Cerebral Vascular Disease
Current Problems of Etiology, Diagnosis, and Treatment

By Joseph F. Fazekas, M.D., Ralph W. Alman, M.D., Rosalie A. Burns, M.D., and Donald Ehrenreich, M.D.

In cerebral vascular disease, difficulties in pathogenesis, diagnosis, and treatment are at present the rule rather than the exception. This discomforting situation is due to our rather limited knowledge concerning the etiology and pathogenesis of vascular disease in general, to the relative inaccessibility of the human brain, and to the resultant paucity of rational therapeutic modalities. It is the purpose of this discussion to review some of the more pressing problems related to cerebral vascular disease.

Problems of Etiology

The essential similarity between atherosclerotic lesions in cerebral vessels and in vessels elsewhere in the body, as well as their not infrequent coexistence, suggests that the etiology of atherosclerosis is everywhere the same. However, there are various observations that challenge this thesis. For example, it is generally accepted that there is a statistically demonstrable relationship between serum lipid levels and the incidence and severity of coronary atherosclerosis; yet among the Japanese and the South African Bantu, both of whom characteristically have low serum cholesterol values, although degeneration of the coronary arteries is relatively infrequent, disease of the cerebral vessels is common. The fact that in any one individual, whatever the serum lipid concentration, atherosclerosis tends to involve some vessels much more than others, also suggests that local factors must be important.

It is not necessary to examine exotic populations in order to demonstrate the selective and sometimes inherited nature of vascular degeneration, nor the inconstant relationship of its lesions to such generalized metabolic abnormalities as hypercholesteremia. It is well recognized that generation after generation of a particular family may apparently be doomed by the early development of either coronary or cerebral vascular disease or both. With all the current enthusiasm for therapeutic reduction of serum lipids by dietary means or drugs, the most ardent proponents of such regimens must concede that many persons fall prey to vascular disease even in the absence of demonstrable abnormality of serum lipids. On the other hand, there are hypercholesteremic individuals who, clinically at least, appear to escape unseathed by vascular degeneration, sometimes for many years.

In addition to local factors and the uncertain influence of blood lipids, hemodynamic forces also are doubtless of major importance in the development of atherosclerotic degeneration. In general, high arterial pressures as well as large blood flow rates appear to augment any tendency toward development of vascular lesions. Arterial hypertension is commonly associated with the accelerated appearance of clinically significant arteriosclerotic lesions.

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degeneration, whereas vessels that carry blood under relatively low pressure, i.e., pulmonary circulation and systemic veins, rarely show sclerotic or atheromatous changes except in the vicinity of a patent ductus arteriosus or arteriovenous fistula.

The foregoing comments serve to emphasize the great complexity of vascular disease as regards etiology and to indicate that degenerative arterial lesions probably represent the resultant of various factors that, individually, predispose toward or protect against atherosclerosis. With all the discussion of the "primary" factor in the development of vascular lesions, reflection will make obvious that, where more than one factor is necessary, none can be considered primary. Basic questions yet to be answered concern the mechanism of lipid deposition in the arterial subintima; whether cholesterol accumulation is the ultimate result of long-continued imbibition by the endothelium and is therefore primary, or whether the initial lesion is a subintimal hemorrhage with fibrin deposition later followed by cholesterol precipitation; and whether the cholesterol of the atheromatous plaque is synthesized by the damaged arterial wall. Finally, one may inquire, perhaps facetiously, whether the subintimal atheroma may not, in fact, represent reinforcement of degenerated intima so that, at least until the plaque causes hemodynamic insufficiency, it acts as a homeostatic device rather than a true lesion.

Problems of Diagnosis

The differential diagnosis of cerebral dysfunction is based upon neurologic manifestations, which depend for the most part upon the anatomic location of the underlying disorder rather than its nature. Hence, cerebral ischemia of vascular origin may cause precisely the same signs and symptoms as those of any other type of disturbance involving the same cerebral areas. Not infrequently, the differentiation between brain tumor and cerebral vascular disease may cause considerable difficulty. While all are agreed that it is of the utmost importance to recognize intracerebral hemorrhage, particularly when the use of anticoagulants is contemplated or when surgical intervention may be attempted, it is generally acknowledged that it may be impossible to identify localized intracerebral hemorrhage by currently available methods. Even after intensive investigation, an unequivocal diagnosis in such cases may still not be possible. Here, all that one can do at present is observe the patient carefully, watching for the development of further manifestations that may eventually reveal the nature of the underlying disorder.

