IV. Brain Edema in Stroke

STUDY GROUP ON BRAIN EDEMA IN STROKE

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SUMMARY A classification of brain edema is provided as well as an extensive review of the animal models from which we have derived most of the basic information we have about the formation and resolution of edema. The clinical aspects of cerebral edema in stroke are discussed and also modern methods for identifying cerebral edema in the human. Attention is given to computed tomography and enhanced CT and advances in their application to this condition.

The classification of cerebral edema introduced by Klatzo, which includes vasogenic and cytotoxic edema, is widely accepted. Vasogenic edema is encountered in a wide variety of focal experimental lesions, including implanted brain tumor. The cerebral blood vessels undergo characteristic changes that permit leakage of proteins and extravasation of the conventional intravenously injected blood-brain barrier (BBB) indicators into the extracellular spaces, particularly in the white matter. In contrast, cytotoxic edema affects either white or gray matter (or both) and is characterized by the accumulation of fluid, usually intracellular, without leakage of proteins or extravasation of BBB indicators. Examples of the cytotoxic type of cerebral edema include triethyl tin intoxication and acute water intoxication. A third type of cerebral edema, defined by Fishman as interstitial edema and termed hydrocephalic edema by Manz, occurs when cerebrospinal fluid is forced into periventricular tissue in hydrocephalus.

Before, one might suppose that edema associated with cerebrovascular lesions would be primarily of the vasogenic type, since both overt injury to blood vessels and a discrete focal brain lesion are present. However, experimentally, the increase in tissue volume and water is found usually to reach a peak prior to the extravasation of protein or of BBB indicators. Clinically, swelling in and around an area of infarction may be present before the radionuclide (RN) scan used to monitor BBB leakage becomes positive. This evidence suggests that brain edema due to focal ischemia begins as a cytotoxic type and is followed by a vasogenic edema. But the pathophysiology of this edema and its pattern of development are sufficiently specific to warrant a separate classification as ischemic brain edema.

Biochemical Measures of Experimental Edema

The most direct method of establishing whether a tissue is edematous is to measure the percent dry weight of a tissue sample. A decrease in percent dry weight is synonymous with a converse increase in percent water content and thus reflects an increase in tissue volume, provided that there is no net loss of tissue mass as would be expected with necrosis or atrophy. The degree of swelling or change in volume can be estimated from percent dry weight using a formula derived...
by Elliott and Jasper. However, to obtain an accurate measure of the change in volume, the percent dry weight of the edema fluid must be included in the calculation (table 1). Water content also can be expressed in terms of dry weight of tissue (table 2).

Sodium and potassium determinations in edematous tissue provide evidence as to the nature of edema fluid. Thus changes compatible with uptake of high-sodium, low-potassium fluid suggest that the edema fluid is derived from plasma, while absence of such changes indicates that shifts of water without electrolytes are involved. A decrease in electrolytes on the basis of wet weight of tissue may denote only a dilution of the normal tissue electrolyte content by extravasated fluid. When expressed in terms of dry weight of tissue, net losses of electrolytes become evident. This applies particularly to potassium since net decreases in brain sodium content are seen only in association with hyponatremia. Expressing electrolyte content in terms of dry weight can be misleading when there is net loss of tissue mass. If electrolyte content and tissue mass change at the same time, apparently normal electrolyte values or even an increase per unit dry weight may be obtained. The various ways of expressing the water and electrolyte data are summarized for normal cat brain in table 2.

A method for measuring brain specific gravity in a non-polar medium has been developed for determination of cerebral edema. Changes in brain water content can be derived from the specific gravity measurements as long as the specific gravity of tissue solids remains constant. Thus the same difficulties encountered in estimating volume changes by means of dry weight measurements exist when specific gravity determinations are employed.

A breakdown of the BBB is usually identified by injecting intravenously substances that normally do not penetrate from blood to brain, and subsequently demonstrating their presence in the affected cerebral tissues. The markers used most often are dyes, like trypan blue or Evans blue, which form complexes with serum protein, and, in effect, make visible the passage of protein across the blood-brain interface. Fluorescent dyes and RISA (radioactive serum albumin) also have been used. When permeability of the barrier is to be investigated in experiments on ischemia, one must ensure that blood flow to the affected parts of the brain has been re-established. Otherwise, failure to demonstrate presence of the marker in brain tissue may indicate simply that it has not been delivered to the ischemic area. While the belief is general that cerebral edema of the vasogenic type develops when a breakdown of the BBB has occurred, recent research has shown that in the experimental animal cerebral edema does not result either from transient opening of the barrier with hyperosmolar solutions or from induced acute hypertension.

In ultrastructural studies, swelling of astrocytic processes and changes in the size of the extracellular space have been considered as indicative of the presence of cerebral edema. The question is debatable whether such morphological evidence can be equated with edema without confirmatory chemical demonstration of increased water content.

### Experimental Models

A classification of experimental models of brain ischemia has been published recently by Molinari and Laurent. These authors discuss in detail the applicability of the various models in the study of human disease and find most of them wanting. Some of the models, with representative references, are listed in table 3.

#### The Gerbil Model: Occlusion of the Common Carotid Artery

**Features and Value**

In recent years considerable progress in the experimental study of regional ischemia has been achieved by the introduction of the Mongolian gerbil (Meriones unguiculatus) as a model. The simplicity of applying carotid clips with an option for their removal or replacement makes it practicable to obtain a large, statistically meaningful amount of data in many directions of experimentation. Anomalies of the circle of Willis in these animals account for the fact that approximately 30% to 50% of those subjected to unilateral occlusion of the common carotid artery develop ischemic brain damage in the homolateral hemisphere.

Pathophysiologically, the gerbil model presents a clear-cut example of regional ischemia, such as is produced by occlusion of a cerebral artery in man; furthermore the resulting data are not "confounded" by multiple factors, as in the popular Levine model, for example, where hypoxia and ischemia, which admittedly differ in their effects upon brain tissue, are used in combination and the findings interpreted sometimes in reference to one, sometimes to the other condition. For similar reasons embolism or acute hypotension, when used as experimental models to study cerebral ischemia, should be recognized as conditions different from "pure" ischemia in which interference with the arterial blood supply constitutes the pathophysiologic event.

#### Table 1 Percent Swelling of Cerebral Tissue* Derived from Measurement of Percent Dry Weight

<table>
<thead>
<tr>
<th>White matter of cat brain</th>
<th>Normal</th>
<th>Edematous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent dry weight</td>
<td>31.8</td>
<td>21.4</td>
</tr>
<tr>
<td>Percent water</td>
<td>68.2</td>
<td>78.6</td>
</tr>
<tr>
<td>Increase in percent water</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Percent swelling when p = 0</td>
<td>48.6</td>
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<tr>
<td>when p = 8</td>
<td>77.6</td>
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</tr>
</tbody>
</table>

*Formula for derivation of percent swelling from Elliott and Jasper:

\[ \text{% swelling} = \frac{P - P_i}{P} \times 100 \]

Where P is percent dry weight in normal tissue, P_i is the percent dry weight of the edematous tissue and p is the percent dry weight of the fluid taken up.

\[ p = 0 \text{ when only shifts of water are involved} \]

\[ p = 8 \text{ when edema fluid has composition close to that of whole plasma} \]

*Dry weight data from Pappius.1

#### Table 2 Dry Weight, Water, Sodium and Potassium Content of Normal Cerebral Tissues of Cat

<table>
<thead>
<tr>
<th>Cerebral Cortex</th>
<th>White Matter</th>
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<tbody>
<tr>
<td>Dry weight, percent</td>
<td>19.2 ± 0.8</td>
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<tr>
<td>Water, percent</td>
<td>80.8 ± 0.6</td>
</tr>
<tr>
<td>ml/kg dry weight</td>
<td>4028 = 158</td>
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<tr>
<td>Sodium mEq/kg wet weight</td>
<td>57.5 ± 3</td>
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<tr>
<td>mEq/kg dry weight</td>
<td>299 = 23</td>
</tr>
<tr>
<td>Potassium mEq/kg wet weight</td>
<td>102 = 4</td>
</tr>
<tr>
<td>mEq/kg dry weight</td>
<td>531 = 31</td>
</tr>
</tbody>
</table>

*Average ± S.D., 9 animals
TABLE 3 Experimental Models of Brain Ischemia

<table>
<thead>
<tr>
<th>Type of Ischemia</th>
<th>Model</th>
<th>Species</th>
<th>Author</th>
<th>Year of Report</th>
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<tr>
<td>Regional</td>
<td></td>
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<tr>
<td>Permanent Ischemia</td>
<td>Middle cerebral artery (MCA)</td>
<td>Cat</td>
<td>Bartko et al.</td>
<td>(15) 1972</td>
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<tr>
<td></td>
<td>clip = hypotension</td>
<td>Dog</td>
<td>Brunson et al.</td>
<td>(16) 1973</td>
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<td></td>
<td></td>
<td>Squirrel monkey</td>
<td>Garcia et al.</td>
<td>(20) 1974</td>
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<td></td>
<td></td>
<td>Macaca mulatta</td>
<td>Crowell et al.</td>
<td>(22) 1970</td>
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<td></td>
<td></td>
<td>Baboon</td>
<td>Meyer et al.</td>
<td>(23) 1972</td>
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<td></td>
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<td></td>
<td>Olsson et al.</td>
<td>(24) 1971</td>
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<td></td>
<td>Hacker et al.</td>
<td>(25) 1973</td>
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<td>Ito et al.</td>
<td>(26) 1975</td>
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<td></td>
<td>Kahn</td>
<td>(27) 1972</td>
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<td></td>
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<td>Siegel et al.</td>
<td>(28) 1974</td>
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<td>Siegel et al.</td>
<td>(29) 1972</td>
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<td>Bremer et al.</td>
<td>(30) 1975</td>
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<td></td>
<td>Brock et al.</td>
<td>(31) 1972</td>
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<td></td>
<td>McQueen et al.</td>
<td>(32) 1970</td>
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<td>(33) 1970</td>
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<td>(34) 1974</td>
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<td>Molinari</td>
<td>(35) 1974</td>
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<td></td>
<td>Molinari</td>
<td>(36) 1974</td>
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<td></td>
<td>de la Torre</td>
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<td></td>
<td>Olsson et al.</td>
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<td></td>
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<td>(24) 1971</td>
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<td></td>
<td>Embolization – microspheres</td>
<td>Rat</td>
<td>Kogure et al.</td>
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<td></td>
<td></td>
<td>Primate</td>
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<td>Macaca mulatta</td>
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<td>(40) 1976</td>
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<td>Transient Ischemia MCA clip = hypotension</td>
<td>Macaca mulatta</td>
<td>Gunn et al.</td>
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<td>Macaca mulatta</td>
<td>Snyder et al.</td>
<td>(42) 1975</td>
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<td>Brierley et al.</td>
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<td>Baboroon</td>
<td>Teraura et al.</td>
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<td>Gerbil</td>
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<td>Unilateral carotid ligation</td>
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<td>Teraura et al.</td>
<td>(44) 1972</td>
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<td></td>
<td>Clamping of brachiocephalic and left subclavian and both internal mammary arteries and pharmacological hypotension</td>
<td>Cat</td>
<td>Hossmann</td>
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<td></td>
<td></td>
<td>Cat</td>
<td>Zaren et al.</td>
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<td>Cat</td>
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<td>Zimmermann &amp; Hossmann</td>
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<td>Cat</td>
<td>Plump et al.</td>
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<td></td>
<td>Cat</td>
<td>Salford et al.</td>
<td>(51) 1973</td>
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<td>Cat</td>
<td>Spector</td>
<td>(52) 1961</td>
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<td></td>
<td>Isolated brain</td>
<td>Rabbit</td>
<td>Yatsu et al.</td>
<td>(53) 1975</td>
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<td>Rabbit</td>
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<td></td>
<td></td>
<td>Rabbit</td>
<td>Schutz et al.</td>
<td>(55) 1975</td>
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<td>Ischemia Secondary to Increased ICP Systemic hypotension and hypoxia</td>
<td>Rabbit</td>
<td>Yatsu et al.</td>
<td>(53) 1975</td>
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<td></td>
<td>ICP increased by infusion of</td>
<td>Rabbit</td>
<td>Marshall et al.</td>
<td>(54) 1975</td>
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</table>

Brierley et al. have suggested that some of the pathological changes in the gerbil are secondary to epileptic seizure activity in the affected animals rather than due to ischemia. However, epileptiform states are observed in less than 50% of the animals that show evidence of infarction, and the nature of the histopathologic changes is the same in animals with seizures as in those without. Although the ischemic damage may be more severe in the animals experiencing seizures, these episodes could be an expression rather than a cause of the more severe ischemic injury. These considerations should not diminish the usefulness of the Mongolian gerbil model for evaluation of changes occurring in acute regional brain ischemia.

**Effects of Hypertension During the Postischemic Period**

Since fluctuations in the systemic blood pressure are a common feature of cerebrovascular attacks associated with ischemia, an investigation of the effects of hypertension superimposed on the ischemic brain should be of considerable clinical importance. Early reports relevant to such studies indicate that an acute elevation in the blood pressure can produce BBB changes in the normal brain, as well as greatly increase the rate of spread of vasogenic brain edema.

