The 2009 Feinberg Lecture
The Continuum of Stroke Research and Policy

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Background and Purpose—This annual Feinberg Award lecture is intended to present examples of the broad scope of stroke-related research and to show how different investigative approaches can advance the field to improve stroke patient’s outcomes. In keeping with one of the objectives of the American Heart/American Stroke Association, this lecture also provides a perspective and highlights opportunities for beginning clinical investigators.

Summary of Report—Clinically, the continuum of stroke research and care can be divided into primary prevention, acute interventions, secondary prevention, and poststroke recovery. From a technical/methodological standpoint, fundamental laboratory studies yield insights into basic disease mechanisms. Applied laboratory studies further explore the biological basis of disease and evaluate possible therapeutic interventions. The results of these laboratory-based observations can inform clinical study design whereas questions raised by clinical observations can be explored in laboratory experiments (ie, “translational” research). Additional information is gained through observational, interventional, and synthetic (eg, meta-analytic) clinical studies. Outcomes/effectiveness research determines how well interventions perform in different “real-world” settings. The discussion provides examples of how several of these approaches can be used to address various research questions. The importance for stroke investigators to contribute to related public policy issues is also reviewed.

Conclusions—This is an exciting era for clinical investigators studying stroke and for those at the beginning stages of their careers. Whether taking a broad-based research approach or working on a specific question, our combined efforts are leading to improved outcomes for patients with stroke, the very goal of Bill Feinberg’s career. (Stroke. 2009;40:3879-3882.)

Key Words: public policy ■ recovery ■ rehabilitation ■ stroke

Dr William M. Feinberg was a superb stroke clinician, educator, and investigator. His interests were broad and extended from the basic aspects of stroke through his work on hemostatic markers to clinical stroke research. He influenced stroke medicine beyond his own specific research interests by trying to improve practice through his roles as chair or contributor to several American Heart Association guidelines and scientific statements. In addition, he was a wonderful role model for young clinicians and investigators. This discussion is intended to reflect themes inspired by Dr Feinberg’s career. First, the opportunity young investigators have to participate in the continuum of stroke research is highlighted based on examples from my own work and experience. Second, the importance of looking beyond personal research or clinical endeavors to contribute to the broader goal of reducing the incidence and consequences of stroke is emphasized.

Figure 1 provides a framework for considering the scope of stroke-related research. From a clinical perspective, the continuum of stroke research and care can be divided into efforts aimed at primary prevention, acute interventions, secondary prevention, and poststroke recovery. From a technical/methodological perspective, fundamental laboratory studies yield insights into basic disease mechanisms. Applied laboratory studies further explore the biological basis of disease and evaluate possible therapeutic interventions. The results of these laboratory-based observations can inform clinical study design whereas questions raised by clinical studies can in turn be explored in laboratory experiments (ie, “translational” research). Additional insights are gained through observational, interventional, and synthetic (eg, meta-analytic) clinical studies. Outcomes/effectiveness research determines how well interventions perform in different “real-world” settings.

Promoting the development of young investigators beginning their careers is a particular focus of the American Heart Association/American Stroke Association. Although there are a variety of pathways to a successful, productive life in research, my mentor, Dr James Davis, had the view that it was important to identify a question of importance but one that was not yet being intensely studied by large numbers of investigators. The poststroke recovery process is one such area. Figure 2 is modified from one of our early clinical...
studies aimed at describing long-term functional outcomes in patients with acute ischemic stroke.\(^1\) The graph underscores two important principles. First, regardless of initial stroke severity, patients with stroke as a group tend to recover with the most rapid improvement occurring over the first weeks and a general tendency to reach a plateau after approximately 3-months, although individuals may continue to recover over more extended periods. Second, functional outcome depends to a great degree on the initial severity of the stroke. Acute interventions such as reperfusion therapy are intended to decrease the volume of injured brain, thereby reducing the associated functional deficit leading to improved functional outcome. Restorative therapies are intended to alter the recovery processes leading to improved outcomes for a given degree of brain injury and initial deficit. A series of laboratory experiments indicate that the latter might be possible.