Similarly, differential diagnosis of the various causes of cerebral vascular insufficiency, i.e., embolism, thrombosis, or stenosis without complete occlusion, poses many problems. Although there are numerous estimates concerning the incidence of these disturbances, it should be recognized that conclusions concerning their relative occurrence must be regarded with reservation unless all investigational modalities have been applied to the evaluation of each individual patient in any series.

Of considerable practical importance is the differentiation, from cerebral embolism or thrombosis, of those cerebral vascular disorders characterized by recurrent transitory episodes of cerebral ischemia. In general, these are in all probability most often based upon narrowing of intracranial or extracerebral channels or both. Where cerebral oxygen delivery is already compromised by such pathologic narrowing of aortocranial or intracerebral vessels, it can be appreciated that further reduction in blood flow of various origins may additionally impair oxygenation of cerebral tissue so that ischemic dysfunction or even infarction may occur.

The factors governing oxygen delivery to cerebral tissue are two: the oxygen content of the arterial blood and the rate of cerebral blood flow, which depends upon the head of pressure, on the one hand, and the cerebral vascular resistance, on the other. The head of pressure, in turn, is governed for the most part by the arterial blood pressure, which is influenced by a large number of extracranial factors.

The cerebral vascular resistance depends
Table 1

**Extracranial Causes of Reduced Cerebral Oxygen Delivery**

<table>
<thead>
<tr>
<th>I. Reduced arterial oxygen content</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Hypoxemia</td>
<td></td>
</tr>
<tr>
<td>1. Decreased atmospheric oxygen tension</td>
<td></td>
</tr>
<tr>
<td>2. Cardiorespiratory disease</td>
<td></td>
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<tr>
<td>3. Reduced oxygen-carrying capacity of blood</td>
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<table>
<thead>
<tr>
<th>II. Reduced cerebral blood flow</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Hypotension</td>
<td></td>
</tr>
<tr>
<td>1. Decreased cardiac output</td>
<td></td>
</tr>
<tr>
<td>a. Decreased venous return</td>
<td></td>
</tr>
<tr>
<td>b. Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>c. Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>d. Valvular disease (e.g., aortic stenosis)</td>
<td></td>
</tr>
<tr>
<td>2. Decreased total peripheral resistance</td>
<td></td>
</tr>
<tr>
<td>a. Carotid sinus or aortic arch reflexes</td>
<td></td>
</tr>
<tr>
<td>b. Drug-induced vasodilatation</td>
<td></td>
</tr>
<tr>
<td>c. Hemodynamic syncope</td>
<td></td>
</tr>
<tr>
<td>d. Hypovolemic shock</td>
<td></td>
</tr>
<tr>
<td>B. Aortocranial arterial stenosis</td>
<td></td>
</tr>
<tr>
<td>C. Increased cerebral vascular resistance</td>
<td></td>
</tr>
<tr>
<td>1. Increased blood viscosity (polycythemia, lipemia?)</td>
<td></td>
</tr>
<tr>
<td>2. Hypothermia</td>
<td></td>
</tr>
<tr>
<td>3. Hypocapnia</td>
<td></td>
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<tr>
<td>4. Hypertension</td>
<td></td>
</tr>
<tr>
<td>5. Increased arterial oxygen tension</td>
<td></td>
</tr>
</tbody>
</table>

| III. Various combinations of the above |  |

upon the total length of the cerebral vascular bed, which may be assumed to be a fixed value in any one individual; upon the viscosity of the blood, which, at most, varies slowly and probably within very narrow limits; and, to the greatest extent by far, upon the caliber of the cerebral vessels, which are capable, by constriction or dilatation, of altering cerebral vascular resistance with remarkable rapidity in accordance with certain extracranial influences. Table 1 presents various disturbances, mostly systemic, that may reduce cerebral oxygen delivery.

