Acute Stroke Therapy at the Millennium: Consummating the Marriage Between the Laboratory and Bedside

The Feinberg Lecture

James C. Grotta, MD

Those of us in the stroke field have a big job ahead of us. When I started attending this meeting 20 years ago, most of the papers related to acute stroke therapy were laboratory related. Now, of course, we are in the era of clinical trials. But in designing clinical trials, we cannot forget the lessons that need to be learned from laboratory research. And it’s the job of the stroke neurologist to marry these 2 together, and that’s the main focus of what I’d like to talk about in the next few minutes.

I’d like to make 4 key points. First, that stroke therapy is difficult. It’s a complex disease, and nobody said it would be easy. There are not going to be any magic bullets for stroke patients. Second, the most critical but ignored lesson from the laboratory is the importance of time. Third, it’s critical to change the role of neurologists in taking care of stroke patients, particularly because of the importance of time. Finally, I’d like to make a few comments about the direction of future stroke research.

The bad news for acute stroke therapy is that as far as translating what we’ve done in the laboratory to clinical reality, stroke has been and always will be difficult to treat. We should expect small advances and many failures, and for every 1 positive clinical trial, we will probably have many negative ones; that’s just the nature of stroke disease. But substantial attenuation of damage is possible.

I will try to show how the hopes of the laboratory have often been dashed by the reality of translation to human stroke by using an autobiographical approach. The basic principle that acute stroke is a treatable disease was demonstrated to me when I was a fellow at Massachusetts General Hospital working with Robert Ackerman, MD, using positron emission tomography in stroke patients, which demonstrated viability of tissue in regions of low blood flow. This was proof in principle that acute stroke is a treatable disease was demonstrated.

In the early 1980s, animal models of global and focal ischemia were developed. The forebrain ischemia model in rats was described by Pulsinelli et al and validated in human cardiac arrest patients by Petito and colleagues, demonstrating delayed cell death in hippocampal regions. We and others showed that such delayed cell death was closely related to calcium influx and binding to calmodulin and that the damage could be attenuated by calcium antagonists.

This was not a universally accepted finding, but our ability to block calcium influx and delay cell death provided the rationale to test calcium antagonists in human clinical trials. The early clinical trials of calcium antagonist therapy were generally negative because of side effects, particularly hypotension, and again, delayed time windows.

Then, of course, Choi and colleagues demonstrated the excitotoxicity of glutamate in neuronal cell culture and that this could be attenuated by calcium antagonists. This led to a number of clinical trials of calcium antagonist therapy, all of which were negative because of side effects, particularly hypotension, and again, delayed time windows. Then, of course, Choi and colleagues demonstrated the excitotoxicity of glutamate in neuronal cell culture and that this could be attenuated by calcium antagonists. This led to a number of clinical trials of calcium antagonist therapy, all of which were negative because of side effects, particularly hypotension, and again, delayed time windows. Then, of course, Choi and colleagues demonstrated the excitotoxicity of glutamate in neuronal cell culture and that this could be attenuated by calcium antagonists. This led to a number of clinical trials of calcium antagonist therapy, all of which were negative because of side effects, particularly hypotension, and again, delayed time windows.

Figure 1 shows the effectiveness of various drugs in our laboratory rat model of focal ischemia with reperfusion, and I’d like to recognize Jarek Aronowski, PhD, who is my colleague in the laboratory and with whom I’ve carried out most of our animal studies in the last 10 years. In the Figure, 100% on the y axis means that there is no difference compared with controls. Calpain antagonists and the blood substitute DCLHb (diaspirin cross-linked hemoglobin) didn’t really attenuate damage very much. Interleukin-1 receptor antagonist had some effect. The antiglutamatergic drugs magnesium, aptiganel, and lubeluzole consistently attenuated damage by about 50%. When we tried FK506, which is a calcineurin antagonist, or Z-VAD, which blocks caspases and apoptotic cell death, and then finally anti-inflammatory drugs like PBN (phenyl-N-tert-butylnitrone), we found even more...
substantial reduction of damage. All the way on the left of Figure 1 is the combination of caffeine and alcohol. While alcohol itself is very damaging, the combination of low doses of caffeine, which can reduce glutamate release via adenosine, and alcohol is the most neuroprotective combination that we’ve been able to find in our laboratory. It may be a little bit disillusioning to think that those billions of NIH dollars that have gone into experimental research may end up with giving our patients the equivalent of Irish coffee through an IV. But the main point is that most researchers who work with animal stroke models would attest that it is possible to obtain substantial attenuation of neuronal damage in these laboratory models.

