MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

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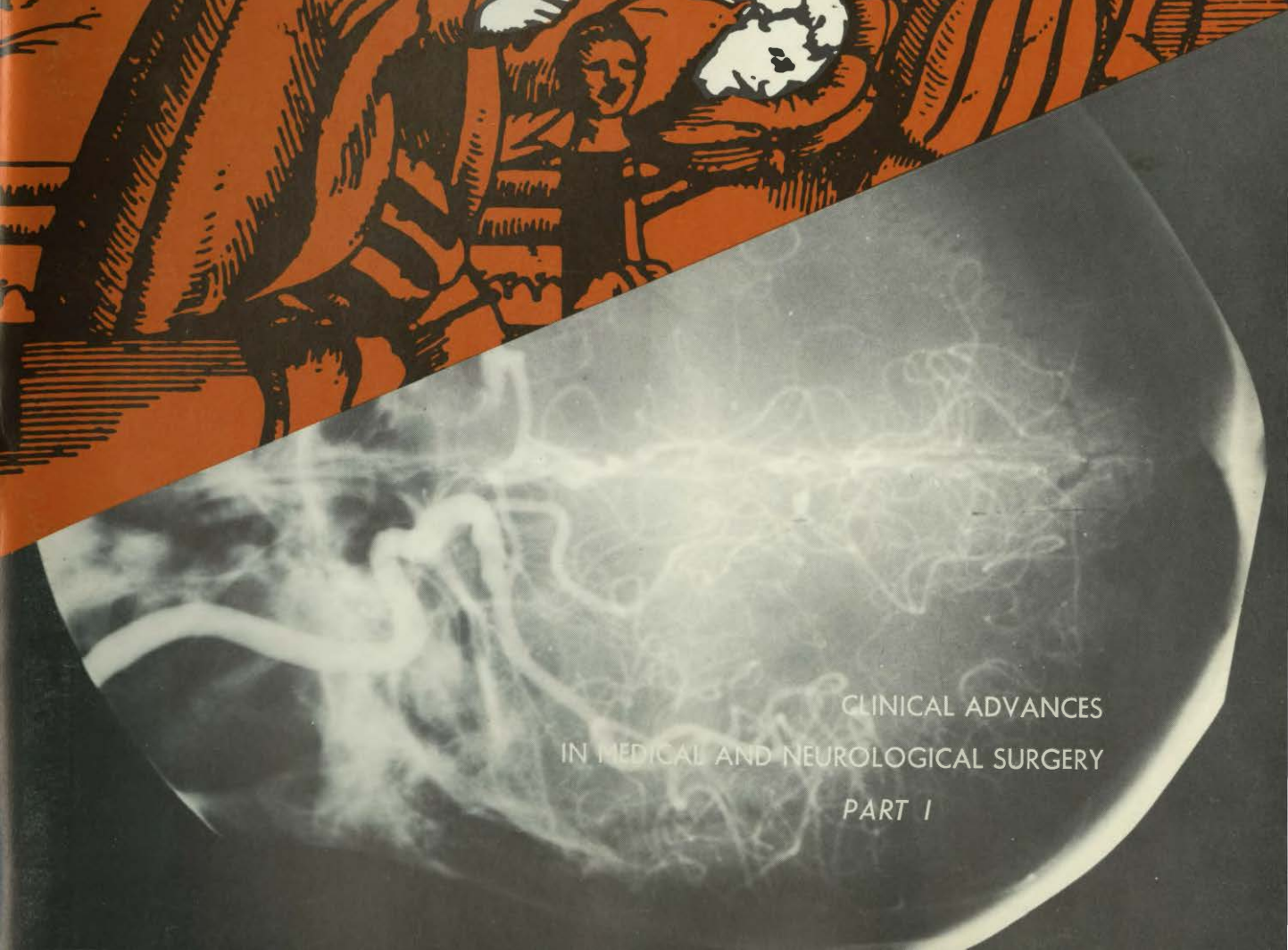
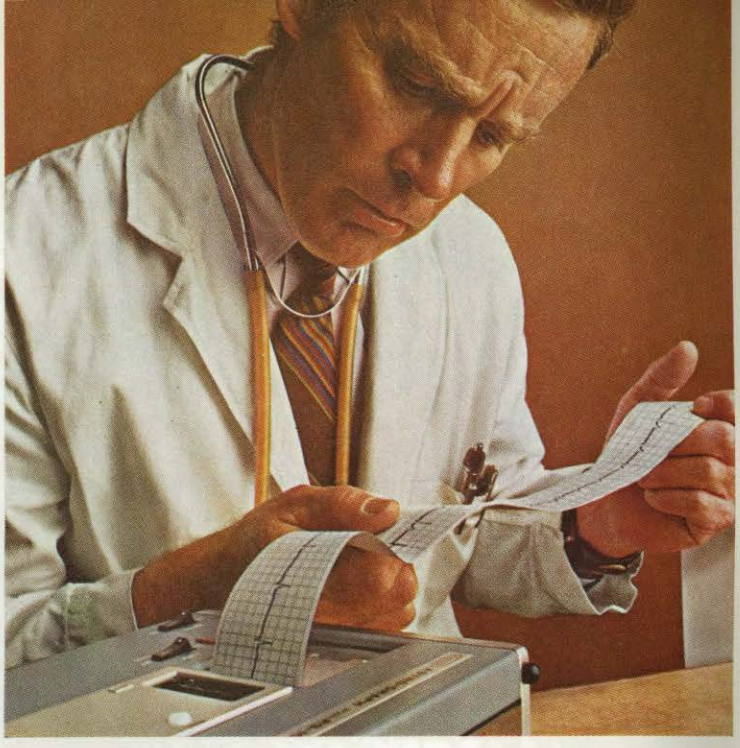


CLINICAL ADVANCES IN MEDICAL AND NEUROLOGICAL SURGERY

PART I

When cardiac complaints occur in the absence of organic findings, underlying anxiety may be one factor



The influence of anxiety on heart function

Excessive anxiety is one of a combination of factors that may trigger a series of maladaptive functional reactions which can generate further anxiety. Often involved in this vicious circle are some cardiac arrhythmias, paroxysmal supraventricular tachycardia and premature systoles. When these symptoms resemble those associated with actual organic disease, the overanxious patient needs reassurance that they have no

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

organic basis and that reduction of excessive anxiety and emotional overreaction would be medically beneficial.