It is evident from this abbreviated review that cerebral hemodynamics may be adversely affected by a wide variety of causes. Although the clinical manifestations of cerebral circulatory insufficiency may be so characteristic as to permit immediate diagnosis, more often than not a serious problem is encountered in attempting to identify the precipitating cause in any one case, particularly because its presence may be masked by homeostatic mechanisms. For example, although intermittent reduction in blood pressure may frequently be implicated as a cause of cerebral ischemia in a patient with underlying cerebral vascular disease, it is not uncommon to find that at intervals such a patient tolerates a rather marked degree of hypotension without experiencing cerebral ischemic symptoms. One may speculate that homeostatic mechanisms, such as represented by increased efficiency of collateral vessels (for reasons unknown) or improved capacity of smaller cerebral vessels to dilate, may be responsible for such unpredictable changes in tolerance. In any event, identification of hypotension as the precipitating cause of cerebral ischemia in such a case may thereby be rendered difficult or impossible.

Although operative and postoperative cerebral infarction appears to be a relatively uncommon complication of surgery, transitory cerebral ischemia may occur under such circumstances far more commonly than recognized. It would appear to be a major problem to identify those neurologically asymptomatic patients who may be particularly vulnerable to cerebral ischemia secondary to the commonly encountered hemodynamic alterations related to surgical procedures or appearing postoperatively.

It may not be generally appreciated that chronic generalized cerebral ischemia may induce a wide variety of personality disorders expressed as chronic anxiety reactions, intellectual deterioration, or behavioral and emotional changes, as well as various symptoms often regarded as "psychogenic" (fatigue, headaches, hallucinations, agitation, or depression).

In not a few instances, there may ultimately appear progressive organic changes that, in association with the clinical picture, exactly duplicate the classical findings of Alzheimer's disease. Even in the absence of cortical atrophy, progressive dementia in some cases may well be of ischemic origin due to disturbances of either the smaller intracerebral
vessels or the large aortocranial arteries. Not infrequently, as illustrated in table 2, there may be measurable reductions in total cerebral blood flow although a good correlation is not always present.

Clinical differentiation between cerebral circulatory insufficiency due to disease of smaller intracerebral vessels and that caused by stenosis of aortocranial vessels is often impossible. In both conditions, the manifestations are those of cerebral ischemia, regardless of the nature of extracerebral precipitating factors; signs and symptoms may often not reliably indicate the specific vessel or vessels responsible or even whether intracerebral or extracerebral in location. This confusion may be related to the development of a relatively efficient collateral circulation and to the inconstancy of anatomic vascular arrangements, as well as to the frequent coexistence of extracranial and intracranial vascular disease. For example, syncope, a common manifestation of cerebral ischemia, may be based upon insufficiency, occlusion, or anomaly of the anterior cerebral, basilar, or carotid arteries and may be precipitated by either peripheral or local factors (mechanical carotid or vertebral artery compression, hypotension, cerebral vasospasm, etc.) which further compromise a limited circulation to those areas concerned with consciousness.

It may be worth while to review certain aspects of cerebral collateral circulation having an important bearing on localization of arterial lesions causing cerebral vascular insufficiency. Not infrequently, alternate sources of blood supply may be indispensable for insuring an adequate cerebral oxygen delivery. Radiography may demonstrate filling by the vertebral-basilar circulation of major intracranial arteries normally dependent upon the internal carotid system, and vice versa. Variations from the classical arrangement of the circle of Willis have been reported in an incidence of nearly 50 per cent. Such deviations also make difficult the specific localization of a cerebral vascular lesion.

In addition to the collateral potentials of the circle of Willis and also its variations as causes of problems of localization, we must include the collateral contributions that may appear to a functionally adequate extent between the distal ramifications of the various major cerebral vessels. That functionally important anastomoses do exist between various intrinsic cerebral arteries has been demonstrated experimentally by Meyer and Denny-Brown, who observed circulatory changes in pial vessels following occlusion of a major cerebral artery. They concluded that the most important factor controlling adjustments in collateral vessels is the intraluminal pressure.
Table 3