In 1982, Dennis Feeney reported that a single dose of \(d\)-amphetamine given 24 hours after unilateral sensorimotor cortex ablation in the rat led to an enduring reduction of the resulting motor deficit.\(^2\) Because the volume of the brain injury was fixed, the experiment suggested that the drug was acting to modulate the recovery process. The observation was subsequently replicated in numerous laboratories and in a variety of different species with a range of brain injuries.\(^3\)–\(^5\) These experiments illustrate several principles.\(^5\) First, the relationship between amphetamine dose and functional outcome has an inverted “U” shape. Recovery improves with increasing dose but then declines as the dose is further raised. Second, the effects of certain drugs (eg, amphetamine) on recovery are dependent on the animal’s training and environment.\(^6\) Third, the timing of the drug administration/training is critical as is the number and frequency of treatment sessions. Fourth, some drugs such as haloperidol impair recovery. Understanding the mechanism of amphetamines’ effects on recovery would not only help predict the potential impact of other drugs on functional outcome after stroke, but also provide insights into the fundamental neurobiological processes underlying recovery. Several lines of evidence suggest that amphetamines on recovery act through modulation of central norepinephrine. First, pretreatment with a neurotoxin that selectively depletes central norepinephrine (\(N\)-[2-chloroethyl]-\(N\)-ethyl-2-bromobenzylamine; DSP-4) impairs motor recovery after later sensorimotor cortex ablation.\(^7\) Previous selective lesioning of the pontine nucleus locus coeruleus, the major source of central noradrenergic innervation, similarly retards recovery after subsequent injury to the cerebral cortex.\(^8\)

The locus coeruleus has widespread projections to the ipsilateral and contralateral cerebral cortex and cerebellum. Locus coeruleus fibers reach the cortex through the dorsal noradrenergic bundle. Figure 3 shows that motor recovery in the rat is impaired by subselective lesions of the dorsal noradrenergic bundle contralateral to a later injury to the sensorimotor cortex.\(^9\) Measurement of norepinephrine levels showed that outcome was correlated with norepinephrine content in the contralateral, but not ipsilateral, cerebral hemisphere. In contrast, rats with or without lesions of the dorsal noradrenergic bundle before an ipsilateral sensorimotor cortex lesion had similar recoveries. Taken together, these experiments and others not only support the hypothesis that amphetamine’s effect on recovery after injury to the cerebral cortex is modulated through central
Table. Impact of Noradrenergic Drugs on Motor Recovery After Focal Injury to the Sensorimotor Cortex in Experimental Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Recovery Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Sympathomimetic</td>
<td>Improve</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Sympathomimetic</td>
<td>Improve</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>Sympathomimetic</td>
<td>Improve</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Sympathomimetic</td>
<td>Improve</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>α2-adrenergic antagonist</td>
<td>Improve</td>
</tr>
<tr>
<td>Idazoxan</td>
<td>α2-adrenergic antagonist</td>
<td>Improve</td>
</tr>
<tr>
<td>Clonidine</td>
<td>α2-adrenergic agonist</td>
<td>Impair</td>
</tr>
<tr>
<td>Prazosin</td>
<td>α1-adrenergic antagonist</td>
<td>Impair</td>
</tr>
<tr>
<td>Phenoxymethylamine</td>
<td>α1-adrenergic antagonist</td>
<td>Impair</td>
</tr>
<tr>
<td>Propranolol</td>
<td>β-adrenergic antagonist</td>
<td>Neutral</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>α1-adrenergic antagonist</td>
<td>Impair</td>
</tr>
<tr>
<td>Clozapine</td>
<td>α2-adrenergic antagonist (low dose)</td>
<td>Improve</td>
</tr>
<tr>
<td></td>
<td>α1-adrenergic antagonist (high dose)</td>
<td>Impair</td>
</tr>
<tr>
<td>DSP-4</td>
<td>Central norepinephrine depletion</td>
<td>Impair</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norepinephrine reuptake blocker</td>
<td>Improve</td>
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</tbody>
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norepinephrine, but that the action is mediated in the cerebral hemisphere contralateral to the injury.

If amphetamine’s effect on recovery is mediated by raising central norepinephrine levels, then other drugs that enhance synaptic norepinephrine release or decrease its metabolism would be expected to be beneficial, whereas those that lower levels or block postsynaptic effects would be expected to be harmful. A series of experiments suggest that this is the case. For example, yohimbine and idazoxan, centrally acting α2-adrenergic receptor antagonists (that act to block autoreceptors on noradrenergic neurons thereby increasing norepinephrine release) enhance motor recovery when given to rats as a single dose after unilateral sensorimotor cortex injury. In contrast, clonidine, an α2-adrenergic receptor agonist, decreases norepinephrine release and impairs recovery. As noted, haloperidol, a dopamine receptor antagonist, interferes with motor recovery when given after cortical injury. Haloperidol, however, also acts at adrenergic receptors. Radioligand binding studies show that haloperidol is a marginally more potent α1-adrenergic receptor antagonist than the atypical antipsychotic clozapine (K_{D} 6.1 versus 9 nM, respectively), whereas clozapine is a significantly more potent α2-adrenergic receptor antagonist than haloperidol (K_{D} 160 versus 3800 nM, respectively). Based on this pharmacology, we hypothesized that haloperidol would impair recovery when given as even a single dose after cortex injury in rats, whereas clozapine would be less harmful or would enhance recovery, a hypothesis that proved true when tested experimentally.

Based on these and other similar experiments, it has been possible to predict the impact of a series of noradrenergic drugs on recovery after experimental cortical injury based on their pharmacological properties (Table).