The benefits of antianxiety therapy

Antianxiety medication, when used to complement counseling and reassurance, should be both effective and comparatively free from undesirable side effects. More than 13 years of extensive clinical experience has demonstrated that Librium (chlordiazepoxide HCl) fulfills these requirements with a high degree of consistency. Because of its wide margin of safety, Librium may generally be administered for extended periods, at the physician's discretion, without diminution of effect or need for increase in dosage. If cardiovascular drugs are necessary, Librium is used concomitantly whenever anxiety is a clinically significant factor. Librium should be discontinued when anxiety has been reduced to appropriate levels.

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in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

Clinical Advances in Medical and Neurological Surgery

Part I

MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

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Clinical Advances in Medical and Surgical Neurology

Sponsored by the School of Medicine, Department of Continuing Education, and the Division of Neurosurgery, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University

DONALD P. BECKER, M.D., *Guest Editor*

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INTRODUCTION

Recently, important strides have been made in clinical neurology and clinical neurosurgery, culminating in improved patient care. The last ten years have witnessed a new sophistication in neuroradiology, and the clear development of neuro-ophthalmology as a subspecialty. The addition of the operating microscope to neurosurgery has improved the quality of the operation which we can provide for our patients. A renewed interest in and study of cerebral vascular disease has aided our understanding of the pathophysiology of this disorder. Of the various clinical neuroscience frontiers that have been forged, an improved understanding of the pathophysiology of brain injury is one of major significance. Much has been learned, both in laboratory and in clinical investigation, concerning the brain's response to insults such as anoxia-ischemia, elevated intracranial pressure, trauma, and neoplasm. Alterations in cerebral blood flow and intracranial pressure in these conditions have been studied, and more recently studies of the brain's metabolic response to insults have been conducted. The clinical goal of improving our treatment of the insulted brain is becoming more of a reality.

It is to these areas that the speakers at the 27th Stoneburner Lecture Series addressed themselves. The Stoneburner Lecturer was Dr. Thomas W. Langfitt, Charles H. Frazier Professor and Chairman of the Division of Neurosurgery at the University of Pennsylvania. Leading us are Dr. Langfitt's pioneering efforts and continuing studies investigating the brain's pathophysiological response to injury. His first lecture, "The Interrelationship of Intracranial Pressure, Cerebral Blood Flow, and Brain Metabolism in Experimental Brain Injury," summarized much of his own work and provided a basic introduction to the program. His second lecture, "Clinical Advances in the Management of Patients with Severe Head Injury," demonstrated how an improved understanding of the brain's response to an insult can improve patient care.

The first part of the program emphasized cerebral vascular disease, and is presented in this issue. The second part of the program related primarily to the clinical care of patients with mechanical brain injury, brain tumors, and seizures, and will be presented in the following issue of the *MCV Quarterly*.

DONALD P. BECKER, M.D.

Professor and Chairman
Division of Neurosurgery
Medical College of Virginia
Virginia Commonwealth University

The Interrelationship of Intracranial Pressure, Cerebral Blood Flow, and Brain Metabolism in Experimental Brain Injury*

THOMAS W. LANGFITT, M.D.

Charles H. Frazier Professor and Chairman, Division of Neurosurgery, University of Pennsylvania, Philadelphia

This presentation will be concerned with some of the relationships between intracranial pressure, cerebral blood flow, and brain metabolism as defined in animal models (Fig. 1). We will also be concerned with the pathophysiological changes that occur among these numerous variables.

We begin with the idea that our greatest concern is with normal brain function. The brain, as we know, functions through the electrical activity of its neurons, but another way of measuring or defining brain function is in terms of metabolism. For our purposes, the brain metabolizes only two substances—oxygen and glucose. Apparently, the brain does not have a store of oxygen nor does it have a significant store of glucose. It is, therefore, dependent upon a constant supply of these metabolites. It is also known that the brain is selectively vulnerable to ischemia, that the brain will not tolerate more than five minutes of cerebral circulatory arrest without irreversible brain damage—a unique feature of the brain. One can put a tourniquet around the arm, totally occlude the circulation to the arm for a period of an hour or two for purposes of doing surgery, and following the removal of the tourniquet, the arm functions perfectly normally. The arm contains bone and muscle, but it also contains nerve and the neuromuscular junction. What is so unique about the brain that permits it to tolerate only five minutes of ischemia, whereas peripheral nerve and neuromuscular junction can tolerate up to two hours of ischemia? This is one of the major dilemmas in our search for the pathophysiological and metabolic basis of brain injury; as of the moment, we do not really have a decent answer.

The cerebral metabolic rate of oxygen utilization and the cerebral metabolic rate of glucose utilization are dependent upon an adequate delivery of oxygen and glucose. The amount of oxygen that is available to the brain is determined by two major factors: the oxygen content of the blood and the cerebral blood flow. The amount of oxygen in the blood is, in turn, determined by the pulmonary function and by the blood oxygen-carrying capacity. Figure 2 shows the familiar oxygen-hemoglobin dissociation curve. As the three curves at pH 7.6, 7.4, and 7.2 reach asymptote, they do so at a partial pressure of oxygen (Pa_{O_2}) in the blood of about 80-100 mm Hg. When the Pa_{O_2} drops below this value, the degree of hemoglobin saturation is significantly influenced by the pH. The normal patient may show a Pa_{O_2} value from 80 up to 140 or 200 mm Hg and the saturation of hemoglobin does not increase significantly, and therefore, in terms of treatment, it does not make much difference whether the Pa_{O_2} is 80 or 200. We must remember, however, that the amount of oxygen available to the brain is a function not only of this value but also of cerebral blood flow. For example, if the cerebral blood flow is at a critical level, and the Pa_{O_2} drops by only a small amount (from 100 to 80), this may be quite sufficient to plunge the brain into hypoxia. It follows, therefore, that in our acutely

* This is an edited transcription of a lecture presented by Dr. Langfitt at the 27th Annual Stoneburner Lecture Series, February 7, 1974, at the Medical College of Virginia, Richmond.