Recent studies carried out in gerbils on the effects of hypertension superimposed during postischemic periods show: (1) much more severe histopathologic changes in the
hypertensive groups, (2) accelerated BBB damage in hypertensive animals, (3) a markedly increased cerebral blood flow (CBF) in the ischemic hemispheres of the hypertensive animals, and (4) evidence of much higher levels of brain lactate in hypertensive than in normotensive gerbils. Still later studies indicate that the opening of the BBB to serum proteins and tracers such as Evans blue or horseradish peroxidase is unlikely to be responsible for the severity of ischemic tissue damage. On the other hand, it appears quite probable that tissue damage resulting from an ischemic insult is compounded by accumulation of metabolic waste products, lactic acid being a prime suspect among them. Accumulation of lactate can be due to increased anaerobic glycolysis as well as to deficient clearance, both of which occur in cerebral ischemia. Earlier studies had demonstrated that significantly elevated levels of lactate persist in gerbils sensitive to infarction as long as 20 hours after release of a one-hour unilateral occlusion; at this time there is no evidence of abnormal glycolysis. This illustrates the extent of the delay in lactate removal, presumably due to oversaturation of the carrier system.

Although an initial clearance of lactate following release of occlusion is relatively rapid in normotensive animals, recent data indicate that in the hypertensive group lactate continues to rise, at least during the first hour following removal of the clip. The reason for this is not understood, but it is tempting to speculate that the intensified damage to structural brain tissue observed in hypertensive gerbils following ischemia may be significantly related to an increased retention of lactate in these animals.

**Pathophysiology of Ischemic Brain Edema (Gerbil)**

The most recent study, using a modified specific gravity measurement method, indicates that an abnormal accumulation of fluid in the ischemic brain tissue is recognizable within five minutes from the onset of arterial occlusion. At one hour after occlusion of one carotid artery, a small but significant decrease is demonstrated in percent dry weight of the affected hemisphere. Although one electron microscopic study of the gerbil reports some increase in extracellular as well as intracellular space after 20 minutes' occlusion, another report demonstrates that fluid accumulation is primarily intracellular. Extravasation of neither blood proteins nor tracers is observed at this time. Thus, the initial stages of ischemic edema may be considered as cytotoxic.

Based on specific gravity measurements, the initial abnormal water uptake progresses and then levels off. In some of the animals (presumably those in whom necrosis has not occurred), the specific gravity returns to normal, indicating that the fluid accumulation per se is reversible. In others, a drastic further reduction in specific gravity is observed with the onset of necrotic changes in the affected tissue. Appearance of trypan blue staining is not a consistent finding in animals that die during the first 17 hours following occlusion, indicating that breakdown in the BBB is not simultaneous with the onset of infarction.

Necrosis, with the breaking up of structural components of brain parenchyma, creates an enlargement of extracellular spaces, which may be distended further by a marked increase in water movement due to lysosomal enzymatic digestion of structural cellular elements and release of osmotically active substances. Fatty transformations within the necrotic areas also can reduce the specific gravity of the brain tissue.

Release of the arterial occlusion and reestablishment of the circulation markedly accelerates the reduction in specific gravity of brain tissue in which necrotic changes already have occurred.

Specific gravity measurements in gerbils subjected to one, three, or six hours of unilateral carotid ligation were made at varying times after release. The cerebral cortex and hippocampus of the animals subjected to one hour occlusion showed no further significant changes in specific gravity during ten hours after release of the clip. After 15 hours of release, however, three types of response could be distinguished. In the first, there was a return to normal control values. In the second, specific gravity values remained little changed after release of the clip. The third type was characterized by a drastic decrease in specific gravity which persisted for as long as one week following release. In the basal ganglia and hippocampus three similar types of response could be recognized after shorter periods following release.

The release of occlusion after three or six hours of ischemia either resulted in no further changes or produced an additional drop in specific gravity. The further drop in specific gravity often occurs in the hippocampus and basal ganglia immediately, and in the cortex, several hours after release but earlier than that following one hour of occlusion.

A recent study clearly demonstrates that in cerebral ischemia the movement of water into the brain tissue and increased permeability of the BBB to proteins are separate and seemingly independent phenomena. The opening of the BBB to serum proteins after occlusion is released, as evaluated by the behavior of Evans blue tracer, is transitory in nature and its incidence and time of occurrence depend on the duration, hence the severity, of the ischemic insult. The longer the condition of occlusion is maintained, the earlier after its release the peak incidence of Evans blue staining is reached and the faster the subsequent fall in incidence of extravasation of the marker occurs. An increased permeability of the BBB to protein tracers is observed to cease after some time although the necrotic changes within the brain parenchyma continue to progress. That such “recovery” of the BBB is not due only to continuing interference with circulation after release of occlusion (no-reflow phenomenon) is clearly demonstrated by the autoradiographic CBF observations which show that the hemispheres with advanced ischemic necrosis and with no abnormal extravasation of protein tracers may exhibit greatly increased CBF.

In cerebral ischemia, necrotic changes are confined primarily to various cellular elements of brain parenchyma such as neurons and glia whereas the capillary endothelium remains strikingly well preserved, even in brain tissue subjected to 18 hours of ischemia. Nevertheless, in spite of this seemingly great resistance to ischemia displayed by capillary endothelium, undoubtedly in stages of advanced necrosis the vascular structures eventually must succumb and the BBB open for passage of plasma constituents. In studies by Olsson et al., extravasation of Evans blue tracer was observed up to 23 days after ischemic infarction.
Electron microscopic observations, using horseradish peroxidase as a tracer, suggest that in cerebral ischemia the mechanism responsible for the increased permeability of the BBB to proteins is a greatly enhanced pinocytotic transport across the endothelium. The presence of numerous peroxidase-laden vesicles in the cytoplasm of capillary endothelium in the brains of animals subjected to ischemia is a characteristic finding in studies of Westergaard et al. Likewise, an increased pinocytotic activity related to extravascular penetration by the protein tracer has been described in hypertension, after portocaval anastomosis, following intraventricular perfusion with serotonin, and as a result of x-irradiation. The factors inducing pinocytosis that results in transendothelial passage of substances such as proteins should be a fascinating subject for future investigations. The study by Spatz et al. might be of interest in this respect. The data indicate that at the time of increased extravasation of protein, total glucose uptake (brain uptake index [BUI]) is not much different from normal (control, 13.3 BUI ± 1.8; ten hours of release, 12.4 BUI ± 1.1). However, passive diffusion is increased from 2.6 BUI ± 1.0 to 5.9 BUI ± 0.65, and so the conclusion can be drawn that carrier-mediated glucose transport is increased. Thus the period of an increased pinocytotic activity and extravascular leakage of proteins appears to coincide with inhibition of the carrier-facilitated transport of glucose.

The observations presented here indicate the complex nature of ischemic brain edema, involving various factors responsible for both cytotoxic and vasogenic pathomechanisms. A concept of ischemic edema such as this suggests the possibility that successful clinical management will require different measures, each appropriate to the particular stage of the pathological process presenting at a given time.

Occlusion of the Middle Cerebral Artery (MCA)

In experimental animal models of acute cerebral ischemia produced by occluding one MCA, histopathologic studies, measurements of water content, and measurements of intracranial and tissue pressure show that cerebral edema regularly accompanies ischemic cerebral infarction. Swelling of perivascular glial cells begins within minutes of the onset of ischemia and by 30 minutes, focal edema of cerebral tissue is measurable by change in water content. Investigators find that water content in the cortex in the occluded area is increased 30 minutes after occlusion, is within normal limits at 60 minutes, and again is increased significantly at 120 and 240 minutes. In the underlying white matter, increased water content is seen at 30, 60, 120, and 240 minutes. In a borderline area, slightly but significantly increased water content is demonstrable in both the cortex and the white matter at 120 minutes, but not at 60 or at 240 minutes. In these experiments, extravasation of Evans blue cannot be detected within four hours of MCA occlusion. Analysis of electrolytes at 120 minutes after occlusion reveals an increase in sodium and a net loss of potassium (dry weight basis) in both the cortex and the white matter — more in the occluded area, but also to a lesser extent in the borderline area.

In a study of the later time course of this model, O'Brien et al. report that infarcted tissue (more than 25% of area necrotic) shows increased water content at four hours (the earliest time sampled) in both predominantly white and predominantly gray tissue. This increase progresses to a maximum at two days. Subsequently, gray matter water content returns to normal, while that of white matter remains elevated. Analyses of ischemic tissue (clipped MCA territory with less than 25% of area necrotic) reveal that both white and gray matter water content increase at four hours, peak at two days, and return to more or less normal by the third day. Nonischemic tissue (opposite hemisphere) at four hours shows a slight increase in water content of both white and gray matter that peaks at two days, and returns to normal by the third day.

Temporal changes in the distribution of pertechnetate, albumin, and sodium differ from those in water content, but brain-blood ratios for pertechnetate and albumin in both ischemic and infarcted tissues are already higher than normal at four hours. This could be due to changes in blood volume. High distribution ratios persist up to 20 days in infarcted tissue, are considerably lower, although present, in ischemic tissue, and in nonischemic tissue samples the ratios are normal throughout this period.

In dogs with normal systemic blood pressure and a clip on MCA, focal areas of infarction develop in 70% of animals and breakdown of the BBB in surrounding areas is demonstrable by trypan blue. No change can be demonstrated in large areas of the cortex normally supplied by the clipped artery where blood flow is probably reduced by not more than 40%. The combination of hemorrhagic hypotension and a clip on the MCA results in marked alterations in the affected cortex measurable 30 minutes after restoration of systemic blood pressure to normal level. These changes consist of increases in water and sodium and a fall in net potassium content. Underlying white matter shows delayed moderate changes in water and electrolyte content similar to those seen in vasogenic edema.

Fluorescein angiography performed at the time of these edematous changes results in diffuse fluorescence of the cortex; the fluorescence is not restricted to the intravascular space.

Several studies of this model in the monkey have been reported. Ultrastructural studies show swelling of astrocytes two and one-half hours after MCA occlusion and gross evidence of edema (midline shift) 12 hours after clipping. Permanent occlusion of MCA (24 and 48 hours) results in only one of 11 brains staining with Evans blue in areas not associated with operative manipulations. However, in these experiments the clip was removed only two minutes before the animal was killed; the low incidence of visualization of Evans blue extravasation may be the result of failure of reperfusion in the ischemic areas.

Little, in an ultrastructural study, demonstrates sequential changes following MCA occlusion. Shortly after vessel occlusion astrocytic swelling begins in the vicinity of the capillaries and spreads in centrifugal fashion. Enlargement of the extracellular space in both gray and white matter is also noted. Six hours after occlusion the next phase begins, characterized by tissue necrosis, rupture of cell membranes, and massive accumulation of fluid. These changes rapidly increase in severity. A significant reduction in mean capillary diameter is noted as early as 90 minutes after occlusion and...
complete obstruction to passage of erythrocytes is evident by six hours. The capillary narrowing is thought to be due initially to compression by swollen pericapillary astrocytes, and later by increased tissue pressure. However, endothelial swelling also appears to be an important factor.

If an animal survives acute induced focal cerebral ischemia, edema generally resolves within three to five days, regardless of the resulting neurologic deficit.78 The time course of ischemic cerebral edema (rapid development to a maximum within one to three days and resolution within a few more days) differs from the longer time course of the transendothelial distribution of other molecules, particularly tracers such as technetium-99m, albumin, dyes, and horseradish peroxidase.18 Thus, the mechanisms that underlie ischemic cerebral edema may be different from those involved in the development of abnormalities of the BBB which allow passage of molecules larger than water.

Transient Global Ischemia

Circulatory Arrest

**Dog.** In the widely quoted study of Gunn et al.,41 the animals subjected to ten minutes of circulatory arrest eight hours earlier have significantly higher total brain water content than do those that are sham-operated. This study is inconclusive, since its statistical significance hinges on the questionable assumption that eight dogs paired as to weight and sex are comparable as to brain water content. When either average water content of the two groups or percent dry weight is compared, the differences are not significant. Snyder et al.42 fail to demonstrate a secondary rise in intracranial pressure up to two hours after 15 minutes of circulatory arrest. Thus the development of cerebral edema in this model remains uncertain.

**Occlusion of Cerebral Arteries**

**Baboon.** Following ten minutes of occlusion in animals with less than 10% of normal blood flow during the occlusion, intracranial pressure increases during and immediately following the occlusion, remaining above 250 mm Hg.43 Three to four hours later, increased water content is demonstrated in both white and gray matter (71.2% and 82.5% respectively). In animals with about 10% of normal blood flow during the occlusion, there is a transient increase in intracranial pressure during the occlusion and normal water content three to four hours later (66.2% and 80.1% for white and gray matter respectively).

**Rhesus Monkey.** One hour's intrathoracic occlusion of cerebral blood supply with systemic hypotension (Arfonad + bleeding) followed by recirculation at high systemic blood pressure (vasoactive drugs) and with rapid adjustment of acid-base imbalance with Tris buffer results in two readily distinguishable groups of animals: one with signs of electrophysiological recovery, and the other in which such recovery is absent.47 The most obvious difference is normal or slightly elevated CBF on recirculation in the group with recovery, and reduced CBF in the animals without recovery (46.1 ml vs. 8.4 ml/100 gm/min respectively).48 Minimal blood flow during ischemia is associated with poor or no recovery, perhaps because of subsequent impairment of reperfusion or because of accumulation of acidic substances from the metabolism supported by small residual amounts of glucose. In all animals intracranial pressure rises immediately after recirculation begins, but remains elevated only in animals without recovery. Morphologically, swelling of perivascular elements is demonstrated at the end of the ischemic period. This becomes more pronounced on recirculation, particularly in animals without electrophysiological recovery. In the one animal (with recovery) recirculated for 24 hours, small infarcts (total volume less than 4%) were present in the inner part of the pallidum and in the boundary zone between territories of ACA and MCA. Earlier experiments19 showed no extravasation of protein during ischemia. No experimental data are given on the effect of recirculation on BBB permeability to proteins.

