I want to thank the Stroke Council, my friends, and colleagues for giving me the privilege of delivering the 2000 William Feinberg lecture. I am particularly honored to follow Lou Caplan. Lou is near the top of the list of individuals who have had the most influence on my career. The subtitle of his classic paper, “What is Wrong with Mr. Jones,” has become the mantra for those of us who believe it is essential to know what we are treating before we know how to treat it; otherwise we run the risk of a “confused vascular analysis.”

I therefore honor Lou by declaring this the millennium of the stroke splitters; I confidently predict that the stroke lumpers will finally be vanquished sometime in the next 1000 years!

The first time I specifically recall being told I was professionally confused was in 1976. I was finishing the third year of my neurology residency at the Cleveland Clinic. My chairman, Jack Conomy, called me into his office to tell me I was confused. He said I really did not want to take an EMG fellowship and that I should go into something more challenging, like stroke. I always took Jack’s advice, and to this day I cannot interpret an EMG.

Shortly after starting my stroke fellowship at the Mayo Clinic in 1977, I noticed that many patients in Rochester, Minnesota, seemed to be on coumadin. I therefore asked Burt Sandok what the rationale was for using coumadin to prevent CVAs. Burt said, “You know, Tony, CVA stands for a ‘confused vascular analysis.’ Why don’t you review the literature and get back to me?” I didn’t realize it at the time, but this seemingly humorous anecdote would serve as the basis for my entire career. That literature review revealed many papers and opinions on coumadin. Even a few randomized clinical trials had been done in the early 1960s. To my surprise, however, there was no proof of the efficacy (or lack thereof) of coumadin despite its widespread use.

This was the dawn of the clinical trial era in stroke, and these early pioneering studies of coumadin are best viewed as exploratory trials. They do not meet modern standards of trial design in terms of sample size, power, or blinding. But “modern” is a relative term, and as we shall see, our notions about clinical trial design keep evolving.

I then learned the academic canard of using the absence of data to publish my first stroke paper: our own “Guidelines for the Management of Transient Ischemic Attacks” in 1978.3 We recommended the use of coumadin for 3 months in patients with new-onset TIAs, because that is when the risk of stroke is greatest and the benefit of coumadin seemed to outweigh the risk, followed by aspirin therapy for 1 year. In fact, it would be many years before the SPAF,4 WARSS,5 WASID,6 and IST7 trials would provide any phase III data on the efficacy of antithrombotic therapy, thereby justifying the publication of evidence-based, as opposed to opinion-based, guidelines. Of note, the trend since the 1960s has been to increasingly restrict antithrombotic therapy to small, well-defined patient subgroups rather than treating all patients in the same way. Indeed, although the efficacy of coumadin for stroke prevention in atrial fibrillation has now been demonstrated, the efficacy of coumadin for atherosclerosis-related ischemic events remains unproven.

I had thus been introduced to my first risk factor for a CVA, or a “confused vascular analysis,” namely, equating expert opinion with proof. A second CVA risk factor, I now realize, was basing treatment on symptoms (ie, TIAs) rather than precise pathophysiology. Looking back, I now find it curious that many physicians were willing to use treatments like coumadin or heparin when there were no efficacy data, yet many now will not use intravenous tissue plasminogen activator (tPA) when there are efficacy data. Does this reflect progress or another CVA risk factor, namely, physician behavior? I suggest that changing entrenched physician stroke behaviors is one of our most difficult challenges in the new millennium.

Shortly after the coumadin incident, my mentor, Jack Whisnant, who is one of the few stroke neurologists I know who can actually spell Cochran Mantel-Haenszel, and Thor Sundt were discussing what to do with a patient with a high-grade but asymptomatic carotid artery stenosis. Jack turned to me and said, “Tony, what do you recommend?” Mindful of my CVA lesson from Burt, I said without hesitation that there were no data supporting endarterectomy and therefore the patient should be managed medically. Upon which Jack turned to Thor and said “fix it.” I felt like a CVA: a “confused vascular assistant.” Paradoxically, however, I was being taught another CVA risk factor: the danger of data dependency. Ultimately, we must be physicians and not statisticians; clinical trials can never describe all of our individual patients, and for some problems, there will never be a trial. In everyday clinical situations, expert opinion and...
experience often must substitute for $P$ values and therapeutic nihilism. Another key challenge for the 21st century stroke physician will be how to balance all of the new data and technology at our disposal with the art of medicine.

