Finding New Drugs to Treat Stroke

Stroke has not been considered a medical emergency because there were no effective therapies. But a deluge of new drugs is now changing that picture

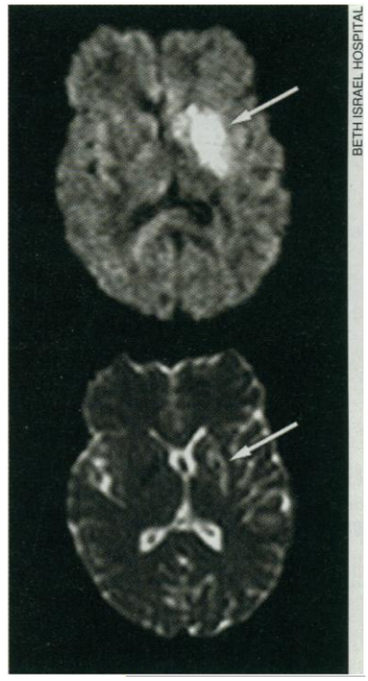
When someone suffers a heart attack, no one doubts that it's a medical emergency. But while the telltale symptoms of a heart attack cause health-care workers to leap into action, most doctors have not viewed stroke—the brain's equivalent of a heart attack—as an emergency. Because there was no effective treatment for stroke, all that physicians could offer a stroke victim was rehabilitation to try to gain back some lost functions. "We were all trained to think, well, the damage is done, so put the patient somewhere in the corner, and we will get them admitted and do some physical therapy when we get around to it," says University of California, San Diego (UCSD), neurologist Patrick Lyden.

But now there is reason for patients and doctors alike to rush to the emergency room when a stroke is suspected. In mid-December, the National Institute of Neurological Disorders and Stroke (NINDS) announced the results of a large clinical trial that showed that the clot-busting drug called tissue plasminogen activator (tPA), if given within 3 hours of the stroke's onset, can boost the percentage of stroke victims who walk away with no permanent disability by 50%. And tPA is just the first trickle in a deluge of stroke drugs coming through the pharmaceutical pipeline.

TPA is directed at the 80% of strokes called ischemic strokes, which occur when blood clots block an artery that carries blood to part of the brain. The treatment is based on the straightforward logic that the sooner blood flow is restored, the less damage there will be. But that is not the only possible approach, because the initial clot is just the first step in a complex cascade of events that causes brain damage. Pharmaceutical companies are developing dozens of drugs aimed at blocking every conceivable step in that cascade. With so many drugs in the works, there may even be a choice of treatments available for stroke within the next 5 years, say neurologists.

"The main lesson of the tPA trial isn't that tPA is the greatest thing since sliced bread for stroke. I think 5 years from now we're not going to be using it" because better drugs will have come along, says James Grotta of the University of Texas Medical Center in Houston, a neurologist and an investigator on the tPA trial. "But it tells us this is a treatable disease, and it has to be treated as an emergency."

Effective emergency treatments for stroke could have an enormous payoff in reduced morbidity and mortality. Each year in the United States alone, 500,000 people suffer a stroke, making it the third leading cause of death (after heart attacks and cancer) and the leading cause of disability. Researchers have been searching for an effective early treatment for stroke for decades. Because most strokes are caused by blood clots, one of the drugs they tried was the clot-dissolving enzyme called streptokinase. But all the streptokinase trials ended the same way: canceled because the drug was making things worse by causing brain hemorrhages.



BETH ISRAEL HOSPITAL

Brain saver. Part of the initial area threatened by a stroke (arrow, *top*) is saved by citicoline treatment *(bottom)*.

At first, the problem seemed to be the difficulty of eliminating the 20% of patients whose strokes are caused not by clots but by bleeding into the brain—patients to whom clot-busters are the last thing you would want to give. But even after computerized tomography (CT) scanning became available in the 1970s to rule out brain hemorrhage, streptokinase still failed to make the grade.

Streptokinase problems

There were numerous opinions about why streptokinase wasn't working. Some researchers blamed its ability to attack both fibrin, the protein that makes up blood clots, and also fibrinogen, the blood protein that gives rise to fibrin. As a result, says Thomas Kwiatkowski, an emergency physician at Long Island Jewish Medical Center and investigator on the tPA trial, "You are at greater risk of hemorrhage, because you don't have your normal clotting mechanism in place." An additional problem may have been in the trial design. The longer a clot sits in a blood vessel, the more it weakens the vessel, making it likely to spring a leak when the clot dissolves. And some of the streptokinase trials administered the drug up to 24 hours after the stroke had begun.