Brain swelling, calculated from changes in water content of cortex and white matter, was absent at the end of ischemia but present in both groups of animals after 45 minutes of recirculation. The swelling then subsided in both groups, but some was present in the only animal without recovery killed six hours after ischemia. After 45 minutes of recirculation, both cortex and white matter had increased water content. After recirculation for other time intervals, considerable variation in water content was observed due to the fact that only one or two animals were killed at each interval studied. Sodium and potassium content of white matter were also variable. In contrast, and in spite of considerable variability, a consistent increase in the cortical Na/K ratio at 24 hours occurred. The changes in the ratio reflect an increase in sodium in both groups of animals and a persistent decrease in cortical potassium content in the animals without recovery.

**Cat.** Similar experiments in the cat48 show again only a small change (from 75.9% to 76.1%) in net water content of brain tissue (probably cortex) at the end of the ischemic period, but a pronounced shift of fluid within the brain, with the extracellular space decreasing from 18.9 to 8.5 volume percent. This finding is of great importance in the interpretation of changes in electrolyte content. Brain water increases to 78.3% after 15 minutes of reperfusion and thereafter the swelling is rapidly reversible (water content 76.6%, 60 minutes after ischemia). Extracellular space gradually expands during reperfusion, approaching normal values within 60 minutes.

Also in the cat, Hossmann and Takagi46 demonstrate that during one hour of ischemia, brain osmolality increases from 308 mosm to 353 mosm causing an osmolarity gradient of more than 50 mosm between blood and brain. The increased osmolarity cannot be accounted for by changes in the concentration of major solutes such as sodium, potassium, glucose, lactate, and pyruvate, indicating that a release of idiosyncratic osmoles from brain constituents has occurred. On recirculation, the gradient rapidly diminishes in animals with functional recovery but remains elevated in those without such recovery. Although it is not possible, on the basis of the data presented, to decide whether failure to restore the brain to normal in the animals without functional recovery is the cause or the result of circulatory impairment, the authors postulate that persistence of the osmotic gradient between blood and brain following a period of ischemia would promote brain swelling which, in turn, would further compromise metabolic recovery. For this reason, they suggest that
therapeutic rise in blood osmolality during the very early stages of recirculation may be an appropriate method for preventing or diminishing the influx of water into the brain.

Occlusion for periods of up to 180 minutes results in cerebrovascular resistance, poor filling is apparent at one hour and grossly evident at three hours. The vascular block is at the level of the capillaries and small arterioles. One should note that in all three sets of experiments, the carotid ligation remained in place after the hypoxic period. The view that vascular abnormality is a primary feature of this model has been challenged by Brown and Brierley" and Salford et al. who observe primarily neuronal alterations after hypoxic exposure of animals with unilateral ligation of the carotid artery. (It should be noted that metabolic alterations noted by Salford et al. suggest that this model is characterized by profound anoxemia rather than by ischemia.) The early neuronal damage without vascular involvement has been confirmed by Levy et al. However, an important difference in the experiments of Salford et al. and Levy et al., as compared to earlier studies, is the removal of the carotid occlusion at the end of the hypoxic exposure.

Cerebral Edema Complicating Subarachnoid Hemorrhage

Cerebral edema appears to be a common complication of ruptured aneurysm and subarachnoid hemorrhage as judged by a measurable increase in regional cerebral blood flow in a series of cases treated with hypertonic glycerol. When subarachnoid hemorrhage is produced experimentally by injecting blood into the subarachnoid space, CSF pressure increases and 24 hours later cerebrovascular resistance increases with a reduction of CBF; these changes persist for one week. The rise in intracranial pressure is associated with swelling of the astrocytic end feet shown by electron-microscopy, and this perivascular edema is decreased, accompanied by increased CBF, following infusions of hyper-
Experimental Intracerebral Hemorrhage

In a now classic paper, it was demonstrated that intracerebral hemorrhage could be produced in experimental animals by distal ligation of the MCA and the subsequent production of systemic hypertension. The authors concluded that massive spontaneous intracerebral hemorrhage in the human is preceded by ischemic infarction in the basal ganglia. This is in keeping with the clinical observation that patients with massive spontaneous cerebral hemorrhage generally exhibit a neurologic prodrome before the onset of deep coma. Investigators subsequently attempted to reproduce this disease by the injection of blood into the brains of dogs. In one such study, the increased intracranial pressure which resulted was diminished by both intravenous mannitol and steroids. Previous studies in the rhesus monkey with cryogenic cerebral lesions treated by intravenous hypertonic urea had shown that a pressure reduction such as this does not necessarily reflect a reduction of cerebral edema, but can be achieved by dehydration of normal brain tissue, and this observation was confirmed recently in the dog, using glycerol as the agent. Another group reports, on the basis of gross observations, that cerebral edema does not occur with this experimental model. More recently, in an experimental model of intracerebral hemorrhage in the primate which also involves ligation of the MCA, the induction of hypertension with noradrenaline produces extensive anemic infarctions but not intracerebral hemorrhage acutely. In chronic lesions, however, hemorrhagic infarction occurs. When hypercapnia is induced five days after injury, intracerebral hematomas develop. The authors conclude that pre-existing cerebral softening is responsible for the subsequent development of cerebral hemorrhage. Since none of these studies adequately addresses the problem of cerebral edema in relation to cerebral hemorrhage, this investigative approach should be pursued further.

Cerebral Embolism

Many different substances have been used to produce embolic injury to the brain, but some of these, such as air or oil would seem to have only peripheral relevance to the problems of stroke. The claim has been made, however, that the use of oil reproduces the pathophysiology of complete, abrupt hemispheric infarction, since it is associated with total anoxia of the hemisphere. The most natural material to use might seem to be blood clots, but this method is difficult and not often used. An interesting indirect method of producing embolic occlusion of the cerebral circulation is by intracarotid injection of the prostaglandin precursor, sodium arachidonate, or of adenosine diphosphate. Although this procedure results in aggregation of platelets and occlusion of the ipsilateral microcirculation, the effects appear to be transient and physiological. Actual anatomic tissue lesions have not been described in reports of the use of this method.

The most popular technique for producing embolic injury is by the intracarotid injection of plastic and silicone spheres. The anatomic lesion produced depends upon the size of the emboli and the species used. In the rabbit, emboli less than 10 micra in size traverse the circulation apparently without causing morphologic damage. Emboli 25 micra to 45 micra in size produce small focal ischemic lesions accompanied by vital staining with Evans blue, provided the dye is in the circulation at the time of the embolization. When the dye is injected three hours after embolization, vital staining is not seen. Emboli of about the same size injected into the right internal carotid artery of the rat produce a large area of infarction in the posterior distribution of the vessel. Emboli of size greater than 70 micra frequently produce multifocal microinfarcts. With even larger (circa 1 mm) emboli, occlusion of major intracerebral vessels has been described in the primate. When elongated (7 mm) emboli are used, gross infarctions are produced. This model gives promise of yielding important data, but is in need of further development. Kogure et al. using microsphere embolization, demonstrate an early, reversible increase in brain water content, with a peak five minutes after microsphere injection, normal values at 30 minutes, and a second rise between four and 24 hours. There is no extravasation of Evans blue during the first 30 minutes after the ischemic insult. In the study of Siegel et al., elevation of the water content of the experimental hemisphere is shown at four, eight, and 16 hours. Distribution space of albumin injected two hours before the animals are killed decreases at four hours (still intravascular) but is slightly above normal at eight hours and significantly so at 16 hours. The authors conclude that necrotic edema is present.

With the intracarotid injection of oil in the dog, McQueen et al. find an immediate rise in water content of the brain, which peaks at 60 minutes after embolization. However, no correlation is evident between brain water content and CSF pressure.

Experimental Hypertensive Encephalopathy

In the rat with chronic hypertension, the brain shows focal microinfarcts which are occasionally hemorrhagic, and the associated blood vessels not infrequently show fibrinoid changes. Many of these animals exhibit convulsions and weight loss. Ultrastructurally, degenerative changes as well as loss of muscle cells are observed in the media of the large subarachnoid vessels. Fibrinoid changes are also seen in small parenchymal arteries and arterioles but not in capillaries and venules. The former vessels are also abnormally permeable to horseradish peroxidase but not to colloidal carbon. The peroxidase is found extracellularly between swollen cells and processes of the neuropil. Neither infarcts nor clinical symptoms are mentioned in the above report. Mice with chronic hypertension are reported to exhibit both electron microscopy and water analyses cerebral edema characterized by enlargement of the intracellular space in the cortex and the extracellular space in white matter. There is no evidence of protein exudation. Infarcts are not seen and the authors state that clinical symptoms are absent.

The acute elevation of blood pressure in normal rats following the administration of angiotensin results in foci of abnormal vital staining with trypan blue in the brain. This dye, like Evans blue, is bound to serum proteins and its presence in brain reflects protein exudation. Similar results are observed in the cat using aramine and Evans blue, and
hypertensive encephalopathy. Early studies indicate excesses, an early sign of infarction, is seen in the hypertensive irreversible. Therefore, some of those lesions may be, in fact, infarctions. This matter needs further study.

Ultrastructurally, the lesion in the rat is associated with enlargement of perivascular foot processes. In the cat, enlargement of the extracellular space of white matter, in addition to astrocytic process swelling in the gray matter, is described and the authors stress the similarity of the lesions to those of ischemic encephalopathy. In the rat with induced seizures and hypertension, passage of peroxidase through the vessel wall into the adjacent, nondilated extracellular space is described. The processes of the neuropil are unremarkable.

In the rat, hypercapnia increases protein permeability in the acute hypertension lesion. The water content of the brain is increased in hypercapnic but not normocapnic rats. Vital staining under these circumstances reflects the exudation of blood proteins, and therefore would indicate that the accumulating fluid has a dry weight equal to that of brain. This is theoretically possible but seems unlikely. In the cat with a cryogenic lesion, there is no measurable decrease in the dry weight of the cerebral cortex in the contralateral hemisphere, but the specific gravity of the tissue is decreased. Had this more sensitive method been used in studying the hypertensive rat, an increase in tissue water might well have been demonstrated. The hypercapnia may have pushed the tissue change to the point of measurability by the less sensitive dry weight method.

In the rat with induced seizures and hypertension there is staining of involved areas only when the Evans blue is given prior to induction of the seizures. When the dye is given one minute after the seizures begin, little or no staining is seen. This is interpreted to indicate that breakdown of the BBB under these circumstances is transient and reversible, in contrast to the findings reported for the dog. Here Evans blue was given before acute hypertension was induced by intermittent clamping of the aorta, and abnormal staining was observed in the brain in seven out of nine instances. Fluorescein-isothiocyanate was given after the blood pressure was lowered and autoregulation was again functioning. This dye, unlike trypan blue and Evans blue, is bound to blood proteins, and therefore would indicate that the extracellular space is also measured in these experiments (table 2). Thus, not all the fluid taken up is due to a further complication in interpretation of data from experiments on ischemia.

This is brought out clearly by a recent report of Hossman. In the cat, sodium content of cerebral cortex increases after one hour of global ischemia from 240 to 272 mEq/kg dry weight, while potassium decreases from 498 to 458 mEq/kg dry weight. Thus, apparently the increase in sodium does not balance the loss of potassium. However, since the extracellular space is also measured in these experiments, intracellular cation concentrations can be calculated. Increase in intracellular sodium is found to be 133 mEq/kg, about double the loss of intracellular potassium which amounts to 64 mEq/kg. Hossman suggests that the observed cell swelling can be explained by an increase in intracellular osmolality. However, it should be noted that assuming the increase in water content (from 75.9% to 78.3%) to be accompanied by sodium concentration of 140 mEq/kg, an increase of 67 mEq Na/kg dry weight would be expected in these experiments (table 2). Thus, not all the fluid taken up is in equilibrium with plasma and CSF.

Changes in Sodium and Potassium Content of Brain Tissue Associated with Ischemia

Only a few experimental studies of ischemia include measurement of sodium and potassium. When the electrolytes are expressed in terms of wet weight of tissue, net changes and/or degree of dilution brought about by the increased water content are not apparent. Shifts of fluid that occur between intracellular and extracellular compartments give rise to a further complication in interpretation of data from experiments on ischemia.

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More recently, the concept of "breakthrough," i.e., forced dilatation with damage to the BBB of the cerebral arterioles, which are no longer able to constrict in the face of the excessive blood pressure, is advanced as another cause. It seems possible that both mechanisms may play a part in producing the syndrome of hypertensive encephalopathy. Studies in acutely hypertensive animals, for example, may show increases or decreases of CBF; in individual animals, heterogeneous zones including both hyperemia and ischemia can be demonstrated. In the dog, a secondary event but does not appear to play a primary role in the pathogenesis of experimental hypertensive encephalopathy.

The frequent citation of lead encephalopathy as an example of hypertensive encephalopathy is wholly unjustified. The edema of lead encephalopathy is extracellular, protein-rich, and involves mainly white matter. It is associated with other cerebral lesions characteristic of lead poisoning and is most likely due to a direct toxic action of lead on the cerebral blood vessels. The vascular lesion is destructive and clearly different from that seen with experimental hypertensive encephalopathy.

Ischemia as one cause. More recently, the concept of "breakthrough," i.e., forced dilatation with damage to the BBB of the cerebral arterioles, which are no longer able to constrict in the face of the excessive blood pressure, is advanced as another cause. It seems possible that both mechanisms may play a part in producing the syndrome of hypertensive encephalopathy. Studies in acutely hypertensive animals, for example, may show increases or decreases of CBF; in individual animals, heterogeneous zones including both hyperemia and ischemia can be demonstrated. In the dog, a secondary event but does not appear to play a primary role in the pathogenesis of experimental hypertensive encephalopathy.
Shorter periods of hemispheric ischemia in Macaca mulatta result in smaller changes in cerebral cortex potassium content: 15 minutes — no change from control, 30 minutes — decrease of 30 mEq/kg dry weight. At the same time increases in sodium are 35 and 40 mEq/kg dry weight respectively, with 35 and 105 mEq expected in terms of increase in fluid content (140 mEq Na/l).

