-focused scope of some of these approaches.
- New technologies are made widely available and affordable to researchers.
- Improved methods for analyzing and interpreting massive amounts of data are developed.
- Knowledge of areas such as genomics, proteomics, post-translational modification, protein-protein interactions, and cell biology is efficiently integrated.

- The ultimate goals of improved clinical diagnosis and treatment are maintained.
- Research takes into account the heterogeneity of clinical stroke by addressing differences in etiology (e.g., genetic and acquired causes), pathophysiology (e.g., ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage), and demographics (e.g., stroke in neonates, women of childbearing age, the elderly, and minorities).

The development of inflammatory changes that occur both in the central nervous system and in the periphery modify stroke outcome. At present there is little known about factors or predisposing physiology that influence the response to ischemia. There is also little known about the initial response to ischemia that influences the predilection for subsequent stroke.

CHALLENGES AND QUESTIONS

- Interdisciplinary postdoctoral training programs must be established to develop a new generation of preclinical and clinical stroke researchers who understand and can apply genomic, proteomic, and bioinformatic approaches. Mechanisms must be devised through which established stroke investigators can obtain sufficient training in genomics, proteomics,

and bioinformatics to use these tools in their ongoing work.

- Because these new technologies are expensive and complex, making them accessible to a broad range of researchers will require considerable centralized coordination and support.
- The traditional strategy of designing experiments to test narrowly focused hypotheses may need to be modified to accommodate the broader and less specific hypotheses that drive genomic and proteomic investigations.
- The comparative nature of expression data dictates that for clinical studies or diagnostic applications, panels of standard reagents will be required to normalize these data and to control for a wide range of variables, including age, gender, ethnicity, concurrent disease, and treatment.
- Gene and protein expression profiles should be compared in clinical stroke and animal models of stroke, as one index for evaluating which models most closely resemble clinical stroke.
- Genomic and proteomic analysis should be used to help resolve the heterogeneity of clinical stroke into biologically and perhaps therapeutically distinct disorders.
- Because of the limited accessibility of brain tissue for diagnosis, genomic and proteomic approaches should be used to help identify peripheral markers of disease to assist in clinical investigation, diagnosis, choice of treatment, and prognostication in stroke.
- Ways must be found to facilitate the analysis and interpretation of the massive amount of data that is typically generated in microarray

experiments; for example, better methods are needed for the visual presentation of these large data sets.

- Improved annotation of genomic and proteomic data, including annotation of pathways in which genes and proteins are involved, is required to facilitate their interpretation and clinical application.
- The acquisition of biologically and clinically useful information will likely require close integration of expression data derived from genomic and proteomic analyses with functional analysis at the level of proteins, organelles, and cells.
- In order to ensure that these powerful new approaches yield clinical benefits, close cooperation will be needed between technical experts and preclinical and clinical researchers at all stages of the investigative process, including experimental design, analysis, and interpretation.

BARRIERS

- Genomic, proteomic, and bioinformatic technologies are prohibitively expensive for most researchers and even for many research organizations.
- There are insufficient opportunities for junior investigators to obtain training for careers in genomics, proteomics, and bioinformatics, or for more senior investigators to learn how to incorporate these approaches into their research.
- There is little interaction between investigators who have genomic, proteomic, or bioinformatic expertise and those studying stroke.
- The new technologies are powerful but also limited; for example, gene

expression cannot be equated with protein expression, protein expression cannot be equated with protein function, and protein function does not necessarily predict cell function.

- Some scientists are reluctant to support or engage in research that they view as not being hypothesis-driven, and these individuals must be convinced of the importance of genomic, proteomic, and bioinformatic approaches.
- Standards for validation of data, even within a single laboratory, are in an early stage of development, and more universal standards that would facilitate data-sharing among laboratories and across technologies do not exist.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Facilitate basic science access to genomic, proteomic, and bioinformatics technology and develop methods of data analysis, interpretation, and standardization as they relate to stroke.

- Develop animal model systems that allow identification of pre- and post-stroke peripheral markers using genomic and proteomic approaches. The goals are to identify gene expression changes and protein changes that are associated with stroke and may predict outcome. Genomic and proteomic discoveries must be placed in the context of pathways through which they function. This informatics issue is a major roadblock in the functional

analysis of discovered genes.

- Use genomic and proteomic technologies in the validation of stroke models at the level of effector molecules.
- Explore and validate use of genomic and proteomic technologies in drug development strategies, to determine common mechanisms of action and identify deleterious side effects. Consider collaborative strategies between academic centers and industry.
- Support central access to genomics, proteomics, and bioinformatics. The expense and complexity of the new technologies severely limits their application. Although access is improving in some respects (e.g., the cost of commercial microarray chips has decreased and the number of academic labs producing chips has increased), the costs of software, instrumentation, and expertise are likely to increase. As to the latter, academic organizations have difficulty competing with large corporations in attracting people in these highly competitive areas. Moreover, some important functions -- such as the capacity to perform large-scale validation studies of microarray experiments and their reproducibility on several distinct platforms -- require widespread inter-institutional cooperation. Other high priorities should, therefore, be the development of (1) centralized, NINDS-supported microarray facilities with abundant access to arrays for basic studies of reproducibility, quality control, and cross-platform comparison, and (2) high-performance computational facilities with dedicated full-time computer scientists, programmers,

- and system administrators.
- Develop tools to analyze and visualize data. Internet-based programs linking genomics and proteomics to biological pathways need to be developed and made available to researchers. Tools for biological problem solving are required for broader solutions to the integration of genomics with proteomics data, the inclusion of experimental results from the biomedical literature, and the resolution of cellular pathways. Clinical databases like Online Mendelian Inheritance in Man (OMIM) exist and an excellent site developed by the National Cancer Institute (<http://cgap.nci.nih.gov>) is available to all investigators interested in cancer. Similar resources in the area of stroke would be widely used.
 - Develop knowledge-based computational tools to model the cellular, molecular, and physiological responses to ischemia by computer modeling techniques (in silico).

Priority 2:

Create a structure for defining stroke at a molecular and mechanistic level. This should include the creation of methods and protocols for the collection of biological samples for genomic, genetic, and proteomic studies linked to current and future National Institutes of Health (NIH) trials. With basic research as a template, identify molecular markers or profiles of stroke and stroke risk in patients to include gene profiling (functional genomics) and inflammatory/cellular mediators.

Specifically, the following parameters should be included in a re-evaluation of the definition of stroke:

- Identification of specific physiological settings (e.g., infection, inflammatory disease, and drug therapies) that influence the response to ischemic injury.
- Identification of peripheral markers that modify stroke outcome, such as cells (lymphocytes, monocytes, neutrophils) that are responsible for the ischemic inflammatory infiltrate and can be sampled from peripheral blood.
- Identification of peripheral changes (such as cytokine levels) that occur in response to ischemia and that influence the predisposition to subsequent stroke and the response to that stroke.

In addition, researchers should:

- Define specific markers in well-established animal models and confirm the utility of these markers in prospective studies in humans.
- Develop protein-based assays (chips) to correlate peripheral changes with genomic alterations in the brain during ischemia. Implement high-throughput mass spectroscopy for proteomic evaluation. Development of databases from subjects without stroke will also be helpful in making meaningful comparisons.

Priority 3:

Recruit geneticists and molecular biologists into collaborations with stroke researchers (both clinical and basic science), with the objective of achieving near-term progress in

capitalizing on current technologies. In parallel, enhance the recruitment of young and mid-career scientists into existing training programs.

Very few people have expertise in these new fields and also in stroke. Moreover, investigators in these fields and stroke researchers typically have limited contact with each other in their institutions, at meetings, and through the literature. However, this sort of combined expertise and interdisciplinary interaction will be critical if genomic, proteomic, and bioinformatic approaches are to be applied to stroke in a useful way.

High priority should be given to the establishment of:

- Postdoctoral fellowship programs for Ph.D.s, M.D.s and M.D.-Ph.D.s that combine instruction in genomics, proteomics, and bioinformatics with either basic laboratory research related to stroke or advanced clinical training in stroke.
 - Short courses involving both didactic and hands-on exposure to these areas for established investigators who wish to use them in their research.
- Interdisciplinary conferences to bring together investigators from each of these areas.

RESOURCES NEEDED

- Funding for interdisciplinary postdoctoral and mid-career training programs in genomics, proteomics, and bioinformatics in relation to stroke.
- Centralized genomic/proteomic/bioinformatic facilities capable of supporting the technology, instrumentation, and personnel required to provide arrays and reagents, large-scale validation, and advanced analysis and annotation of genomic and proteomic data to stroke researchers. Such facilities should include an education and support component specifically to address experimental design issues and utilization of the technology that is effective at both the scientific and financial level.
- Initiatives to encourage the application of these new technologies to basic and clinical stroke research.

Defining Disease II (Imaging)

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STATEMENT OF THE PROBLEM/ PROGRESS REVIEW

The field of neuroimaging has produced major advances in the diagnostic evaluation of cerebrovascular disease during the past 25 years.

Computerized Axial Tomography

The development of computerized axial tomography (CT) in the early 1970s revolutionized the diagnosis of acute stroke, primarily because of its ability to detect acute hemorrhage. Today, CT remains the standard diagnostic imaging procedure in this setting. Intracerebral hemorrhage size on CT has proven to be accurate for prognosis of ICH. Serial CT scanning showing progressive enlargement of intraparenchymal hemorrhage early after onset has identified an important cause of post-hospitalization deterioration. CT scanning has also proven useful in the management of patients following ruptured aneurysms to detect hydrocephalus, re-bleeding, and cerebral infarction.

The accuracy of CT for detecting hemorrhage led to its use as a requirement for determining eligibility for treatment with thrombolytic agents, currently the only approach with demonstrated efficacy in the therapy of

acute stroke. Delayed CT also permitted the visualization of the precise area of the brain that was damaged by cerebral infarction. This has, in many cases, improved differentiation of anterior circulation infarcts from posterior circulation infarcts, permitting more appropriate use of carotid endarterectomy for secondary prevention. Recent attention to CT in the hyperacute period has demonstrated its sensitivity for detecting early signs of cerebral infarction within six hours of onset. However, even with the accepted widespread use of CT for stroke, solid data demonstrating that the use of CT improves patient outcome is lacking in most instances.

Magnetic Resonance Imaging

Proton magnetic resonance imaging (MRI) is noninvasive and provides improved resolution and tissue contrast for detecting ischemic changes, vascular anomalies, and evidence of prior hemorrhage. MRI is widely used in the clinical evaluation of transient ischemic attacks and stroke, and has shown increased sensitivity over CT for detecting small and posterior fossa infarcts. Its sensitivity in detecting acute intracranial blood remains unknown, primarily due to a lack of studies in this area. The development of diffusion-weighted MR imaging and its

quantitative correlate of regional measurement of the apparent diffusion coefficient (ADC) has made it possible to visualize cerebral ischemia very early after onset, before CT- and other MRI-detectable changes occur. While much still needs to be learned about the biological basis of this signal, clinical practice is defining its sensitivity, specificity, and temporal evolution for diagnostic purposes. Yet, studies prospectively demonstrating that the increased sensitivity of MRI for early and small lesions actually improves patient outcome or reduces costs remain to be carried out.

Arteriography

Catheter arteriography remains the gold standard for defining the anatomy of intracranial and extracranial blood vessels. The pathophysiological relevance of arteriography has been demonstrated empirically by the close correlation between the degree of arteriographic carotid stenosis and the subsequent risk of stroke in medically treated patients. Arteriography has also been extensively used for the diagnosis of and surgical treatment planning for aneurysms and arteriovenous malformations and for the diagnosis of vasospasm after subarachnoid hemorrhage.

Noninvasive Visualization of Vessels

Due to the invasive nature of arteriography and the small, but real, complication rate, a great deal of effort has been devoted to the development of alternative techniques to visualize the vasculature. These alternative methods also have the potential to provide more rapid images, with the possibility of use

at the bedside. Carotid duplex Doppler ultrasound has been developed into a useful screening tool of the extracranial carotid arteries for severe stenosis and can be used to study the characteristics of the carotid plaque. However, variations in machine and operator characteristics make it necessary to perform validation studies versus arteriography in each individual laboratory. Transcranial Doppler ultrasound of the intracranial vessels is also widely used to detect intracranial stenosis and occlusion, though its accuracy and clinical utility remain to be fully established. Flow-sensitive MR techniques also provide information about the cerebral and cervical blood vessels and have found widespread application, including screening for aneurysms. Use of rapid-sequence CT following intravenous bolus injection of X-ray contrast agents also has recently been used to study the cerebral and cervical vessels. The accuracy and clinical utility of MR and CT angiography versus catheter angiography remains to be formally established by appropriate studies.