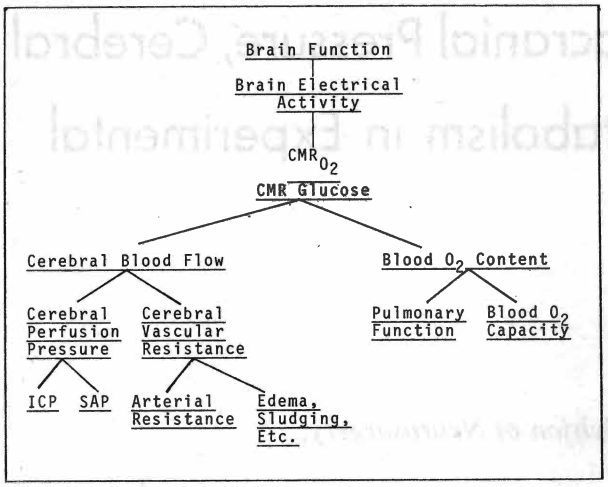

Fig. 1.

brain-injured patients, it is necessary to keep the Pa_{O_2} at 100 mm Hg or above. When the Pa_{O_2} is markedly decreased (to a value of 40 or 50 mm Hg), the pH value is of definite significance. At an alkalotic pH of 7.6 and about 40-50 mm Hg, one can see that hemoglobin is 85% saturated; whereas in acidosis, it is about 60% saturated. The important factor here is that in alkalosis, the hemoglobin hangs onto the oxygen; it will not release the oxygen as effectively as in acidosis. Therefore, in a situation where there is systemic hypoxia, a low Pa_{O_2}, and a reduction of cerebral blood flow approaching a critical value, the pH of the systemic blood becomes a tremendously important factor. It is quite possible, as the patient passes from an acidotic to an alkalotic pH, for the brain to be again plunged into hypoxia because at that alkalotic pH, the hemoglobin will not give up the oxygen as well as it did when the pH was acidotic.

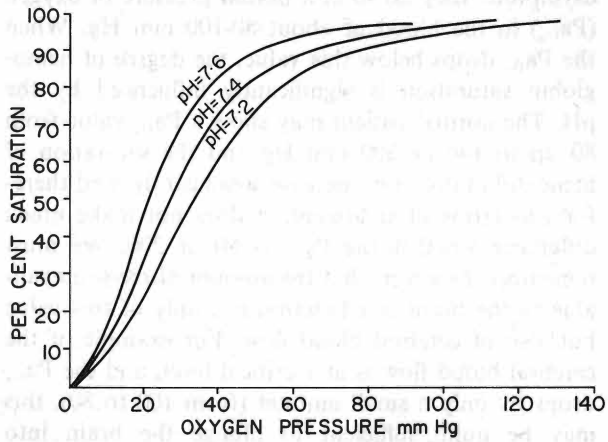

Fig. 2.

What are the factors which govern the flow of blood through the brain? The two major ones include the cerebral perfusion pressure—ordinarily defined as the inflow pressure (the carotid artery pressure) minus the outflow pressure (the jugular vein pressure)—and the cerebral vascular resistance (Fig. 1). The cerebral perfusion pressure, in turn, is influenced by the systemic arterial pressure (SAP) and the intracranial pressure (ICP). The cerebral vascular resistance, under normal circumstances, is primarily a function of arterial resistance; they are therefore called the resistance vessels, the arteries, and the arterioles. Also, under pathological conditions, cerebral vascular resistance is tremendously influenced by events that occur within the microcirculation in the capillary bed, in the form of such things as edema of the wall of the capillaries and sludging of the intravascular blood.

Figure 3 shows Poiseuille's equation for the flow of Newtonian fluids through a system of rigid tubes. This is only roughly applicable to a vascular bed but is helpful to us as we proceed through this discussion. Flow "Q" is directly proportional to the perfusion pressure and to the fourth power of the radius, demonstrating that the diameter or the radius of the cerebrovascular bed is extremely important in governing the flow through it. If we substitute "R" resistance for "R" radius, we come up with a rather simple Ohm's law for the cerebral circulation, which says that the blood flow is equal to the inflow pressure minus the outflow pressure divided by the resistance $\left(I = \frac{E}{R}\right)$. Under normal circumstances, the perfusion pressure is defined as the carotid artery pressure minus the jugular vein pressure. It is very important, how-

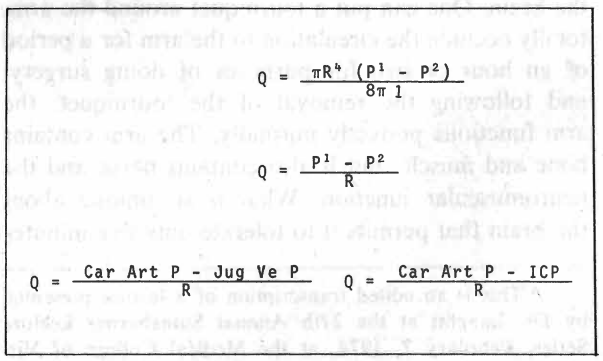

Fig. 3.

ever, that in the presence of increased intracranial pressure, this relationship no longer holds. This is because it has been well demonstrated that as the intracranial pressure rises, the cerebral venous pressure rises in concert, and the two pressures are essentially equal to all levels of elevated intracranial pressure. It has become the convention to say, therefore, that the perfusion pressure across the brain, in the presence of increased intracranial pressure, is equal to the carotid artery pressure minus the intracranial pressure again divided by the resistance.