The focus of my fellowship was natural history studies. Jack told me “Study the natural history of carotid occlusion; I think Barney [H.J.M. Barnett] will need that to calculate the sample size in the EC/IC bypass trial.” With the help of many others, I later also studied the natural history of carotid siphon stenosis,8 proximal vertebral artery stenosis,9 and distal vertebral basilar artery stenosis.10 We learned that patients with carotid siphon stenosis had a lot more heart attacks than strokes (or should I say “brain attacks?”) and that distal vertebral artery stenosis had a much worse natural history than proximal vertebral artery stenosis. I did not pursue the natural history of middle cerebral artery stenosis only because it was rather rare in Rochester, Minnesota, and Cleveland, Ohio. However, I did write my first paper on middle cerebral artery occlusion, which we unexpectedly precipitated with an extracranial/intracranial (EC/IC) bypass for middle cerebral artery stenosis11; happily, in recent years, my research has shifted to opening the middle cerebral artery rather than closing it.

I was impressed that all these sites of arterial occlusion had different natural histories. Internal carotid occlusion had a benign natural history in most patients.12 Yet at the time, it was standard practice to send patients after a single TIA or minor stroke who were subsequently found to have an ipsilateral carotid occlusion for an EC/IC bypass. Of course, if the EC/IC study subsequently disproved the bypass—or did it? Most patients with internal carotid occlusion have normal cerebral blood flow because of good collaterals, but a small percentage have impaired perfusion reserve.13 We did not fully understand this in 1980, and the technology did not widely exist to routinely assess cerebral blood flow and perfusion reserve in patients with internal carotid occlusion. It was easier, and certainly more lucrative, to send all patients off for surgery.

I had learned 2 more CVA risk factors that would haunt later clinical trials, namely, the difficulty of estimating outcome in a control group and the danger of confusing anatomy with physiology.

These early adventures taught me that we cannot treat lesions with different natural histories in the same way and expect to get the same results. Yet, how well have we applied this and other lessons learned during more than 30 years of stroke clinical research? Certainly a major risk factor for a confused vascular analysis remains the design of clinical trials. How many drugs have gone to trial because they worked in animal models, only to fail in man?14 Was it the drug or the trial? We almost certainly have abandoned more than 1 good drug because of poor clinical trial design.

Consider that for many years, we all did trials with 48-hour or even longer time windows. During all those years, it never occurred to us that “time is brain.” It was as though we had learned something about sample size but not much else since the coumadin trials of the 1960s. Incredibly, it was not until 1995 that the NINDS investigators galvanized us with the observation that acute ischemic stroke had to be treated much earlier.15 This now seemingly self-evident but seminal insight has revolutionized acute stroke management. Similarly, consider that although CT scans have been done in acute stroke since 1976, the ECASS criteria were unheard of until 1995.16

Are there other simple but essential lessons staring us in the face? In my view, a prime candidate is that 30 years of failed acute stroke trials should have taught us that we cannot continue to rely on randomization alone, especially with most sample sizes well under 2000 patients, to account for the complex heterogeneity of acute ischemic stroke. To do so seriously underestimates the enemy. By not applying this lesson to clinical trial design or routine clinical practice, we only increase our risk of a CVA.

There can no longer be any doubt that clinical features alone are insufficient to diagnose stroke etiology and subtype. In TOAST, in which the diagnosis of stroke subtype was made by neurologists interested in stroke, the initial clinical impression agreed with the final diagnosis in only 62% of patients; the main difference was the performance of diagnostic tests.17 In a study we published with Marc Chimowitz,18 only pure sensory stroke involving 2 or more regions of the body and pure motor hemiparesis associated with subcortical infarction of $<1.5$ cm on CT had positive predictive values exceeding 90% for small-vessel disease.

In 1988, we first learned in the Burroughs Wellcome iPA trial that patients who appeared to be excellent candidates for intravenous thrombolysis based on clinical and CT criteria had widely disparate sites of occlusion on angiography, and indeed, 20% had no visible occlusion.19 In PROACT II, 19% of patients selected for angiography had no visible occlusion.20 Predicting the site of arterial occlusion in the posterior circulation stroke is equally complex.21

The fact that we cannot accurately predict the site of arterial occlusion with a neurological examination and CT scan is especially relevant to thrombolytic therapy, since we know intravenous iPA is much more effective at opening small-branch occlusions than large-vessel occlusions.22 Furthermore, the efficacy of thrombolytic therapy in patients without angiographic occlusion is controversial. We now have other treatment options to consider as well, such as intra-arterial thrombolysis or combined intravenous and intra-arterial thrombolysis. Such decisions cannot be made without vascular information.