Physiological Imaging

The development of positron emission tomography (PET) in the mid-1970s launched the modern era of physiological imaging in cerebrovascular disease. Physiological neuroimaging of cerebrovascular pathophysiology in humans provides a critical translational link to laboratory research. The relevance of information derived from cellular and animal models to human disease can be determined and, vice versa, human pathophysiological data can be used to design more appropriate experimental systems. PET remains the

standard for quantitative, accurate, regional measurements of cerebral blood flow and metabolism. Its complexity and expense have thus far precluded widespread general use in cerebrovascular disease, but this may change with the growth of PET facilities for oncology imaging. PET has provided important new insights into the pathophysiology of both acute and chronic cerebrovascular disease. MRI and CT approaches have also been developed for examining cerebral blood flow and related hemodynamic parameters, and are much more widely available than PET, though their accuracy has not been conclusively established.

Imaging of Acute Stroke

The development of clinically practical physiological imaging in acute ischemic stroke has led to a great deal of interest in trying to identify brain tissue that is viable early on but will go on to die if left alone. Accurate identification of this physiological “ischemic penumbra” would be extremely valuable because it would facilitate clinical trials and allow clinical care of acute stroke to be targeted to those patients who can benefit from treatments designed to salvage tissue. A variety of measurements, including cerebral blood flow and nonquantitative perfusion alone or in combination with other tissue signatures, have been proposed for this purpose. However, few validation studies have been conducted to show that these techniques can accurately identify viable but doomed tissue.

Methods for portable imaging of physiological change, primarily using optical imaging methods, are also under current development. While these

approaches afford the promise of providing diagnostic information at the bedside or in the ambulance, significant technical and methodological challenges remain to be met before they can be considered for clinical application.

Recent advances in understanding the cellular and molecular changes that accompany ischemic events in animal models have provided many new insights into the mechanisms of ischemic injury. Concomitant with this is a need to develop imaging methods that will allow these processes to be visualized in human patients. Because of its high sensitivity, PET imaging with radio-nuclide tracers is most likely to meet this need, though efforts to link paramagnetic contrast agents to molecular markers for use with MRI are also underway.

Imaging of Chronic Cerebrovascular Disease

While much of the interest in brain imaging in cerebrovascular disease has focused on its use in the evaluation and management of patients presenting with acute stroke, there are numerous opportunities for imaging methods to contribute to the evaluation and management of chronic cerebrovascular disease. Applications include optimization of pharmacological therapy, stratification of patients for prophylactic procedures such as extracranial-intracranial bypass surgery, and the use of sequential imaging to better define the natural history of cerebrovascular disorders.

Recovery of function from stroke is of paramount importance to patients and families, yet the mechanisms of recovery remain poorly characterized, and it is

unclear which interventions influence outcome. Functional imaging methods could potentially assist in this issue by providing direct visualization of brain function, even in the absence of overt behavioral manifestations, though the validity of imaging markers for neural activity in the setting of cerebrovascular disease also needs to be validated.

CHALLENGES AND QUESTIONS

In the next decade, neuroimaging will advance the treatment of cerebrovascular disease in two important ways.

First, neuroimaging of cerebrovascular pathophysiology in humans will provide a critical translational link to laboratory research. Direct translation of the results of mechanistic and preclinical pharmacological studies in experimental systems to therapeutic interventions in humans have not met with much success. While there are many potential reasons for this, the differences in pathophysiology between human and animal model systems undoubtedly contribute. Neuroimaging provides the methodology to directly test whether specific mechanisms identified in animal systems are important in humans. Similarly, a better understanding of human pathophysiology can lead to the development of improved animal models. Furthermore, studies of drug delivery and of the biological effects of different treatment interventions will be of value to screen potential therapies for efficacy and to determine the proper parameters for dose, duration, and time window. This approach will require not only the use of currently available technology but also the development of new methods to image molecular, cellular, and functional processes.

Second, neuroimaging will provide predictive information to stratify clinically similar patients into different outcome groups. Since neuroimaging provides both physiological and structural information about cerebrovascular disease over and above that available from conventional risk factors and the clinical examination, it can be used to further improve the prediction of outcome for both acute and chronic cerebrovascular disease. Such outcome measures may initially include anatomic endpoints such as reduction of infarct size, but must eventually rely on clinically relevant outcomes such as functional status or subsequent stroke. This predictive information can be used in two important ways to advance clinical treatment trials. First, selection of patients based on physiological or structural criteria can identify groups of patients most likely to benefit from a given treatment. Second, if a predictive factor is demonstrated to be reliably and precisely related to an important clinical endpoint, it can be used to stratify enrollment or, in the best of circumstances, as a surrogate marker in Phase 2 or Phase 3 trials.

Data obtained in individual cases or small series demonstrate the feasibility of all of these approaches. For example: (1) neuroimaging of ischemic stroke has demonstrated that the evolution of damage takes place over hours, not minutes, (2) neuroimaging of intracerebral hemorrhage greater than six hours old has failed to document any evidence of ischemia, (3) imaging of the carotid arteries is necessary for selection of patients for carotid endarterectomy, and (4) PET measurement of oxygen extraction fraction determines stroke risk in patients with symptomatic carotid

occlusion and has provided a basis for an intervention trial.

The challenge is to further implement these approaches more widely. More extensive studies are needed to define the pathophysiology of human cerebrovascular disease in all ages, encompassing acute and chronic ischemia, atherosclerosis, hemorrhage, and recovery in populations. The value of neuroimaging to predict outcome under a variety of different conditions must be validated by rigorous studies, most likely requiring prospective multicenter trials. This validation approach, while accepted for therapeutics, represents a new direction in the evaluation of imaging.

BARRIERS

The following barriers to achieving these advances were identified:

- Lack of integration between basic and clinical research in the study of the pathophysiology and treatment of cerebrovascular disease.
- Inadequate infrastructure to support prospective hypothesis-driven clinical cerebrovascular research employing neuroimaging, including timely access to scanners, technical support, and financial support.
- Lack of training in research neuroimaging methods for both clinical investigators and basic scientists.
- Poor communication and collaboration between centers engaged in cerebrovascular neuroimaging research.
- Insufficient methodology for image analysis of complex 4-dimensional data sets.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Define the relevant pathophysiologic mechanisms in human cerebrovascular disease as determined by molecular and functional neuroimaging, and integrate this knowledge with appropriate data from experimental systems to develop new therapeutic approaches.

This priority employs neuroimaging as the critical translational link between lab experiments and human disease. It employs existing methodology and supports the development of new methods for elucidating the pathophysiology of human disease and testing specific mechanistic hypotheses derived from animal model systems for their relevance in human disease. This approach uses neuroimaging as a scientific measurement to study pathophysiology and thus requires careful validation studies for accuracy and a clear understanding of the biological basis of each neuroimaging modality and measurement. The goal is to integrate this information as a means to develop new treatment strategies.

Priority 2:

Identify and prospectively validate neuroimaging markers of tissue injury for prediction of clinical outcome in large patient samples.

This priority refers to existing markers of vascular, physiological, and functional derangement, as well as the development of new markers of function and injury. The application is to all aspects of acute and chronic

cerebrovascular disease, including pre-symptomatic vascular disease, ischemic stroke, intracerebral hemorrhage, and aneurismal subarachnoid hemorrhage. This approach uses neuroimaging for clinical prediction and thus requires well-designed studies free of bias that provide empiric proof of accuracy in the clinical setting in which it will be applied.

Priority 3:

Identify neuroimaging markers of potentially salvageable brain tissue in acute stroke.

This priority refers to the application of existing or novel neuroimaging measures of vascular and/or parenchymal function to determine the potential for response to therapy. Pursuit of this priority will further refine the concept of the “ischemic penumbra” and will seek to expand the treatment window for patients presenting with symptoms of acute stroke.

RESOURCES NEEDED

- Support for round-the-clock, dedicated cerebrovascular imaging

research centers to conduct prospective hypothesis-driven studies, including imaging of hyperacute stroke.

- Support for multicenter prospective studies using neuroimaging methods to characterize the natural history of cerebrovascular diseases and to establish their predictive validity in clinical practice.
- Establishment of an NIH-based clearinghouse for expertise and data exchange, to capitalize on existing resources and to facilitate collaborations and industrial partnerships.
- Support for additional formal fellowship training in research neuroimaging methods for clinical investigators and basic scientists, and for visiting scientist fellowships, to promote cross-education among those already established in the field.
- Support for satellite meetings in cerebrovascular imaging, to occur in conjunction with international meetings such as the American Stroke Association's International Stroke Conference.

EXHIBIT I

Specific Areas for Future Research

1. Multicenter studies to determine if the application of diffusion MRI and magnetic resonance angiography, as opposed to CT, in acute stroke results in improved patient outcome and/or reduced healthcare costs.
2. Multicenter studies with standardized methodology in patients who are more than three hours post-acute ischemic stroke, to determine if neuroimaging accurately identifies brain tissue that will die if untreated but would regain or maintain function if treated with t-PA.
3. Careful validation studies of CT and MR vascular and perfusion imaging modalities against arteriography and quantitative cerebral blood flow measurements, incorporating a wide variety of patients with cerebrovascular diseases, including atherosclerosis, vascular malformations, and aneurysms.
4. Development of imaging techniques that can be performed in the emergency room or at the bedside, simply and rapidly.
5. Development and validation in relevant animal models of new molecular and physiological tracers and data analysis techniques for differentiating viable from nonviable tissue in acute ischemic stroke.
6. Multicenter studies with standardized neuroimaging methodology in patients who are more than three hours post-acute ischemic stroke, to determine if parenchymal and/or vascular neuroimaging accurately identifies patients at risk for intravenous or intra-arterial thrombolysis-induced intracerebral hemorrhage.
7. Studies to determine the relative sensitivity and specificity of CT and MRI for detecting acute parenchymal and subarachnoid hemorrhage.
8. Studies to determine the neuroimaging correlates of post-hospitalization deterioration and mortality following intracerebral hemorrhage.
9. Studies of neuroprotective drugs, to determine if they can penetrate the ischemic penumbra in humans at sufficient concentrations to be effective.
10. Studies of cerebral blood flow measurements with varying degrees of induced hypertension and cardiac output augmentation with different drugs in patients with subarachnoid hemorrhage with vasospasm.
11. Studies that incorporate a large number of ischemic stroke patients with different infarct sizes and clinical severity, to determine: a) if neuroimaging findings in the acute period can accurately predict ultimate infarct volume, b) if ultimate infarct volume or change in lesion volume from the acute to the chronic phase correlates with clinical outcome as measured by neurological, functional, or cognitive measures, and c) if there are neuroimaging findings

- that can improve the predictive value over the clinical examination performed in the acute period, using standardized methodology.
12. Studies of patients treated with t-PA, to determine if there are neuroimaging findings that accurately identify tissue that has been salvaged from ischemic damage.
 13. Development of rapid-analysis methods for multi-modality image data suitable for clinical application.
 14. Studies that use functional imaging methods to localize and quantify regions of volitional neural activity in patients with deficits, to assess the effects of interventions such as forced use or pharmacological therapy on recovery, or to interface with bionic devices.
 15. Studies that explore imaging of disseminated neuronal loss (e.g., by N-acetylaspartate levels detected by magnetic resonance spectroscopy or C-11 flumazenil PET).
 16. Studies that, under circumstances in which carotid endarterectomy is not to be performed for asymptomatic carotid stenosis, perform hemodynamic or plaque imaging and follow to determine if any of these tests accurately predict subsequent stroke.
 17. Studies that correlate noninvasive imaging with quantitative assays of blood flow and metabolism in disease-relevant animal experiments.