If the vascular resistance, the denominator R, remained the same during a change in perfusion pressure, cerebral blood flow would passively follow changes in perfusion pressure, whether the perfusion pressure was decreased by decreasing blood pressure or decreased by increasing the intracranial pressure. We know that this is not true because of the phenomenon of autoregulation. Autoregulation is a ubiquitous physiological phenomenon which occurs in the brain, in the pulmonary circulation, the heart, gastrointestinal tract, and in the kidney. The one conspicuous organ which does not autoregulate is the skin. We define "pressure" autoregulation as a change in the diameter of the resistance vessels where blood flow remains constant in the presence of a change in perfusion pressure. According to Ohm's law of the cerebral circulation, if one reduces the perfusion pressure, the cerebral vessels dilate, thereby maintaining blood flow and if one increases the perfusion pressure, the cerebral vessels constrict, thereby maintaining the same blood flow. The origin of this particular type of autoregulation is somewhat uncertain, but our own data, as well as those of many others, would suggest that it is probably myogenic in origin and that it is probably a vascular reflex of the small arteries and the arterioles of the organ.

In man, normal cerebral blood flow is between 50–55 ml/100 gm/min. What one sees in man is a constant blood flow, even as the mean arterial blood pressure is slowly decreased, until the mean arterial pressure reaches a value of approximately 50–55 mm Hg at which point cerebral blood flow falls off abruptly; the reason it does so at this level is that the blood vessels are now maximally dilated, and they cannot dilate any further in response to the continued decrease in perfusion pressure. It is only at this point that blood flow bears a passive relationship to perfusion pressure.

One of the questions which we asked ourselves sometime ago was whether or not the cerebral vessels autoregulate in the same manner to increased intracranial pressure, decreasing perfusion pressure, as they autoregulate to decreased arterial pressure, decreasing perfusion pressure. This seemed extremely important because so many of our patients with a wide variety of brain insults develop intracranial hypertension. In fact, one could probably say that increased intracranial pressure, as a cause of decreased perfusion pressure, is more common in our patients than decreased blood pressure, or at least we can say that the blood pressure is more readily correctable.

Douglas Miller conducted a series of experiments with dogs in our laboratory, in an attempt to demonstrate the relationship between autoregulation and increased ICP. In these experiments, a hollow screw was put into the torcular Herophili of the dog and an extracorporeal shunt run from the torcular Herophili to the jugular vein; the remaining venous outflow from the dog's head was occluded. Either an electromagnetic flow meter or a bubble flow meter can be used to measure blood flow through the shunt. This gives one a continuous measurement of cerebral blood flow (CBF). Further studies have shown that we are measuring total or nearly total CBF from the hemispheres and the diencephalon in this preparation. Some of Miller's data are seen in Figure 4. First, he decreased the arterial pressure by bleeding the animal and measured the CBF over a wide range of perfusion pressures. He was then able to develop an autoregulatory curve, reflected by the open circles. This is a typical curve of autoregulation showing that there is no significant change in CBF until the mean arterial pressure is reduced to about 50 mm Hg. In the same preparation, he then raised the arterial pressure back to normal by reinfusing blood. While the arterial pressure was constant, he raised the intracranial pres-

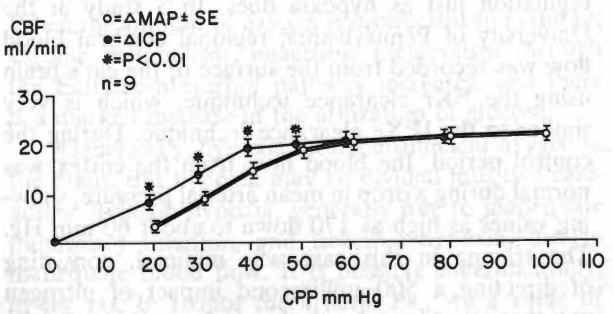

Fig. 4.

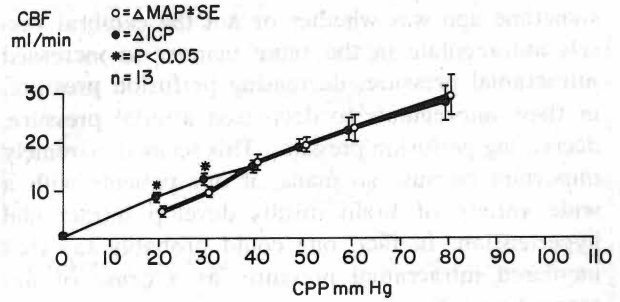

Fig. 5.

sure, thereby reducing the perfusion pressure. That, then, is represented by the upper curve, the autoregulatory curve for increased intracranial pressure. One can see that the cerebral vessels do, in fact, autoregulate just as well to increased ICP as they do to decreased SAP and, for unexplained reasons, they autoregulate somewhat better to increased ICP. These animals were then subjected to a period of brain hypoxia by reducing the Pa_{O_2} to values of about 15–20 mm Hg for a period of ten minutes. In other words, the animals were subjected to brain insult. The exact procedure was repeated. Figure 5 shows a pressure passive system. Following the cerebral insult, autoregulation was destroyed and the blood flow followed the perfusion pressure passively whether the pressure was decreased again by either decreasing blood pressure or by increasing intracranial pressure.

The importance of these kinds of data is that they demonstrate that when autoregulation is intact in a patient, he will tolerate large decreases in blood pressure, shock, or large increases in intracranial pressure without significant cerebral ischemia. If, however, the patient has had a brain injury of some kind and autoregulation is defective, the brain becomes much more vulnerable to either decreased blood pressure or to increased intracranial pressure.