In contrast to cerebral cortex, the white matter, following 60 minutes of global ischemia (Macaca mulatta), shows no significant changes in sodium and potassium content per unit of dry weight and after 120 minutes of focal ischemia (cat). The decrease in potassium is 40 mEq balanced by an increase in sodium of 39 mEq/kg dry weight.

It is difficult to interpret the electrolyte data on reperfusion following 60 minutes of global ischemia in Macaca mulatta, because of the small number of animals used and the considerable variability of results. In the animals that recover functionally, swelling and sodium content appear to decrease after three hours of reperfusion from a peak at 45 minutes of reperfusion. In animals without recovery, after three hours of reperfusion, loss of potassium amounts to 134 mEq while increase in sodium is 188 mEq/kg dry weight. Water content, sodium, and potassium remain more or less unchanged in the white matter.

A strikingly different picture is presented by isolated canine brain subjected to ischemia. When expressed in terms of dry weight, both sodium and potassium increase in cerebral cortex after 30 minutes of ischemia; there is a further increase in sodium after 15 minutes of reperfusion and then a gradual decrease at 75 and 120 minutes of reperfusion. Potassium follows the same general trend. The increase for 30 minutes of ischemia and 15, 75, and 120 minutes of reperfusion are as follows: Na increase, 95, 263, 114 and 31 mEq/kg dry weight; K increase, 62, 52, 79 and 22 mEq/kg dry weight. Na increase expected in terms of increase of water, 135, 260, 180 and 63 mEq/kg dry weight. Thus, under these conditions, the sum of Na + K (157, 315, 193, and 53 mEq) approaches closest to the expected increase in cation content.

All the experiments described above deal with what may be considered as the early, and at least partly reversible, phase of the ischemic or postischemic state. Severe ischemic insult which causes irreversible changes and necrosis results in massive loss of potassium in cerebral cortex and a gain of sodium which both balances the loss of potassium and accounts for the sodium in the fluid taken up. Thus, at six hours after occlusion of MCA and five hours after a period of hypotension, the loss of potassium in dog cortex amounts to 211 mEq/kg dry weight while the gain of sodium is 449 mEq/kg dry weight. On the basis of the increase in water content (1.86 l/kg dry weight), and assuming concentration in swelling fluid to be 140 mEq/l, one would expect a sodium increase of 261 mEq/kg dry weight. The figures at 24 hours are as follows: gain in water, 266 l, increase in Na, 737 mEq, and loss of K, 324 mEq, all per kg dry weight. The expected increase in sodium, 373 mEq plus sodium expected to replace the potassium (324 mEq) totaling 697 mEq is reasonably close to the actual increase (737 mEq). The changes in white matter are of a different order of magnitude. Five hours after the hypotensive period superimposed on MCA clipping, there is no net loss of potassium, and sodium increases by 49 mEq/kg dry weight. On the basis of increase in water content, an increase of 58 Na mEq would be expected. At 24 hours the loss of K is 44 mEq, the gain in sodium 124 mEq; with gain in water of 0.84 l/kg dry weight, a gain of 118 mEq Na would be expected.

Brunson et al. report that Na content in ischemic tissue of cat (induced by MCA clipping) is double that to be expected on the basis of increased water content. This result agrees well with the data of Shibata et al.

In summary, assuming that the changes observed do not reflect differences in the experimental models used, during ischemia initially (at 15 and 30 minutes), uptake of sodium corresponds to increase in fluid and there is little change in potassium content. By 60 and 120 minutes the tissue loses considerable amounts of potassium but the sodium increase is less than would be expected. In tissue which has sustained severe ischemic damage and becomes infarcted, massive loss of potassium is balanced by gain in sodium, and in addition, an influx of sodium accompanies the influx of fluid.

The isolated canine brain behaves differently inasmuch as net content of both tissue Na and K rises, the sum of the two contributing to the expected cation content of the edema fluid.

**Effect of Lactate on Cerebral Edema**

Several reports suggest that accumulation of lactate may contribute to development of cerebral edema. Gilboe et al. find that anoxic isolated dog brains, on reperfusion, become more edematous than do ischemic ones, and attribute this to abnormally high amounts of lactate which accumulate in the anoxic preparation.

Myers and Yamaguchi report that food-deprived monkeys show no brain injury following ten minutes of cardiac arrest, while fed or glucose-infused animals develop brain edema and other signs of severe brain damage. Again, the accumulation of lactate in high concentrations (> 15—20 moles/g) in the brains of fed or glucose-infused animals is seen as the cause of the damaging effects of the circulatory arrest under these conditions. Similarly, Yamaguchi and Myers find that anoxia does not produce brain edema in food-deprived monkeys, although it injures the nuclear structures of the brain stem, while hypoxia causes cerebral edema and damages structures in the hemisphere. Prolonged hypoxia is shown to increase lactate concentration in brain.

**CBF Changes Secondary to Edema**

In experimental models of MCA occlusion, an additional decrease of CBF takes place hours to days after the occlusion, at times when intracranial pressure increases as a result of accompanying edema. The decreases of CBF probably are related to heightened cerebral vascular resistance, perhaps caused by the increases of intracranial pressure. Lesser degrees of edema, insufficient to bring about rises of intracranial pressure because of compensation by displacement of cerebrospinal fluid and intracranial structures, may cause focal increases of vascular resistance. Secondary decreases of regional CBF such as have been described for other models of edema may result from compression of venous structures or impairment of the reactivity of regula-
Edema can develop in remote, nonischemic parts of the brain when sequential ischemia is severe and the resultant infarct large, \[\ldots\]

**Effect of CBF Restoration on Experimental Edema**

Ischemic cerebral edema produced by experimental MCA occlusion is worsened by anything that intensifies the effect of the ischemia, such as hypoxia or systemic hypotension. Reactive hyperemia likewise may worsen the edema and perhaps cause extension of an infarct if the hyperemia develops within several hours after the onset of ischemia. Hyperemia from reperfusion can lead to extravasation of protein tracers. Presumably hyperemia developing with or without hypertension augments transudation of water and proteins through endothelium in response to the higher intravascular, particularly intracapillary, pressure. However, hyperemia occurring later, i.e., several days after the onset of ischemia, does not produce a catastrophic reaction of massive edema and brain swelling, and may aid in resolution of the cerebral edema that developed earlier. Restoration of CBF to an ischemic zone of the brain may be followed by the restoration or preservation of function of ischemic neurons and a minimization of neurologic disability; alternatively, if there is worsening of ischemic cerebral edema, increased neurologic disability may result.

**Effect of Pretreatment with Parachlorophenylalanine (PCPA) on Cerebral Edema, Neurotransmitter Levels, and Stroke Mortality in the Gerbil**

Carotid ligation in the gerbil produces signs of cerebral infarction in 40% to 50% of animals. The subsequent increase of tissue water in the infarcted hemisphere is associated with a depletion of serotonin (5HT), dopamine (DA) and norepinephrine (NE), presumably due to presynaptic release. Since 5HT may contribute to the process of cerebral edema formation, the effect of pretreatment with PCPA, a tryptophan hydroxylase inhibitor, was evaluated and found to significantly reduce the incidence of cerebral infarction; brain 5HT levels were also significantly lower in the PCPA-treated animals than in the nonPCPA-treated controls. PCPA does not prevent the increase in water content in the brains of animals with infarction. Thus, pretreatment with PCPA does not appear to influence the development of cerebral edema once cerebral infarction becomes established.

**Edema Remote from Lesion**

In experimental models of MCA occlusion, if the subsequent ischemia is severe and the resultant infarct large, edema can develop in remote, nonischemic parts of the brain, even in the opposite hemisphere. The mechanisms involved in the production of remote edema are unknown, but may have a neurogenic basis, or may be related to release of vasoactive agents within the ischemic area of the brain. Remote edema may be one factor in the development of secondary remote ischemia which has been called "diaschisis." Summary of Experimental Studies

1. Experimental observations indicate that cerebral edema regularly accompanies ischemia and infarction. This is demonstrated by biochemical evidence of an increase in tissue volume, an increase in tissue water, or a change in tissue specific gravity, and confirmed by microscopic and ultrastructural appearance.

2. Although details of the development of ischemic cerebral edema vary with the species and experimental technique used to produce ischemia, a characteristic pattern of events can be discerned. Within minutes of arterial occlusion, the water content of the brain begins to increase. This occurs before microscopic or ultrastructural appearance of tissue destruction is evident, although swelling of astrocytic processes may be observed. Subsequently intracellular water (and salt) continue to accumulate, although in some species an increase in extracellular fluid can be observed to begin in less than one hour. Only after several hours of ischemia is the BBB altered to permit extravasation of protein markers and spread of extracellular edema. Although in some areas tissue destruction may lead to loss of capillary structure, the endothelial cells with their tight junctions are markedly resistant to necrosis. Pinocytotic processes, however, are activated in the endothelial cells, leading to transport of protein markers. Thus, while elements of both cytotoxic and vasogenic edema are apparent, the overall process is sufficiently distinctive to warrant designation of *ischemic edema* as a special form of cerebral edema.

3. Areas of immediate research interest can be identified:

a. The possible role of increased intracellular osmolality warrants investigation. If cellular osmolality does increase in ischemia, is this simply the result of proteolysis or are other factors involved? What therapeutic strategy could be employed? Can proteolysis be reduced? Will increasing serum osmolality counteract this change?

b. The reported role of lactate in determining the extent of ischemic damage and edema is important. If lactate per se is one of the pathogenetic factors, can it be controlled?

c. The chief pathway for transport of fluid and serum components into the brain during the extracellular phase of edema seems to be pinocytosis. Pinocytosis may also function in resorption of edema. Are these two processes separately determined? Can the activity of the pinocytotic mechanism be inhibited or enhanced?

d. Cerebral edema invariably accompanies ischemic necrosis. Massive edema can lead to distortion of brain tissue and death. But, what effect does circumscribed brain edema associated with smaller infarcts have upon neurologic function? This question, recently raised, has not been adequately answered.

**Cerebral Edema Associated with Stroke in Man**

**Human Pathology**

Ischemia describes a condition in which there is a diminution in the blood supply to a given organ resulting from func-
The majority of those with an increase greater than 20% as determined by the weight method is the same as that of half of the patients with increases between 10% and 20% and of secondary brain stem hemorrhages were seen. About one-half this degree of swelling can be tolerated. In 19 cases the edema develops slowly, as with a benign tumor, almost showing a mean hemispheric weight increase of 20% (range, 15.0% to 24.3% ± 9.0%). The fixed normal hemisphere weighs 544 gm ± 53 gm. A weight increase greater than 20% was defined by this means. Quantitative figures can be obtained also by comparing the weights of the two hemispheres. Nine patients dying within four days of ictus showed a mean hemispheric weight increase of 20% (range, 15.0% to 24.3% ± 9.0%). The fixed normal hemisphere weighs 544 gm ± 53 gm. A weight increase greater than 20% occurring rapidly generally is fatal in the human, but when the edema develops slowly, as with a benign tumor, almost twice this degree of swelling can be tolerated. In 19 cases with an acute weight increase of less than 10%, no instances of secondary brain stem hemorrhages were seen. About one-half of the patients with increases between 10% and 20% and the majority of those with an increase greater than 20% showed these hemorrhages. The time course of the swelling as determined by the weight method is the same as that reported with linear measurements. Atrophy was demonstrable after one month. During the intermediate period between maximal swelling and demonstrable atrophy, histologic evidence of edema often can be shown. The persistent edema in this period may be counterbalanced by the onset of atrophy, the net result being a hemispheric weight which does not differ from that of the opposite hemisphere. The earliest recognizable histologic change in ischemic infarction is a spongy enlargement of the neuropil and pericapillary spaces. Accompanied later by signs of necrosis in neurons in the form of a homogeneous cytoplasmic eosinophilia. Acute inflammation in anemic infarction is minimal and follows a time course similar to that of the gross swelling. In the acute phase of anemic infarction, it is often impossible to accurately define the extent of the lesion by conventional histologic methods. When this can be done, the changes in the adjacent tissue are usually minimal and of questionable significance. A small amount of proteinaceous fluid is usually demonstrable in definite areas of infarction in the acute phase but only rarely does the adjacent white matter show a massive protein-rich extracellular edema.

It would seem that ultrastructural studies might provide a means for both defining the extent of the infarct and determining the nature of the changes occurring in the adjacent tissues. The question has not been resolved by ultrastructural studies performed on human brains perfused within 30 minutes of death, nor has it been clarified, as far as we are aware, in experimental studies. Failure to accomplish this probably relates to the tremendous problem of tissue sampling which would arise in any such attempt and to the difficulty of preparing central white matter for electron microscopic studies. Since ultrastructural changes observed with ischemia are similar to artifactual changes that occur postmortem or at biopsy, satisfactory ultrastructural studies of cerebral infarction in man are not possible with present techniques.

While morphologic demonstration presents difficulties, it is entirely reasonable to suppose that if fluid has leaked into an infarcted area, it will also pass into the adjacent tissues. Chemical information derived from experimental studies suggests that this is the case. With the exception of the isolated canine brain, tissue necrosis is associated with a decrease of tissue potassium measured on a dry weight basis. One may generalize from studies reported on edematous tissue in the cat, in the dog with cryogenic injury and in the lead-poisoned rat, that this decrease in tissue potassium is not found in white matter in vasogenic edema. Of the references cited on chemical changes in experimental ischemic brain injury, the only one in which the claim is made that the tissue being analyzed lies outside (adjacent to) the area of infarction is in the dog with MCA occlusion. Forty-eight hours after removal of the clip, a statistically significant increase in sodium and water was seen in both white and gray matter. In neither white nor gray matter was this accompanied by a statistically significant decrease in tissue potassium measured on a dry weight basis. These observations support the view that edema occurs in the white matter adjacent to an infarct and probably also in the gray matter. To designate this edema as vasogenic would require demonstration that the edematous tissue contains blood proteins.
Clinical Hypertensive Encephalopathy

Hypertensive encephalopathy is defined medically as a syndrome associated with malignant or severe hypertension. It is characterized by headache and neurologic symptoms and signs such as decreased level of consciousness, seizures, and transient focal neurologic deficits and is accompanied by retinal vascular spasm and often by papilledema. If untreated, the condition may progress to death. With improved medical treatment of hypertension, the syndrome is becoming rare.