Epidemiology and Risk Factors

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STATEMENT OF THE PROBLEM

Stroke is the third leading cause of death in the United States today but current understanding of its etiology and variations (among groups and over time) is insufficient to provide the foundation needed for effective strategies to reduce stroke mortality and morbidity in the foreseeable future. Stroke remains a challenging disease to address with epidemiological methods for several reasons, including:

- Stroke is heterogeneous and comprises a number of pathological conditions; these conditions share the common manifestation of brain injury caused by disease of the cerebral vasculature. There are two major challenges: accurate detection of stroke cases, and distinguishing between stroke subtypes. Separation of hemorrhage from infarction has been dramatically improved and is currently easily accomplished by brain imaging.
- Distinguishing among cerebral infarction subtypes remains problematic and has been only partially improved by intensive, sophisticated, and comprehensive clinical and laboratory evaluation of each stroke patient. Such evaluations depend upon modern “high tech” methods and neurological sophistication not universally available, thereby preventing (or at least impeding) comparisons between populations.
- To examine the frequency and determinants (epidemiology) of these stroke subtypes in different populations and geographic locations, it will be necessary to devise a strategy for stroke subtype determination that is independent of the risk factors themselves. This will permit examination of risk factors, recurrence rates, and outcomes of the various subtypes in different populations over time.
- There are major confounding factors, including ethnicity, socioeconomic status, geographic region, and gender, which complicate study design and limit our ability to generalize results.
- Characteristics strongly related to stroke incidence and mortality, such as race, are confounded by a variety of social and cultural factors, such as education, level of medical care, and others that are difficult to enumerate or quantify.
- The understanding of stroke epidemiology lacks data on basic dimensions such as the role of incidence versus case-fatality of stroke; information is particularly lacking in specific stroke subtypes. Such data are key to explaining the large observed differences known to exist between populations defined by

race/ethnicity, geographic region, or socioeconomic status. In addition, an understanding of the risk factors for stroke is only now beginning to emerge, with the majority of current data limited to specific population groups (most notably northern whites).

CHALLENGES AND QUESTIONS/ BARRIERS

Lack of Data

While there are selected exceptions (the Framingham Heart Study, the Rochester, Minnesota Epidemiology Project, the Northern Manhattan Stroke Study, the Atherosclerosis Risk in Communities study, the Cardiovascular Health Study, and others), further advances in stroke epidemiology will require additional detailed population-based data on stroke risk and outcome. Particular issues include: (1) the selection of study designs to collect data to establish incidence, outcomes, and the role of risk factors (cohort, case/control, etc.), (2) the evaluation and inclusion of individuals with a broad representation of confounding factors (ethnicity, geographic region, etc.), and (3) inclusion of a sufficient sample to provide meaningful study of differences in subgroups defined by age, ethnicity, gender, and other factors, where different factors are likely to be playing substantially different roles.

Lack of Accurate Subtype-Specific Data

As noted above, the processes underlying stroke differ by disease subtype, and specific studies may be needed within broad subtypes such as

infarction or hemorrhage. This implies a need for sufficient resources to draw meaningful inferences within subtypes, and the need to develop classification procedures that are not defined by the risk factors for the disease under study.

Poorly Defined Racial/Ethnic and Socioeconomic Factors

Race/ethnicity is substantially confounded with socioeconomic status and cultural factors, and attempts to provide adjustments require the quantification of socioeconomic status beyond the education/income/occupation measures currently employed. Cultural contexts needed to understand differences by race/ethnicity and socioeconomic status include measures of discrimination, stress, acculturation, language barriers, differences in access to healthcare, and others.

Poor Understanding of the Epidemiology of Outcome Following Stroke

Improving our understanding of the prevention of secondary or subsequent stroke events among those with prevalent disease is necessary. The risk factors for subsequent stroke may differ substantially from the risk factors for the first stroke, and a deeper understanding of these factors is critical to preventing such subsequent events.



In addition to subsequent stroke events, epidemiology of outcome as characterized by cognitive and functional disability following stroke is lacking. The identification of factors associated with positive functioning outcomes is the first step of interventions that may maintain or improve the life of

the stroke patient, as well as caregivers, following stroke events.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Characterize the public health burden of stroke and establish subpopulations for special emphasis.

The foundation approach to characterizing the public health burden of stroke is to develop a national, population-based surveillance system to establish incidence rates for stroke, both overall and by stroke subtype. This surveillance system needs to be prospectively designed to provide detailed information on incidence rates, with strata defined by age, geographic region, and race/ethnicity. These strata-specific incidence estimates will serve as the foundation to estimate the proportion of the well-known differences in stroke mortality rates between these strata that are attributable to differences in incidence (rather than case fatality, which will be addressed below), as well as the case-mix of stroke subtypes between these strata. Of equal importance, this resource will provide the mechanism to prospectively track temporal changes in incidence, allowing for appropriate shifts in resources and research efforts in response to changes in the incidence rates (both overall and by stroke subtype), as well as shifts between the strata defined by demographic factors.

A well-designed surveillance system naturally results in a sizable cohort of stroke patients. The follow-up of this cohort will serve the secondary aim of

establishing the magnitude and determinants of the public health burden associated with the post-stroke period. Specifically, the cohort can be used to estimate the costs associated with long-term treatment, and the mortality, recurrence, and morbidity (including both recovery and cognitive decline) associated with the stroke event. For each of these domains, the cohort can also be used to establish the determinants that place stroke patients at risk for differential outcomes.

Finally, links between the national surveillance cohort and administrative databases can be investigated, to provide determinants of cost-effectiveness and patterns of resource utilization on the national level.

Priority 2:

Establish the new determinants of stroke and its consequences and identify subgroups with varying risk.

The current understanding of the determinants of stroke and its consequences is only partially successful in providing prognostic information on stroke incidence, mortality, morbidity (including recovery and cognitive decline), recurrence, and subclinical disease (including silent cerebral infarction). For each of these domains, additional case/control and cohort studies are needed to refine the information and understand the prognostic factors. Issues that need to be addressed include:

- The establishment and description of new and novel determinants of disease, including infection, inflammation, and coagulation.

- The identification of specific subgroups at differential risk.
- A better understanding of existing (“traditional”) factors.
- Improved understanding of the role of genetics and gene-environment interactions in stroke and their consequences.

Each issue needs to be addressed overall as well as within strata defined by ethnicity, gender, stroke subtype, age, geographic region, and socioeconomic status.

Priority 3:

Integrate epidemiology into clinical management and prevention.

The hypotheses addressed in epidemiological studies need to be designed so that the results collected are useful to the anticipated users of this information. Specifically, studies should be designed to meet the information needs of investigators from the fields of policy development, randomized clinical trials and primary prevention, systems development, and the lay public and healthcare workers at all levels. In addition, hypotheses should be developed to address issues raised in related fields, including cardiovascular disease, peripheral vascular disease, subclinical disease, and brain injury.

Finally, there is a need to establish systems for data sharing by other investigators and clinicians.

RESOURCES NEEDED

- Continued research efforts on the epidemiology of stroke, specifically to expand efforts in (1) the continued development of population studies (cohort, case control, etc.) for elucidation of risk factors, and (2) the development of a population-based surveillance system for estimating incidence and outcome following stroke.
- The development of mechanisms for linkage of information collected in the epidemiological studies, including the development of methods and infrastructure (i.e., Internet-based sharing systems) for sharing stroke data by “outside” investigators. As part of the resource, consistent documentation, ideally with common definitions, needs to be developed for domains assessed in the studies.
- The development of links with epidemiological databases from other sources (e.g., insurance companies and health maintenance organizations), including improved methods for clinical informatics.
- Research approaches that ensure access to patient data while protecting patient confidentiality.

Prevention of First and Recurrent Stroke

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STATEMENT OF THE PROBLEM

Epidemiological studies carried out over the last decade have clearly identified factors associated with increased risk of ischemic stroke and intracerebral hemorrhage. In addition, clinical trials have identified interventions that can reduce initial and recurrent stroke risk. Both vascular risk factors and stroke-specific factors, such as atrial fibrillation and carotid stenosis, have been demonstrated to be prevalent and modifiable. However, recent work has shown that a significant proportion of stroke-prone individuals do not receive appropriate therapy, despite the dissemination of evidence-based recommendations. This is likely due to a combination of factors, including failure in patient compliance, lack of adherence to evidence-based guidelines by healthcare providers, and the inability of the healthcare system to provide adequate resources.

Additionally, while the prevalence of stroke risk factors varies across populations in the United States, the greatest burden of risk factors is borne by an underserved segment of the population. Thus, those at greatest risk are the least likely to benefit from recent advances in initial and recurrent stroke prevention.

Current issues in first and recurrent stroke prevention focus on:

- Recognition that well-defined stroke risk factors are highly prevalent and that modification of risk factors is inadequate in the U.S., especially in minority populations.
- Evidence that initial and recurrent stroke risk can be reduced through implementation of interventions demonstrated to be effective by randomized clinical trials.
- Acceptance that the degree of compliance with current stroke prevention recommendations varies across the U.S., but is generally poor, particularly in areas underserved by the healthcare system.

Effective risk factor modification offers great potential to significantly reduce stroke incidence and recurrence. An understanding of why proven therapies are not being used, especially in vulnerable populations, is essential for designing and testing implementation strategies. The current challenge is to take what has been learned through cardiovascular prevention research and incorporate it into stroke prevention interventions. The efficacy of these strategies to modify a risk factor, affect an intermediate endpoint, or reduce stroke incidence can then be tested.

CHALLENGES AND QUESTIONS/ BARRIERS

- Recognizing that there are limited research and healthcare resources, it is unclear whether stroke prevention strategies should utilize the “mass” or the “high risk” approach. Risk stratification models may be one strategy for quantifying risk and targeting specific populations.
- Other than medical therapies for hypertension and atrial fibrillation, little is known about the impact of cardiovascular risk factor modification for prevention of recurrent strokes.
- The emergence of methods for detecting subclinical disease (i.e., genetic studies, carotid intima-media thickening, C-reactive protein, silent stroke, and white matter disease) has led to uncertainty in the definitions of primary and secondary prevention. It remains unclear which populations, if any, should be screened for “silent” cerebrovascular disease. The method and type of intervention may vary significantly based on the stage of disease and the population affected.
- The low rates of compliance with established prevention guidelines indicate that there are obstacles to implementing these guidelines. Failure to adequately address stroke prevention issues may be due to patient noncompliance, a lack of awareness on the part of the healthcare provider, or an inability of the community or healthcare system to provide diagnostic or therapeutic resources. Patient values and preferences vary based on socioeconomic status, race/ethnicity, and gender, and these need to be

assessed in evaluating our understanding of noncompliance. In addition, it is important to determine the most cost-effective strategies to educate healthcare providers about first and recurrent stroke prevention and to develop better methods of integrating this information into routine clinical practice.

- There has been little stroke-specific research examining how to best measure the impact of prevention interventions. In order to detect a significant effect on stroke rate, particularly in low-risk populations, expensive clinical studies with large sample sizes would have to be undertaken. The use of intermediate endpoints, such as changes in the level of a biological marker or reduction in a calculated stroke risk score, may facilitate the design of novel studies to assess the impact of specific interventions in pilot trials.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Improve implementation of existing, proven stroke prevention guidelines by (1) identifying barriers to such implementation by assessing the individual, healthcare providers, and the healthcare system, (2) studying methods of overcoming these barriers, and (3) supporting the development of research evaluating the effectiveness of innovative initial and recurrent stroke prevention interventions, especially in underserved populations and minority racial/ethnic groups.

Appropriate management (behavior modification, lifestyle changes,

management of vascular risk factors, and medical/surgical therapy) may reduce initial and recurrent stroke risk and improve both the length and quality of life. Despite proven benefit, however, patients commonly fail to achieve accepted goals for risk factor modification before and after stroke. The reasons for failure to implement guidelines need to be explored in a variety of healthcare settings. One issue may be the dissociation between population and individual benefit. Special considerations may need to be given to younger populations and to individuals without traditional risk factors.

Once barriers have been identified at the three points in the prevention paradigm (individual, healthcare provider, and healthcare system), studies should evaluate novel interventions to improve initial and recurrent stroke prevention. Interventions aimed at the individual may include education, behavior modification, attention to health state preferences, use of support groups, empowerment, and incentives. Healthcare providers may benefit from education, clinical informatics, and incentive programs. Modification of healthcare systems may include changing access patterns, implementing quality assurance programs, and restructuring patient care reimbursement. In the design of these studies, it is essential to measure the clinical efficacy and cost-effectiveness in a variety of healthcare settings, especially in medically underserved and minority racial/ethnic groups. The use of intermediate endpoints in the design of pilot studies may provide justification to proceed with larger confirmatory clinical trials.

Priority 2:

Develop and examine the effectiveness of quantitative risk factor assessment tools that can identify stroke-prone individuals who need aggressive risk factor management and initial and recurrent stroke prevention intervention, with particular emphasis on underserved populations and minority racial/ethnic groups.

Identifying and treating those at highest risk of developing cerebrovascular disease remains a major challenge and a public health imperative. The use of risk assessment tools by healthcare providers and individuals can contribute greatly by identifying even low-risk persons likely to benefit from intervention. Risk assessment tools that include innovative markers of risk can improve upon conventional models. These assessment tools must be flexible, in order to incorporate new risk factors and to allow for calculation of risk in the case of missing data (incremental models). The development of these tools must take into consideration issues of risk-factor measurement (such as discrete vs. continuous variables), as well as validation in many racial/ethnic groups.