Trauma to the brain in animals abolishes autoregulation just as hypoxia does. In a study at the University of Pennsylvania, regional cerebral blood flow was recorded from the surface of the cat's brain using the ^{85}Kr clearance technique, which is very similar to the ^{133}Xe clearance technique. During the control period, the blood flow from the cortex was normal during a drop in mean arterial pressure, showing values as high as 170 down to about 60 mm Hg. The trauma in this case was minimal, consisting of directing a 500 millisecond impact of nitrogen gas through a nozzle at the surface of the brain. It was minimal in the sense that there was no histological damage of the brain; the blood brain barrier was intact, and the EEG alteration was slight and immediately reversible. Autoregulation, however, was impaired, as demonstrated by the fact that following the trauma, when arterial pressure was again varied over a wide range, the characteristic picture of abolished autoregulation, was seen.

There is a second and equally important type of autoregulation which we term "metabolic" autoregulation, to be distinguished from pressure autoregulation. We can define metabolic autoregulation as a change in the diameter of the resistance vessels in order to meet the metabolic demands of the tissue. A good example of this is a change in cerebral blood flow in the region of the brain during an epileptic attack. Before the seizure occurs, blood flow is set for a given metabolic rate of oxygen. During the seizure, the tremendous increase in neuronal activity is accompanied by intense vasodilation, markedly increasing the blood flow to that region of the brain appropriate to the increased metabolic demands of the epileptic tissue. Whereas pressure autoregulation is a physiologic phenomenon, most likely a physiologic vascular reflex, metabolic autoregulation, by contrast, is presumably a chemical phenomenon, probably due to a change in extracellular pH at the level of the resistance vessels, the small arteries and the arterioles. As the neuron increases its activity, it produces more lactate and hydrogen ions. The hydrogen ions rapidly diffuse out of the neuron, through the extracellular space, and into the vasoactive vessel; the focal acidosis causes the vessel to dilate. The linkage in autoregulation, then, is apparently a hydrogen ion linkage. This means that if metabolism changes, a change in blood flow will follow which will be proportional to the change in metabolism as long as metabolic autoregulation is intact.

An excellent example of this rule can be demonstrated by what happens in hypothermia (Fig. 6).

Hypothermia		
	CBF (ml/100gm/min)	CMR_{O_2} (ml/100gm/min)
37°C	50	3.50
30°C	25	1.75

Fig. 6.

In hypothermia, the primary change is decrease in brain metabolism. Under normothermic conditions of 37°C, CBF is 50 and the cerebral metabolic rate of oxygen utilization (CMR_{O_2}) is 3.5 ml/100 gm/min. When one decreases the CMR_{O_2} to half that value, 1.75, by decreasing the temperature to 30°C, CBF falls at the exact same rate—from 50 to 25. If one did not know about the fall in CMR_{O_2}, seeing only that the blood flow had decreased by one-half, he would say that the brain was about to become ischemic because the CBF was at a critical level. This is not true because CMR_{O_2} has decreased the same amount. Even though CBF is markedly reduced, it is perfectly adequate for the needs of the hypothermic brain.

We have stated that pressure autoregulation is sensitive to various types of brain injury. The same statement can be made about metabolic autoregulation; thus, with certain kinds of insults, an *unlinkage* occurs between metabolism and blood flow and they go their separate ways. Figure 7 shows some selective data from our patients to demonstrate this fact. All of these patients were unconscious; most of them had severe head injuries. In all of these patients the CMR_{O_2} is reduced. The normal value of 3.5 is reduced to as low as one-third of that value and even lower in two of the patients. The first patient (BJS) shows a metabolism that is one-third of normal but the mean CBF is 114 ml/100 gm/min, the highest mean hemisphere blood flow we have seen in our series. In this circumstance, the patient has a condition which we defined a number of years ago as "vasomotor paralysis"—in which there is no metabolic or pressure control of the cerebral vessels; the tone of the cerebral vessels has been destroyed. They passively dilate, thereby increasing cerebral blood flow. It is impossible to influence this process because both the pressure and the metabolic control of the blood vessels has been destroyed. We see the same thing in the second patient (ED) with a CBF about 50% above normal, the CMR_{O_2} again about one-third normal. The third patient (JL) has a normal CBF, but it would not be normal if metabolic autoregulation were intact because the CMR_{O_2} is only one-half normal.

Patient	CBF	CMR_{O_2}	Outcome
BJS	114	1.05	Dead
ED	77	1.42	Dead
JL	52	1.76	Alive, well
EF	34	0.76	Alive, demented
MF	32	0.87	Alive, well

Fig. 7.

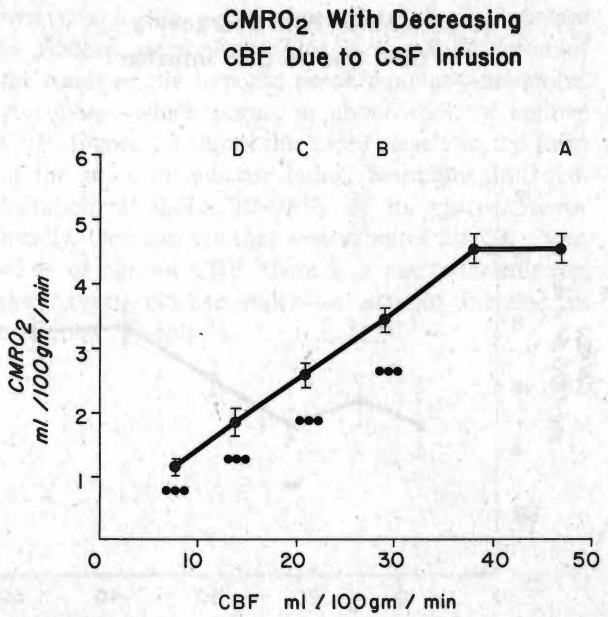

Fig. 8.

