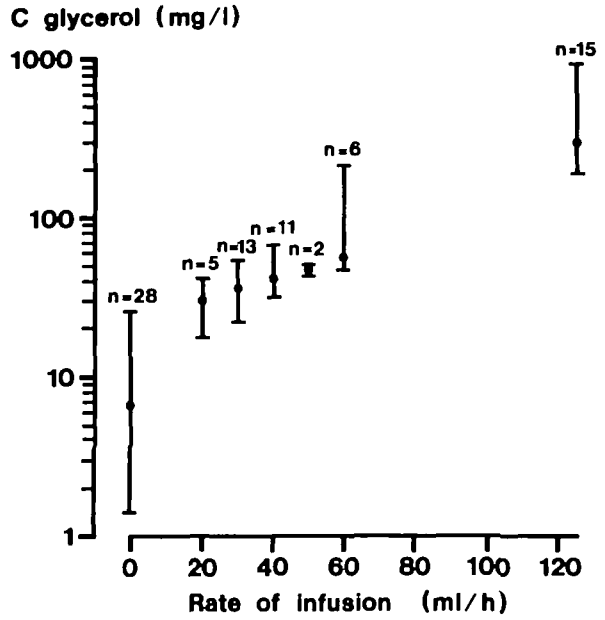

FIGURE 1. *Graph showing dependence of serum concentration of glycerol on the infusion rate of a 10% glycerol solution. Bars represent the ranges and circles represent the medians of the glycerol levels in stroke patients. For those patients whose glycerol levels were measured repeatedly at the same infusion rates, only the median values were used in this figure.*

Although there is no theoretical reason to expect that a critical "osmotic threshold" must be exceeded before changes in the cerebral volume can occur,[12] several authors have concluded that an increase of plasma osmolality by 30–35 mosm/kg is necessary to move water from brain to blood.[12] Increases of plasma osmolality by at least 10 mosm/kg are deemed necessary to exert a reliable osmotherapeutic effect.[5]

Among our patients, none with continuous glycerol infusions and only two of 15 with discontinuous administration of 500 ml over 4 hours reached serum glycerol concentrations near 10 mmol/l (921 mg/l). This is due to the short half-life of glycerol in blood, 0.18–0.87 hours.[13]

Our observations led us to the conclusion that in the clinical trials cited (except for the study by Friedli et al[6]) the majority of patients did not develop glycerol serum levels high enough to dehydrate brain tissue. Similarly, Larsson et al[7] did not observe "any significant rise in serum osmolality" after infusion of 50 g glycerol over 6 hours in two healthy volunteers, which may explain the conflicting clinical findings. The minimum serum concentration of glycerol required to produce direct metabolic effects on impaired brain tissue has not been determined.

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Treatment of "Progressive" Stroke

To the Editor:

My comments are provoked by the article by Slivka and Levy[1] on the natural history of progressive stroke in patients treated with heparin. They apply as well to any study of the treatment of progressive stroke and to studies of the utility of heparin.

Therapeutic decisions and trials should be solidly grounded on a bedrock of pathology and pathophysiology and not on studies of patients designated by time course.[2] Progressive stroke, or stroke-in-progress, is an artificial, descriptive term, the current definition of which depends on when the meter is started.[3] A man who develops right arm weakness at 11 AM and, by 2 PM, has gradually developed a right hemiparesis qualifies as "progressing" when seen by doctors at 1 PM. Had that same patient arrived at 3 PM, and stabilized by then, he might be classified as a "completed stroke" by doctors assuming that he would not worsen further. What if that same patient then developed aphasia on day 5? Would his doctors erase the term "completed"? Perhaps they should have chosen "completing" instead. All stroke patients whose deficits are not maximal at the outset progress at some time. The term "progressive" is now applied only if there is worsening after medical care begins.

Progression or, more simply put, getting worse refers to the patient's brain function. The ischemic zone functions less well or gets larger for reasons that include 1) thrombosis of a stenotic artery; 2) propagation of a clot to block branches; 3) embolization of a clot; 4) collateral failure; 5) hypoperfusion due to hypovolemia, fall in systemic blood pressure, or decreased cardiac output; 6) hypoxia; 7) brain edema; 8) seizures; 9) local metabolic changes in the ischemic region set in motion by the original ischemia (e.g., influx of Ca^{2+}, excitotoxic amino acids, free oxygen radicals); 10) intercurrent systemic complications such as pneumonia or urosepsis or those from drugs such as Haldol; and 11) herniations or shifts in brain contents. Heparin is not known to

have any direct effect on brain function; as far as is known, it mostly affects blood clotting. Heparin might influence reasons 1, 2, and 3 relating to coagulation, but would not influence the other causes of worsening listed above. Is it reasonable to judge the effectiveness of heparin by whether the patient worsens and by the degree of worsening? By preventing clot formation, propagation, and embolization, heparin might prevent worsening in stable patients or minimize the severity of worsening.

Treatment with heparin and other drugs that affect coagulation should be studied in groups of patients with defined vascular occlusive lesions. With modern diagnostic technology, it should be possible to monitor the lesion in the involved artery. The presence of new, transient, or lasting deficits and their severity can also be compared in large groups of patients with similar arterial lesions, some receiving the study treatment, some not. A search for a single panacea to treat patients with progressing stroke is doomed to fail. Clinicians must identify the pathology and pathophysiology in their individual patients and treat these problems logically and specifically. Trials can be designed in patients sharing specific pathologies and pathophysiologies to study therapy more systematically.

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The following is in response:

To the Editor:

We appreciate the thoughtful comments of Dr. Caplan concerning our article.[1] We entirely agree with his thesis that decisions regarding treatment for stroke should be based on an understanding of pathophysiological mechanisms. We also recognize that in many cases stroke etiology cannot be defined with certainty, particularly in the acute setting or when multiple possible etiologies are present in an individual patient.

Even though the definition of progressive stroke is purely clinical and depends on when the patient is first seen, a practical patient-management issue remains regarding the question of whether clinical progression after stroke can be arrested or reversed. We acknowledge that many different mechanisms might underlie progression of a clinical deficit. Perhaps the most important distinction, however, is between mechanisms corresponding to potentially irreversible pathological processes (e.g., clot progression or embolization, herniation, or biochemical ischemic effects) and those representing readily identifiable reversible systemic dysfunction (e.g., hypotension, arrhythmias, seizures, or electrolyte or glucose abnormalities). While it is desirable to tailor treatment to the underlying pathophysiology, defining processes such as clot progression or biochemical changes may not be possible even with modern diagnostic technology. Furthermore, application of diagnostic techniques can be time consuming and may not always be practical in critically ill patients. Thus, even were complete elucidation of the underlying pathophysiology of worsening possible (e.g., with magnetic resonance imaging, spectroscopy, transcranial Doppler, positron-emission tomography, single photon emission computed tomography, or angiography), time constraints might take precedence over pathophysiological understanding.

Because heparin is often used for progressive stroke, and because heparin has the potential to produce devastating consequences, we believe a prospective clinical trial should, and probably will, be done to determine definitively whether heparin should be given to patients with progressive deficits following stroke. We also believe that our study serves an interim purpose in the attempt to correlate clinical features and degree of anticoagulation with clinical outcome or bleeding complications.

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Treatment of "progressive" stroke.

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Stroke. 1991;22:694-695
doi: 10.1161/01.STR.22.5.694
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628