Priority 3:

Support research designed to identify and evaluate innovative stroke prevention treatments and strategies.

There is great promise that future epidemiological studies will identify new stroke risk factors. Pharmacological research could help identify new agents capable of modifying these factors, and subsequent randomized clinical trials could then evaluate the efficacy of these

new prevention treatments or strategies. For example, recent evidence that HMG-CoA reductase inhibitors and angiotensin-converting enzyme-inhibitors play multifunctional roles in preventing stroke has increased the number of potential medical therapies. Next-generation antiplatelet agents and thrombin inhibitors may similarly expand the role of antithrombotic therapy in first and recurrent stroke prevention. New antiinflammatory agents may help reduce the risk of stroke and retard atherosclerosis progression. In addition, there may be specific dietary and lifestyle practices that will prove to help reduce the risk of stroke. These and other as-yet-unproven therapies need further investigation through randomized clinical trials. Further successful results could lead to important modifications of future comprehensive stroke prevention recommendations.

RESOURCES NEEDED

- Expedited funding for studies that will identify barriers to stroke prevention implementation and for pilot trials (with subsequent definitive multicenter trials) to evaluate novel interventions that may overcome these barriers.
- Programs to perpetuate those interventions that are found to be beneficial, once clinical trials have been completed.
- Comprehensive “stroke systems” that consolidate prevention, acute management, education, and rehabilitation services within a defined network, in order to test the prevention interventions.
- Support for the development of a national, population-based stroke surveillance system, and for the removal of barriers (such as confidentiality issues, inefficiencies of retrieval, and lack of validation) that are limiting access to high-quality administrative data.
- Improved and expanded training in stroke prevention for non-neurologists and stroke specialists.
- Partnerships with industry, government, and volunteer organizations in the implementation of strategies to prevent initial and recurrent stroke.
- Expanded translational research to increase the number of recognized risk factors that are subject to modification.
- Support for the development of novel statistical methods, such as incremental modeling, to assess stroke risk and to develop risk-stratification tools.
- Coalitions to develop consolidated vascular prevention guidelines that will help simplify messages for primary care providers and the public.

Acute Stroke Treatment

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STATEMENT OF THE PROBLEM

The problems associated with acute stroke care are found in three related and often overlapping areas:

- Acute care infrastructure
- Research infrastructure
- Therapeutic innovations

Acute Care Infrastructure

Problems with acute care infrastructure are found in a number of different areas, including the number of individuals who are treated, the time it takes for them to get treatment, and the experience level of the teams that treat them.

One option for improving the overall care of individuals with stroke is to center this care around community hospitals, with support and coordination for tertiary centers designated as comprehensive stroke centers.

Community-Centered Care

People with symptoms of stroke typically present at their community hospital first; it is unlikely that they will all present to a single, tertiary stroke center. For this reason, health care systems should focus on community-based infrastructure.

With regard to how long it typically takes people to respond to the symptoms of stroke and seek treatment, continued public education efforts will be critical. NINDS and voluntary health agencies have already provided support for such programs, but it is important that future educational efforts urge the public to see the symptoms of an acute stroke as an emergency situation, and also encourage emergency personnel to deliver these individuals to the best, closest facility.

The quality of care currently varies among community hospitals. Ideally, a stroke center should include a round-the-clock stroke team, the ability to triage patients appropriately, and immediate CT scanning. However, these services are not offered at many community facilities. Consequently, too many hospitals are currently accepting stroke patients without adequate preparation or resources.

For these reasons, designated stroke centers could be very helpful; however, further translational research will be needed to ensure that appropriate methods are used for designating centers, monitoring their performance, and improving their patient care.

Stroke Center Designation

Many groups consider the designation

of stroke centers as an appropriate solution to the problem of hospitals that are not sufficiently prepared to manage stroke patients. A system for this designation has been considered a high priority, and as a result, the Brain Attack Coalition published guidelines for stroke centers in June 2000. However, the official authorization of stroke centers is still a subject of ongoing discussion. Who should be in charge of this authorization? NINDS or a professional society are both options, though it will likely take a multi-disciplinary effort to ensure that appropriate guidelines are implemented.

It is believed that the designation of stroke centers would be valuable to the field, since it is already known that the prompt use of thrombolytics improves outcomes and stroke centers that are well-equipped, well-staffed, and prepared are able to deliver these drugs more quickly. However, considerable translational research will still be needed in order to demonstrate the long-term benefits of stroke centers on patient outcomes. As part of this effort, centers will need support for the collection of appropriate outcome and process data.

Research Infrastructure

At present, stroke research is also hindered by the lack of a research infrastructure that can enable the translation of basic science findings to clinical phases of development. The development of centers or programs that could conduct studies and provide a framework within which collaborations could form has very broad support. Research centers could also contribute to the development and testing of therapies.

The identification of one or more entities that would be responsible for the administrative functions of a stroke research center is another unresolved issue. Commercially sponsored translational research typically focuses on a single, potentially profitable agent. In contrast, the type of translational research infrastructure that is needed would enable hypothesis-driven research to be conducted. In an appropriate framework, the findings from these studies could be translated into projects with significant clinical relevance.

In terms of funding for translational research, it is unlikely that this type of infrastructure would be funded privately. Research progress in acute stroke is likely to be incremental, and pharmaceutical companies are often skeptical that treatments for acute stroke will be profitable. For these reasons, they may hesitate to devote resources to these specific research needs.

Cooperative Clinical Trials

The concept of cooperative clinical trials emerged from cancer research centers, where the collaboration of several centers has been necessary to investigate rare forms of the disease. Individual institutions that treat stroke patients are in a similar situation: they may not see enough patients to support a clinical trial, in some cases because the affected individuals are not reaching the hospital in the limited time frame required to enroll in a study. Cooperative clinical trials in stroke could help centers to overcome this obstacle and would have the additional benefit of bringing good researchers and their ideas together.

Device Trials

In terms of the testing of devices, we believe that a paradigm shift in how stroke treatment and prevention research is conducted is needed. As an example, high-risk patients may be referred for several different procedures that involve devices, such as carotid stenting, intracranial aneurysm therapy, and endovascular coiling. However, comparison studies of these approaches (e.g. surgery vs. endovascular coiling) have not yet been conducted.

In addition, clinical researchers have proposed a number of additional medical devices for use in ischemic stroke therapy. These devices typically remove clots mechanically or deliver therapeutic hypothermia. The device industry traditionally has brought such products to market under regulations that are significantly different and less stringent than those that govern pharmaceutical products. However, with the increasing need for additional Phase 1 and 2 studies, these small companies, which have limited resources, are beginning to look for academic collaborators who can organize and manage such trials. These collaborations can complement the needs of academic researchers, who often find it difficult to organize such trials alone because they are not sufficiently familiar with the device field, device regulations, or the related branch at the Food and Drug Administration (FDA).

Diversity Issues

The study of diversity issues as they relate to acute stroke treatment is also an important priority, since the Centers for Disease Control and Prevention have demonstrated that healthcare outcomes

are disparate across minority groups and geographic regions. Since we do not have a complete understanding of why these disparities occur, more research in this area will be needed.

Therapeutic Innovations

Diagnostic Issues

Another significant issue related to stroke therapy is the amount of time and effort needed to make a reasonable and confident diagnosis of stroke. Timing issues are critical in caring for patients, yet clinicians do not have a diagnostic tool for stroke that works well and is rapidly available. This problem is compounded by the fact that the presentation of stroke is often complex. Better diagnostic tools and designated stroke centers could both help to facilitate difficult diagnoses.

Combination Therapy

Another issue facing clinicians and researchers is the number of single treatment agents that have not performed well in clinical trials. The results to date indicate that the complex cascade of events following brain ischemia may not be easily interrupted by a single agent. For this reason, the concept of combination therapy, which has improved cancer treatment, should also be explored for stroke.

Although the testing of treatment agents in combination may be a reasonable approach, combinations have not been studied in humans and have been seldom studied in animals. Many factors have influenced the evolution of these studies: traditional factorial designs require prohibitively large numbers of patients,

involvement of pharmaceutical companies in these trials may be limited because of competition issues, and studies based on empirical evidence have encountered difficulties in the review process. Successes in cancer chemotherapy suggest, however, that combination therapy will almost certainly be necessary to develop effective treatments for stroke. Enhanced funding for trials of combination therapy and improvements in the capability of centers to conduct trials of hyperacute therapy are critical needs. Incorporation of thrombolytics and potentially synergistic therapies should be considered a high priority as these studies move forward. For these reasons, NINDS should make the evaluation of combination chemotherapy for hyperacute stroke a key priority over the next five years.

Endpoints

As treatments are considered and improved, it will be important to address quality of life endpoints. Often, researchers and clinicians consider the treatment of stroke as an acute issue, but endpoints are often measured several months after initial treatment has taken place. A 90-day endpoint, for example, is affected by interventions used acutely, but is also affected by follow-up treatment that was performed in the weeks and months following the stroke. Thus, reconsideration of time points may be needed such that researchers can maximize the number of endpoints that can be analyzed, with the least impact from co-morbid conditions.

BARRIERS

Acute Care Barriers

Reimbursement

Reimbursement for acute stroke care is a critical issue, and it will likely impact the implementation of new research findings in the future. Although thrombolytic drugs may be covered by insurance, insurers do not always appreciate the complex medical management that is required to administer these drugs. However, more recently they have begun to recognize the considerable cost savings that can be achieved with the application of thrombolytics.

Infrastructure

As described previously, an infrastructure for acute stroke treatment is needed -- in particular, one that is based on community hospitals and community response teams. More facilities are needed that can respond quickly and effectively when individuals present with symptoms of an acute stroke; such approaches should also be cost-effective for the centers. Caring for most stroke patients in an intensive care unit, for example, is not likely to be productive for most patients or cost-effective for the hospital.

Professional Staff

Another critical need in the field of acute stroke research (and in stroke

research in general) is the expansion of the scientific and clinical workforce. Both fundamental pre-clinical and translational research will be required to address the problems outlined in this report. Traditional training mechanisms are available to the young investigator, but no programs specifically develop stroke researchers. In an effort to encourage professionals to enter the field of stroke research, NINDS has created loan repayment programs. However, these programs may not persuade enough people to choose a career in stroke. NINDS could further enhance these efforts by fostering a program that recruits and trains clinical investigators specifically focused on stroke. Once an interest in stroke research has been stimulated, such young investigators will transition to more traditional training programs and grants. As an additional option, stroke centers could also contain a professional development component to expand the workforce.

In addition to the problem of recruitment and training of new investigators, additional training of neurologists is also needed. Exposure to developments in stroke therapeutics, especially in emergency care, endovascular methods, and critical care, would enhance the ability of neurologists to treat individuals who present with a possible stroke. Similarly, clinicians who are not neurologists often care for stroke patients. These emergency medicine and primary care physicians would also benefit from training in the recognition and management of stroke. This information should be incorporated as early as possible into the medical education system.

Research Barriers

An efficient system for the introduction of safe and effective devices for treating stroke is a high priority. In the past, companies that develop these devices have hoped for a rapid approval of their products, in order to recoup their research investments as quickly as possible. Traditionally, safety standards for these devices were considered to be higher than were the required standards of efficacy. However, efficacy is still a critical concern, and there is agreement in the field of stroke therapeutics that new devices should not be used prior to a demonstration of efficacy. However, efficacy trials can be both large and time-consuming, and device companies tend to be small, start-up businesses that have difficulty supporting such studies. In order to resolve this problem, several steps will likely be required, including: 1) enhanced interactions with the device companies, to familiarize them with the complex requirements of device approval, 2) improved awareness at FDA of the requirements and design of good efficacy trials, and 3) new methods of conducting efficacy trials to enhance their efficiency.

Another barrier to research is the lack of good intermediate markers that can be correlated with ultimate clinical outcome following stroke. We understand how stroke affects an individual's function and leads to lesions that are apparent on brain imaging, but we know very little about other changes. Such changes, if identified, might be used in place of the typical stroke outcome measures (patient function and lesion size).

Along these same lines, there is a critical need to develop markers of stroke that

complement traditional stroke scales. Brain imaging is still in early development, and will require considerable further investigation. Novel markers of ischemia, possibly including serum or cerebrospinal fluid tests, will be required to facilitate rapid bedside diagnosis and staging. Exciting areas of research are underway, including the characterization of serum markers that may differentiate cerebral hemorrhage from ischemia. Such a test could stimulate the development of ways to begin stroke therapy in the field, at an earlier time point following stroke onset.