Diagnostic Modalities for Cerebral Circulatory Insufficiency

1. Peripheral artery examination:
   - Radial, temporal, common carotid pulsations
   - Brachial blood pressures
   - Neck vessel bruit
2. Carotid artery compression test
3. Ophthalmodynamometry
4. Electromyelgraphy:
   - Resting
   - Hypoxic challenge (7 per cent O₂, hypotension, carotid compression)
5. Quantitative cerebral circulation studies:
   - Cerebral circulation time
   - Cerebral blood flow measurements
   - Quantitative response to hypoxia, CO₂, and carbonic anhydrase inhibitors
6. Angiography:
   - Extracranial and intracranial visualization
7. Internal carotid and vertebral artery pressure measurements

a localized reduction of which results in vascular dilatation and increased flow from collateral channels having a higher head of pressure. Various other factors stimulating these circulatory readjustments include reduction of oxygen tension and accumulation of acid metabolites (pyruvic, lactic, and carbonic acids). These principles should apply equally to communications between branches of various intracerebral vessels and to communications between these vessels and certain extracranial collateral sources. It may be interesting to point out that although the intracerebral vessels appear not to be influenced by the autonomic nervous system, the caliber of the extracranial arteries is largely dependent upon sympathetic nerve supply for tone. This fact, in conjunction with the presence of communications between intracerebral and extracranial vessels, may afford some rationale for blockade or removal of the stellate ganglion, particularly in patients with occlusion or insufficiency of a major aortocranial vessel. The probable inconstancy of communications between intracranial and extracranial vessels may explain the uncertainty of therapeutic benefit from these procedures and the disagreement about their efficacy.

Various investigational modalities are applied in attempts to establish the diagnosis of cerebral circulatory insufficiency and, if present, to identify the vessels involved. Table 3 lists some of these procedures. Unfortunately, our experience has demonstrated that tests for cerebral vascular insufficiency tend to be somewhat unreliable when they fail to demonstrate abnormality. Least subject to misinterpretation are the presence of a bruit in a neck vessel, failure to visualize major extracranial vessels radiographically, and direct measurement of internal carotid or vertebral intrarterial pressure.

Until the present time, measurements of pressure gradients between the aorta (as approximated by femoral or brachial artery pressures) and the internal carotid or vertebral arteries distal to their origins have been made only during surgical exposure of these vessels, although significant gradients have also been assumed on the basis of bruit, sensitivity to carotid compression, and more or less refined methods of ophthalmodynamometry. It is, however, technically not difficult to perform percutaneous puncture of the internal carotid artery at the base of the skull and, with appropriate recording devices, to determine accurately the blood pressure within this vessel. One can conceive of few circumstances that would impair the reliability of conclusions drawn from such measurements, which, in some instances, may make radiographic observations unnecessary. The major exception is the occasional real or apparent failure of the procedure due to misdirection of the needle or complete occlusion of the vessel.

Inasmuch as a large proportion of strokes appear to be caused by stenosis of extracranial (aortocranial) vessels, it is extremely important to visualize or otherwise assess the role of these arteries in the production of cerebral ischemic lesions and, if possible, to determine the precise location of stenosis. The results of contrast radiography are somewhat disappointing, however, insofar as intracranial vascular disease is concerned. Angiography, although at the present time considered one of the best available diagnostic aids, more
often than not fails to support even an obvious clinical diagnosis of intracranial cerebral vascular disease. For example, in an unselected series of 41 cases in which the diagnosis of middle cerebral artery occlusion had been based upon careful clinical study, angiograms supported the impression in only three instances while demonstrating that an occlusive lesion was actually present in the internal carotid artery in six cases. Twenty-nine angiograms in this group were normal, suggesting that although ischemic infarction in the distribution of the middle cerebral artery may well have been responsible for the clinical picture, actual occlusion of the vessel had not occurred and that ischemia was therefore nonocclusive or due to occlusion of nonvisualized small radicals. In the same series, clinical diagnosis of aortocranial vessel occlusion was substantiated by angiography in only 40 per cent of the cases (internal carotid artery, four of 11; basilar artery, two of four).

A limited number of observations suggests that in the presence of a significantly reduced total cerebral blood flow, failure of response of the cerebral vascular resistance to administration of 5 per cent carbon dioxide or carbonic anhydrase inhibitors may strongly indicate rigidity or maximal dilatation of the smaller intracerebral vessels, particularly when disease of the larger vessels can be excluded on the basis of normal aortocranial pressure measurements or angiography. Nevertheless, insofar as the intracerebral vessels are concerned, it must be admitted that there are few or no satisfactory means of differentiation between occlusive and nonocclusive intracerebral ischemic infarction.

It must not be supposed that cerebral angiography, as well as various other diagnostic modalities, is wholly worthless because of frequent failure to provide unequivocal information. Positive findings can be demonstrated often enough to make mandatory the application of these studies in every clinically questionable case, since one cannot predict in advance whether or not they will clearly establish a specific diagnosis. It is important to recognize the weaknesses of various diagnostic tests, however, in order to avoid compounding the problems of diagnosis by reason of misplaced confidence.

