Survival of the Ischemic Brain: A Progress Report

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SUMMARY The number of patients with cerebral infarctions increases as the population ages, despite campaigns against hypertension, the greatest risk factor. Cerebral ischemia initiates events that are presumed to defer the stage of irreversible injury. These events cause an increase of perfusion around the central ischemic zone and trigger the Bohr effect, both of which preserve tissue viability. Almost simultaneously, mitochondrial function fails, resulting in insufficient energy for the enzyme systems to control Na and K ion equilibrium. At the same time, protein synthesis slows and cellular respiratory enzymes decrease their activity, initiating an irreversible state of tissue change. Tissue fatty acids increase as a result of dissolution of cell membrane lipoprotein structure. Barbiturates reduce the extent of experimental infarction. Resperine and aminophylline are also effective, but there are no corroborative clinical trials. That ischemic brain damage may be the result of toxic substances in the ischemic tissue represents a new concept.

THE PAST 25 YEARS has witnessed an enthusiastic awakening of interest in the problem of cerebral vascular diseases. The demonstration that arteriosclerotic lesions of the extracranial arteries were frequently responsible for strokes lead directly to an appreciation of the significance of certain symptoms and signs in diagnosis, as well as to a more dynamic classification of stroke, which focused upon pathogenesis and management (transient ischemic attack, progressing stroke and completed stroke) and to carotid endarterectomy as a means of preventing cerebral infarction. Simultaneously, medical prophylaxis of cerebral infarction by anticoagulation was described. This form of therapy remains controversial despite many published studies. Evaluation of therapy required studies on the natural history of the various types of occlusive and hemorrhagic cerebral vascular diseases; though difficult to interpret, these studies sharpened our understanding of the clinical and pathologic problem. Epidemiologic studies gradually identified a few obvious risk factors in cerebral vascular disease similar to those in arteriosclerotic heart disease that eventually resulted in a modestly successful campaign against hypertension, which is clearly the most important risk factor, as well as an endorsement of dietary weight control and increased physical activity.

There now appears to be evidence that modest inroads have been made in reducing the number of cerebral infarctions by means of the various modalities described above, as well as by the use of drugs that inhibit platelet aggregation. Despite these hard-won achievements, the number of patients with cerebral infarction continues to increase with the age of the population. It is now apparent that, short of finding a means of eliminating atherosclerosis, hypertension and valvular heart disease, the number of patients with symptomatic cerebral vascular diseases will continue to increase. It is also clear that our ability to treat the patient who has already had a "stroke" has not improved measurably in the past 25 years, although there have been benefits of better nursing care, more sophisticated life-system monitoring techniques and improved medical management of the various systemic disorders that frequently coexist in the patient with stroke. The true clinical problem is proper management of cerebral ischemia to prevent ischemia from becoming infarction.

Insight into the biology of cerebral ischemia has been acquired from studies of patients with strokes and from animal models of cerebral ischemia. Progressively more definitive means of studying cerebral blood flow, biochemical measurements on ischemic brain tissue, histochemical and immunofluorescent staining techniques, electron microscopy and electrophysiologic measurements have resulted in a better understanding of the biology of cerebral ischemia. Studies using these techniques have begun to permit some insight into the sequence of events in cerebral ischemia, and have afforded an opportunity to devise pharmacologic techniques to influence those events. This has been achieved together with an enormously improved understanding of normal cerebral circulatory and metabolic functions, their controls and how they are affected by disease.

The circulatory physiologic events in cerebral ischemia have been well documented and can be reviewed briefly:

1) Cerebral blood flow (CBF) is reduced in the center of the infarct and increased in the surrounding ischemic zone. The hyperemia (sometimes termed "luxury perfusion") is secondary to increased H+ ion concentration in brain parenchyma from lactic acid and CO2.

2) Autoregulation is impaired, resulting in predictable clinical consequences.

3) There is an inconsistent alteration in vascular reactivity to PaCO2 changes. "Intracerebral steal" is observed in patients with middle cerebral artery occlusion. Prolonged hypocapnia does not influence the clinical course.
4) CBF is decreased in non-infarcted areas of the same hemisphere and intact hemisphere (dischis
sis)? 52, 58, 60, 61, 75, 84, 85
5) There is a significant impairment of cerebral recirculation after ischemia (no-reflow phenomenon) due to swelling of capillary endothelium, swelling of perivascular glia and increased blood viscosity due to coagulopathy. 86-94
6) Tissue survival during total ischemia is enhanced by washing out residual blood in cerebral vessels at the onset of ischemia. 94-103 Though the mechanism for this is not understood, it suggests that one deleterious effect of ischemia may be an accumulation of “toxic” substance rather than substrate deficiency alone.

The sequence of many biochemical and histologic events in ischemia has also been established from experimental stroke models. Experimental limitations relate specifically to the necessity of immobilizing all cerebral metabolic and enzymatic activity instantaneously. A perfect model does not yet exist, and modalities for stopping tissue metabolic activity are under intensive study. A solution will provide a quantum leap in stroke research.

The evidence suggests that cerebral ischemia initiates events that defer the stage of irreversible injury. Vascular occlusion is followed by the circulatory events previously described, i.e., immediate reduction or loss of substrate (O2 and glucose) delivery and increase in “waste” products. O2 storage is insignificant so that anaerobic glycolysis is almost instantaneously initiated, even though neuronal mitochondria may continue to function until tissue PO2 is about 5 torr. 103-106 The consequent increase in tissue lactate also increases tissue PCO2. The latter is liberated from the –HCO3 buffer system by lactate and is also derived from retained tissue CO2. 107-111 These events are responsible for the increased perfusion around the central ischemia zone; in addition, they stimulate the Bohr effect. 112-115 Both mechanisms preserve tissue viability.