Given this experience, it’s hard to believe that in the year 2000 we still have not routinely incorporated vascular diagnostic testing into acute stroke management. The core imaging technology remains a CT scan; a CT angiogram, carotid ultrasound, transcranial doppler, or MR angiogram is rarely done emergently. Emergency cerebral angiography is out of the question in most hospitals. It is time to take the next great “technological leap” and incorporate vascular testing into the routine assessment of acute ischemic stroke.

But, hardening back to the EC/IC trial, documenting the anatomic site of occlusion in addition to clinical and CT findings will prove insufficient to optimize patient selection for acute stroke therapy. The 21st century will finally see the emergence of a pathophysiologic approach to acute stroke management. We will finally learn how to measure brain salvageability and thereby better define the elusive “thera-
TABLE 1. Intra-Arterial Thrombolysis: Estimated US Market for Middle Cerebral Artery Occlusion

- 700 000 Strokes per year
- 80% Ischemic = 560 000 per year
- 33% Arrive at ED < 6 h = 185 000 per year
- 33% MCA occlusion = 61 000 per year
- 33% Eligible for IA = 20 000 per year
- Estimated prevalence = 100 per 100 000
- Orphan indication < 200 000 persons

ED indicates emergency department; MCA, middle cerebral artery; and IA, intra-arterial thrombolysis.

percutaneous window.” Perfusion and diffusion MR currently hold great promise in this regard, but there will be new technologies as well.23

I am concerned that if we keep designing “brass ring” stroke trials to treat all patients, we will get results that help no patients. The “one drug fits all strokes” CVA is reflected in the unrealistic marketing assessments of stroke drugs (AKA “net present value” or NPV) done by many pharmaceutical firms new to stroke research. There are 700 000 strokes per year, right? Third leading cause of death, right? Huge market, right? Then ask Genentech why 4 years after FDA approval, <2% of acute stroke patients are getting intravenous tPA.

Bruce Wallin of Abbott now refers to acute stroke as an orphan disease. He exclaimed this insight one day during an NPV analysis of intra-arterial prourokinase for middle cerebral artery occlusion. All the clinical investigators in the room scoffed, myself included. But then it dawned on me that referring to middle cerebral artery occlusion as an orphan disease was a perfect way to focus the pharmaceutical mind on the heterogeneity of acute ischemic stroke (Table 1).

Given such sobering numbers for middle cerebral artery occlusion, it is not surprising that the entire continent of Australia could not recruit enough patients with basilar artery occlusion to complete a randomized trial of intra-arterial urokinase.24 Indeed, based on such numbers, I am often told that intra-arterial thrombolysis will never help many patients. But such criticisms, even if true, miss the main message of the PROACT trials,20,25 which is that some patients with major ischemic stroke due to middle cerebral artery occlusion can be helped even beyond 3 hours, but not by treating them the same way as lacunes.

The main reason we are treating <2% of patients with intravenous tPA is the 3-hour window. Right now, of the 4000 ischemic stroke admissions in Cleveland each year, only 19% arrive at hospital within 3 hours of onset, and only 1.8% of patients get intravenous tPA. Cleveland Operation Stroke has set an intravenous tPA target of 5% over the next 2 years, but even this modest goal has required a massive, citywide mobilization effort. Not to minimize the critical importance of time, as well as the needed changes in our stroke care delivery systems, such real world data suggest to me that it will be extremely difficult to ever treat more than 10% of all acute stroke patients with intravenous tPA (or any drug) if we remain confined to a 3-hour window. So the key finding of PROACT, bolstered by the recent perfusion/diffusion MR data, is that there is hope beyond 3 hours. But to crack the 3-hour barrier, Greg del Zoppo, Mike Pessin, Randy Higashida, and I had to design a radically different kind of stroke trial. How different? Well, consider that PROACT I and PROACT II are the only randomized clinical trials to replicate the rat model of middle cerebral artery occlusion in humans.

Having successfully completed PROACT I and PROACT II (an 8-year process), we were subjected to yet another CVA when we applied for licensure for intra-arterial prourokinase with the Food and Drug Administration (FDA). The FDA had actively participated in the design of PROACT II and had indicated that they would consider licensure of prourokinase based on this single phase 3 trial as long as certain requirements were met; unfortunately, they neglected to tell us that one of those requirements was a P value of 0.0025 (that’s correct, 0.05 squared). Obviously, our P value of 0.043 fell short (but then, so does virtually every clinical trial ever published).