Some of the factors we are most interested in are: What constitutes a critical level of Pa_{O_2}, a critical level of mean arterial pressure, and a critical level of CBF for brain function? How much can we reduce the oxygen content of the blood or the cerebral blood flow before hypoxic tissue damage occurs? There is currently an argument as to what criteria should be used in determining hypoxic tissue damage. Two of these criteria are a decrease in high-energy phosphates (ATP and phosphocreatine) and an increase in anaerobic glycolysis. Normally, most of the glucose that is metabolized by the brain is done so aerobically. When the amount of oxygen is insufficient to maintain aerobic metabolism, anaerobic metabolism through the Embden-Meyerhof pathway increases, and there is a marked increase in the utilization of glucose.

Generically, hypoxia means insufficient oxygen to the brain. But hypoxia may be divided into two categories: hypoxic hypoxia, generally due to inadequate pulmonary function, and ischemic hypoxia, due to inadequate blood flow. It is possible experimentally, in the rat, to reduce the arterial Pa_{O_2} to a value of about 25–30 mm Hg at which point a decrease in

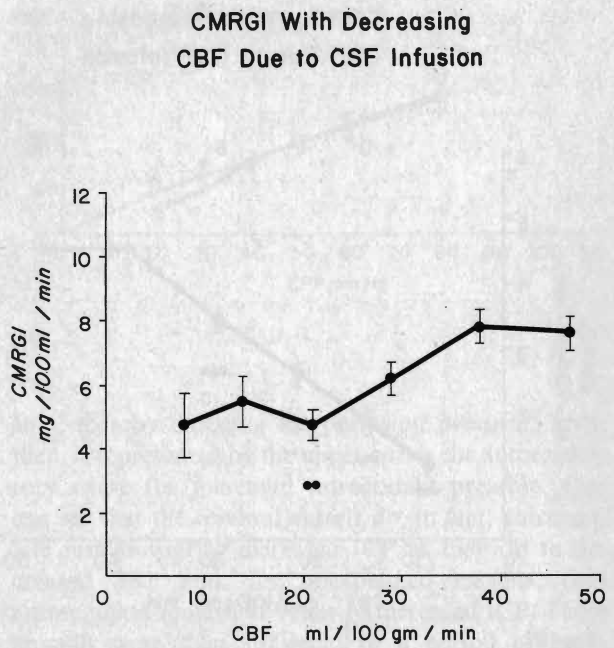

Fig. 9.

phosphocreatine occurs. ATP does not change because the phosphocreatine is converted to ATP temporarily. This process, which is a derangement in oxidative phosphorylation in the mitochondria, is one criterion of hypoxic damage. Again, in rats, if the arterial Pa_{O_2} is kept constant but the blood

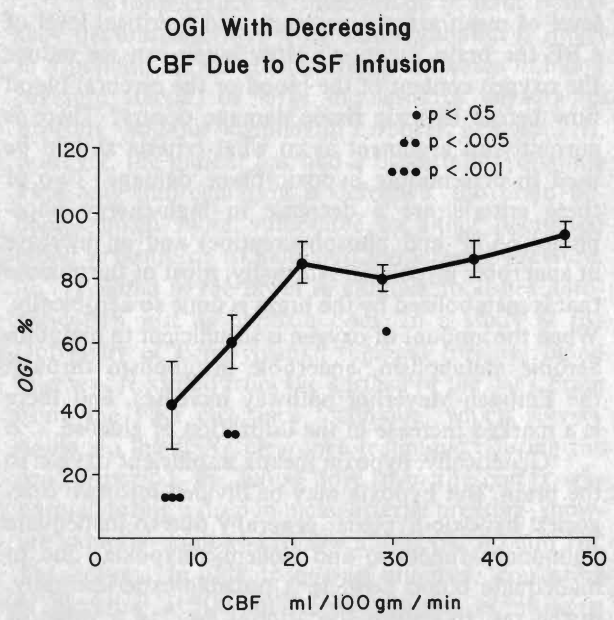

Fig. 10.

pressure is dropped, in order to find out what the critical mean arterial blood pressure is for the maintenance of adequate oxidative phosphorylation, the value is about 30 mm Hg, at which point we see a drop in phosphocreatine and ATP and an increase in AMP and ADP.

There have been a number of studies in recent years, both in man and in experimental animals, which show that the critical value for cerebral blood flow is approximately 45% of normal. According to Dr. Sundt's studies on patients undergoing endarterectomy, when the CBF dropped to a value of 18 or 19, about 45% of normal, there were EEG changes characteristic of brain ischemia.

There is another new concept regarding the linkage between metabolism and cerebral blood flow. We have said that in metabolic autoregulation, the primary change occurs in metabolism and blood flow follows due to hydrogen ion linkage. In some of our patient studies, we found evidence to suggest a reverse mechanism—when blood flow decreased due to increased intracranial pressure, metabolism seemed to decrease with the decrease in blood flow. Teleologically this is extremely important because it means that if one decreases the CBF slowly enough over a period of time, the metabolism will decrease by some unknown mechanism.

Studying the autoregulation curve in the dog with the experimental design described previously, where cerebral blood is measured continuously by the torcular outflow technique, we found that when the mean cerebral perfusion pressure was decreased to about 50 mm Hg by elevating the ICP, blood flow remained constant, but below a perfusion pressure of 50, blood flow began to fall. We had been concerned mostly with the horizontal portion of the curve and had not paid much attention to the falling portion. What we did, therefore, was to increase the intracranial pressure very carefully in small increments in order to produce 10% decreases in CBF. At each one of these levels, we measured the cerebral metabolic rate of oxygen and glucose. Figure 8 shows the data regarding the CMR_{O_2}. On the abscissa, we have CBF beginning with the normal value of close to 50; CMR_{O_2} is on the ordinate. We see that when CBF has been decreased to about 70% of control, CMR_{O_2} begins to fall and follows CBF down to approximately one-fifth of control. This decrease in CMR_{O_2} occurs at values of CBF 70% of normal, far above those values required to provide the brain with an adequate amount of oxygen. At this point, therefore, it seems clear to us

that the decrease in cerebral metabolism is not a manifestation of brain damage; rather it appears to be due to some kind of metabolic control mechanism which tends to turn off the brain as the oxygen supply is reduced, a protective mechanism intrinsic to the brain.