Almost simultaneously, three other events are known to occur: Tissue cAMP increases precipitately, 116-119 tissue norepinephrine falls 119-124 and the level of ATP, the ATP/ADP ratio and the energy charge of the S’s-adenosine PO4 system and of other cerebral high-energy compounds, such as guanine nucleotides, all decrease simultaneously, reflecting failure of mitochondrial function. 125-128 The first two changes may well provoke other events inimical to cell survival. cAMP is a protein kinase activator that may alter the integrity and survivability of the cell membrane. 135, 136 The adrenergic discharge may also adversely affect cell metabolic activity or constrict collateral arteries. 117, 117, 118 The decrease in tissue energy charge and alteration of the tissue redox state results in insufficiency energy for the enzyme systems to control cellular ionic equilibrium so that, in effect, power failure occurs. K+ ions leak out of cells and are replaced by NA+ ions, and tissue HOH increases. 134, 135-142 Edema of this type is reversible if the energy state can be improved. 134

Almost simultaneously, there is a decrease in protein synthesis, 130, 143-146 with alteration in tissue amino acids and an increase in tissue NH3. 132, 147-149 Cellular respiratory enzymes show decreased activity 150-152 and the tissue moves into a stage of irreversible change, reflected by an increase in tissue fatty acids associated with dissolution of the lipoprotein structure of the cell membrane. 153-155

The above observations have stimulated the development of strategies aimed at enhancing tissue survival by decreasing those metabolic activities involved in cell function so that sufficient energy potential will remain to preserve cell membrane integrity and prevent cell autolysis.

Evidence demonstrates that barbiturates reduce the extent of experimental infarction, an effect that may have direct clinical applicability. 156-158 The mechanisms responsible for this protective effect have been the subject of much interest and study. Several explanations have been suggested: 1) improvement of CBF and brain glucose use in stage of recirculation; 159 2) no relation to reduced energy requirements of the tissues; 160 and 3) prevention of the initiation of the chain-spreading, free-radical reactions. 161, 162 Other drugs, such as reserpine, which depletes tissue stores of monoamines, and aminophylline, which inhibits the ischemia-induced rise of cAMP, are also effective in favorably altering the biochemical evidences of progressing ischemia, 163 but there have been no corroborative clinical trials.

Interest has been focused on the concept that ischemic brain damage is not so much a function of substrate deprivation as it is an effect of “toxic substances” in the ischemic tissue. It has been suggested that the central nervous system is particularly susceptible to free-radical degenerative processes 161, 162, 164, 165 because membrane lipids undergo pathologic free-radical reactions in the presence of oxygen. The lipid damage is catalyzed by derivatives from mitochondrial and endoplasmic reticulum electron transport systems and extravasated red blood cells. These hypotheses, which represent a radical departure from the traditional view of the mechanism of tissue damage in ischemia, await experimental confirmation.

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Research Related to Validation of Treatment Modalities by Large-scale Clinical Trials

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SUMMARY The history of randomized, controlled, clinical trials is reviewed. Cooperative clinical trials are reviewed and summarized, and specific needs for future trials are identified. Improved policy on resource allocation decisions for clinical trials vs other forms of research is necessary, particularly as such trials begin to translate improved therapeutic knowledge into community level disease control.

IN 1949 Sir George Pickering, in his presidential address to the Section of Experimental Medicine and Therapeutics of the Royal Society of Medicine, said:

Therapeutics is the branch of medicine that, by its very nature, should be experimental. For if we take a patient afflicted with a malady, and we alter his conditions of life, either by dieting him, or by putting him to bed, or by administering to him a drug, or by performing on him an operation, we are performing an experiment. And if we are scientifically minded we should record the results. Before concluding that the change for better or for worse in the patient is due to the specific treatment employed, we must ascertain whether the result can be repeated a significant number of times in similar patients, whether the result was merely due to the natural history of the disease or in other words to the lapse of time, or whether it was due to some other factor which was necessarily associated with the therapeutic measure in question. And if, as a result of these procedures, we learn that the therapeutic measure employed produces a significant, though not very pronounced, improvement, we would experiment with the method altering dosage or other detail to see if it can be improved. This would seem the procedure to be expected of men with six years of scientific training behind them. But it has not been followed. Had it been done, we should have gained a fairly precise knowledge of the place of individual methods of therapy in disease, and our efficiency as doctors would have been enormously enhanced.1

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Treatment of atherosclerosis and hypertension has changed dramatically since Sir George made that statement. Therapeutic evaluation has improved since then, but much improvement lies ahead, and the attitudes against systematic assessment of therapeutic safety and efficacy still persist, though they are not as strong as in the 1940s.

The history of clinical trials is temporally parallel to the history of the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA). The first paper that fully described methodologic standards for the clinical trial was published by Sir Austin Bradford Hill in 1951.2 In 1959, Professor Greenberg published his important methodologic advice on the conduct of cooperative field and clinical trials.3 By the mid-1960s, the Heart Special Projects Committee, a primary review group of the National Heart Institute, had prepared standardized recommendations for use by staff members of the Institute in planning and administering cooperative clinical trials in the cardiovascular field.

Throughout the history of large-scale trials, the ethical basis of the methods has been debated and discussed. In 1951, Bradford Hill said:

The first step in such a trial is to decide precisely what it hopes to prove, and secondly to consider whether these aims can be ethically fulfilled. It need hardly be said that the latter consideration is paramount and must never, on any scientific grounds whatever, be lost sight of. If a treatment cannot ethically be withheld then clearly