The second point I’d like to make is that the most important lesson of these animal stroke models is the brief time window we have for effective neuronal salvage by reperfusion or neuroprotection. We need to recognize and make the most of the brief time window we have to treat patients with acute brain injury. In these data from our own laboratory in young rats, if we occlude the middle cerebral artery for variable durations of time, then reperfuse and measure infarct volume shown on the y axis, we can leave the artery occluded for up to 60 to 90 minutes before any damage occurs (see Figure 2). After that, substantial infarction becomes visible. Opening the artery within 2 or 3 hours will reduce damage, but after 2 to 3 hours, reperfusion produces no reduction of damage compared with just leaving the artery permanently occluded and, in fact, may even make things worse. In spontaneously hypertensive rats, which may permanently occluded and, in fact, may even make things worse. In spontaneously hypertensive rats, which may clarify a little more of what we see in our aged stroke population, this time window is even briefer: 90 to 120 minutes. If we start neuroprotective therapies (for instance, lubeluzole) within this time window, we can get substantial attenuation of damage, but when these drugs are started beyond this point, nothing beneficial happens.

How does this time window relate to our clinical trials? The only conclusive positive clinical study of reperfusion was exactly predicted by animal models, and that is that patients must be treated within 3 hours. This has been further corroborated in recent post hoc analysis of our NINDS rtPA data by Marler et al, which demonstrates a falloff in response to rtPA the longer after stroke onset the treatment was begun within the 3-hour time window. We are going to hear later this morning the results of reperfusion trials where therapy was carried out to 6 hours, and hopefully at some point, we will have therapy to offer people beyond 6 hours. But I think the basic lesson remains true: the earlier we start, the better, and the earlier we treat patients even within the 3-hour time window, the more response we are going to get.

The same is true with neuroprotective therapy. Carmela Picone, MD, Sandra Hanson, MD, and Tom DeGraba, MD, when they worked in our laboratory, measured calcium influx into neurons as detected by its binding to calmodulin, which correlates very well with ultimate cell death and functional outcome. In a focal-ischemia animal model, within 2 hours, calcium binding to calmodulin becomes maximal, so that the time window at least for the early events related to calcium after ischemia is also very short. All the various drugs that we’ve tested in the laboratory need to be started early in order to produce neuroprotection. In the case of lubeluzole, when started 15 or 30 minutes after occlusion, or even up to an hour afterward, we found some benefit. But beyond that, there was no effect. With PBN, a very effective spin-trap agent, we can get some effect up to 2 hours, and the combination of alcohol and caffeine can be given out to 2 hours. There are over 100 studies in the literature that show the efficacy of MK801 (dizocilpine). A random sampling of these could find none in which MK801 could be given beyond 2 hours and still reduce infarct damage.

This is how I foresee the way we should translate laboratory studies into our clinical trials, at least with neuroprotec-
We have to remember that we are trying to achieve neurorational trial design, we need to start our therapies early, and that no one of our outcome measures really gives the full picture of outcome. But to reiterate the most important component of outcome remains to be seen, but I really don’t think it’s going to add much to our behavioral outcomes. Then, of course, we need to have a good measure of behavioral outcome. In the NINDS rtPA trial, we used the global statistic, which combines a number of different outcome measures. We didn’t include quality of life, but I think that does need to be built into our clinical trials now. The global statistic isn’t all that difficult to understand. To illustrate, those of you on the left side have another, and those in the center have another, and none of you see that from behind I die, and that has to occur by giving our therapies within the first few minutes.

Now, how can we carry this out? I think that it requires changing the role of neurologists entirely. Treatment really means empowerment. This meeting has doubled its size in the last few years, and I think this reflects that the stroke community has felt empowered now that we have treatments we can offer our patients. It is disconcerting to read editorials about why new acute stroke therapies should not be given, written by people who have never been in the emergency department treating patients. I think all of us who have been treating patients recognize that they do get better as a result of our therapies. Both the clinical trial evidence and our personal bedside experiences have galvanized the stroke community. But we need to keep our momentum by maximizing early intervention rather than falling back to the traditional role of neurologists as probers and sifters. Treating a larger number of patients early rather than relying on expensive and time-consuming diagnostic studies to identify those few patients with limited salvageable tissue later in their course will benefit the most number of patients. That means we are going to have to be running to the emergency department and changing how we usually practice neurology. Neurologists will have to become friendly with the previously unfamiliar terrain of the emergency department. The usual practice patterns of neurologists who love to do EEGs and electromyograms and obtain multiple scans and other diagnostic tests before we treat, while comfortable and appropriate under certain circumstances, is going to have to change to a more proactive approach for acute stroke.