Hypertensive encephalopathy is a disease which, paradoxically, is better characterized pathologically in the experimental animal than in the human. This point is well illustrated by reference to a recent book on the pathology of cerebral blood vessels. In the section on hypertensive encephalopathy, the disease is defined clinically and this is immediately followed by a description of experimental models without intervening discussion of the changes expected in the human at autopsy. In the index of Minkler's three-volume textbook of neuropathology, the only listed reference to the subject consists of a few paragraphs in the chapter on renal disease.

It has been reported that the centrum semiovale of the brains of hypertensive patients has a higher than normal water content. Histologically, myelin pallor and regressive changes in astrocytes are seen. The authors interpret these findings as degenerative signs and indicative of old cerebral edema. In none of the patients was there a clinical diagnosis of hypertensive encephalopathy.

A study of the brains of 12 patients with clinical symptoms suggestive of hypertensive encephalopathy has been published. Only two of the cases are reported in detail, and both show cerebral swelling with tonsillar herniation. In one patient there is an acute anemic infarct and in the other a hemorrhagic infarct. Of the remaining ten cases, two show massive hemorrhages. Focal areas of softening or glial scarring are occasionally found. These data support the view that the brains of hypertensive patients may be edematous, but not that cerebral edema is the cause of hypertensive encephalopathy.

The view that hypertensive encephalopathy in the human is primarily associated with severe diffuse cerebral edema can be documented only by reference to the literature of the last, and the early part of the present, century and one cannot help feeling uncomfortable about this. It must be admitted, however, that the lack of publications may reflect improved methods of managing hypertension. Since 1940 the incidence of hypertensive encephalopathy has markedly decreased.

In the years 1954 to 1963, the clinical diagnosis of hypertensive encephalopathy was made 43 times in a large midwestern medical center. However, when strict clinical criteria were applied and when patients with gross cerebral lesions and cerebrovascular insufficiency were eliminated, only three patients in the group were considered to be examples of true hypertensive encephalopathy. Even if the presence of severe cerebral swelling in hypertensive encephalopathy is conceded, the question of the relative role of infarction in such cases still remains and can only be resolved by careful histologic studies of the brains.

Neurological Syndromes Secondary to Edema

Massive Infarct with Herniation

As in experimental models of acute cerebral ischemia, edema secondary to ischemic cerebral infarction in humans is maximal two to four days after onset of infarction. The development and resolution of edema may be manifested by transient worsening of a mild or moderate neurologic deficit that subsequently improves. However, ischemic cerebral edema is unlikely to be responsible for a sudden massive increase in neurologic deficit two to five days after the onset of an ischemic process that has apparently stabilized; a situation such as this is more likely to be related to further embolization or thrombosis.

More common, perhaps, than transient worsening of a neurologic deficit are a progressive impairment of consciousness and an increasing severity of a neurologic deficit related to edema in and around an extensive infarct of a cerebral hemisphere. Massive swelling of one hemisphere most often occurs with occlusion of a major vessel when there is an anomaly of the circle of Willis or when collateral circulation is reduced for some other reason. It is apt to be associated with an increase of intracranial pressure and a side-to-side pressure gradient, may cause shifts of midline structures, tentorial herniation, and eventual death. If tentorial herniation does not occur, the patient may survive. Unfortunately, such patients usually are left with severe deficits.

Cerebellar Hemorrhage and Infarction

During the past decade, treatable syndromes of acute brain stem compression secondary to cerebellar hemorrhage or cerebellar infarction have received specific attention. The beginning of cerebellar hemorrhage is heralded by headache, dizziness, vertigo, severe and repeated vomiting, and inability to stand or walk. On examination, the most common clinical findings are truncal and extremity ataxia and nystagmus; other symptoms include dysarthria and nuchal rigidity. Usually strength is well preserved, although Babinski signs may be present. As brain stem compression develops, paralysis of conjugate lateral gaze, peripheral facial weakness, pupillary changes, impaired consciousness, and, finally, decerebrate posturing occur. Recognition of the condition within the first hours after hospital admission may permit lifesaving neurosurgical intervention. Pathologically a cerebellar hemorrhage acts as a mass lesion producing cerebellar herniation as well as direct brain stem compression. Information is lacking as to whether edema adds to the clinical picture. In contrast, the brain stem compression occurring with cerebellar infarction is due to swelling in and around the infarct. The initial manifestations, including headache, drowsiness, dizziness, nausea and vomiting, gait ataxia, dysmetria, dysarthria, and nystagmus may be similar to the clinical picture of cerebellar hemorrhage. Other findings such as diplopia, ocular bobbing, and skew deviation may be present. In many untreated cases, a steady deterioration occurs with death supervening on the third to sixth day. Prompt surgery is usually advised; but, in some instances, medical therapy for edema (mannitol and steroids) appears to stabilize the patient and permit spontaneous recovery.

Cerebellar hemorrhage and infarction both constitute
medical emergencies. In the past, angiography coupled with ventriculography has been required to confirm the diagnosis and demonstrate the size of the lesion and the extent of brain stem displacement. The procedure of choice now is computed tomography, which is capable of giving a more precise delineation, permits identification of hemorrhage, and can be repeated as frequently as necessary.

Procedures for Diagnosing Edema in Stroke

Radiographic contrast procedures, such as angiography or pneumoencephalography, may show the effects of local or generalized cerebral swelling caused by edema. The mass effects are difficult to distinguish from those of other cerebral lesions, and an appropriate interpretation of contrast studies depends on evaluation of the clinical history and neurologic findings.

An important recent development, computed tomography, particularly if used in conjunction with radionuclide scanning and enhancement, holds promise as a method for delineating edema during life. This promise has not yet been completely fulfilled in the stroke patient. Nevertheless, these methods are of sufficient importance to warrant detailed description.

Radionuclide (RN) Scanning

The radiopharmaceutical most frequently used in emission scanning of the brain is technetium-99m. The image produced by this technique usually consists of a photograph of the entire head but tomographic cuts can also be obtained. The image size can be measured by planimetry and a quantitative estimate of the tissue change made by comparing its density to the vertex density. With appropriate instrumentation, the image can also be transformed into a computer print-out providing quantitative figures. This technique has been used to study cerebral circulation in the human. With computed emission tomography, the edema adjacent to a brain tumor has been quantitatively determined. In the same patient, the CBV also was measured using technetium-labelled red blood cells, and was found to be diminished in the edematous tissue. Following steroid therapy, the edema declined and the blood volume increased.

The pertechnetate ion (Tc-O4) is weakly bound to serum protein, but is bound more firmly in the human than in rodents. In normal rats, 132 minutes after injection of technetium-99m, its loss from the blood stream is tenfold relative to serum protein and its distribution in both scalp and brain is not the same as that of serum protein. Under abnormal conditions, in the cat with occlusion of the MCA, the uptake of Tc-O4 and of albumin have a parallel course in the first week. In the dog with a cryogenic cerebral lesion, the distribution ratio of plasma to edema fluid is the same for Tc-O4 and albumin four hours after injection. These observations support the view that the abnormal image in RN scans is related to protein exudation. However, the same ratio is found for the chelated form of technetium and for chloride. It appears that the uptake of Tc-O4 and of serum protein represent the same phenomenon, i.e., breakdown of the BBB, but are not necessarily causally related.

Anemic cerebral infarction appears not to be a promising area in which to study cerebral edema by means of the RN scan. To begin with, the technique is applicable in only about one-third to one-half of the cases, since the remainder have normal scans during the period of maximal swelling. Moreover, the peak incidence as well as the peak intensity of positive scans occurs two to four weeks postictus, while gross swelling is no longer demonstrable after two weeks. The positive image may be related to the extravascular distribution of the indicator through damaged BBB and its sequestration by abnormal tissues. Increases of blood volume may also be important, particularly weeks to months later when there may be no neovascularization associated with healing. In experimental infarction in the cat, the time course of the water increase and the Tc-O4 uptake in infarcted tissue are parallel for the first two days but after that the water uptake declines while the Tc-O4 uptake persists.

Among patients with blood in the spinal fluid, the number showing positive RN scans during the edema period is larger by one-third to about one-half. Examination of the spinal fluid, however, cannot differentiate a small intracerebral hemorrhage from a hemorrhagic infarct. In a series of stroke cases studied by both CT and RN scans, seven instances of intracerebral hemorrhage were diagnosed by the CT scan. Of these, only two showed a positive RN scan and the pattern of the latter was indistinguishable from that seen in anemic infarction. It thus appears that cerebral hemorrhage is not promising as a disease entity for studying cerebral edema with the RN scan.

Computed Tomography

The general principles of computed tomography were covered in a previous report in this series. Although most of the published data have been obtained with the instrument manufactured by the Electric Musical Instruments Company of Great Britain, this is not the only equipment that can produce these scans. The abbreviation "EMI scan" is phonetically pleasing and will undoubtedly continue to be used in the clinic, but "CT scan" is the preferred term. Quantitative data from the CT scan are expressed as linear coefficients of attenuation. Since all matter absorbs and scatters radiant energy, an attenuation coefficient will always be positive. In the scale used with the EMI scanner, a 1% change relative to the linear attenuation coefficient (μw) of water corresponds to 5 EU (EMI units). This is also called the attenuation number. Since other tomographic scanning instruments may use the same convention, "EU" is not an appropriate designation. It has, therefore, been suggested that this unit (the attenuation number) be represented by the symbol "h" in honor of Godfrey N. Hounsfield, the inventor of the EMI scanner. This usage is adopted in the present review.

By convention, water is assigned a value of 0 h and any substance, such as air or fat, with a μw less than that of water will have a negative h value. The attenuation number of normal brain has been reported to vary from 12 h to 30 h; the values for white matter are lower than those for gray matter. The standard deviation of the attenuation number (inherent in methodological variation), as determined by measurements of water in a phantom, is 2.5 h.

Attenuation of x-rays by matter takes place at the atomic level rather than the molecular and is a function of the
The density of edematous brain is reported as varying from 7 h to 17 h. These values were obtained from analyses of foci of diminished density surrounding edema-producing lesions such as tumors and hemorrhages. A more recent study in which the postmortem brain is compared with the antemortem scan reports that the foci of diminished density surrounding hemorrhage, tumor, and abscess correspond to histologically recognizable edema. In this study, which also involves experimental work with the rhesus monkey, the mean density of the edematous tissue ranges from 11.1 h to 16.4 h. In a biopsy study, where the presence of edema was chemically verified, a mean of 12.1 h with a range of 9.5 h to 13.7 h, is reported. In an in vitro study of formalin fixed brains with hemorrhages and with metastatic tumors, a mean density of 12.6 h with a range of 8.3 h to 16.6 h is found. This tissue also shows an increased water content and a diminished specific gravity. It can, therefore, be concluded that in CT scans the areas of diminished density seen surrounding hemorrhage, tumor, and abscess correspond to histologically recognizable edema.

Isolated human white matter has an in vitro attenuation number of 15.0 h and a dry weight of 29.3 gm%. Since attenuation is linearly related to concentration, and water = 0 h and 0 dry mass, then a change in dry mass of 1.0 gm% will produce a change in attenuation number of 0.5 h (fig. 1). Vasogenic edema is primarily a disease of white matter. The edematous white matter surrounding tumors has a dry weight of 20.1 gm%. This gives for edematous tissue a predicted attenuation number of 10.4 h, assuming that the change is due purely to dilution. The actual measured attenuation numbers for two samples of isolated edematous tissue are 8.8 h and 11.1 h.

Because the in vivo attenuation numbers cited are generally higher than the predicted value of 10.4 h, one must consider the possible reasons for this discrepancy. Since isolated gray matter has an attenuation number of 19.1 h, one reason might be the inadvertent inclusion of uninvolved gray matter in the CT scans. Inclusion of 50% uninvolved gray matter in the scan would give an attenuation number of 14.8 h. That measurements from the human CT scan are in error by so much is unlikely, but this could be an important factor in those from the rhesus monkey. At least three additional factors will influence the attenuation number of edematous cerebral tissue. These are changes in electrolytes, proteins, and lipids. While it may be dangerous to draw firm conclusions at this time, the problems can at least be defined.

The relationship is linear between the concentrations of sodium and potassium chloride in the range of 25 to 150 mEq/kilo and the in vitro attenuation numbers ranging from 25 h to 150 h. The slopes (and 95% confidence limits) are: for sodium chloride, 0.0449 ± 0.0131 and for potassium chloride, 0.0742 ± 0.0168. Thus, changes in tissue potassium will have a considerably greater effect on the attenuation number than will changes in tissue sodium.

Biopsy studies of the edematous white matter surrounding brain tumors show a sodium concentration of 88.3 mEq/kilo wet weight of tissue. The value for normal white matter is 60.0 mEq/kilo wet weight. Insofar as edema fluid has a dry mass, this is included in the measured dry mass of edematous tissue and influences the attenuation number according to the slope of the line describing the dilutional effect (fig. 1). But the elements added in the dry mass of the edema fluid increase the predicted attenuation number as well in proportion to their own attenuation numbers. An increase in tissue sodium of 2.83 mEq/kilo will increase the attenuation number by 0.12 h by virtue of its own attenuation number but 0.1 h of the increase is included as part of the mean change thus giving a net increase of 0.02 h (0.12 h − 0.1 h), which is negligible.