Figure 9 shows some of the data for the glucose —not quite so impressive, but again we see a decline in the cerebral metabolic rate of glucose with decreasing CBF. When we look at the area of the curve where CBF is 15 ml/100 gm/min, we see that this is the point where there is an increase in glucose metabolism. This is a manifestation of the onset of the hypoxic tissue damage—anaerobic glycolysis—which occurs at about 45% of control CBF. Figure 10 shows this more clearly in the form of the so-called glucose index. Normally the brain metabolizes about 90–95% of its glucose aerobically. One can see that at a value of 20–22, about 45% of control CBF, there is a marked change in the oxygen glucose index—a marked increase in anaerobic glycolysis.

Arteriography of Cerebrovascular Disease*

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Advances in reconstructive vascular surgery have increased the importance of accurate angiographic demonstration of the extracranial vascular tree. The limitations of the clinical examination are well recognized and make it essential that complete angiography be obtained prior to contemplated surgery. The locus of cerebral involvement may be determined clinically, but the site and extent of vascular disease in a surgically accessible location must be confirmed. The role of the angiographer is, therefore, twofold: Firstly, he must be able to safely perform complete angiography with adequate evaluation of the multiple sites of possible involvement; secondly, he must be aware of the pathophysiological changes which may occur and recognize the techniques and pitfalls he may encounter in delineating these changes. The present communication will describe the more common findings observed during angiography, along with some pitfalls the angiographer and clinician may encounter.

The example of carotid stenosis in Figure 1*A* certainly would be considered by most to be a surgical candidate with a remaining internal carotid lumen of less than 1 mm; however, the patient shown in Figure 1*B*, with smooth carotid artery stenosis narrowing the lumen by approximately 60%, may not be a candidate for operative intervention. Extracranial surgery was originally performed based on a theory of decreased cerebral blood flow, relative to an arbitrary degree of narrowing of the proximal arterial lumen. Thus, factors such as hypotension or cardiac arrhythmias which would result in decreased flow were considered to produce cerebral symptoms in the territory supplied by the stenotic vessel. This "stenotic theory" is now considered to play a minor role in the production of symptoms of cerebral ischemia (1). A significant change has occurred in recent years, so that now the patient with an "ulcerated plaque" and recurrent symptoms distal to this lesion is considered to be the prime candidate for extracranial carotid artery surgery. These ulcerated plaques are considered to be a source of cerebral emboli from clumps of blood elements or atheromatous materials which have developed from an area of irregularity and ulceration in a preexisting plaque. This explains the recurrent episodes of cerebral ischemia and the symptoms that may be present with a minor plaque or stenosis. Several examples of ulcerated plaques are seen in Figure 2. It is imperative that the carotid artery be evaluated carefully in multiple angulations, since these ulcers may at times be quite small and seen in only one projection. It is true, however, that most of the atherosclerotic disease and subsequent ulcer formation is on the posterior wall and the critical view is a lateral projection.

Another common problem in evaluating the extracranial carotid artery is the presence of an "irregular" plaque. This is a somewhat arbitrary designation and indicates only that there is no single focal area of ulceration (Fig. 3). The angiographer must be completely aware that the ulceration itself, however, may be filled with debris at the time of the contrast injection and should not be surprised if the pathological sample shows a much more irregular and ulcerated lesion. Additionally, a perfectly smooth carotid stenosis angiographically may at the time of surgery have a focal area of ulceration. Some authors consider that an irregular plaque cannot be differentiated from an ulcerated plaque

* Presented by Dr. Vines at the 27th Annual Stoneburner Lecture Series, February 7, 1974, at the Medical College of Virginia, Richmond.

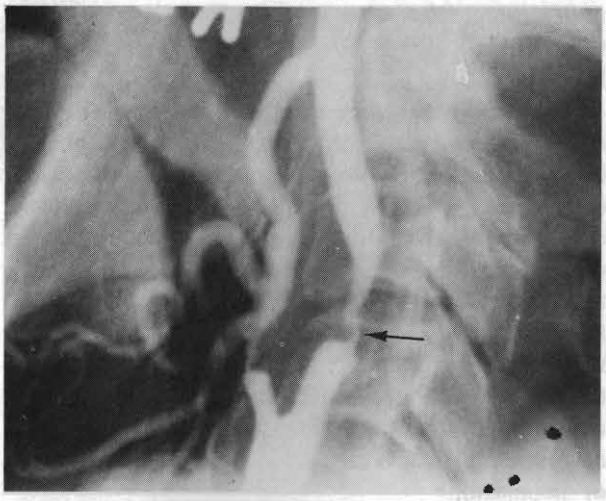


Fig. 1*A*—Severe internal carotid artery stenosis.

and that both should be treated as possible sources for cerebral emboli. This finding has been estimated to occur in 10–30% of the cases, but one might consider that this incidence could be reduced by utilizing multiple projections of the carotid bifurcation (2). Thus, one should examine the carotid bifur-