Lastly, the views of the individuals with stroke are an important concern for the field of acute stroke treatment. A meaningful result to a clinician or a healthcare system may be very different than a meaningful result to a patient. Clinicians may focus on basic functions, like movement, speech, and vision, or activities of daily living such as cooking, bathing, and dressing. By contrast, a patient may be much more concerned about regaining speech and the ability to comprehend language, read, or watch television. Additional research is needed on patient responses to stroke-induced deficits and patient perceptions of disability.

Therapeutic Innovation Barriers

Diagnostics -- the "EKG"

When individuals present in the clinic with conditions that mimic stroke, considerable effort is spent on separating the cases of true stroke from these "mimics." A simple, reliable, and accurate serum marker might allow faster diagnosis and facilitate the triage

of all patients. Similarly, improvements in brain and vessel imaging might also aid in the accurate diagnosis of stroke and, importantly, identify patients most at risk for hemorrhage.

Combination Therapy

As described in a previous section, a renewed emphasis on combination therapy is needed in the field of stroke. Although pharmaceutical companies may encounter proprietary roadblocks to cooperation, methods must be identified that will allow these studies to move forward. NINDS could aid in this effort by investing in two types of research: 1) methodological investigations into how to design efficient trials of combinations, and 2) combination trials themselves.

Time Constraints

Brain tissue dies rapidly after stroke; thus, the speed with which therapies need to be introduced presents a major barrier to effective treatment. More research is needed on the mechanisms of cell death after stroke, so that therapies that delay this degeneration can be developed. With such therapies in hand, effective treatments could be offered to a larger number of patients.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Reperfusion: therapeutic agents that open blood vessels in more patients and that do so better, faster, and more safely, are greatly needed.

It is quite possible that devices available in the future will aid in the removal or dissolution of clots. However, such devices must be rapidly deployed by healthcare practitioners, and at present, the time required for this deployment limits their potential utility. Trials must be designed to test the efficacy of these devices, and teams must be created that are ready to mobilize and use these interventions in an appropriate but realistic time frame (under one hour), in order to achieve patient benefit.

Lytic drugs that are more powerful and versatile and that open more arteries with fewer hemorrhages are greatly needed.

In addition to a need for new drug therapies, clinicians still do not know the best method for delivering these therapies. The best delivery model should be defined, and it may involve a network system, stroke teams, or single centers. The Brain Attack Coalition has already proposed one model (comprehensive and basic stroke centers linked in a network) that could be tested in a rigorous design.

Studies are also needed to identify ways to reduce hemorrhage. Current options include using safer lytics with or without concurrent cytoprotection, and improved patient selection. Devices to induce hypothermia may also reduce the rate of hemorrhage and augment the beneficial effects of thrombolysis.

Priority 2:

Biology and pathobiology: a paradigm shift to a focus on brain blood vessels is needed.

The primary events that cause ischemic and hemorrhage stroke -- the intraluminal molecular and cellular pathological processes within the brain blood vessels, particularly those of the aging brain -- are largely uncharacterized. The neuroscience of stroke -- ischemia, cellular injury, inflammation, necrosis, apoptosis, neuronal reorganization and repair -- are usually secondary events. Since they are of fundamental importance in the development of stroke, the intraluminal generation of thrombus, the lodging of that thrombus, lysis of the thrombus (or not), and the interplay of endothelial cells, platelets, and other cellular constituents of blood should be thoroughly explored.

In addition, pathology of the blood vessel walls also underlies the problem of brain hemorrhage. The basic vascular pathology of this form of stroke is even less well understood than is the pathology of ischemic stroke, and should be more fully investigated.

Priority 3:

Clinical trials and establishing the utility of cytoprotection: a shift is needed from single agent trials to combination trials.

A number of clinical trials have suggested that a single cytoprotectant is unlikely to work as an effective treatment for stroke. The design of these trials has been subject to considerable debate, however. Regardless of those questions, the pathobiology of ischemia suggests that a multi-modal approach may be more successful. Combination therapies have already proven to be highly successful in other fields of treatment, including cancer chemo-

therapy and acute myocardial infarction. This area of research may require NINDS leadership, as proprietary issues related to the development of therapies by pharmaceutical companies may slow the formation of research collaborations. As combination trials get underway, two types of research will be needed. Initially, multi-modal therapies should be tested in Phase 2 and Phase 3 trials. A second goal will involve improvements in primary trial design such that efficiency is enhanced.

As mentioned previously, the combinations that are most likely to be effective may involve the addition of a putative cytoprotectant to thrombolytic therapy. Multiple types of thrombolytics, such as those applied intravenously and intra-arterially, should be studied as part of this effort. In addition, multiple cytoprotective agents, with or without thrombolysis, could also be evaluated. Another consideration in the development of combination therapies is a reperfusion strategy; approaches that include such a plan may be more likely to succeed.

RESOURCES NEEDED

Continued Investments in Stroke Research

Stroke is the second leading cause of mortality in the world, and a greater investment of NINDS/NIH in stroke grants and contracts would enhance the progress in this field.

The funding mechanisms used by NINDS in past have worked well; rapid turn-around contract mechanisms, along with creative requests for applications

have led to the rapid evaluation of multiple interventions, including hemodilution, naloxone, and t-PA. In contrast, current grant mechanisms may not facilitate the rapid application of new ideas, due to the time required to develop applications and move through the review process. The new Specialized Program of Translational Research in Acute Stroke (SPOTRIAS), supported by NINDS, may help to resolve some of these issues, but this type of program should be strengthened and enhanced. NINDS is also encouraged to streamline the review process and time-to-funding, and is also encouraged to commit a sufficient level of support for the development of stroke centers.

Stroke Center Certification

The certification of stroke centers is another critical need in the field. As plans to develop centers move forward, it will be important to consider that the ability to bring stroke centers closer to patients may be a more productive goal than bringing patients to stroke centers more rapidly. Certification of these centers, also described above, should recognize competence for both basic (intravenous t-PA) and advanced stroke care (endovascular treatment).

Further, designated stroke treatment centers would also have a critical role to play in the development of a consortium to conduct clinical trials – both to test new therapies and to help identify more meaningful outcome measures.

As they are developed, the certified stroke centers would need to be subject to a system of checks and audits similar to the trauma system. Voluntary

compliance with guidelines has not worked well, and not all hospitals that have agreed to meet the guidelines developed by NINDS have followed them in practice. As a result, patients are taken to hospitals that claim to be ready to provide stroke care, but are not. This issue is a sensitive one in the field of acute stroke care, however there are potential solutions to this problem. Collegial pressure can be effective in encouraging centers to follow guidelines, as can linking identification of a center to reimbursement or participation in clinical trials.

Development of Emergency Department Investigators and Protocols

In the field of cardiology, most patients enrolled in trials of acute myocardial infarction treatments are identified first by investigators in emergency medicine departments. In that field, advances in therapy have been transferred smoothly to clinical practice because emergency medicine physicians provide the initial clinical care.

For stroke, initial clinical care is also provided by emergency medicine physicians. However, this group has not moved forward as rapidly with stroke research protocols as they have with cardiology protocols. Given that the success of emergency room interventions (t-PA) is established, that more urgent interventions are needed, and that emergency personnel may be the best equipped to administer these interventions, it will be important for research to be fostered among these investigators.

Education and Telemedicine

The training of established clinicians in stroke care is an important goal, and financial incentives for physicians who are already in practice may help to facilitate this training. However, a more achievable approach may be the education of residents and medical school students. For practitioners at some community hospitals, telemedicine may help to facilitate the application of urgent interventions, by enabling them to achieve an increased understanding of stroke treatments. Along these lines, public education is also an important goal, and can aid in the recognition and treatment of stroke.

Endpoints; Surrogate Markers of Outcomes

Individuals with stroke need to be identified more quickly than they are at present, so that treatments can be provided faster and more safely. To achieve this goal, a rapid, reliable, sensitive, and specific marker of stroke is needed. Ideally, a fingerstick test would be developed that would allow paramedics to diagnose strokes in the field. Rapid identification of individuals with stroke would accelerate the overall medical response: medics could transport more quickly, the stroke team could assemble more rapidly, and needless additional testing could be avoided. Several candidate markers are already available and many appear promising enough to proceed with clinical validation. NINDS could provide needed support for the development of such markers.

New Ideas from Basic Scientists

Researchers must be encouraged to explore new areas of biology and pathobiology, such as:

- How do the microvascular and macrovascular endothelium within the brain differ from those structures outside the brain?
- How do the interactions of the endothelium with constituents of the blood differ from those same interactions with blood vessels outside of the brain?
- What happens to the structural elements and to endothelial-cellular interactions in the setting of experimental manipulation?
- How do structure and interaction change with advancing age?
- What do the new ultra-structural and molecular biological techniques offer to the study of brain micro and macro blood vessels?
- How might discoveries in brain vascular biology relate to human disease? How do they relate to currently-approved drugs, such as antiplatelet drugs, anticoagulants, lipid-lowering drugs, antihypertensive drugs, and glucose-lowering drugs?

Links Between Basic and Clinical Scientists

Advances in the treatment of myocardial infarction typically have involved the use of a device in combination with appropriate medical management. This is the result of effective translation of basic science findings on compounds such as aspirin into informative clinical trials.

Small, project-type mechanisms that link clinical trials investigators with basic scientists are needed. This type of program could lead to productive collaborative relationships and information exchange between these very different groups of investigators. If designed well, the process can speed the development of animal models and the testing of therapies, by facilitating basic science studies that closely replicate the clinical situation.

The movement of an idea from basic proof-of-concept work through to clinical deployment requires an array of resources not found in most stroke centers. In other diseases, however, the "center" model has worked, notably in cancer therapeutics.

In order for an effective center for translation to be developed, the resources needed would include a stroke response team trained to give urgent stroke therapy and a biostatistical unit available to guide the development of new therapies and diagnostics. Such centers are also ideal places to train new clinician-investigators, so a fellowship core could be included as well. Other services that might benefit basic investigators are the collection and storage of blood and other human tissues for future use. NINDS could foster the development of such centers, using SPOTRIAS or other mechanisms. As in basic investigation, the potential future benefits of such research activity cannot be predicted; it is certain, however, that such centers could provide the critical elements needed to efficiently translate basic discoveries into public health benefits.

Improved Research Infrastructure

In some ways, a renewed focus on community-based healthcare is new. However, prior NINDS trials have used centers that led community-based networks. For example, in the rt-PA for Acute Stroke Trial, most of the patients were entered at community hospital emergency departments by stroke teams from an academic medical center. Due to time constraints, acute stroke trials require immediate treatment in the emergency department where the patient presents.

The Brain Attack Coalition proposed designated stroke centers, a system in which a comprehensive stroke center would lead a network of primary stroke centers. The SPOTRIAS center grants could be fashioned to support such an infrastructure. These community networks could, then, provide the support for a variety of trials. Also, such centers could also participate in the collection and storage of blood and other specimens for use in genetic studies. An inevitable benefit of these centers would be an increase in the number of treated patients, in and outside of clinical trials.

Clinical Trials

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STATEMENT OF THE PROBLEM

There is no substitute for randomized clinical trials to define the benefits and risks of interventions for stroke prevention and treatment. Given the burgeoning understanding of the diseases causing stroke, the number of potential interventions, and the magnitude of stroke's burden on society, there are too few stroke trials. The overall goal of NINDS-sponsored clinical trials in stroke is to decrease the burden of neurological disease due to stroke and vascular diseases of the brain, with the corollary objective of gaining new knowledge about biology and pathophysiology. It is no exaggeration that NINDS-sponsored trials in stroke over the past two decades have been landmark trials that influence daily the management of stroke patients throughout the world. But we must move in new directions and accelerate the advances in cerebrovascular disease.

Research Areas

Stroke is caused by several different disease processes, each with distinct interventional strategies for prevention, acute care, and recovery. Primary prevention refers to interventions undertaken prior to the clinical

occurrence of a stroke or transient ischemic attack. In contrast, secondary prevention refers to treatment to prevent stroke in those who have survived an initial stroke or transient ischemic attack (about 20 percent of incident strokes occur in those with prior stroke or transient ischemic attack). The distinction between primary and secondary prevention is blurred, since many strokes are unrecognized by patients and their physicians; apparently asymptomatic, subclinical or "silent" strokes detected by MR imaging are common in the elderly. Potential interventions for prevention include treatment of traditional and novel risk factors (e.g., hypertension management, lipid lowering using the statin class of drugs, folate supplementation for elevated homocysteine, and others) and antithrombotic agents.