A possible solution to both those problems emerged in the 1980s, when the new drug tPA, which is more specific for fibrin than streptokinase is, began to show promise for treating heart attacks. "There was a lot of hope that tPA would work better than streptokinase for stroke," says neurologist John Marler, a program director at NINDS. Despite the hope that tPA would cause fewer bleeding problems than streptokinase, Marler was still committed to the idea that treatment would be most effective within the first few hours of the stroke, but he knew it would not be easy to do that. "We faced a vicious circle, in that stroke patients weren't rushed into the emergency rooms ... because whenever you started to do that, people would say there is nothing we can do for them," Marler says.

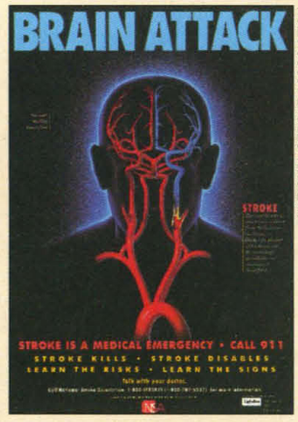
But he was determined to break that cycle and get patients in early for a tPA trial. He searched for medical centers willing to give it a try and set up a successful pilot study at three centers in the late 1980s. This was followed by the full-scale trial, including 624 patients treated at nine medical centers. The results—31% of the patients treated within 3 hours showed full or nearly full recovery 3 months after the stroke, compared to 20% of the untreated patients—were reported in the 14 December 1995 *New England Journal of Medicine*.

The study compared treatment within 90 minutes to treatment within 3 hours and showed no difference in outcome between the two groups, a very encouraging finding, says Kwiatkowski: "The logistics of enrolling a patient within 90 minutes are so difficult that if this trial ended up showing benefit only at 90 minutes, I would say ... it will be very difficult to translate this into practice." Three hours is still "formidable," he says, but "doable." Genentech is running a

Educating the Public—and Health Workers—About "Brain Attacks"

Last December, stroke researchers got a long-awaited piece of good news. For the first time, a clinical trial had shown that prompt treatment, in this case with the clot-busting drug tPA, dramatically boosts a stroke victim's chance of full recovery. Other stroke drugs in the pipeline could do even better (see main text). But for stroke victims to benefit from this pharmaceutical revolution, there must be a parallel revolution in the way the health-care system handles stroke.

The tPA study showed that the therapy needs to begin within hours of the stroke, and patients are rarely treated that promptly now because of the prevailing view that stroke is not a medical emergency. Changing that attitude was one of the major challenges facing neurologist John Marler of the National Institute of Neurological Disorders and Stroke (NINDS) and his colleagues in the tPA trial. But now, others can benefit from the lessons learned by those pioneers, says NINDS director Zach Hall: "There is a model in this study for everybody to find out how they should organize their own hospital, and exactly what they should do."



New message. Posters like this seek to raise public awareness that stroke is an emergency.

The first hurdle in stroke treatment is to get stroke patients to the hospital fast, a challenge that requires stroke victims to call the emergency number 911 and paramedic teams to mount a quick response. "The data are fairly convincing that if a patient calls their primary-care doctor instead of 911, their treatment is delayed between 12 and 24 hours," says neurologist Patrick Lyden, who headed a tPA trial site at the University of California, San Diego. But patients are often blasé about the symptoms of a stroke—which include numbness, weakness, and loss of balance. Public education about stroke through advertising would help, but it is so expensive that the centers didn't do much of it, says trial investigator Thomas Brott, of the University of Cincinnati.

The tPA trial sites instead concentrated their efforts on improving the emergency response to stroke once a victim has called 911. Because the medical system has thought of stroke as untreatable, "emergency medical services could be very slow in responding to a call for stroke," says Washington University neurologist Chung Hsu, who directs the emergency stroke team at Barnes Hospital in St. Louis. To change that, the trial organizers had to reach the 911 operators and paramedics. "We had to visit each fire station where the medics hang out and convince them that stroke is an emergency," says Lyden.

A posttrial analysis showed that this strategy did quite well at getting patients to the hospital: Roughly 50% of stroke victims who came to the nine centers within 24 hours of their strokes arrived within the first 3 hours, although not all of those patients qualified for the trial, says NINDS's Marler. Brott is convinced that number can be improved through the slower process of public education, because local news coverage of the trial improved arrival times in Cincinnati.

But getting the patient to the hospital is only half the battle. There, emergency room personnel, computerized tomography scan operators, and other technicians have to be ready to leap into action. Achieving that change, says Lyden, is just a matter of informing them that "a stroke is really a code blue," which is hospital jargon for a life-threatening situation requiring immediate action.