There is a linear relationship between the concentration of human serum albumin in the range of 0.5 to 6.0 gm% and the in vitro attenuation number. The slope of this line is 1.1 h. Edematous white matter in the monkey with a cryogenic le-
The albumin-globulin ratio in edema fluid is 1:6. Assuming that the globulins have the same effect as albumin on the attenuation number, the net increase in attenuation number in this tissue due to the plasma proteins is 1.5 h. This should not be ignored.

The attenuation number of gray matter is greater than that of white. This is reflected in the tissue specific gravity which is greater in the former than in the latter, but not by the dry mass which is greater in white than in gray matter. It has been suggested that the lower attenuation number of white matter relative to gray is the result of the higher lipid content of the former. Normal human gray matter has a total lipid content of 5.7 gm% and white matter 17.8 gm%. If the above proposition is correct, then an increase in total lipid of 12.1 gm% has reduced the attenuation number by 4.1 h, or a 1 gm% change in lipid is associated with a 0.3 h change in attenuation number. This will have been produced by a mixture of compound lipids with a composition as indicated in figure 2. Projecting the line to the y intercept gives an attenuation number of 21.0 h for lipid-free brain.

Cholesterol has a calculated attenuation number of 11.9 h. The phosphorus content of the phospholipids makes it doubtful that their attenuation number would be negative. Therefore, if the lower attenuation number is to be attributed to the complex lipids indicated, it would necessarily be due to the galactolipid fraction. Since the compound lipids of the brain apparently have a net negative attenuation number, and assuming that the attenuation number of the class as a whole is approximated by the value in figure 2, the effect of dilution will be to increase the attenuation number by 1.9 h. This increase will not be part of the decrease shown in figure 1, since the assumption in drawing this line is that dilution will only decrease the attenuation number.

Another lipid factor which should be considered is the transformation of compound into neutral lipids since these should have a lower attenuation number than the compound polar lipids. Free lipid is sometimes histologically demonstrable in the white matter surrounding tumors and this tissue contains esterified cholesterol. Peritumor edematous white matter has a lipid content of 13.40 gm% and 1.19 gm% higher than the predicted value for dilution. The in vivo attenuation number of human adipose tissue is —42 h, but this tissue contains protein and electrolytes in addition to fat. The calculated attenuation number of glycerol trioleate is —60.5 h. Assuming that the transformed lipids have a similar density and attenuation number, 1.19 gm% of lipid will produce a 1 h decrease in attenuation number by virtue of its own attenuation number and an increase of 0.8 h from its dilutional effect, giving a net decrease of 0.2 h. This may be ignored.

While it is known that the edema fluid surrounding tumors contains serum proteins, their concentration has not, to our knowledge, been determined. The reported mean attenuation numbers for peritumor edematous tissue are 12.1 h and 11.8 in vivo and 8.8 h and 11.1 h in vitro. The fact that these figures are generally higher than the 10.4 h predicted for dilution (fig. 1) suggests that the serum proteins play a role in producing this higher figure for dilution. Histologic studies indicate a much higher protein concentration of the edema fluid associated with hemorrhage and abscess than with tumor. The corresponding attenuation numbers, 15.9 h for hemorrhage and 15.4 for abscess, are also higher.

In a study of the edematous tissue from five intracerebral hemorrhages and two metastatic lesions, a significant correlation was not found between the dry mass and attenuation number. There was, however, a linear correlation between the dry mass and the attenuation number of normal white matter. The failure to obtain a linear correlation with edematous tissue may be related to the facts that the brains used for this study were fixed in formalin, and that in vitro CT scans were employed. On the other hand, it could also reflect varying amounts of neutral lipid in the edematous tissue and differences in the concentration of protein in the edema fluid. There is need for studies of individual cases to correlate changes in water, electrolytes, lipids, and plasma proteins in fresh tissue and in vivo attenuation numbers.

In the first week after nonhemorrhagic infarction, the CT scan is positive in 50% of patients and equivocal in 31%. In the first 24 hours after ictus, a positive le-
sion appears as an irregular nonhomogeneous area of reduced density (6 h to 14 h). At the time of maximal swelling (1 to 3 days), the majority of demonstrable lesions are homogeneous and half of them are well defined. This pattern suggests that the edema occurs principally within the infarct. In this time period, about one-third of the patients show, in addition to the lesion itself, CT evidence of a mass effect.

In terms of absolute values, there is no difference in the attenuation number of the infarct for the following time periods: less than 24 hours, one to three days, and four to six days. These values are 1.0 h to 10.7 h lower in the infarcted area than in the homologous area of the opposite hemisphere. At the periphery of the infarct, the magnitude of this difference remains the same at all time periods, but in the center of the infarct (within white matter), the difference increases from 5 h to 10 h between the first two time periods. These relatively large decreases in the attenuation number of white matter in the first week postictus suggest that neutral lipids are being formed in rather considerable amounts. This matter should be explored.

In hemorrhagic infarction, patchy areas of decreased and increased density are evident, with a peak absorption appreciably less than that of a parenchymal hematoma. A correlative study of the CT scan, water content, and specific gravity in formalin-fixed brains of stroke patients included acute, subacute, and old lesions, as well as hemorrhagic infarcts. As might be anticipated, there is no correlation between attenuation numbers and the water content of the tissues. At the 5% level of probability, the mean water content of the infarcted tissue is higher than normal and the mean attenuation number lower. The mean specific gravity of cortical infarcts, but not of white matter infarcts, is lower than normal. Since old lesions are included, free lipid may well play a significant role in these figures.

Because extravasated blood appears as an area of greater density, CT scanning is superior to any other technique in demonstrating the presence and site of hemorrhage within the brain. The density is directly proportional to the hematocrit; clotting is unnecessary. Areas of diminished density adjacent to that of the hemorrhage correspond to foci of edema. In this condition, unlike infarction, the primary lesion and the edema are spatially separated. The edema, as judged by this method, is minimal in the first two days after ictus and maximal after several days. In some instances, it seems to persist for 3 to 4 weeks.

If the boundaries of the primary lesion can be defined, the cerebral edema can be quantitatively measured by means of the CT scan. Simple inspection of the cathode ray image is one method of doing this. Using this method to study the effects of combined chemotherapy and radiation on primary brain tumors, it is reported that the edema diminished in five of the 13 patients who showed clinical improvement, but in only one of 32 who showed clinical deterioration. The area of edema can also be measured by planimetry. Using the latter technique, peritumor edema was reported to decrease over a period of weeks following treatment with steroids and furosemide. A third method consists of measuring with computer-assisted techniques the density of concentric rings around the lesion. The CT scan provides the means to measure cerebral edema in the living patient; the techniques require further improvement.

Many disease processes in the brain, such as an old stroke, are relatively stable. In these cases a brain obtained at autopsy can be safely compared with a CT scan obtained several weeks or months earlier. The same is not true for the cerebral swelling associated with acute stroke. With anemic infarction, this occurs over a one-to-three-day period and by the end of the second week is not grossly demonstrable; the edema associated with hemorrhage follows a similar time course. In order to make meaningful correlations between histologic patterns and the CT scan in these cases, the scan must be obtained shortly before the patient's death. The situation in which this is possible happens infrequently. The problem could be solved by the use of CT scans of postmortem material. The postmortem CT scan of the brain in situ shows an increase in attenuation number of the CSF and of the gray matter but no change in white matter. These findings are in keeping with controlled studies of the edema associated with cryogenic lesions in the cat in which it was shown that during the postmortem period, cortical water and sodium increase relatively rapidly and potassium decreases. Normal and edematous white matter show little change. As mentioned above, a CT scan can also be obtained from the removed brain placed in a phantom. Difficulties in positioning can be overcome by using gelatin rather than water as the supporting medium. Absorption coefficients for fresh edematous brain tissue as well as for various tumors are very similar in vivo and in vitro.

CT scans are reported for the baboon and can be obtained easily in the rhesus monkey. The means for performing controlled experiments with the ordinary EMI scanner are thus available and should be pursued.

Enhanced Computed Tomography

The intravenous infusion of iodinated contrast material is an important adjunct to computed tomography. The absorption values of normal and pathological tissues are increased in proportion to vascularity, vascular permeability in relation to time, and the blood iodine level. It is to be anticipated that the problems of delivery of the indicator to the tissue and the results will be similar to those of the RN scan. Thus, vascular malformations and malignant tumors show marked enhancement, low grade gliomas less enhancement, and acute strokes often enhance poorly.

The linear relationship existing between the attenuation number measured in vitro and the iodine concentration is such that 100 gm% iodine equals 13 h. Hypaque 60 M in a dose of 1.2 ml/kg body weight produces a plasma level of about 300 gm% of iodine. The use of iodinated contrast media rarely results in the visualization of major blood vessels in normal patients. In glioblastomas, the contrast media is not retained in the blood vessels.

Three patterns of enhancement as a function of time have been described in cerebral lesions. The first of these is a high initial increase in attenuation of about 15 h, followed by a sharp decline within 15 minutes, with little residual attenuation at three hours. This type is believed to define a vascular lesion in which the blood vessels are relatively im-
permeable. It is seen with meningiomas and acoustic neuromas. The second pattern shows the same initial increase and decline but with high residual attenuation at three hours. This is believed to typify a vascular lesion in which the blood vessels are relatively permeable and is seen with arteriovenous malformations. The third pattern consists of a rise in enhancement over the first 15 minutes, followed by a slower rise during the next hour to a maximum of 3 h to 7 h. This is seen with gliomas. Residual attenuation may or may not remain at three hours, presumably depending upon the degree of vascular permeability in a given tumor.

Both normal and edematous tissue show an enhancement of 2 h to 3 h in the first 15 minutes with no essential change at three hours. The initial values are lower for the edema group. The primary lesions in the edema group are: three gliomas and two meningiomas. One glioma shows a pattern indistinguishable from that of the edema group. The fact that the pattern of the edema group is the same as that of the normal is in keeping with the view that the blood vessels in the edematous area are not hyperpermeable and that the source of the edema fluid is the lesion itself.

A single case of cerebral infarction shows a pattern similar to that of the edema group, and intracerebral hemorrhage has been reported to show no enhancement.203

Cerebral Blood Flow, Intracranial Dynamics and Metabolic Changes Accompanying Cerebral Edema

Experiments on edema, primarily of cerebral white matter, produced in rats by administration of triethyl tin sulfide, have shown that CBF per unit brain weight is reduced before the intracranial pressure increases as cerebral tissue volume expands by imbibition of water.188 When making in vivo measurements it is important to recognize that an increase in intracranial pressure may be due to: (1) increased volume of brain tissue as a result of increased fluid content alone (cerebral edema) and/or (2) an increase in the other intracranial contents such as intracranial blood volume (CBV) or cerebrospinal fluid volume (CSFV).184 Accompanying the restoration of blood flow following brief occlusion of the blood supply to the brain, intracranial pressure may become temporarily increased due to reactive hyperemia without cerebral edema; but if the interval of cerebral ischemia is prolonged, progressive cerebral edema results.28 44 When cerebral edema occurs, cerebrospinal volume and cerebrovascular pressure increase, cerebrovascular resistance likewise increases, while CBV and cerebral perfusion pressure both decrease. Cerebral edema may initially be associated with an increased cerebral oxygen consumption (CMRO₂) despite slowing or suppression of EEG. It has been suggested that this situation may be due to uncoupling of oxidative phosphorylation, since known uncouplers, such as 2,4-dinitrophenol, also consistently produce cerebral edema.44

In patients with cerebral edema following head injury or stroke, generally similar patterns of blood flow and intracranial dynamics are observed.44 205 When hyperosmolar agents such as mannitol or glycerol are infused, regional CBF and CBV increase, while CSF pressure becomes decreased, despite the fact that in many cases the CSF or intracranial pressure is not elevated.205 206 As the CSF pressure decreases, the EEG improves and, in patients with cerebral infarction. CMRO₂ decreases as the EEG improves.207 209

In experimental animals, as CSF pressure rises, the cerebral vessels dilate, cerebrovascular resistance decreases, and CBF is maintained constant, a phenomenon termed "CSF pressure autoregulation." Ultimately, this autoregulatory process is impaired, possibly due to development of cerebral edema210 and CBF becomes reduced.211 212 Eventually, when intracranial pressure approaches arterial pressure, a pressor response occurs as a result of ischemia of the brain stem (Cushing phenomenon). Ultimately, when intracranial pressure equals arterial pressure, cerebral perfusion pressure becomes zero and CBF ceases.211 213 However, the perfusion pressure of ischemic brain tissue may be less than that of nonischemic brain tissue and perfusion may cease before intracranial pressure equalizes systemic blood pressure.

Effects of Cerebral Edema on EEG and Cerebral Evoked Responses

While many publications deal with the vulnerability of EEG and evoked responses to cerebral ischemia, hypoxia, brain trauma, and cerebral compression by mass lesions, the assumption that these changes are causally related to, rather than associated with, edema remains unproved. Nevertheless, when cerebral edema is present, abnormalities of the EEG and evoked responses are usually present also.

Some of the best evidence that brain edema is associated with EEG abnormality is found in studies of cerebral edema experimentally induced by administration of triethyl tin sulfide.182 Likewise, in experimental cerebral edema caused by cerebral ischemia, the EEG is consistently abnormal in those animals with increased intracranial pressure but not in those whose intracranial pressure is normal.44 These studies suggest that cerebral edema itself does not alter either the EEG or behavior unless compression of the microcirculation reduces regional blood flow. For example, in experimental groups of acute or chronic animals exposed to triethyl tin but with normal intracranial pressure and without reduction of CBF below 23.1 ml/100 gm brain/min, the EEG appears normal. The only animals showing both abnormal EEG and behavior are those in the acute group with increased intracranial pressure as well as edema. These animals are obtunded, show generalized slowing of the EEG, and the CBF is reduced to 13.2 ml/100 gm brain/min. Animals in the acute group with normal intracranial pressure are alert and have normal EEG, but are paretic.