In addition to clinical and subclinical stroke (i.e., temporally discrete, focal brain lesions), vascular disease of the brain is increasingly appreciated to play a role in progressive cognitive decline in the elderly, albeit through mechanisms incompletely defined at present. Future clinical trials testing interventions aimed at vascular diseases causing stroke should include cognitive assessment and quality of life measures in addition to

counting stroke events. Clinically recognized stroke events represent only the tip of the iceberg of vascular injury to the brain.

Treatments and diagnostic procedures of uncertain value are widely used for treatment or prevention of stroke. The need for testing of such widely practiced procedures and treatments depends on their intrinsic risk, as well as their total cost to society. Clinical trials of certain widely used procedures offer a potential win-win situation: whatever the outcome of the trial, stroke patients benefit. “Positive” results justify the wider use of such procedures, while “negative” results discourage their use, saving money and avoiding needless risks. While scientifically less attractive (in a perfect world, treatments would not be widely used without adequate validation of benefit), “negative” trials are consistent with and mandated by the primary mission of NINDS clinical trials.

Scientifically, there is more appeal in clinical trials that evaluate new interventions that emerge from laboratory research and/or from epidemiological studies. Use of t-PA and the neuro-protectants for acute stroke are examples of such interventions that have been evaluated in recent clinical trials. When testing these types of novel interventions, a “positive” outcome is required to impact patient care, although “negative” results can significantly shape future research directions.

Diagnostic procedures are increasingly expensive and are sometimes risky. It is particularly challenging to assess their overall value in clinical trials because their potential benefit to patients is often

linked to the availability of established treatments, whose use, in turn, depends on the results of the diagnostic test. Trials of diagnostic procedures should be reserved for situations where the costs or risks are high and the management implications are important (based on availability of validated interventions). Ongoing studies of MR imaging to predict potential late-responders (i.e., more than three hours from stroke onset) to t-PA are an example. Not only must the accuracy of the MR technique be determined, but also the incremental benefit afforded to all the patients who undergo the procedure (whether treated with t-PA or not) must be characterized. An inherent difficulty in studying diagnostic tests is the standardization of procedures at different clinical sites; this difficulty is also encountered in their eventual application to clinical use, but is particularly challenging during early phases of development and application.

Collaboration Issues

Barriers to collaboration between pharmaceutical and medical device companies and NINDS exist concerning validation of new agents and diagnostic procedures. Proprietary interests often necessitate added complexity in a clinical trial, primarily because of regulations that must be followed to gain FDA approval. Government participation in the clinical testing of a drug for stroke is not entirely welcomed by pharmaceutical companies for many reasons, including uncertainty about whether collaboration in a government-sponsored trial threatens future profits, and concerns about the control and publication of trial data. In addition, when similar agents are available for prevention or treatment of stroke,

pharmaceutical companies are often reluctant to undertake the large trials necessary to compare two different, potentially active agents. For example, the control of blood pressure has well-established benefits for stroke prevention; does the specific type of antihypertensive agent make a difference?

Social and Economic Issues

Primary prevention of stroke is a complex issue that must consider patient preferences, societal values, and medical economics, in addition to the biology of the disease. There is often a disparity between what is good for public health and what is accepted by people, patients, and physicians.

For example, treatment of hypertension remains underutilized in our relatively affluent society, even after more than two decades of high-quality trials have shown profound reduction in stroke and despite the availability of generally well-tolerated antihypertensive drugs.

In contrast, an area of notable success in primary prevention of stroke has been the use of warfarin in patients with atrial fibrillation. Of more than two million Americans with this cardiac rhythm disturbance, which predisposes to stroke, almost half are now treated with warfarin following the NINDS-sponsored Stroke Prevention in Atrial Fibrillation (SPAF) trials and other clinical trials. This has prevented tens of thousands of strokes yearly. For these patients, the number-needed-to-treat for one year with warfarin to prevent a stroke is typically about 40; in other words, they are at relatively high risk. For the average middle-aged person

with mild hypertension, the risk of stroke is lower; the number-needed-to-treat for one year to prevent one stroke is several hundred.

One key to more widely applied interventions for primary stroke prevention will be reliable identification of relatively high-risk populations, which are more likely to accept the need for preventive therapy.

In addition, primary prevention trials concerning vascular disease of the brain should not focus exclusively on stroke outcomes, but rather on more global measures of the healthy brain potentially impacted by interventions. Vascular factors may have a major role in age-related cognitive impairment and are more common and perhaps even more important than clinical stroke events. In short, large primary prevention trials involving people at particular risk, to test interventions aimed at vascular disease of the brain in all of its manifestations, are warranted.

Clinical trials also need to be more efficient and economical. Novel design strategies that test multiple interventions in factorial designs, incorporate futility monitoring and innovative statistical design when appropriate, and use more sensitive global outcomes as well as potentially more sensitive outcomes such as cognition and quality of life, must be further developed. Large “simple” trials are appropriate to address certain issues; however, they need to be balanced with more complex trials that also seek to incorporate study of the disease process.

Progress has been slowed unnecessarily by the slow recruitment of patients in stroke trials. Many trials have taken

several years to recruit participants; other than a lack of organization, there is little excuse for this, given the huge number of Americans with cerebrovascular diseases. Currently, answers that should take a few years to obtain can take a decade or more. In addition, the relatively high cost of clinical trials has limited the number and types of trials sponsored.

To address these issues, the development of a clinical trial network, including both academic and practicing physicians, and an infrastructure along the lines successfully used in oncology and cardiology, should be explored.

Increased efficiency will also require the development and inclusion of important new trial methodologies. For example, there is a need for trial designs that can accommodate the complexity of acute stroke. Questions to consider in such trials might include the best ways to develop combination therapy for acute stroke while determining the correct dose and duration of treatment and also accounting for drug interactions. In addition, it might be helpful to develop adaptive designs with real-time data retrieval and adaptive treatment allocation to optimize learning about the research question. Also, it would be important to be able to maximize the information that can be obtained from each patient and the benefits to patients that can be obtained from each trial. Another consideration could be a decision-theoretic termination rule, for stopping a trial at the earliest point at which sufficient information is available to conclusively answer the research question or, when appropriate, to determine futility.

Inadequately Explored Areas

Primary reliance on investigator-initiated clinical trials has led to uneven clinical study of the different aspects of stroke. For example, several clinical trials have evaluated stroke prevention in patients with atrial fibrillation and in patients with cervical carotid atherosclerosis, whereas no trials have been conducted in intracerebral hemorrhage. Less common causes of stroke relevant to young adult and pediatric patients (e.g., arterial dissections) are unlikely to be brought to trial given current mechanisms. Recent availability of funding for pilot clinical trials has allowed testing of methodological innovations important for study of less common stroke subtypes.

Future Needs


In short, too few clinical trials have been conducted in stroke prevention and treatment, given the burden of the disease and the availability of potentially efficacious interventions. Some of the specific areas that need more research include:

- Primary prevention of vascular-mediated brain injury (including ischemic and hemorrhagic stroke).
- Acute treatment of intracerebral hemorrhage.
- Acute treatment of ischemic stroke beyond three hours from onset.
- Efficacious treatment of transient ischemic attack.
- Secondary prevention of stroke due to cerebral small artery disease.
- Prevention of vascular dementia.
- Rehabilitation for all kinds of vascular brain injury.

In order to accomplish all that needs to be done in stroke trials, the clinical trial process needs to be more efficient, economical, and expedient, without inhibiting individual investigator enthusiasm and innovation.

CHALLENGES AND QUESTIONS

Some of our major challenges:

- Large primary prevention trials to investigate several interventions to prevent vascular-mediated brain injury in a population at risk, and large trials testing rehabilitation methods, are sufficiently complex that leadership by NINDS will likely be required for expeditious organization and execution.
- lication of methodologies for large simple trials with outcomes that measure quality of life and brain health will require innovation and modification of traditional clinical trial paradigms.
- Inclusion of common outcomes that focus on cognition and quality of life in all clinical trials sponsored by NINDS is necessary to allow the magnitude of treatment effects to be compared across trials.

NINDS could take a major step toward reducing the cost of clinical trials and increasing recruitment by developing a clinical trial investigator network to recruit participants for multiple trials. Such a network could involve both academic and practice-based physicians and could obviate the need to rebuild the clinical site recruitment infrastructure from scratch for each new trial. More efficient use of trial machinery should result in less expense. Because of the relative maturity of development of

stroke clinical trials and the large number of patients, stroke research may be more readily adaptable to the clinical trials consortium concept than are some other areas of neurologic research. In the future, expansion of the consortium or the parallel development of consortia for other areas of neurology may be useful.

Other issues that must be considered are:

- Outcome measures. Are there better, more meaningful outcome measures than those used in current stroke trials? Functional measurements, quality of life, cognitive status, and patient preferences regarding interventions have not been explored thoroughly, especially with regard to their use in large, simple trials.
- Design strategies. What novel design strategies could be applied to reduce the sample size of clinical trials? Possibilities include the use of clinically meaningful outcome combinations, simultaneous testing of multiple interventions, and more stringent futility monitoring.
- Balance between simple and complex trials. What is the optimal "large, simple" clinical trial design that incorporates baseline risk factors, medical history, and genetic linkage and biomarkers?

BARRIERS

Barriers to improved clinical trials include:

- The lack of an established, large clinical trial investigator network to participate in multiple clinical trials in several aspects of stroke.
- Inexperience with more efficient methodologies for reducing the

- cost of clinical trials.
- The reluctance of pharmaceutical companies to collaborate in government-funded stroke research.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Identify needed clinical trials in stroke prevention, acute treatment, and recovery.

The NINDS should undertake leadership in organizing large, simple clinical trials for primary prevention of vascular injury to the brain (including hemorrhagic and ischemic stroke), and for evaluation of rehabilitation therapies for patients with vascular brain injury. The NINDS should encourage and support investigator-initiated clinical trials addressing areas such as the following:

- Acute treatment of intracerebral hemorrhage.
- Acute treatment of ischemic stroke.
- Treatment of transient stroke.
- Prevention of stroke caused by small cerebral artery diseases.
- Prevention and treatment of vascular dementia.

This list should be reviewed regularly by a working group and updated as understanding of stroke advances. The goal would be to more rationally prioritize trials in different areas of stroke as well as to take advantage of specific research opportunities.

Priority 2:

Organize an NINDS-based clinical trial investigator network to execute

clinical trials expeditiously and efficiently.

Such a network could involve scores or even hundreds of clinical investigators (and sites) who would enroll patients in several ongoing trials, enhancing rapid and less expensive recruitment due to economies of scale. Inclusion of community-based (i.e., non-academic) investigators would permit access to a broader range of participants in a "real-world" setting. The network would minimize the need to re-create the various components of trials every time a trial is proposed (whether institute- or investigator-initiated). The organization and management of this network would require considerable effort and expense; its performance and value would require critical evaluation periodically to assure that its objectives are being met.

Priority 3:

Encourage novel clinical trial methodology.

The "pre-review" process that is now being developed by the NINDS Clinical Trials Group should be expanded in order to assist investigators in the initial submission of the highest-quality grant applications and encourage the use of efficient designs and novel outcomes. For planning grants, the review process should be accelerated.

Additional Priorities

The NINDS and the stroke research community should:

- Take the initiative in promoting the best possible human subject protection.

- Define further the barriers to collaboration with pharmaceutical companies in stroke trials and initiate discussions with such companies on ways to overcome those barriers.
- Explore and encourage the development and inclusion of comprehensive, uniform, and validated outcome measures (e.g., cognitive function, quality of life measures) as well as the assessment of patient values and preferences regarding interventions.
- Explore, as appropriate, the development and validation of innovative biomarkers for clinical stroke outcomes as potential means of decreasing the sample size and expense of future clinical trials.
- Develop additional, carefully substantiated cost-effectiveness data to support the need for more stroke clinical trials, as justified by their impact on decreasing the burden of neurological disease.
- Explore means to include pediatric stroke patients, as appropriate, in clinical stroke trials, as well as to investigate treatments for types of stroke that occur specifically in pediatric populations.

RESOURCES NEEDED

Priority 1:

- A Stroke Clinical Trials Advisory Group (including a budget for

conference calls, yearly meetings, and staff liaison) to prioritize clinical trial research and identify opportunities.

- Adequate NINDS staff to develop and supervise institute-initiated clinical trials.
- Funding for investigator- and institute-initiated stroke trials.