The FDA did concede that middle cerebral artery occlusion is a serious and life-threatening condition for which there is no approved therapy beyond 3 hours. The FDA is also aware that stroke centers are currently forced to use intra-arterial tPA, for which we have no phase III data, or to do nothing for these devastated patients. Nonetheless, the initial FDA recommendation was to conduct another placebo-controlled, randomized trial to confirm the results of PROACT II. Let us consider for a moment what this would entail. Another placebo-controlled trial with 2:1 randomization and 90% power to detect a 15% absolute treatment benefit will require 400 patients with acute middle cerebral artery occlusion. It took 2.5 years at 54 major centers in North America to recruit 180 patients with acute middle cerebral artery occlusion in PROACT II. Only 13 centers randomized 5 or more patients, and that was before we had any ethical issues posed for a placebo group by a positive trial. The FDA has thus far refused to accept historical controls, even though we have argued that the dismal natural history of mainstem middle cerebral artery occlusion is well established. We estimate it would take 3 years at 80 international sites and cost $20 million to complete PROACT III. Recent discussions with the NINDS indicated they would be 2 years before such a trial could be launched, assuming first-round funding approval. So it would be at least 5 more years before we had an NINDS-funded answer on intra-arterial prourokinase. Now, I am not saying we cannot or should not do a PROACT III. I just want to clarify any confusion out there as to what it currently takes to get a new treatment for acute stroke to market. I suggest we need to find a better way.

I shudder to think that the “easy” trials of thrombolysis have been done. How are we going to do these next studies? How are we going to study new intravenous thrombolytic agents, intra-arterial thrombolysis, combined intravenous and intra-arterial thrombolysis, mechanical thrombolysis, cytoprotective agents, combination therapy, and restorative therapy when we have limited patients, limited resources, and limited time? The international stroke community needs to put politics aside, prioritize the essential research questions,
and divide the work. To this end, I am pleased to announce that several world leaders in clinical stroke research are exploring the feasibility of an international consortium analogous to GUSTO designed to expedite essential stroke clinical trials.26

While we continue to design better stroke trials, the time has already come to move key concepts of clinical trial design into routine clinical practice. The goal of the neurological stroke examination at the turn of the last century was to localize brain function. The goal of the neurological stroke examination as we enter the next century is to preserve brain function. While complementary, these goals require different information. The traditional neurological examination may satisfy Current Procedural Terminology coding and the Health Care Financing Administration, but it does not give us the data we need in a readily understandable format to make informed treatment decisions in acute ischemic stroke. Consider that in all clinical trials, a quantified assessment of baseline stroke severity has been an essential element in patient selection and outcomes. For this purpose, a stroke scale such as the NIH stroke scale is far superior to the traditional neurological examination.27 The NIH stroke scale provides a “common language” for acute stroke, one understood by the emergency department physician and neurologist alike. It takes <7 minutes to do the NIH stroke scale, and now anyone can be certified in the NIH stroke scale by the National Stroke Association (about 400 health professionals took the National Stroke Association certification examination in the last year). Yet in a recent study of community physician behavior in Cleveland done by Irene Katzan and colleagues,28 an NIH stroke scale was documented in only 40% of patients who received intravenous tPA. Why is this? Simply put, physician behavior is hard to change.

As we enter the new millennium, the emphasis on quality improvement and outcomes by payors may finally provide the incentive for physicians to change their ways. Currently, there is no standardized way to report outcomes after acute stroke. Even within clinical trials, a “good outcome” has been variously defined. In the community, chaos reigns. Charting “doing OK” at some arbitrary time point after stroke onset is hardly sufficient to assess stroke outcomes. A modified Rankin score, NIH stroke scale, or Barthel scale at 3 months would be far preferable. Why not use the same outcomes examinations in clinical trials and clinical care?

In Cleveland, we have been trying to change physician behavior related to acute stroke for almost 4 years. In Cleveland, the use of intravenous tPA and the designation of “stroke centers” has become highly politicized and contentious, as evidenced by a recent headline in the Plain Dealer (Figure). We are now piloting a community-wide stroke outcomes project with Genentech as part of Operation Stroke. The Academy of Neurology has also launched a community-based stroke outcomes pilot project, which, I am proud to say, has been spearheaded by one of our former stroke fellows, Judy Hinchey. The goal should be to use this information to change the standard medical record in stroke patients instead of just creating additional work and “research projects” for already busy clinicians. Without such change, we will just perpetuate more CVAs.