This correlation of EEG abnormality with reduction of cortical flow is in good agreement with experimental studies of occlusion of the MCA in the baboon188 which indicate that cortical evoked potentials are not altered until regional flow values are below 16 ml/100 gm brain/min, and in the cat,188 activity of individual neurons has not been observed below 18 ml/100 gm brain/min. Likewise, the EEG becomes altered or abolished in man when regional CBF is lowered below 18 ml to 20 ml/100 gm brain/min.114 115 The alteration of cerebral evoked responses has been correlated with ultrastructural changes in the synaptosomes compatible with release of neurotransmitters.124

Studies of focal vasogenic edema in the cat117 also indicate that edema per se is not responsible for slowing (delta waves) in the EEG. These studies suggest that disturbances of the mesencephalon and diencephalon secondary to brain
swelling are responsible for delta waves seen in this preparation.

Treatment of Cerebral Edema in Stroke — Experimental and Clinical Findings

Cerebral edema with increased intracranial pressure and transtentorial herniation with consequent brain stem compression are among the most common causes of death within the first week following cerebral infarction.\textsuperscript{144} It is generally agreed that the risk of death after cerebral infarction and intracranial hemorrhage is greatest during the first week, and if the patient is stuporous or comatose the prognosis is poor.\textsuperscript{218} Following cerebral infarction, maximal cerebral edema occurs about the fourth day and declines thereafter so that by the fourth week it is slight or absent.\textsuperscript{142}

Hyperosmolar Agents

Although much has been written about the effects of hypertonic solutions, including glucose, sucrose, urea, mannitol, and glycerol in increased intracranial pressure, relatively little work has been carried out concerning the treatment of cerebral edema associated with stroke. Since the brain responds like a modified osmometer, an osmotic gradient between brain and blood must be produced to result in a water shift that reduces brain volume and intracranial pressure.\textsuperscript{4} Osmotic gradients obtained by the parenteral administration of hyperosmolar solutions tend to be shortlived because all the solutes mentioned, after a few hours' delay, tend to enter normal brain and when the plasma level falls, there is the possibility of a rebound increase of intracranial pressure. It has been shown in the cryogenic model that hypertonic solutions dehydrate the normal rather than the edematous brain.\textsuperscript{8, 90, 91, 916} On the other hand, in the ischemic-anoxic model and in experimental triethyl tin edema it has been shown that abnormal brain tissue is dehydrated by hyperosmolar agents.\textsuperscript{8} In clinical studies of stroke, the zones of ischemia rather than the normal areas appear to respond first to administration of hyperosmolar agents.\textsuperscript{200}

Glycerol

Cantore and associates\textsuperscript{206, 217} first described the successful use of glycerol in reducing cerebral edema and intracranial pressure associated with brain trauma and brain tumor. Tourtellotte et al.\textsuperscript{222} reviewed the literature concerning the potential long-term nontoxic effectiveness of glycerol in reducing cerebral edema and confirmed its favorable therapeutic action without rebound.\textsuperscript{206} The clinical effectiveness of glycerol in reducing cerebral edema and increased intracranial pressure without rebound, particularly in patients with cerebral infarction, was reported by Meyer et al.\textsuperscript{244} and later confirmed in some controlled trials including a double-blind evaluation of glycerol therapy in acute cerebral infarction.\textsuperscript{286, 287} Inconclusive results of a clinical study of glycerol treatment in acute stroke are reported by Larsson et al.\textsuperscript{288} who treated their patients within the first six hours of stroke onset. Both groups improved, but improvement was no greater in the glycerol-treated cases than in those treated with intravenous 10% glucose. Unfortunately, for reasons not stated in the study, the authors were unable to produce the hyperosmolality of the serum expected following the glycerol infusion.\textsuperscript{228}

Glycerol is administered orally in doses of 1.5 gm/kg body weight per 24 hours, or intravenously dissolved in isotonic saline or glucose as a 10% solution, in doses of 1.2 gm/kg body weight per 24 hours. It must be given cautiously to patients with diabetes or in dehydrated states since it has gluconeogenic properties and, if such cases are not followed closely, may elevate serum glucose to dangerously high levels with the possibility of producing a state of nonketotic hyperosmolar hyperglycemia.\textsuperscript{290} If given intravenously, the concentration should not exceed 10% and the rate of infusion should not exceed 500 ml over a four-hour interval, since, if it is given more rapidly, hemolysis may result.\textsuperscript{200}

In patients with brain edema, glycerol reduces intracranial pressure as well as dehydrates normal brain tissue by its hyperosmolar action and, of all available hyperosmolar agents, shows the least equilibrium concentration in the brain with little or no rebound rise in intracranial pressure, since after crossing the BBB, it is metabolized by the brain.\textsuperscript{206, 217} In patients with recent ischemia or hemorrhagic infarction, intravenous infusion of 10% glycerol in normal saline increases serum glycerol levels to 33.1 millimols, reduces CSF pressure, and increases regional CBF and CBV in the ischemic zones with a redistribution of blood from the hyperemic to the ischemic zones.\textsuperscript{206, 217} suggesting that glycerol may act directly on ischemic brain edema. These intracranial hemodynamic and hydrodynamic changes are accompanied by EEG and clinical evidence of improvement.\textsuperscript{200, 217}

Despite the increase in CBF following glycerol infusion in patients with acute cerebral infarction, in those diabetics with stroke, hemispheric oxygen consumption and respiratory quotient decrease, while glucose consumption either remains constant\textsuperscript{206} or increases.\textsuperscript{206} CSF glycerol levels increase and an uptake of triglycerides and fatty acid by the brain is noted for the first time. The infarcted brain releases inorganic phosphate (Pi) into cerebral venous blood; glycerol therapy causes the brain to take up Pi. The clinical, hemodynamic, and metabolic results, taken together, suggest that glycerol has a beneficial metabolic as well as hyperosmolar effect on ischemic brain, improving oxidative metabolism and lipid synthesis.

Dextran 40

Reports indicate that following experimental cerebral infarction in animals,\textsuperscript{244, 245} dextran 40, a low molecular weight form of dextran, temporarily improves flow in ischemic areas of the brain. However, any beneficial effects tend to be evanescent and are ascribed to improved rheological properties of the blood rather than to a reduction of cerebral edema. Likewise, intravenous therapy with dextran 40 is reported to be of possible benefit in patients with acute cerebral infarction, but here again any favorable effect is ascribed more to disaggregation of platelets, with better flow to the ischemic brain, than to reduction of cerebral edema.\textsuperscript{244, 245} Mortality of patients in the acute stage of severe stroke is significantly reduced, although survivors are severely disabled.\textsuperscript{244}
Mannitol

Intravenous administration of mannitol, usually given as a 25% solution, has been shown to reduce cerebral edema and intracranial pressure, and to increase CBF in patients with cerebral edema due to trauma, cerebral infarction, and hemorrhage. In patients with cerebral edema caused by trauma, but not in those with cerebral infarction, the cerebral metabolic rate for oxygen also increases. A rebound increase of intracranial pressure above the pretreatment level may occur when the mannitol solution is discontinued. Intravenous administration of hyperosmolar mannitol plus dexamethasone does not appear to benefit patients with stroke when compared retrospectively with those receiving either dexamethasone alone or no antiedema therapy.

Phosphodiesterase Inhibition

The methylxanthene derivative, pentoxyfilline (3,7-dimethyl-1-[5-oxohexyl]-xanthene) (Trental) is reported to reduce edema associated with cryogenic cerebral lesions in cats. Intravenous injection of pentoxyfilline, administered 24 hours before or immediately after cerebral edema has been produced by a standard freezing lesion, reduces the cerebral edema, particularly in gray matter. The claim is made that the drug inhibits the enzyme phosphodiesterase, thereby increasing levels of cyclic AMP. In the cat, pentoxyfilline administration has been shown to increase CBF and the regional tissue PaO2 of the cerebral cortex. The beneficial effects claimed for pentoxyfilline in cryogenic cerebral edema cannot be accepted without reservation. The amount by which the weight increase is lessened in the damaged hemisphere of drug-treated animals is not statistically significant, nor is the lesser water increment in the white matter, the principal site of edema in this experimental model.

When gerbils are pretreated with pentoxyfilline, signs of ischemia in the area of distribution of the occluded unilateral common carotid artery are delayed in onset for up to one hour, compared to untreated animals in which signs appear immediately after occlusion. The onset of the late-appearing neurological deficit is coincident with the development of cerebral edema. Pentoxyfilline is therefore successful in delaying for a time the development of edema in ischemic brain; possibly this delay is related to the half-life of the drug. Cerebral hemispheric cyclic AMP levels are bilaterally increased in both pentoxyfilline-treated and control animals subjected to unilateral common carotid artery occlusion and are unaltered in sham-operated controls. Thus, the postulate that pentoxyfilline may owe its antiedema action to an effect on cyclic AMP metabolism requires further investigation.

The ultrastructural effects of the drug in the normal and ischemic gerbil have also been described. Animals receiving a single dose of the drug after 30 minutes of bilateral carotid occlusion and studied by electron microscopy show reduction of edema in the cerebral cortex and hippocampus at the end of 96 hours. By 120 hours, however, treated animals are morphologically the same as the ischemic controls. Ischemic animals given continuous treatment show essentially normal ultrastructure at 120 hours. In both normal and ischemic animals receiving pentoxyfilline, hypertrophy of neuronal mitochondria is observed.

Pentoxyfilline (Trental) is extensively used in Europe to treat patients with cerebrovascular and peripheral vascular disease. The claim that it is effective in the treatment of stroke is based on the statement that, in a double-blind investigative comparison with nicotinic acid, 172 out of 217 patients with cerebrovascular insufficiency and "psychiatric cases" responded to therapy. The patients were treated for six to eight weeks with a follow-up of more than two years. Neither the term "psychiatric cases" nor "cerebrovascular disease" is defined, nor are the criteria specified for determining a good clinical response. Clinical investigations with better controls are required.

Hyperventilation and Aminophylline

A decrease of CBF and CBV can be produced in normal brain by reducing arterial carbon dioxide tension (PaCO2), as by hyperventilation. Thus hyperventilation to the stage of hypocapnia has been suggested as a therapeutic measure to allow compensation for cerebral edema developing after ischemia. In experimental animal models of acute cerebral ischemia, and in a controlled study in humans, no benefit has been shown. Similarly, aminophylline, which is a vasoconstrictor of normal cerebral vessels, has been advocated for the treatment of cerebral ischemia, but no clear advantage has been demonstrated to date.

Hypothermia

Hypothermia has long been used in neurosurgery and cardiovascular surgery to protect the brain against ischemia and resulting cerebral edema. Hypothermia reduces intracranial pressure, intracranial blood volume, brain volume, CBF, cerebral oxygen consumption, and metabolism, increases cerebrovascular resistance, prolongs cerebral survival time following ischemia, and minimizes cerebral edema. Cerebral PaO2 available to the brain is not altered by hypothermia, and, following circulatory arrest, cortical PaO2 levels decrease at a slower rate than during normothermia, confirming the protective effect of hypothermia against ischemia.

During profound hypothermia, measurements of regional CBF indicate much greater reduction of CBF in white matter compared with gray matter, suggesting that the protection against ischemia is relatively greater in those areas of brain with the higher metabolism.

Systemic hypothermia has been shown also to reduce the edema associated with cryogenic lesions in the rhesus monkey, in the cat, and the dog. Conversely, raising the body temperature of the rhesus monkey to 104 F for a two-hour period increases this edema by 40%. The authors conclude that in human diseases known or thought to be associated with cerebral edema, fever should be vigorously treated.

Barbiturates

Anesthesia with barbiturates at the onset of experimental cerebral ischemia has been shown to be partially protective against subsequent infarction. However, the dose of barbiturates required is large, and deep anesthesia must be achieved; protective effects are evident only if respiration is...
maintained by mechanical ventilation. The protective effects of barbiturates may be related to depression of neuronal metabolism, so that individual neurons are better able to withstand prolonged periods of hypoxia and hypoglycemia. Alternatively, decreases of CBF induced by barbiturates in nonischemic regions of brain, with resultant decreases of blood volume, may permit better compensation for focal ischemic cerebral edema so that lesser increases of vascular resistance occur in ischemic regions of the brain; or the barbiturates may protect against the development of edema, as with cold injury, perhaps because of a lesser production of lactate and other acidic metabolites by cellular elements.

**Diuretics**

The diuretic action of intravenous hypertonic solutions is independent of their effects in reducing intracraniual pressure and presumably in dehydrating cerebral tissue, since these are seen after nephrectomy. Other diuretics reported to reduce cerebral edema may be acting directly on the brain. It has been reported that peritumor edema in humans is diminished following treatment with ethacrynic acid. Acetazolamide is reported to reduce the edema associated with cryogenic lesions in cats when this is combined with excision of the lesion. On the other hand, in cats with MCA occlusion, treatment with acetazolamide was found to be harmful rather than beneficial. The treated animals showed more infarction and edema than did the untreated animals. This is attributed to an increase in CBF in nonischemic tissue and a subsequent increase in intracranial pressure. Treatment with furosemide reduces the edema associated with cryogenic lesions in both cats and squirrel monkeys. In the cat, neither furosemide nor acetazolamide has an effect on the specific activity of cerebral tissue sodium at four hours after injection of $^{24}$Na, but diminishes the sodium specific activity of the tissues at two hours, the effect being more pronounced in white matter than in cerebral cortex, suggesting that both drugs are acting through their influence on CSF formation. Furosemide and acetazolamide inhibit CSF formation and decrease specific activity of sodium in the CSF. Such inhibition may allow faster drainage of the extravasated edema fluid through channels which normally accommodate considerable amounts of bulk CSF flow. Furosemide is also used clinically in combination with steroids in the treatment of peritumor edema. As far as we are aware, there has been no controlled study of the use of this group of diuretics in stroke patients.