Priority 2:

- Adequate NINDS staff and budget for organization of a clinical trial investigator network, including ongoing supervision of contractual arrangements and human subject assurances.

Priority 3:

- Statistical and methodological consultation with extramural experts, as needed, during the pre-review phase of clinical trial applications, working with investigators toward novel, economical approaches to trial design, monitoring, and interpretation.

The co-chairs of this session thank Dr. Barbara Tilley for additional contributions to this session's report.

Recovery and Rehabilitation

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STATEMENT OF THE PROBLEM

- Stroke is one of the major causes of long-term disability among adults, and its prevalence will continue to rise as the population ages.
- Improving function and quality of life are the primary targets of rehabilitation interventions. Depending on the location and extent of brain damage, stroke survivors can have a variety of chronic deficits. Among these are severe motor, sensory, cognitive, communicative, executive, mood, emotional, and social problems. It is well established that any one of these can substantially impact the quality of life, not only in patients, but also in caregivers.
- Recent laboratory and clinical developments indicate that current rehabilitative procedures can be optimized, potentially yielding enormous clinical benefits.
- Neural events related to brain injury (e.g., trophic factor upregulation) create a remarkably long window of opportunity for greatly enhancing normal plasticity and recovery of function.
- Rehabilitation research is an “orphan” line of investigation that has been ignored by most biotechnology and pharmaceutical companies, despite the possibility

that treatments for neuroprotection or plasticity being developed by these companies might require behavioral interventions to be successful.

- Preventive measures are modestly effective, acute thrombolytic therapy applies to only a small proportion of stroke survivors, and neuroprotective interventions remain to be established. Thus, it is likely that most survivors will have some degree of residual functional deficits; effective management of these deficits remains a major challenge of stroke rehabilitation research.
- Stroke survivors who have already sustained a stroke (and are beyond help from treatments aimed at the acute or subacute phases) represent the overwhelming majority of stroke survivors; they and their caregivers are hopeful that research will one day help them.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Investigate the neurobiology of recovery.

Rationale

- Basic research will improve understanding of the mechanisms

underlying stroke recovery (including compensation or restitution of function).

- This understanding will help direct the development of rational therapeutic interventions.

Objectives

- Develop strategies to promote collaboration between basic scientists and clinicians to define brain mechanisms underlying recovery in both acute and chronic stroke using animal models and human studies.
- Validate animal models in multiple species, including mice and primates, with behavioral outcome measures sensitive to chronic deficits in sensorimotor and cognitive domains.
- Establish valid and reliable markers for the events underlying stroke recovery in humans, and their predictive role in directing rehabilitation strategies. Possible modalities include fMRI, transcranial magnetic stimulation, and positron emission tomography.
- Perform epidemiological studies to establish predictors of recovery and responsiveness to new therapies.
- Heighten understanding of patterns of recovery after stroke. This includes the natural course of cognitive and affective disorders and their influence on functional recovery and quality of life.
- Develop consensus guidelines that address issues (e.g., outcome measures) specific to the design of recovery studies.

Priority 2:

Promote evidence-based investigations of innovative therapies compatible with principles of neural plasticity and learning.

Rationale

- Animal models and human studies suggest that the type, location, and extent of stroke injury may critically influence outcomes, but there is almost no systematic data to guide the medical or rehabilitation community in using this information to tailor individual therapy.
- Factors that affect responsiveness to rehabilitation therapies -- age (including developing brains), comorbidity, gender, race/ethnicity, socioeconomic status, and the physiological and clinical features of stroke -- are not well understood.
- A persuasive body of data suggests that environment and activity affect recovery from stroke and also critically influence the utility of restorative cellular and pharmacological interventions. For example, animal models indicate that rehabilitative motor skills training, environmental enrichment, and exercise after stroke markedly enhance functional recovery and cellular and structural brain changes. New innovative approaches to motor retraining (e.g., treadmill training with partial body weight support, robot-assisted training, and constraint-induced therapy) in human stroke survivors suggests that these approaches improve motor recovery and self-reported function. Use of pharmacological agents (e.g.,

d-amphetamine), and in the future, progenitor cells and growth factors, may complement motor retraining to improve stroke recovery.

Objectives

- Employ a multidisciplinary effort that combines cellular and pharmacological interventions with rehabilitation programs.
- Develop science (e.g., regarding timing, duration, frequency, specificity, dosing, environment) to maximize benefits of rehabilitation training and minimize potential adverse effects.
- Define attributes of physical, cognitive, and communicative rehabilitation interventions that promote recovery/compensation.
- Develop interventions to manage depression.
- Develop a dissemination plan that includes training of rehabilitation professionals who can impact delivery of evidence-based rehabilitation interventions.

Priority 3:

Evaluate the organization of rehabilitation services.

Rationale

- The delivery of rehabilitation care is inconsistent across communities; it varies according to reimbursement schema and sites of care, and it generally lacks quality assurance.
- Current healthcare models tend to focus rehabilitation services during the subacute stroke recovery period and not during later phases.

- Many stroke survivors receive limited therapy and are then discharged to the community, where they often remain chronically disabled, socially isolated, and at risk for common post-stroke rehabilitation complications such as falls, disuse atrophy, and cardiovascular deconditioning.

Objectives

- Investigate determinants of variations in access to stroke rehabilitation services and their quality, intensity, and duration.
- Explore and evaluate new options for timing and sequencing of rehabilitation care.
- Evaluate relationships between stroke rehabilitation structures, processes, and outcomes.
- Create common outcome measures across the continuum of stroke care.
- Evaluate the cost-effectiveness of rehabilitation services.

RESOURCES NEEDED

- A network of basic and clinical research scientists, including industry representatives, to design and implement trials of recovery and rehabilitation; opportunities for this network of scientists to attend NIH-sponsored workshops for education and training.
- Funding of clinically relevant animal models of stroke and stroke recovery that address the significance of pre-existing conditions such as aging, hormonal imbalance, obesity, diabetes, inactivity, pre-existing brain dysfunction, and other comorbidities.

- A consortium for clinical trials that includes personnel and facilities, to maintain a continuum of sites of care to access stroke survivors in the community.
- NIH-directed policies to support recruitment of stroke survivors with cognitive and communication problems.
- Training and recruitment of new investigators, reflective of the multidisciplinary team; in particular, training programs that combine neurology, physical medicine, and rehabilitation.
- Funding of mechanisms to create and evaluate a common battery of stroke outcome measures applicable across the phases of stroke recovery and different sites of stroke care.
- Mechanisms for interinstitutional collaboration with the Center for Medicare and Medicaid Services, the Agency for Healthcare Research and Quality, and the Department of Veterans Affairs, to implement quality indicators of rehabilitation care.
- Interinstitutional collaboration with federal agencies and insurance carriers, to support rehabilitation research within the administrative infrastructure of clinical practice.
- Consideration of the unique requirements for rehabilitation research across multiple sites of care and often without the capacity for double blinding.

Health Services Implementation

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STATEMENT OF THE PROBLEM

A major goal of NINDS-supported research is practical: to reduce the burden of neurological disease for the U.S. population. This practical goal can only be realized when the research results are implemented appropriately and well in real-world practice. The broad aims of health services implementation research are to (1) help patients and healthcare workers interpret clinical research so they may understand which interventions lead to valued outcomes, (2) identify when valued interventions are not being used optimally, and (3) develop, test, and promote practical ways to implement those interventions.

Failing to address these three issues leads to a variety of specific problems:

- Not considering important outcomes can (1) cause investigators to under- or overestimate the value of interventions, and (2) lead patients, physicians, and policy makers to misjudge whether an intervention is right in a given circumstance.
- Not assessing patterns of care can (1) lead to an inappropriate estimate of the effectiveness of intervention efforts in a population, and (2) diminish the perceived value of a practice improvement effort

when physicians are unaware of deficiencies.

- Not developing, testing, and promoting interventions aimed at improved practice can (1) leave providers to their own devices to develop practice improvement strategies -- a task for which they may be ill-prepared, (2) cause interventions to be implemented that do not, in fact, work, and (3) decrease the likelihood that results of clinical trials will be incorporated into patient care.

CHALLENGES AND QUESTIONS/ BARRIERS

There are general challenges and barriers to the three issues outlined above.

Challenges to Measuring Outcomes

- Comprehensive measurement of important outcomes is not the norm in clinical research studies, as many clinical investigators are not familiar with the techniques of outcomes measurement.
- There are many stakeholders involved in judging the value of interventions (including clinicians, patients, administrators, payors), and which outcomes are deemed important depends on perspective.

Challenges to Evaluating Current Practice Patterns

- Evaluating practice patterns requires examination of a representative sample of patients and practitioners.
- Administrative data, while easily accessible, is often not sufficient for this purpose.

Challenges to Developing, Testing, and Promoting Health Services Interventions

- Health services implementation is often perceived as being separate from the research enterprise (an administrative or advocacy/marketing task).
- Health services implementation research is challenging. It involves working in typical practice sites, requires large sample sizes at multiple sites to achieve generalizability, and requires adequate power to demonstrate changes in outcomes that have high variability.

RESEARCH AND SCIENTIFIC PRIORITIES

Priority 1:

Measure outcomes that people care about.

- Develop and apply outcome measures that are accurate, reliable, and easy to measure.
- Present results in a standardized way that facilitates cross-study comparisons and meta-analysis (both in the primary reports and via data repositories).

Priority 2:

Identify when care is inconsistent with best evidence.

- Describe current practice patterns and trends over time.
- Study patterns in communities representative of the U.S. population.
- Pay attention to systematic discrepancies (such as by age, race, gender, and ethnicity).
- Identify barriers to changing practice patterns. Consider:
 - * Patient barriers such as lack of knowledge, inconvenience, and cost.
 - * Physician barriers such as lack of knowledge of best evidence, failure to identify appropriate candidates, community norms inconsistent with best evidence, and lack of visible benefits.
 - * System barriers such as lack of access to necessary medical resources and insufficient reimbursement for services.

Priority 3:

Develop, test, and promote ways to optimize practices based on best evidence.

- Develop innovative, generalizable health services approaches to implement practices based on best evidence, such as interventions aimed at the health system.
- Perform health services trials to test interventions aimed at improving community practice in generalizable settings.
- Partner with practice organizations, payors, professional societies, advocacy groups, and others to

promote the dissemination of effective health services interventions.

- Explore therapies that are under-utilized, including preventive strategies such as warfarin for atrial fibrillation, acute strategies such as intravenous t-PA for acute ischemic stroke, and recovery strategies, including early rehabilitation services.

APPROACHES TO ADVANCING THESE PRIORITIES

Advances in diminishing the burden of stroke in the U.S. require that we overcome the classes of barriers mentioned above. The three research priorities speak to overcoming the barriers. Studies performed within the framework of these priorities will serve to advance the uptake of clinical practice based on best evidence.

The three research priorities are derived from experience in health services implementation research that suggests this effort is most effective when it proceeds in a logical sequence. Such a sequence is listed in Statement of the Problem: (1) identify interventions that lead to valued outcomes, (2) identify "targets of opportunity" (i.e., community practices that are not optimal), and (3) develop, test, and promote practical ways to implement those practices.

Each step in this sequence can be addressed with a variety of methodological tools. Identifying interventions that lead to valued outcomes may be as simple as evaluating a clinical trial with crucial outcome measures. When a single study is not sufficient, other approaches can be considered, such as evidence synthesis based on meta-analysis and/or decision modeling.

Identifying "targets of opportunity" can be accomplished by performing population-based surveillance studies to examine whether there are significant discordances between practices supported by best evidence and actual practice. These studies can also be used to identify barriers that may impede optimal practice. In specific circumstances, other issues and research methods may be relevant. For example, where cost is an important consideration, cost of illness and cost-effectiveness studies can be employed.

The quintessential approach to evaluating clinical interventions, including health services interventions, is the randomized controlled trial. Substantial progress has been made in advancing the science of health services implementation trials. When a randomized controlled trial is not feasible, other designs, such as before and after studies with concurrent controls can be reasonable alternatives.

Integration Session

*Co-Chairs: John M. Hallenbeck, M.D.,
and Richard J. Traystman, Ph.D.*

INTRODUCTION

The brain does best if ischemia can be prevented and it does second best if ischemia can be reversed within the first few hours. Ischemia and hemorrhage set into motion many injury mechanisms and injury-modifying mechanisms. We need to understand these mechanisms in exquisite molecular detail. We must find better ways to subdue vessel activation as it begins to threaten thrombosis or hemorrhage. We must find ways to block or attenuate the *systems* of injury mechanisms that extend brain damage in acute stroke. We need to understand recovery and repair mechanisms and learn how to promote them. We can assemble the expertise and apply the technology to do these things.

