Ischemic stroke is a common cause of permanent brain injury. It frequently causes severe disability and can strike at the very essence of an individual, the mind. Any intervention that significantly improves the outcome of patients with acute cerebral ischemia would revolutionize stroke therapy. In this issue of the Journal of Intensive Care Medicine, Wechsler [1] systematically discusses the most recent clinical and preclinical trials of treatment for acute ischemia. The promise of the strategies described is encouraging. However, the article is also a reminder that, despite the medical advances of the twentieth century, the twenty-first century may arrive before any effective treatment is refined to prevent acute ischemic neurological deficits from developing into permanent brain infarction.

The twentieth century has seen major advances in stroke prevention. Effective antihypertension regimens have surely prevented thousands of disabling ischemic strokes as well as intracranial hemorrhages. Endarterectomy and anticoagulation have probably lessened the frequency of major stroke in patients with transient ischemic attacks caused by tight stenoses of the internal carotid artery. Anticoagulation has certainly prevented stroke in patients who are at high risk of forming a cardiac thrombus as a result of atrial fibrillation, recent myocardial infarction, ventricular aneurysm, or rheumatic heart disease. In contrast, our ability to reverse the course of a stroke in progress is limited to implementing the preventative measures listed above. In general, modern stroke therapy attempts to 1) optimize hemodynamic, respiratory, and metabolic parameters; 2) ascertain the probable vascular pathology responsible for the stroke; 3) prevent further infarction caused by the vascular lesion with endarterectomy or anticoagulation; and 4) prevent and treat complications of stroke (i.e., cerebral edema, seizure, aspiration pneumonia, pulmonary embolus, and depression).

Modern stroke therapy is derived from detailed clinicopathological correlations between various vascular lesions and their associated stroke syndromes. Unless the "magic bullet" that prevents all types of ischemic brain injury is forthcoming, new therapies will intervene in the pathophysiological processes that cause stroke. Attempts to increase cerebral blood flow and decrease viscosity may significantly improve collateral flow in the distribution of a slowly occluding artery with a rich collateral circulation. However, this same therapy may be ineffective if an embolus suddenly plugs an otherwise normal artery with only sparse collaterals. Similarly, timely clot lysis with tissue plasminogen activator may completely cure an embolic occlusion and only postpone the inevitable in the atherosclerotic occlusion. As experimental therapies enter the clinical armamentarium it will be much more important to identify accurately the vascular cause of a patient's ischemic symptoms. For example, agents that markedly depress neuronal metabolism may protect a large number of neurons in ischemic cortex, but such aggressive measures will not be helpful and will be contraindicated in a patient with a complete hemiparesis because of a lacunar infarct in white matter.

Each new therapy may be expected to work best in a specific clinical situation and during a specific time interval. These considerations will make randomized drug trials difficult to design because different types of cerebrovascular events may need to be examined independently; emergency cerebral angiography may be necessary to establish the underlying vascular pathology; timing of therapy may be critical; and traditional informed consent may be unobtainable because of the patient's brain dysfunction. This latter concern, which is unique to brain injury studies, may prohibit important studies from being performed in this country. A national, medical-ethical-legal consensus on the importance and appropriate design of brain protection drug studies in patients with acute stroke or cardiac arrest is desperately needed. These studies will require the most sophisticated medical attention and need to be conducted in North America, where intensive care is especially advanced.

The therapies described by Wechsler [1] fall into two major categories: 1) those that increase blood...
flow into an ischemic zone and 2) those that preserve ischemic neurons from dying. Ischemic neurological deficits resolve if blood flow is promptly restored or they fluctuate if flow increases and decreases around a requisite level. In general, complete ischemia lasting more than a few minutes sets in motion a process that leads to permanent brain infarction; incomplete ischemia is probably reversible for considerably longer periods. Therefore, therapies that increase cerebral blood flow through collaterals (e.g., hypervolemic hemodilution, cerebral vasodilators) or through resolution of the vascular obstruction (e.g., tissue plasminogen activator, endarterectomy, angioplasty) are limited only by their adverse effects and the time window during which the patient's ischemic deficit is reversible.

In some experimental paradigms irreversible neuronal death occurs hours or even days after an ischemic insult. Interestingly, prolonged anoxia and circulatory collapse occur in cold-water drowning victims but do not necessarily lead to severe brain injury. These phenomena suggest that the metabolic processes set in motion by ischemia may be subject to control. Knowledge about the processes that follow brain ischemia but precede neuronal death has led to clues about how to intervene in stroke. Recently, scientific evidence from various fields converged to produce an attractive hypothesis to explain the unique susceptibility of brain to ischemia and the nature of delayed neuronal death [2]. During ischemia a number of events conspire to produce an immense excitatory neurotransmitter action that causes excessive movement of calcium into neurons. The calcium overload impairs cellular metabolism and triggers the activation of a myriad of enzymes that might cause neuronal destruction even if blood flow is restored. In addition, there is some evidence that the initial burst of excitatory neurotransmission is self-perpetuating and leads to neuronal death with a delay as long as 48 hours. In some animal stroke models, agents that block excitatory neurotransmission have proved to be remarkably effective in preventing infarction [3–5]. Most important, their effectiveness is not limited to the first few minutes after the stroke but may be beneficial hours later. The rationale for calcium channel blockers in brain protection is somewhat similar, but the evidence is less impressive, and the agents presently available block only one of at least three types of calcium channels. Consequently, they only partially prevent neuronal calcium accumulation, and their benefit in stroke treatment is probably more related to their vaso-dilatory action. More complete calcium channel blockade with combinations of blockers should be more effective in preventing neuronal death in stroke.

It is exciting to consider that blockade of calcium channels or excitatory neurotransmission may provide extremely effective brain protection in patients who have suffered recent stroke or cardiac arrest. The maximal benefit of such drugs may require temporary, high-dose therapy that will shut down neuronal function and necessitate careful life-support management during their administration. In the future we may see the implementation of an aggressive brain protection regimen in concert with thrombolytic agents to restore blood flow. The challenge will be to train and motivate the necessary human resources to ensure timely, safe, and appropriate stroke management. Carrying out the necessary clinical research studies will require an immense cooperative effort between neurologists and intensivists. Nevertheless, the rescue of functional brain tissue for a stroke patient is a goal worthy of Herculean efforts.

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References