Having worked out the formula, Lyden says he can spend half a day with administrators of a community hospital and give them a full picture of what they need to do and how to do it. And the burden of spreading the word doesn't fall on the tPA investigators alone; in an effort to prepare the way for further clinical trials of potential stroke drugs, the National Stroke Association's Clinical Trials Acceleration Program sends teams to hospitals to help them reorganize their staff and emergency services, and provides public service announcements for local media or hospital newsletters.

Of course, these days health care is driven by the bottom line, so the cost of these steps will certainly be an issue. The tPA group hasn't yet completed its cost-benefit analysis of the therapy, but James Grotta, who headed a trial site at the University of Texas Medical Center in Houston, says a switch to the new approach needn't be costly. "It is a matter of education more than it is hardware," he says. "We can do it with what we have; we just need to disseminate the information." He predicts the new approach will actually save money in the long run, for the cost of administering tPA—or, in the future, other drugs—should be more than offset by the improved chance that the patient will be free of any need for rehabilitation or long-term care. If so, the stroke education campaign will pay off in more ways than one.

–M.B.

large trial to find out whether tPA treatment is still effective between 3 and 5 hours after the stroke.

Despite its positive results, the tPA study underscores the risks of tPA treatment; 6% of the tPA-treated patients experienced life-threatening bleeding into the brain, compared to fewer than 1% of the controls. But even with that risk of bleeding, patients treated with tPA in the NINDS trial fared better than controls did. And Genentech is now developing a more fibrin-specific drug that may further reduce the risk of bleeding.

Welcome as the tPA finding is, clinicians and basic researchers alike know that the drug is not an ideal stroke treatment on its own. For one thing, dissolving the clot and letting blood back into oxygen-deprived brain areas is not entirely benign. "When you open the clot up and all the blood comes back, that is a really high-risk period," says Harvard University neurologist Walter Koroshetz.

When the blood vessels are opened, white blood cells called granulocytes are drawn to the injury site, where they stick to the blood-vessel walls and dump out a damaging cocktail of protein-dissolving enzymes and free radicals, highly reactive chemicals with unpaired electrons. In addition, the sticky granulocytes can partially reclog the blood vessels. A number of companies are developing strategies to block this so-called reperfusion injury—compounds that "scavenge" or neutralize free radicals, and antibodies that prevent granulocyte binding to blood-vessel walls. Such drugs may someday team up nicely with tPA. "When you open up the blood vessels, that's when you'd like to have a free-radical scavenger and the white cell–adhesion blocker," says Koroshetz.

Another problem with tPA treatment is the necessary delay before treatment can

begin. Stroke victims must reach the hospital and have a CT scan to rule out brain hemorrhage before they can be treated—and all that may have to happen within 3 hours of the stroke if the tPA is to be safe and effective. As a result, "everyone is looking for a compound that is easy to use and could be used to preserve brain cells even before the patient reaches the hospital," says neurologist Thomas Wessel, associate director for clinical development at Belgium-based Janssen Pharmaceutica.

New drug hopes

Toward that end, pharmaceutical companies and clinicians are placing their hopes on a host of experimental drugs that act on the destructive biological processes set in motion by the clot, rather than on the clot itself. Such drugs shouldn't be dangerous to people with hemorrhagic strokes—indeed they may help save brain tissue in that category of strokes as well. And that means they may eventually be given by paramedics in the field when a stroke is suspected, but before the type of stroke is known. That prompt protective treatment might in turn extend the time window for later treatments, such as tPA, says Koroshetz: "If you give a neuroprotective agent and can slow the [cell death] process down, you may buy another couple of hours, and that would let you treat more patients."

These drugs, along with those aimed at blocking reperfusion injury, are intended to save cells just outside the stroke's core. The core is ground zero for the stroke—neurons there are totally deprived of oxygen and die within minutes. But surrounding the core is a region called the penumbra, which, like the partially lit penumbra in a lunar eclipse, is not entirely blacked out. It still gets 20% to 50% of normal oxygen levels, via blood vessels unlinked to the clot. This residual circulation allows the cells to hang on for a while, although they will succumb eventually if circulation isn't restored. It should also allow these so-called neuroprotective drugs to reach the penumbra and possibly lengthen the grace period.