Space will not permit a detailed discussion of the miscellany of less frequently encountered disorders that may further impair oxygen delivery to the brain in patients with cerebral vascular disease and that constitute problems as regards their diagnosis and the evaluation of their importance as contributing factors. Traditionally, such dissimilar entities as hypoglycemia, fever, or smoking, are suspected to increase cerebral dysfunction in cerebral vascular disease. The mechanisms by which they operate are not always immediately evident and, in some instances, their alleged role in augmenting the symptoms of cerebral ischemia may be questioned.

Problems of Management

The management of patients with cerebral vascular disease is attended by no fewer problems than those that arise in relationship to etiology, diagnosis, and localization; in fact, problems of management are likely to depend directly upon the more basic uncertainties.

Little can be said concerning the medical management of identifiable cerebral hemorrhage except that it is seldom successful. In view of the extensive damage to brain tissue, which usually occurs with great rapidity, there is presently little reason for optimism although limited success has been reported to attend prompt neurosurgical treatment of hematomas localized in the temporal lobe area.

The suggestion that a basic disturbance in vascular degeneration is intimal fibrin deposition has stimulated investigation of fibrinolytic activity of the blood under a variety of situations and the use of thrombolytic agents for both therapeutic and prophylactic purposes. With regard to occlusive cerebral vascular disease, reports regarding their efficacy have been inconclusive.

The use of anticoagulants in the management of patients with cerebral vascular disease has undoubtedly been stimulated to a certain degree by reports of beneficial effects in patients with coronary vascular disease.
**Table 4**

*Acute Hypotension and Cerebral Hemodynamics*

<table>
<thead>
<tr>
<th>Young normotensive subjects</th>
<th>Age</th>
<th>MAP</th>
<th>CBF</th>
<th>CVR</th>
<th>CAVO₂</th>
<th>CMRO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with malignant hypertension</td>
<td>40</td>
<td>179</td>
<td>89</td>
<td>60.3</td>
<td>3.0</td>
<td>5.75</td>
</tr>
<tr>
<td>Subjects with cerebral vascular disease and hypertension</td>
<td>66</td>
<td>133</td>
<td>87</td>
<td>39.4</td>
<td>3.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

*Significant difference, p < 0.05.

MAP indicates mean arterial blood pressure in millimeters of Hg; CBF, cerebral blood flow in milliliters per minute per 100 Gm. of brain; CVR, cerebral vascular resistance in millimeters of Hg per milliliter of blood per minute per 100 Gm. of brain; CAVO₂ cerebral arteriovenous oxygen difference in volumes per cent; CMRO₂ cerebral oxygen consumption in milliliters per minute per 100 Gm. of brain; C, control; E, experimental.

Even today, however, there appears to be considerable difference of opinion regarding the therapeutic value of these agents in coronary disease, despite numerous studies extending over more than a decade.²⁵ One of the greatest deterrents to the use of anticoagulants in cerebral vascular disease is the previously mentioned difficulty in differentiating between intracerebral hemorrhage and cerebral vascular occlusion. In spite of this difficulty, anticoagulants have been widely used in the management of patients with cerebral vascular disorders. Although reports in the American literature were at first somewhat encouraging, more recent studies have questioned the value of these drugs when administered to patients with acute cerebral vascular occlusion and suggest that they offer little as long-term therapy in preventing recurrent ischemic cerebral infarction.²⁶

According to Millikan²⁷ and Fisher,²⁸ anticoagulants significantly reduce the incidence of transient cerebral ischemic episodes in patients with vertebral-basilar insufficiency and should be administered in such instances for a period of 3 to 4 months after the onset of symptoms. It is difficult, however, to understand why such drugs should be effective, since they do not alter the rate of cerebral blood flow nor reduce blood viscosity. Indeed, recurrent ischemic attacks may continue to occur despite satisfactory anticoagulation. One must be aware that this disorder is characterized by a relatively high spontaneous re-
patients with malignant hypertension and with cerebral atherosclerosis were less capable of compensatory reduction of cerebral vascular resistance and that signs and symptoms of cerebral ischemia developed with blood pressure values within the normal range.