We need to do this because these changes will have demonstrable benefit for our patients. We all know the results of the NINDS rtPA trial when treatment was started within 3 hours. In combining the 2 parts, good outcomes are increased from 27% to 42%, and, importantly, the bad outcomes are reduced from 47% to 37% (Figure 4). And, in my opinion, this is the way we need to look at results in clinical trials. Some of the drugs that we give, including rtPA, have a downside, and we need to be sure that we examine both the benefits as well as the downside simultaneously. Now that we have effective therapy, it’s interesting to look back and compare the responses of rtPA in animals compared with

---

Figure 3. Comparison of paradigm for testing neuroprotective drugs in the laboratory (top) versus proposed paradigm for clinical trials (bottom). DWI indicates diffusion-weighted imaging; NIHSS, NIH Stroke Scale; and QOL, quality of life.

Figure 4. Distribution of outcomes on NIH Stroke Scale (NIHSS) (top), Barthel index (middle), and Rankin scale (bottom) in parts 1 and 2 combined of the NINDS rtPA Stroke Study.
humans. There are some striking similarities. Work just published in *Neurology* from Chopp’s laboratory found that in a rat model, rtPA is associated with a 56% improvement in the neurological score. In the NINDS trial in stroke patients, the drug was associated with a 62% improvement in functional outcome. In the laboratory studies, rtPA reduced infarct volume by about 33%, and in the NINDS clinical trial, rtPA reduced infarct volume by about 38% (Figure 5). It’s going to be very important, as we develop positive therapies, to look back at what our experience was in the laboratory to try to see what parts of the laboratory experience were most useful in deciding whether these drugs work or not. The rtPA data suggest that both in the laboratory and at the bedside, our behavioral and functional outcomes are at least as good and probably even more sensitive at detecting response to therapy than just simply measuring infarct volume.

I know that what I’ve said about the need for speed and diagnostic tests is somewhat controversial and of course has been debated in the pages of the *New England Journal of Medicine* this last year between myself and some of my esteemed colleagues. The bottom line of this debate really boils down to how much information we need to obtain on our patients before we treat them. At the University of Texas–Houston Medical School (UT-Houston), we also believe that the more we know about the patient, the better, but we don’t want to delay our therapy in order to obtain that information. The best idea would be to obtain the information as we are treating the patient. We have been fortunate that Andrei Alexandrov, MD, joined our group, and so we now can obtain emergency transcranial Doppler (TCD) on most patients whom we see urgently. Figure 6 is a TCD from a patient who was seen about an hour or so after a stroke and was started on therapy. You can see there is initially no flow in the middle cerebral artery, but after 45 minutes into the therapy, there was a loud pop from an embolic signal and then recanalization of the middle cerebral artery with reestablishment of flow. Had this not occurred, we would have taken the patient to angiography to finish the job with intra-arterial therapy. Tom Brott, MD, and Joe Broderick, MD, developed a protocol over the last few years, now being evaluated at a number of sites, combining intravenous therapy followed by intra-arterial therapy to see whether we can increase the benefit in patients who have middle cerebral artery occlusion.

I might add that such endovascular therapy should some day be carried out by appropriately trained stroke neurologists. As stroke therapy matures, we need to take back some of the activities that we have previously relinquished to our colleagues in radiology and critical care. Stroke is too large a public health problem, and there are too many stroke patients for advanced care to be limited to the hands of only endovascular neuroradiologists and critical care intensivists. Specifically, we need to develop programs to train and eventually credential and certify stroke neurologists to carry out endovascular therapy and critical care management of our stroke patients.

Our experience with urgent thrombolysis at UT-Houston over the last few years demonstrates how a successful urgent-therapy program can work. I’ve benefited from having a wonderful team of fellows, and I want to thank them for the work that they have done in getting patients treated (Figure 7). In the first year after the approval of rtPA, we treated an average of 2 to 3 patients per month. By improving our patient recognition and triage by working with the Houston Fire Department Emergency Medical Services and our emergency medicine department, we now are treating 6 to 8 patients per month, which represents almost 20% of the 500 strokes we see each year. I think that treating 25% of patients within 3 hours is not an unrealistic goal if we reorganize our priorities and focus on getting patients in rapidly. Outcomes in these treated patients are similar to those that were reported...
in the NINDS trial. We are treating more patients with intra-arterial therapy, particularly those who, according to our vascular imaging methods (usually TCD), have middle cerebral artery or basilar occlusion. Once intravenous rtPA is started in these patients, if their CT scans are normal, we’ll take them to angiography for possible intra-arterial therapy as just described, but this approach remains to be proven effective.