**Steroids**

Adrenal corticosteroids have been studied in various animals as potential therapy for cerebral edema developing in experimental models of acute cerebral ischemia. Dexamethasone is ineffective in reducing cerebral edema in rats made hypoxic after occlusion of one carotid artery, in rats with microemboli injected into one carotid artery, and in squirrel monkeys with one MCA occluded. Dexa- me-thasone and methylprednisolone have been ineffective in reducing cerebral edema in cats with one MCA occluded; however, pretreatment with dexamethasone has been found effective in preventing or delaying the development of ischemic cerebral edema in cats studied two hours after MCA occlusion. In gerbils with unilateral carotid artery occlusion, dexamethasone was shown to be effective in one laboratory but ineffective in another. In general, adrenal corticosteroids are not as useful for the treatment of ischemic cerebral edema as for other types of edema. In experimental MCA occlusion, corticosteroids appear to be more effective in altering the parenchymal distribution of large molecules, such as protein tracers, than in modifying the degree of ischemia; similarly, corticosteroids are more effective in modifying cerebral edema in the nonischemic experimental models that also produce changes in the distribution of protein tracers. Corticosteroids may not influence the size of cerebral infarcts resulting from ischemia, but may prevent massive cerebral edema with shifts of intracranial structures, herniation, and death.

It has been reported also that steroids decrease the edema associated with acute hypertension in x-irradiated rabbits. Samples of brain tissue taken from the rhesus monkey seven days after MCA occlusion show diminished water after steroid treatment. The authors specifically report that no clinical improvement is observed in these animals. Data on cryogenic brain injury have relevance to the vasogenic edema of cerebral hemorrhage and hemorrhagic infarction in the human. Using tissue specific gravity measurements, negative results are reported for mice with cryogenic lesions treated by steroids. Suppression of this edema with steroid management is reported in the cat. In these experiments the edema was assessed by measurements of weight changes and albumin uptake in the whole damaged hemisphere. In another study, suppression is again reported on the basis of water changes in tissue samples. It is also reported that this edema in the rabbit is reduced by steroid therapy. In this study, changes in total hemispheric water and electrolytes are described.

In the rhesus monkey, on the other hand, steroids do not reduce the edema associated with cryogenic injury. Changes in water and electrolytes of the total hemisphere as well as uptake of albumin and Evans blue were measured. The authors attribute the lack of response to steroids in the rhesus monkey to the presence of acute inflammation in the lesion. Lesions produced by the application of liquid nitrogen to the intact skull of dogs and monkeys are associated with an intense acute inflammation and resolve as collagenous scars. Lesions produced in cats by the Klatzo technique, on the other hand, are associated with little acute inflammation and resolve as glial scars. Claussen et al. also report that there is an inverse relationship between the presence of inflammation and a favorable clinical response to steroids in humans with metastatic brain tumors. In experiments in which tissue specific gravity measurements of white matter are used to assess the edema associated with cryogenic injury in cats, results with steroid therapy are negative. These authors used liquid nitrogen to produce the lesions. Examination of histologic preparations from these animals, which were kindly supplied by the authors, shows a degree of acute inflammation comparable to that seen in the rhesus monkey. These results support, but do not prove, the hypothesis that the response of cerebral edema to steroids is determined in part by the presence of inflammatory cells in...
the primary lesion. On balance, it appears that experimental data do not support the view that steroid management is beneficial in experimental stroke.

The use of steroids in the treatment of patients with acute stroke has been disappointing. Early enthusiastic reports of benefits obtained with cortisone are not confirmed in a controlled study carried out by Dyken and White. Moreover, these investigators were disturbed by a possible adverse effect of the steroid used (cortisone, 300 mg/day). Because of the great success that the synthetic steroids, especially dexamethasone, have had in the therapy of cerebral edema due to brain tumors and other intracranial lesions, many physicians have adopted this drug for the treatment of patients with stroke. However, controlled double-blind studies on the effect of dexamethasone therapy in strokes have had conflicting results. A positive double-blind study of dexamethasone in the treatment of stroke patients is reported by Patten et al. In their complete series of patients, the average neurological score of patients on steroid therapy improved 12%, while those on placebo worsened by 12%. In other controlled clinical studies, dexamethasone has shown no benefit. Bauer and Tellez included 54 patients with stroke in a double-blind study to evaluate dexamethasone. These authors conclude that, when comparisons are made of patients with similar levels of consciousness, no difference is found between patients receiving the drug and those receiving placebo treatment. In a similar study, Norris reports that patients receiving steroids do somewhat worse than those treated with placebo. In a retrospective study of 227 stroke patients, Candelise et al. cannot find any beneficial effect of steroid therapy on ten-day survival rate. Wright finds no effect of dexamethasone on death rate, time of discharge, or necessity for chronic hospitalization in elderly patients treated with dexamethasone as compared to untreated patients on an adjacent ward. Gilsanz et al. find the results obtained with the use of 10% dextrose for six days in 30 patients with acute ischemic infarctions to be far superior to those observed in 31 similar patients treated with dexamethasone.

Agreement now appears to be universal that dexamethasone does not help patients with massive intracerebral hemorrhage. In the series of Patten et al., the three patients with intracerebral hemorrhage were included in the placebo group by chance. The last study, which is positive in regard to the effect of dexamethasone, has been criticized on the basis of failure to exclude patients with intracerebral hematoma. However, recalculation of their results after exclusion of this group still shows an apparent beneficial effect of dexamethasone.

In most series, few adverse side-effects of short-term dexamethasone therapy are noted. Norris reports that hematomas and infections as well as serious exacerbations of diabetes occur more commonly in the group treated with steroids, but Bauer and Tellez find gastrointestinal hemorrhages in their placebo and not in their steroid groups.

The inclusion in a double-blind study of stroke patients who are bright and alert and have no evidence of developing cerebral edema might hide a beneficial effect of steroids. Rubinstein states that patients believed to be developing herniation after cerebral infarction show appreciable improvement in consciousness but less improvement in other neurological manifestations if treated with high doses of dexamethasone after 72 hours as compared with untreated (double-blind) controls. Candelise et al. although unable to demonstrate the effectiveness of dexamethasone, state that "supported only by scattered single observations," they believe that there is often a clear-cut response to dexamethasone in terms of level of consciousness and survival in young patients with massive internal carotid occlusion or massive embolic infarction. However Bauer and Tellez analyzing their data in terms of the patients' level of consciousness, can find no evidence that steroids are beneficial, even in the patients most likely to have cerebral edema.

One is faced with an anomaly: a very large number of physicians use dexamethasone in treating patients with stroke and, on personal interview, report specific instances in which they believe a patient who appeared to have a sudden decline attributed to the development of cerebral edema seemed to brighten and improve following administration of the steroid. Wright, although reporting no effect on death rate with the use of dexamethasone, observes an early stimulating effect of the drug. Perhaps these salutary effects of the steroid are due to a direct action on neuronal systems or to its activity as a euphoriant, rather than to acute anti-edema action.

Another factor to be considered is the dosage of dexamethasone used. For example, the results of treating acute head injury with dexamethasone had been considered equivocal, similar to those reported in patients with stroke. However, recent studies from several neurosurgical centers, particularly in Europe, indicate that a clear-cut effect of steroids in severe closed head injury can be seen if dexamethasone is given in very high doses, beginning with a loading dose of 60 mg to 100 mg given intravenously. In particular, it has been found that the complication rate for very high doses given over short periods of time is only slightly greater than for lower doses, except for an increase in the instances of hyperglycemia which are reversible with cessation of treatment.

It has also been learned that glucocorticoid therapy combined with furosemide, a drug that acts on sodium retention, produces a more effective therapeutic response in patients with various forms of cerebral edema than do antiinflammatory glucocorticoid steroids by themselves. These latest reports suggest the need for double-blind studies of both high dose steroids and the combination of dexamethasone and furosemide as therapeutic agents in patients with cerebrovascular disease.

Discussion and Recommendations

During the past decade, substantial insight has been gained into the pathophysiology of edema accompanying experimental ischemic and other models of vascular disease. In man, as in the animal models, cerebral edema appears to occur with regularity during the first week or two following vascular insult. Yet our understanding of both the clinical importance and the pathogenetic mechanism of this process in man depends almost entirely on analogy with our animal models—models which admittedly are imperfect replicas of the human disorder.
A major problem has been our inability in the past to estimate with any accuracy the extent of ischemic brain edema during life. The indirect measures of breakdown of BBB and increased intracranial pressure may give misleading results. In purely extracellular edemas such as those accompanying brain tumors, the BBB is altered and the distribution of extracellular markers may reflect the extent of the edema, and consequently a brain scan with a gamma emitting tracer (RISA, radioactive mercuhydrin, Tc⁹⁹) is useful. But in ischemic brain edema, the extracellular phase and the breakdown of the BBB are late events, often occurring well past the major phase of intracellular edema. In man too, the brain scan does not usually become positive until several days after a stroke. Since the earlier intracellular phase of ischemic brain edema may be more important clinically and may be reversible, the information to be derived from a brain scan is far from optimal. Another approach has been the measurement of cerebral spinal fluid pressure. This may result in artifacts due to the use of lumbar intrathecal pressure determinations as indices to intracranial pressures. But even the direct measurement of intracranial pressure may be misleading since it can be influenced by cerebral blood volume and other factors unrelated to the edema. It can be fairly argued that the progress in animal studies has resulted in part from the development of a general consensus that edema must be measured directly as an increase in tissue water and tissue volume.

The importance of a direct in vivo measure of ischemic brain edema in man is well illustrated by the difficulty in interpreting the poor results obtained with therapeutic modalities such as corticosteroids. When corticosteroids are used in the treatment of edema secondary to brain tumors, the effect is often dramatic. Yet in double-blind studies in patients with stroke, the usefulness of corticosteroids has been equivocal. In these studies, the end point has been a clinical evaluation of "improvement" during treatment. Such data do not permit one to analyze treatment failure appropriately. Are failures due to the inability of steroids in the dosage used to alter the degree of ischemic brain edema? Are beneficial effects of steroids on the edema masked by the overriding effect of tissue necrosis in determining final clinical outcome? While animal experiments suggest the first explanation, we cannot be sure.

Fortunately, the means of accomplishing this goal of estimating both tissue swelling and tissue water content during life may now be at hand. Computed tomography has the potential of accomplishing both goals. While a rough beginning in its use has already proved productive, there is much to be learned and developed before this technique can provide a true estimate of ischemic brain edema in man. The increasing resolution provided by the new "generations" of these instruments will help in realizing this goal. With increased resolution and improved enhancement, the ability to recognize circumscribed tissue swelling will be improved. But exploitation of the full potential of this methodology will depend on carefully planned studies. The Study Group on Brain Edema in Stroke considers the development of this technique to be the most important goal in understanding ischemic brain edema in man and recommends that the following endeavors be given a high priority:

1. Improvement in ability to recognize circumscribed tissue swelling by CT scan including use of enhancement techniques. Such improvement requires correlation of the scan with postmortem morphometric estimates. Although initial studies of this type have been reported, much remains to be done as CT resolution, enhancement techniques, and ability to interpret scans improve.

2. Improvement in ability to estimate changes in tissue water content in a situation in which other tissue components such as structural lipids are also changing chemically, thus confounding interpretation of CT density measurements. Further biochemical research is indicated into specific changes in brain lipids and proteins during the evaluation of stroke in experimental models, at time of surgery, and in postmortem human material, as is also correlation of CT density measurements with these chemical changes.

3. Serial CT scans in patients with stroke to evaluate development of edema, especially in its early phases. Since serial scans demand a considerable economic outlay, these studies will require financial research support even though they make use of what has become an ordinary diagnostic tool. Since serial scans are not part of the neurological routine, informed consent is also required.

Therapeutic Studies

While steroids, diuretics, and osmolar agents are widely used in the treatment of stroke, the Study Group on Edema in Stroke cannot recommend either for or against the use of such agents at this time. Results of the studies summarized are either equivocal or not as yet fully explained.

The Study Group considers, however, that several carefully designed therapeutic trials are justified at this time. In suggesting such trials, the Study Group recommends adherence to the following experimental conditions:

1. All studies should be randomized and double-blind. Since informed consent is required in all cases, these may, in practice, require use of another treatment as control.

2. Studies should be confined to patients with ischemic brain disease. Specifically, every effort should be made to exclude patients with intracranial hemorrhage. In past clinical trials, combining patients with stroke of these two etiologies in one experimental group has led to difficulty in interpreting results.

3. CT scans should be carried out before and after treatment to identify at least major edema.

4. End point criteria should include, in addition to survival, the quality of survival, change in neurological status, and CT scan.

The following clinical trials are recommended as having high priority:

1. High dose steroid therapy. This recommendation is based on its reported success in head injury — another condition in which steroids in conven-
tional doses have proved disappointing.
2. Combination therapy — steroids plus furosemide. This is in fact widely used clinically, but has not been properly evaluated in ischemic brain edema.
3. Hyperosmolar agents, especially glycerol. Although some reports have been discouraging, others are very enthusiastic.
4. Phosphodiesterase inhibitors. These relatively safe drugs, which are vasoactive and alter certain forms of experimental edema, should be evaluated more fully in patients with stroke.
5. Pretreatment with steroids in patients undergoing revascularization procedures.

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