Despite the implications of these well-documented observations, disastrous results are frequently reported following efforts to restore blood pressure to so-called normal values in patients with incipient or known cerebral vascular insufficiency. We are often confronted with patients receiving hypotensive agents to reduce systolic hypertension of atherosclerotic origin. It should be evident that little is to be gained by efforts at reduction of systolic blood pressure in the absence of diastolic hypertension.

In the patient with essential hypertension and cerebral atherosclerosis, in whom cerebral vascular resistance is disproportionately elevated as compared to blood pressure and cerebral blood flow therefore reduced, attempts to restore blood pressure to accepted normal values may also be hazardous. The problem of therapy under such circumstances is likely to be complicated by the coexistence of renal or cardiac disease, upon which continued severe hypertension may have a markedly deleterious effect. Certainly, in such instances, acute reduction of blood pressure should be avoided, and a more gradual approach toward reasonably reduced levels appears warranted.

In summary, it would seem that hypertension may not infrequently represent a homeostatic mechanism and that attempts to restore a "normal" state quickly may nullify certain beneficial effects. In many cases, hypertension may indeed be "essential."

This concept would seem to suggest an answer to the problem of management of those patients with cerebral vascular insufficiency who have a normal or even low diastolic pressure. In view of their elevated cerebral vascular resistance, these patients may justifiably be considered as having relatively insufficient blood pressure and a cerebral oxygen delivery constantly hovering near the critical limit. One is therefore tempted to administer vasopressor agents for the purpose of raising the blood pressure and thereby improving cerebral perfusion. It should be appreciated, however, that the administration of sympathomimetic drugs to normotensive subjects is associated with an increase in cerebral vascular resistance, at least paralleling the rise in blood pressure and sometimes exceeding it so that there may result even a slight reduction in over-all cerebral blood flow. It is uncertain whether this "Bayliss effect" represents a disproportionate response of the cerebral vessels directly to the vasoressor drug or rather to the elevation in blood pressure.

In spite of the foregoing, it may be advisable to administer sympathomimetic drugs to normotensive patients with symptoms of cerebral vascular insufficiency, although in doses that will cause at most only slight blood pressure elevation, in order to obviate those minor blood pressure reductions that may fre-
quent further jeopardize cerebral oxygen delivery. These alterations may be precipitated by such common occurrences as straining efforts, coughing, or sudden changes in body position, any of which may temporarily reduce cerebral oxygen delivery.

Pharmacologic alteration of hemodynamics in cerebral vascular insufficiency logically may also include administration of agents that tend to dilate cerebral vessels. As indicated in table 5, only carbon dioxide36-39 and parenterally administered carbonic anhydrase inhibitors40 are capable of improving cerebral oxygen delivery by dilating cerebral vessels without impairing arterial oxygenation or reducing blood pressure.40-42 Even these agents may be of limited effectiveness in certain patients in whom, because of chronically reduced cerebral blood flow, there has already been maximal, but not entirely compensatory, cerebral vasodilatation. The table demonstrates that some "vasodilators" actually increase the resistance of the cerebral vessels while others, although their administration is associated with decreased cerebral vascular resistance, induce an at least equivalent reduction of blood pressure so that cerebral blood flow remains unchanged or may even be slightly reduced.

Several unanswered questions concerning management of cerebral vascular disease are based upon epidemiologically and experimentally derived inferences regarding the role of lipids in the development of coronary artery disease. Is there any justification for the employment of dietary or chemical means for the control of blood lipid levels in patients with cerebral vascular disease? If not justified after cerebral vascular deterioration has occurred, at what age should such measures be instituted for prophylactic purposes inasmuch as vascular lipid deposition, according to pathologists, begins at birth? We are not aware of any well-controlled data that indicate that dietary manipulation or administration of substances inhibiting endogenous cholesterol formation (estrogens, triparanol, thyroxin and its analogues, or nicotinic acid) have significant therapeutic or prophylactic value as far as established cerebral vascular disease is concerned.

Although the problem of management of cerebral vascular disease has not been satisfactorily solved by the medical approach, reports in the literature on the value of extracranial vascular surgery (i.e., endarterectomy and bypass procedures) appear to be extremely promising.17, 43, 44 Operative intervention is advocated in those patients experiencing signs and symptoms of cerebral ischemia and in whom stenosis can be demonstrated angiographically in one or more of the extracranial vessels. The patients falling into the above category can be classified into three separate groups: those with acute occlusive vascular disease, those having recurrent transient attacks of cerebral circulatory insufficiency, and those having suffered previous cerebral infarction.