There are some interesting impediments to why urgent stroke therapy is not being carried out more widely. When I travel around the country and give talks about the use of thrombolysis, I’m struck that some stroke fellowship programs sometimes don’t even allow their fellows to treat patients with rtPA. It’s distressing even in our own program at UT-Houston to see that our neurology residents often finish their training without feeling comfortable selecting and treating patients with rtPA in the emergency department. We don’t put enough emphasis on training our residents in giving rtPA. Now, why is that? It escapes me. The closest parallel to acute stroke therapy in terms of a neurological emergency is status epilepticus. If we look at an article from Epilepsia in 1994,21 the time frame for developing either neurological deterioration or mortality from untreated status epilepticus is not too dissimilar to what we see with stroke. Every neurology resident will drop whatever they’re doing if they’re called to the emergency department about a patient in status epilepticus. The same approach has to be taken with stroke patients who arrive at our emergency departments within 3 hours. The same response has to be expected. And we cannot expect neurologists in private practice or elsewhere to be doing this for free. We get up in the middle of the night and go to the emergency department and spend 2 hours of our time because emergency physicians are not going to carry out this therapy without the expertise of the neurologist to select the patient. Well, if our expertise is so important, then it should be reimbursed. However, there is no billing code for intravenous rtPA stroke therapy. The one code that does exist, transcatheter therapy, bills for about a thousand dollars but does not reimburse for anything other than intra-arterial therapy. It does not reimburse at this rate for intravenous therapy. The endovascular radiologists, neurologists, or neurosurgeons who are giving intra-arterial therapy have a code for administering lytic therapy in that fashion, but there is no code that reimburses more than a standard consultation fee for intravenous therapy. I went back and reviewed our billings for the last 14 patients we’ve treated with intravenous rtPA. Whereas we billed $15,000 for that work for those 14 patients treated in the middle of the night, we collected a total of $3000. In my opinion, our professional organizations need to take on this responsibility, as well as the educational one, to be sure that neurologists get reimbursed for reorganizing their lives to carry out effective acute stroke therapy.

Finally, I’d like to make a few predictions that I think will come true before I retire in another 10 or 15 years. I hope I’ve made it clear that if we stick to the lessons from the laboratory, effective neuroprotective therapy is likely to be found and demonstrated for at least some patients with ischemic stroke. I only had a chance to briefly touch on cardiac arrest at the start of my talk, but there are data in animal models of global ischemia showing that therapies targeting apoptosis and delayed cellular death and anti-inflammatory therapies will be effective for reducing consequent brain damage. I also think we’ll have effective therapies for intracerebral hemorrhage (ICH) and for enhancing recovery after stroke.

Let me make a few comments about ICH. Lewis Morgenstern, MD, who started as a fellow in our program and I’m proud to say is now codirector of our stroke program at UT-Houston and an esteemed colleague, carried out a single-center trial of surgical therapy for ICH.22 The results reflected what had been found in small trials elsewhere, that surgical evacuation alone really doesn’t do very much for patients with ICH. We need to come up with a better treatment approach for this large component of our stroke patients. So we’ve gone back to the laboratory to find out what’s going on in the brain to result in poor outcomes in these patients. Of course, we’re not alone in this effort, and it’s gratifying to see the large number of studies that are now addressing this problem. In the model that we use (again, these are studies carried out in our laboratory by Jarek Aronowski, MD, and more recently by Susan Hickenbottom, MD, and Teddy Wein, MD),23 we’ve found that there is substantial cellular death in the area around the hematoma, and after several hours, this becomes prominent out in the parenchyma. More recently, Andrew Demchuk, MD, has obtained tissue from human patients undergoing clot evacuation at our center and has seen the same sort of activation of the transcription factor nuclear factor-κB (NF-κB), which activates inflammatory processes in the brain. There is robust activation of NF-κB within hours around the hematoma, and after several hours, this becomes prominent out in the parenchyma. More recently, Andrew Demchuk, MD, has obtained tissue from human patients undergoing clot evacuation at our center and has seen the same sort of activation of the inflammatory transcription factor NF-κB in perivascular regions around the hemorrhage within hours of ICH. This suggests that NF-κB activation and consequent inflammation are reasonable targets for neuroprotective therapy in patients with ICH, perhaps combined with surgical evacuation.