OVERARCHING THEMES

Several overarching themes emerged from the 15 Roundtable Meeting breakout sessions. In particular, the stroke community needs to focus on:

- Capitalizing on advances in genomics and proteomics.
- Facilitating multidisciplinary collaboration on projects.
- Integrating multiple mechanisms, i.e., promoting systems analysis.
- Improving access to bioinformatics tools.
- Standardizing data analysis and methodology.
- Developing a better infrastructure to support research.
- Encouraging collaboration and cooperation among researchers,

rather than competition.

- Developing better animal models of stroke, and improving translation from basic research into clinical trials.
- Facilitating interactions between basic scientists and clinicians.
- Developing and testing combination therapies.
- Improving the training of stroke researchers, including options for postdoctoral and mid-career professionals, and multidisciplinary approaches.

Several of these themes are discussed below.

GENOMICS AND PROTEOMICS TECHNOLOGIES

Many of the overarching themes are best discussed in the context of the impending genomic and proteomic revolution.

New genomics and proteomics technologies, such as DNA and protein chips, together with miniaturization down to nanostructures, hold tremendous potential for providing personalized medical care to the individual patient that is based on predicted molecular mechanisms. If we can successfully filter and digest cryptic, non-intuitive data and connect it to clinically relevant information, the resultant molecular profiling should suggest many hypotheses that can be tested at both preclinical and clinical levels. For optimal translation, every effort should be made to increase the

relevance of preclinical models to clinical disease. Some crucial points are addressed below.

Genomics and proteomics technologies will operate in a major new research paradigm.

Data analysis will require multi-disciplinary teams, including computer scientists skilled at mining databases, biostatisticians, bioengineers, molecular and cellular biologists, pharmacologists, and basic and clinical stroke researchers.

In the most enthusiastic scenario, genomics and proteomics may turn into a major engine that leads and drives much of stroke research. The molecular mechanisms, systems of mechanisms, and targets derived from human tissue samples may activate stroke research on a pathway that begins at the bedside, goes to the bench (e.g., cell culture systems, transgenic models), and then goes back to the bedside for clinical trials. Developing hypotheses and designing research based on molecular mechanisms derived from human rather than animal tissues may help to resolve some of the difficulties that have been encountered in translating preclinical stroke research into approved clinical applications.

Genomics and proteomics technologies may require a systems biology approach to understand gene and protein interactions.

These technologies will involve a “combinatorial explosion,” raising many questions about how combinations of factors interact and influence each other. Such an approach is appropriate for a multifactorial problem like the

progression of brain injury during acute stroke. Data derived from the new technologies should encourage the study of the interrelationships among molecular mechanisms of injury and their effects on all brain structures, rather than a preoccupation with a circumscribed area of interest, which has tended to characterize current stroke research. This approach to research should encourage a more global view.

To realize the full predictive value of genomics and proteomics analysis, we need massive clinical and population analyses (a bioinformatics database) that will identify and validate the predicted batteries of disease-relevant molecular markers (biomarkers and surrogate measures). This must be accomplished before the markers can be used in routine clinical diagnosis, individualization of therapy, and prognosis.

- Massive correlative bioinformatics-driven analyses will probably need to be performed at five different levels to make clinical applications possible. These five levels are: DNA, RNA, protein, 3-dimensional localization and context of proteins in cells and tissues, and drug responses. Integration of clinical and basic research will be necessary to optimize this process.
- We should standardize data analysis and data sharing nationally, and perhaps internationally, so that biologically relevant information from different sources related to stroke can be easily compared. The NINDS could take a role in promoting this. (This could perhaps be done in cooperation with other institutes. For example, it would be valuable to have data on molecular

mechanisms of cellular signaling related to cell proliferation versus growth arrest and apoptosis from the National Cancer Institute (NCI), and data on molecular mechanisms in healthy and diseased vasculature from the National Heart, Lung, and Blood Institute (NHLBI). It would also be valuable to have interinstitutional promotion and funding of multidisciplinary teams). Efforts should also be made to standardize the collection of samples from patients during clinical trials so they can be banked in anticipation of future studies. For example, blood samples should include both cells and plasma.

- Such analyses will be very expensive and will probably require an infrastructure of both private biotechnology companies (proprietary databases for profit) and academic centers (information freely available). Examples of cooperation do exist; the SNP Consortium (composed of pharmaceutical companies, academic laboratories, and Wellcome Trust) intends to make 300,000 human SNPs available in the next few years. One hope for SNP patterns is that they can be used as markers of disease susceptibility (pharmacogenetics) or drug responsiveness (pharmacogenomics). If so, knowledge of these SNPs could facilitate the drug development process and medical care by allowing better diagnosis of diseases and treatment of patients.

We don't know yet whether genomics and proteomics technologies will follow the development pattern of personal computers, resulting in miniaturized lab-on-a-chip devices in every lab and clinic,

or whether they will remain expensive “mainframe” instruments found only in central locations. The NINDS should decide (perhaps with other institutes) what role it might appropriately take in facilitating the availability of this technology for stroke researchers and how best to assist with their education to exploit the full potential of these technologies. For example, three years ago NCI established a joint initiative with FDA, the Tissue Proteomics project. The stated goal of the project is to “originate and complete technology for studying proteomic networks and signal pathways in small quantities of microdissected human tissue cells directly from biopsy specimens.” It is oriented toward immediate, patient-based clinical applications. NCI might be a good strategic partner for NINDS in this area.

One possible effect of the genomics/proteomics paradigm is that research groups will increase their cooperation and reduce competition, since input from many laboratories and clinical centers will be necessary to build the bioinformatics database. Currently, however, data submitted to the database does not remain proprietary, so it may be difficult to ensure that individual research effort is recognized and rewarded. Our research community will need to address this problem.

A proliferation of injury mechanisms during acute brain ischemia has been revealed by conventional research approaches during the past decade. This list is likely to expand exponentially as a consequence of this new research paradigm. We may have to devise ways to counteract and control multiple injury mechanisms at the same time in order

to achieve a marked attenuation of progressing brain damage in acute stroke. One approach to this that could be facilitated by the new research paradigm is the discovery and characterization of master regulatory switches and molecular mechanisms that simultaneously counteract multiple mediators of injury and confer resistance to ischemic brain damage.

STROKE MODELS

Discussion of stroke models permeated many of the Roundtable Meeting breakout sessions.

The scientific research community has developed many varieties of stroke models over the past years. These models encompass stroke, subarachnoid hemorrhage, intraventricular hemorrhage, vasospasm, and global ischemia. These models have been developed for two reasons: one, to try to recreate the human disease in an animal, and two, to create a model that allows us to study and dissect mechanisms of formation of injury and mechanisms of neuroprotection from injury.

For example, in developing animal models of focal ischemia (middle cerebral artery occlusion), there are different methods available to occlude the vessel. It can be coagulated, clipped with a neurosurgical clip, clogged with thrombo emboli, or blocked with a thread or filament. There are both similarities and differences between these models of middle cerebral artery occlusion, and there is always the question of whether any of them actually represent a model of human disease. However, each of these models can be studied to examine mechanisms of injury

and mechanisms of neuroprotection. This can equally be stated for other models of injury as well.

The question is, why have these animal models not predicted stroke outcome in clinical trials? This issue arises often, given the number of negative clinical trials. For many of the animal models, specific pharmacologic agents have been protective, yet when these same agents were used in patients in clinical trials, the results were disappointing. In the past, most have placed fault on the animal models, saying they are not appropriate models of human disease and therefore results obtained in the animal may not have been predictive of a drug's efficacy in humans.

Fault may also be placed on the clinical trials, however. One problem is that trials may be organized in a way that is not completely based on preclinical data. For example, why design a clinical trial such that a drug must be given at three hours after the stroke event, when no preclinical studies have looked at the efficacy of the drug at that time? Preclinical data for the drug may have shown effectiveness when administered prior to ischemia, or at reperfusion, but the drug had never been administered at three hours following ischemia. Another possible issue is drug dosing. What may be an effective dose in animals may not be the most effective in humans.

Thus, fault can be given to both the researcher, who may not study a drug completely from a dose/response analysis or a window of opportunity analysis, and to the clinician, who may design and perform a clinical trial not based on appropriate preclinical data.

BASIC SCIENTIST AND CLINICIAN INTERACTION

The problems seen in carrying animal model data to clinical trials points out the need for strong interaction and collaboration between the basic scientist and the clinician, another overarching theme of the Roundtable Meeting breakout sessions.

Basic scientists and clinicians must work together to design proper clinical trials based on appropriate preclinical data. They need to discuss precisely what information the clinician needs in order to design an appropriate clinical trial, and which animal experiments the researcher must do to allow the clinician to base the design of the trial on those data. This collaborative relationship is critical for the design of both preclinical studies and the clinical trial itself. The proper integration and collaboration of researchers and clinicians will clearly lead to better translational research for the good of the stroke patient.

COMBINATION THERAPY

Ischemia results in brain injury, and over the years many potential mechanisms of injury and neuroprotection have been identified. But as the mechanisms of neuroprotection each have been dissected out, not one has been found to be capable of completely ameliorating the injury produced. Therefore, it seems reasonable that no single agent will be found that, when administered alone, will ameliorate all injury or completely protect the brain. It is more likely that agents will be given in combination (combination therapy) as a "cocktail," with effects on several different protection mechanisms. One might have

to administer, for example, an O₂ radical scavenger and an excitotoxic amino acid antagonist together, in order to protect the brain better than either agent could do individually.

The preclinical studies required to determine which agents to administer, at what dose, and the timing of administration of the agents, however, are extremely complicated. To perform dose/response curves for two or more agents in combination with dose/response curves for windows of opportunity is time consuming and complex.

There is also the question of who would fund such studies. These types of studies traditionally have not fared well at NIH Study Sections. They are perhaps not reductionistic, molecular, or mechanistic enough, not to mention innovative enough, to do well. Thus, there may have to be a change in the culture concerning how these types of grant proposals are reviewed, in order to appreciate and foster these types of studies.

MULTIDISCIPLINARY TRAINING AND RESEARCH PROGRAMS

Stroke is a disease of the vasculature, of the blood vessels. Perhaps we need to return to the study of the vessels and their elements to discover new potential cures for stroke. Areas that need to be studied more carefully include methods to unclog vessels, mediators released from the clot in the vessels, the cerebral endothelium and its responses, reperfusion, hyper- and hypoperfusion, vascular inflammation, and new, unique agents to vasodilate cerebral vessels.

In order to accomplish all this, we need to have individuals trained in these areas, and/or we need to attract individuals from other fields (e.g., neurology, neurosurgery, neurosciences, physiology, radiology, pharmacology, pathology, molecular biology, genetics, biomedical engineering, and micro-circulation) into the area of stroke research. This would bring individuals with the best creative minds and with techniques from different areas to study stroke.

Postdoctoral programs and programs for mid-career individuals who want to redirect their efforts towards stroke and cerebrovasculature are needed to attract individuals into the stroke field. How do we attract and train the vascular wall biologists, for example, to direct their attention to the field of stroke? Stroke involves multidisciplinary activities, and perhaps interdepartmental or even inter-university individuals. How do we foster these multidisciplinary, intra- and inter-university approaches to the study and understanding of stroke?

This will not be easy to accomplish, but one way to be successful is through collaborative grant mechanisms. The SPRG strongly encourages the NINDS, NHLBI, and other institutes, within or outside the NIH, to facilitate the

development of new, innovative programs to accomplish the goals outlined above.

Along with this comes the challenge of implementing clinical trials. Clinical trials are complicated, multidisciplinary, multi-institutional, and very expensive to perform. The SPRG recommends that the NIH and industry work together to creatively move stroke trials forward. Developing stroke databases of epidemiological, genetic, and imaging data are similarly challenging and would benefit from collaborative efforts among the NIH institutes and industry.

These are difficult challenges that need to be addressed. However, one thing is certain: there are many individuals, clinicians and researchers alike, from many different fields (as evidenced from attendees at the Stroke PRG Roundtable Meeting) who are poised to work together to advance our understanding of stroke mechanisms and translate that understanding into better prevention, diagnosis, and treatment of this major cause of death and disability in the United States. These intellectual resources, combined with the necessary fiscal resources, will provide a powerful impetus for alleviating the devastating effects of stroke on our society.

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Stroke Progress Review Group Roundtable Meeting
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