Fortunately, the major risk factors for a CVA are all modifiable: we need to standardize stroke clinical trial methodology (Table 2). Consensus is needed on the most appropriate measures of outcome. Sample sizes should be based on a realistic treatment effect compared with a well-defined control group. Baseline variables having a significant influence on outcome, such as stroke severity, should be stratified. Importantly, more focused trials in homogeneous patient subgroups must be performed.29 The acute stroke evaluation should be modernized, standardized, and quantified (Table 2). Clinical examinations should more closely parallel clinical trial methodology. Vascular testing and a pathophysiological assessment must be incorporated into acute stroke management so that we can tailor therapy to “what is really wrong with Mr. Jones.” The pharmaceutical industry needs to make a long-term commitment to stroke (Table 2). Marketing estimates should be segmented, and stroke should not be viewed as a single disease process. Clinical trials should be developed in close cooperation with investigators using standardized methodologies. The NINDS should look for innovative ways to streamline the grant process and should expedite applications for major clinical trials. Proactive and mutually beneficial guidelines for interaction with the pharmaceutical industry should be developed. The FDA should improve communications with investigators and industry during clinical trial development (Table 2). FDA policies for accelerated approval of new therapies for serious and life-threatening conditions other than AIDS and cancer should be reviewed. Lastly, and most importantly, we need to change physician behavior related to acute stroke (Table 2). Appropriate incentives, including financial compensation, need to be provided so community physicians are encouraged to treat more patients, collect outcomes data, and participate in stroke quality-improvement projects.30,31

The new millennium signals new thinking about acute stroke. Change is apparent when my older colleagues refuse to take the stroke service but the young house staff clamor for it. Ultimately, physician behavior will change only when we train a new generation of “strokeologists” who think about
TABLE 2. Confused Vascular Analysis (CVA): Risk Factor Modifications

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<tr>
<th>CVA Risk Factor</th>
<th>Risk Factor Modifications</th>
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<tr>
<td>Clinical trial design</td>
<td>Standardization</td>
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<td>Appropriate sample size</td>
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<td>Stratification</td>
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<td>International consortium</td>
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<td>Acute stroke evaluation</td>
<td>Quantification (NIHSS, Rankin)</td>
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<td>Standardize assessment</td>
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<td>Time from onset</td>
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<td>Severity (NIHSS)</td>
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<td>CT (blood, early signs)</td>
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<td>Vascular (US, CTA, MRA)</td>
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<td>Pathophysiology (DW/PWMRI)</td>
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<td>Tailor therapy (lytic, cytoprotective, multimodal)</td>
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<td>Pharmaceutical industry</td>
<td>Realistic marketing (NPV process)</td>
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<td>Long-term commitment to stroke</td>
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<td>Preclinical development (STAIR)</td>
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<td>FDA</td>
<td>Coordinate divisions (drugs, biologics, devices)</td>
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<td>Review accelerated approval process</td>
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<td>NINDS/NIH</td>
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<td>CME (Operation Stroke)</td>
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<td>Residency and fellowship training</td>
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NIHSS indicates NIH Stroke Scale; US, ultrasound; CTA, CT angiography; MRA, magnetic resonance angiography; DW/PWMRI, diffusion-weighted-perfusion-weighted MRI; ASO, arteriosclerosis obliterans; STAIR, Stroke Therapy Academic Industry Roundtable; DVT, deep venous thrombosis; and CME, continuing medical education.

acute stroke in an entirely new way. We need to encourage the new enthusiasm about stroke among our young house staff by revamping residency programs and offering comprehensive training to qualified applicants regardless of specialty. I have been very encouraged, therefore, to see the American Academy of Neurology, the Joint Section of Cerebrovascular Surgery, and the American Society of Interventional and Therapeutic Neuroradiology work together to develop standardized training guidelines for cerebrovascular specialists with an appropriate balance between cognitive and interventional skills.

In closing, I hope my analysis has not added to the confusion but has instead provided a blueprint for a new kind of stroke care in the new millennium. One thing is clear: I did not envision in 1976 when Jack Conomy told me to take up something more challenging how prophetic that advice would seem 24 years later.

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