I’d like to end with a few words about recovery after stroke. We’ve been collaborating with Tim Shallert, PhD, in Austin, Tex, and have shown that when you cast the unaffected forelimb of a rat after a stroke and force overuse of the affected forelimb, both histological and behavioral outcome are worse.24 This is also seen to a lesser extent if you cast the affected limb and totally immobilize it. These are things that we don’t usually do to our patients, but these studies...
demonstrate the principle that what we do with our patients during the recovery phase after stroke is important in the amount of recovery they make. Understanding the biology of this plasticity should become an important research priority.

In closing, like David Letterman, I’d like to list the top 10 things I think we should focus on in the next few years:

1. We need to reorganize stroke care delivery by neurologists, emergency departments, and paramedics so that acute stroke is treated as a dire emergency. That also means increasing public awareness, developing designated stroke treatment centers analogous to trauma centers, and improving reimbursement for stroke care.

2. We need to safely augment what we’ve already achieved with thrombolysis, perhaps with better thrombolytic agents, intra-arterial drug delivery, and mechanical clot disruption, adding anticoagulants or perhaps the newer antiplatelet agents and adding neuroprotective drugs. We are trying to mount studies now of very early therapy combining potent neuroprotective drugs with thrombolysis.

3. We need to develop programs to train and certify stroke neurologists to carry out endovascular therapy and critical care of stroke patients.

4. We need to understand and develop treatments for reperfusion injury, particularly after cardiac arrest. Therapies aiming at apoptosis are particularly relevant for this condition and need to be tried, and they have a chance of success if we can develop good clinical trials.

5. We need to develop nontoxic multimodality neuroprotective cocktails. We then need to test them and combine them with thrombolysis, and we have a big job in convincing pharmaceutical companies and regulatory agencies of their logic and necessity. I think that most of us in the neuroprotective field believe that this is ultimately how the efficacy of neuroprotection will be demonstrated. These neuroprotective drugs need to be safe enough that they can be administered on the way to the hospital before brain imaging in order to save valuable time.

6. We need to improve our clinical trial design, including more-thorough phase II pilot studies to determine maximal dose, choice of end points, and sample size estimates before we move on to pivotal trials. We need seamless transit from phase II to phase III similar to what was done in the NINDS trial, where momentum is not lost as the data are analyzed and decisions are made to go on to phase III. We need to increase the sample size of our phase III trials, particularly with neuroprotective drugs, to see a 5% to 10% absolute difference in outcome. We need to use doses that are effective in animals models, standardized stroke severity, and most importantly, early administration.

7. Development of online measures of cerebral physiology and cellular viability, as well as determining if they are useful, is a high priority. At this point, their utility is still hypothetical. Hopefully, these tools will help us, without delaying therapy or as we are treating patients, to decide when to stop and who to move on with.

8. We need to focus our research on understanding the biology of recovery and translating that knowledge into rational rehabilitation strategies and pharmacological augmentation of the brain’s natural adaptive mechanisms.

9. We need to evaluate surgical decompression, hemi-craniectomy, clot evacuation, and other heroic measures such as hypothermia for massive infarcts and ICH. Hemi-craniectomy has caused excitement in the stroke community by producing strikingly good outcomes in some patients with otherwise fatal strokes.

10. We need to understand the pathophysiology of secondary brain injury after ICH and then develop scientifically based therapies for that condition.

In conclusion, I’d like to thank all of the fellows who have worked with me over the years and who have made the work that’s come out of the UT-Houston Stroke Program possible. They are too numerous to thank individually, but it’s been the most gratifying part of my job professionally to train these fellows and watch them develop their own research interests. I’d also like to thank the nurse-coordinators who have helped carry out our clinical trials; Jarek Aronowski, PhD, who has helped with the laboratory work I’ve described; and William Fields, MD, and Frank Yatsu, MD, for hiring and mentoring me. Finally, I’d like to remember Bill Feinberg, MD, after whom this lectureship is named, and thank the American Heart Association for selecting me to give this lecture in his honor.

References

14. Grotta J, Clark W, Cossut B, Pettigrew LC, Mackay B, Goldstein LB, Meissner I, Murphy D, Larue L. Safety and tolerability of the glutamate...


**Key Words:** American Heart Association • rtPA • thrombolysis • neuroprotection • clinical trials • research
Acute Stroke Therapy at the Millennium: Consummating the Marriage Between the Laboratory and Bedside: The Feinberg Lecture
James C. Grotta

Stroke. 1999;30:1722-1728
doi: 10.1161/01.STR.30.8.1722

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/30/8/1722

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/