Moving across the continuum from basic or applied experimental studies to humans (Figure 1), we found that many of the drugs that could affect postbrain injury recovery are frequently given to patients after stroke. Determining whether the putative detrimental drug effects found in laboratory animal models are similar in humans cannot be determined by randomized, controlled trials, so any inferences must rely on observational studies. These types of studies find that, when considered as a group, drugs having a negative functional impact when given after brain injury in animal models of locomotor recovery also lead to poorer outcomes when given to humans recovering from stroke, even after adjustment for comorbidity and other potential confounders.

In contrast to evaluating potentially harmful drugs, testing pharmacological therapies that might enhance poststroke recovery in clinical trials is ethically feasible but logistically challenging. Given the important interaction between drugs and training effects, control of concomitant physiotherapeutic interventions is critical, but not easily accomplished. Issues such as drug dose, timing of the intervention as well as its duration and intensity, patient comorbidity, and the location and extent of brain injury, among other factors, may be significant. It is therefore not surprising that the results of small clinical trials of the effects of amphetamine on poststroke recovery in humans have been inconsistent, but mostly negative. The Amphetamine Enhanced Stroke Recovery Trial, a National Institutes of Health-supported pilot clinical trial, is attempting to address some of the issues necessary for the design of a large prospective trial.

This discussion has so far highlighted how it is possible to start from an observation in the laboratory, develop an understanding of the biology underlying the observation, and then move to the clinic to determine whether those principles can be applied to human disease. The ultimate goal is to identify and test new treatment approaches and potentially novel therapeutics (ie, efficacy studies). Another area of research is focused on effectiveness rather than efficacy (ie, determining how therapies, many of which are based on the results of randomized trials, affect patient outcomes as used in routine clinical practice; Figure 1). For example, if amphetamine combined with physical therapy was found to improve poststroke gait recovery in a controlled clinical trial, would the benefit be similar as it was used for a broad patient population by healthcare providers in various clinical settings? Would there be safety issues that were not apparent from the trial? Because the clinical efficacy of amphetamine/physiotherapy has not been established, questions regarding effectiveness are premature. There are, however, other therapeutic interventions for stroke that provide examples of what can be learned from effectiveness research.

A variety of organizational features of care are associated with improved outcomes or fewer complications in patients being evaluated or treated for stroke. In 1998, we conducted the first statewide assessment of hospital-based stroke treatment capabilities in the United States in North Carolina. Although reimbursable diagnostic tests were generally available, only 40% of hospitals had intravenous tissue plasminogen activator treatment protocols, 18% a stroke unit or its equivalent, 18% a stroke rapid response system, and only 27% offered stroke-related community education programs. Moreover, there was a geographic disparity within North
Carolina with a lack of hospitals providing these services in entire regions of the state. The North Carolina statewide assessment was repeated 5 years later in 2003. Although there was an interval increase in the availability of certain diagnostic tests, there was essentially no change in the organization of care. These types of studies have direct implications for the development of health policy. For example, in North Carolina, the sequential surveys were used to support legislation adopted in 2006 establishing a Stroke Advisory Council that was charged with developing a state-wide stroke care system.

Those of us having careers in academic medicine are also citizens and therefore have a responsibility to use our knowledge to advocate for policies that can have a direct impact on the health and well-being of our patients and communities. For example, with the support of its Grass Roots network and along with coalition partners, the American Heart Association and its volunteers advocated for a doubling of the National Institutes of Health budget in 1998, a goal that was achieved in 2003. This type of activity has obvious and direct implications for the careers of new investigators. With the doubling, there was an intentional expansion in the numbers of new investigators with a goal of increasing research capacity. The National Institutes of Health budget, however, contracted after 2003 because further adjustments did not account for medical inflation. More new investigators were then submitting an increased number of applications but competing for less funding. The result was that the proportion of funded to submitted grants dropped dramatically, leading to the conclusion by a group of universities and research institutions that “a generation of science [was] at risk.”

It is the responsibility of each of us, particularly those at early career stages, to become involved as advocates for the importance of biomedical research so that sustainable levels of federal funding can be secured in the future. Similar efforts are required to support national programs through the Centers for Disease Control and Prevention as well as state-based initiatives aimed at reducing the burden of cardiovascular disease and stroke. It is also important to have a voice in the ongoing national debate on healthcare reform and the role of comparative effectiveness research.

This discussion highlighted 2 themes inspired by Bill Feinberg’s career. First, this is an exciting time for young investigators who have wonderful opportunities to make significant contributions across the entire continuum of stroke research. Second, through advocacy and other activities, it is important take a broad view of how individual efforts can help achieve the shared goal of decreasing stroke and its consequences. As Bill Feinberg did and as his career exemplifies, we can all make a difference.

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Disclosures
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References