"There are a lot of approaches in the works," says Washington University neurologist Dennis Choi, "and they don't depend on one common strategy or mechanism." One is to block "excitotoxic" death, triggered when neurons are deprived of normal levels of oxygen, become energy-starved, and lose the electrical charge that maintains the normal properties of their membranes. As a result, they begin haphazardly dumping out neurotransmitters, including the powerful excitatory neurotransmitter glutamate. Too much glutamate causes calcium ions to flood into neurons, activating enzymes that destroy cell membranes and generate damaging levels of nitric oxide and free radicals.

Companies are targeting drugs at every step of this excitotoxic cascade, starting with the receptors through which glutamate exerts its effects. Compounds directed at the NMDA subclass of glutamate receptor had some of the most promising results in animal studies. But in humans they proved ineffective or caused worrisome side effects, most notably psychotic symptoms similar to those caused by the illicit drug PCP, which also acts through the NMDA receptor.

One drug, Cerestat, made by Massachusetts-based Cambridge NeuroScience, is still in the running, however. At last month's meeting of the American Academy of Neurology in San Francisco, neurologist Keith Edwards of the Southwestern Vermont Medical Center reported that in a small trial of 132 patients aimed primarily at determining an appropriate dose for the drug, the highest dose of Cerestat tested doubled (from 19% to 40%) the number of patients with moderately severe strokes who recovered completely. The side effects of Cerestat were mild and transient hallucinations, said Edwards, that didn't present a big problem. "If I had something that was going to make a stroke patient better, those side effects wouldn't slow me down," says neurologist Steven Warach of Harvard Medical School, who participated in the Cerestat trial.

Future NMDA receptor–blocking drugs may be even more benign. While the first such drugs block either the glutamate binding site or, like Cerestat, the channel in the receptor through which ions flow, the latest of them block the site where the neurotransmitter glycine binds to boost the receptor's activity. In small early trials they appear to have fewer psychotic side effects.

But the NMDA receptor is only one target for blunting excitotoxic damage. Companies are developing drugs that stop sodium influx into cells, which can trigger glutamate release and also allows damaging calcium into cells; drugs that block calcium channels directly; and still others that soak up damaging free radicals, block NO accumulation, or quiet neurons by mimicking the inhibitory neurotransmitter GABA. Even the neuron-nurturing proteins known as neurotrophic factors, some of which have been shown to protect neurons in culture against damage by stroke-related insults such as excitatory amino acids, free radicals, and NO, are entering human trials.

Among the drugs from this varied group that are farthest along in trials are lubeluzole, a blocker of NO accumulation made by Janssen, which has shown some benefit for stroke patients; Parke-Davis's fosphenytoin, a new version of phenytoin, better known as Dilantin, a sodium-channel blocker that has been used safely for epilepsy for 60 years; and citicoline, a drug from Interneuron Pharmaceuticals of Lexington, Massachusetts, that prevents the accumulation of free fatty acids, which participate in the chemical reactions that generate free radicals. Citicoline made a big splash at last month's neurology meeting with the report that it boosted by 50% the number of patients who completely recovered from strokes.

While clinicians await official FDA approval of tPA for stroke, which may come as early as this fall, they are eagerly watching the new wave of drugs moving through the pipeline. And as soon as some of these new approaches pass clinical trials, they are likely to be tested in combination. In 5 years or so, predicts UCSD's Lyden, paramedics in the field will be administering a cocktail of drugs to combat excitotoxicity and reperfusion injury. "That combination will prolong the window of intervention"; says Lyden, "then in the hospital the patient will be receiving a clot-busting compound." And with all those new weapons poised to treat a stroke, stroke victims will have plenty of incentive to call the emergency number 911.

–Marcia Barinaga

A PARTIAL LIST OF DRUGS IN OR NEAR CLINICAL TRIALS

Drug	Company	Action
Aptiganel (Cerestat)	Cambridge NeuroScience	NMDA receptor ion-channel blocker
ZD 9379	Zeneca	NMDA receptor glycine-site blocker
GV 150-526A	Glaxo Wellcome	NMDA receptor glycine-site blocker
Fosphenytoin (Cerebyx)	Werner-Lambert Parke-Davis	Na channel blocker
BW619-C89	Glaxo Wellcome	Na channel blocker
SNX-111	Neurex Werner-Lambert Parke-Davis	Ca channel blocker
Clomethiazole	Astra	Stimulates inhibitory GABA receptors
Lubeluzole (Prosynap)	Janssen	Interferes with nitric oxide's effects
Tirilazad	Upjohn	Radical scavenger
Citicoline	Interneuron	Reduces free fatty acids
Enlimomab	Boehringer Ingelheim	Blocks granulocyte adhesion
bFGF	Scios	Growth factor