Good results are claimed in the first group of patients (i.e., with acute cerebral ischemia due to thrombotic occlusion of one of the major extracerebral arteries) provided the procedure is performed promptly (within 24 hours of the "stroke"). In view of the known extreme susceptibility of the brain to ischemia, one must assume that in those patients improved by surgery there was a slow reduction in the size of the lumen of the vessel and that the occlusion was not complete or that either intracranial or extracranial collateral circulation had maintained oxygen delivery at levels sufficient to obviate irreversible damage and to permit recovery of function upon restoration of a more adequate blood supply.

It is as difficult to evaluate the efficacy of surgery as that of anticoagulants in patients with recurrent cerebral ischemia due to vascular insufficiency. Little is known regarding the natural history of this disorder and the incidence of spontaneous remissions. Some patients have been free of symptoms for as many as 3 years without any form of therapy. In such cases, we believe that the development of collateral circulation is the most likely explanation for the prolonged remission. It is possible, however, that early correction of stenosis or occlusion of extracerebral vessels

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may improve or accelerate stabilization of cerebral oxygen delivery in some instances in which collateral circulation is inadequate.

There are many perplexing problems regarding the indications for surgical attack upon stenosed or occluded aortocranial vessels. It should be recognized that, despite occlusion of one or even more of the four primary channels of cerebral blood supply, total cerebral blood flow and function may remain normal by virtue of increased efficiency of the remainder or of collateral circulation. Moreover, it may be little appreciated that a significant margin of safety is included in the normal cerebral blood flow of 55 to 60 ml per 100 Gm. of brain per minute, and that normal cerebral metabolism and function may proceed in spite of a gradually achieved 40-per cent reduction. In such instances, the widening of the cerebral arteriovenous oxygen difference reflects the ability of the brain to continue its normal rate of oxygen utilization in the face of slowed circulation.

Furthermore, the pathologic processes that culminate in aortocranial stenosis usually proceed quite slowly, so that an effective collateral circulation is given the opportunity for development. It would seem not to have been conclusively established that endarterectomy or bypass procedure will improve the total cerebral oxygen delivery beyond that maintained by adequate dilatation of smaller cerebral vessels and the effective assistance of collateral vessels. In other words, the changes in pressure gradient resulting from successful operative intervention may merely restore the original hemodynamic arrangement without necessarily producing an improvement in over-all blood supply. Unfortunately, there has been too little quantitative evaluation of the results of aortocranial vascular surgery, most of the conclusions regarding its efficacy being based upon clinical impression and not always entirely objective.

Summary and Conclusions
Problems related to pathogenesis, diagnosis, and management of cerebral vascular disease have been reviewed. The problem of etiology cannot be resolved until the various factors that predispose toward or protect against cerebral vascular degeneration can be identified and their relative importance assessed. Differential diagnosis of various cerebral ischemic disorders is often difficult and sometimes impossible; that of intracerebral hemorrhage poses a particularly worrisome problem. The presence of circulatory anomalies and the existence of extensive collateral circulation may interfere with determination of the primary locus of cerebral vascular insufficiency. Radiographic visualization of both extraenial and intracranial vessels, as well as certain other procedures, may be helpful but is not always reliable. Numerous, sometimes obscure, extracranial factors may sufficiently reduce cerebral oxygen delivery so that where local circulatory impairment exists, ischemic dysfunction or even infarction may result. The diagnosis of incipient cerebral ischemia in patients undergoing elective surgery and in those having various functional psychiatric disorders may depend on an accurate evaluation of the neurovascular circulation.

The medical management of patients with cerebral vascular disease (by diet and anticoagulant or other drug therapy) has received its impetus largely from experience gleaned from observations on patients with coronary vascular disease. Attempts at transfer of this experience may be misleading with regard to use of certain drugs and even hazardous. The disappointing results of vaso dilator agents and reduction of blood pressure in patients with cerebral vascular disease require consideration of cerebral hemodynamic and metabolic principles for understanding. Finally, there has been too little objective physiologic evaluation of the results of aortocranial vascular surgery on cerebral oxygen delivery to formulate definitive conclusions concerning the efficacy of such procedures.

References
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