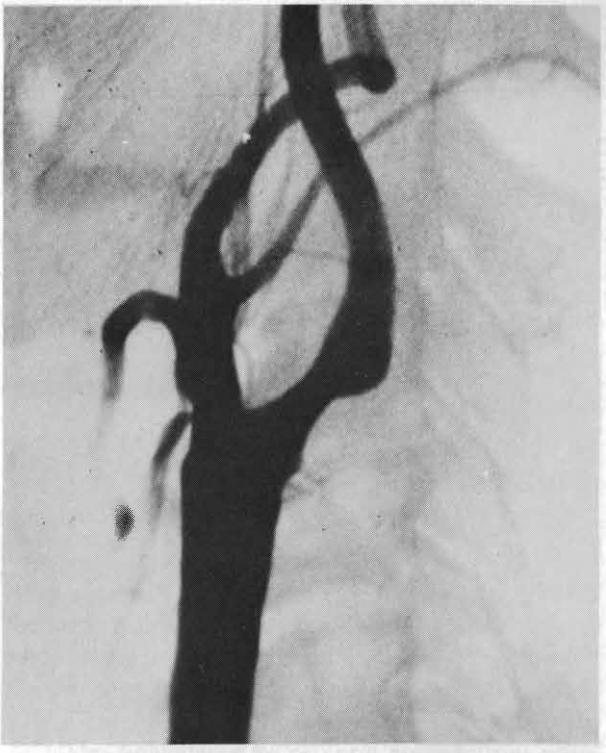
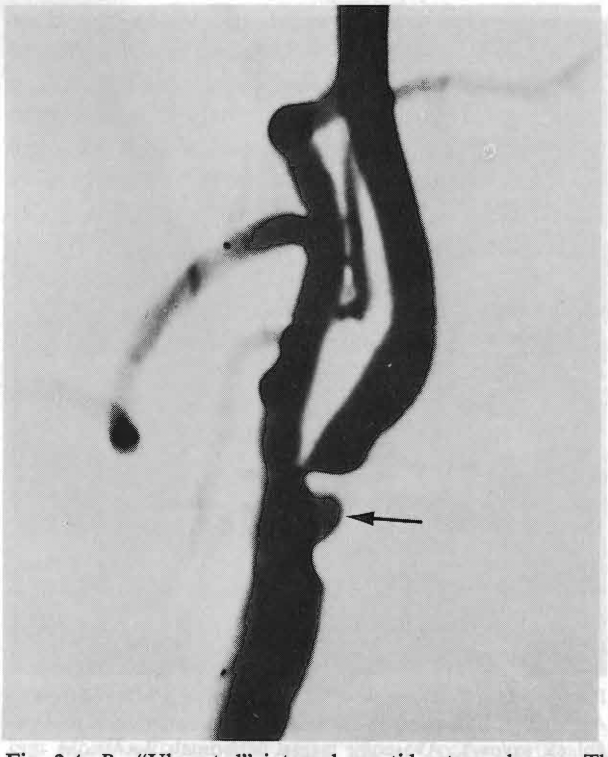


Fig. 1*B*—Moderate internal carotid artery stenosis with smooth borders.



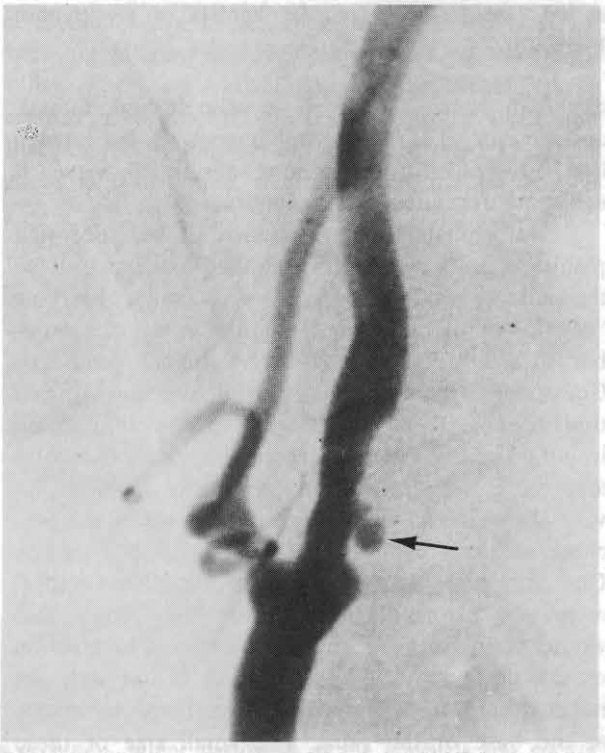


Fig. 2*A, B*—"Ulcerated" internal carotid artery plaques. The atherosclerotic plaque projects into the arterial lumen with the collection of contrast in the "ulcer" crater (arrow).

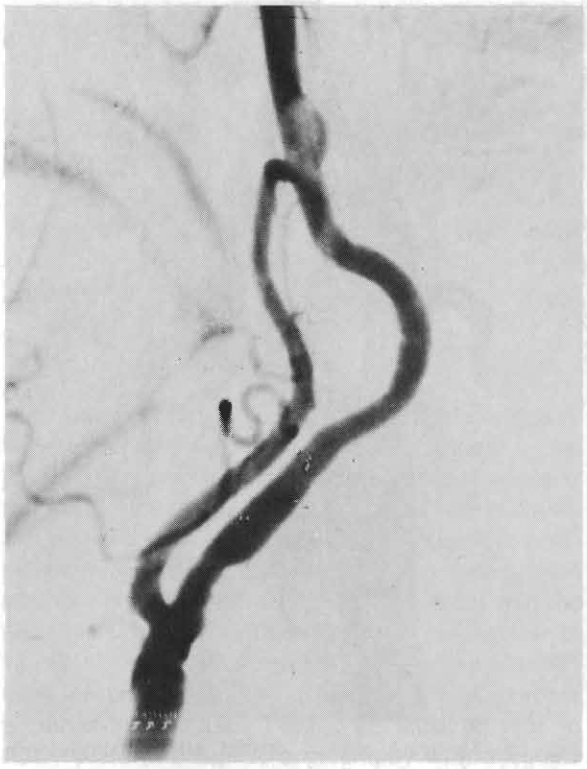


Fig. 3— Irregular internal carotid artery plaque. There is mild stenosis with irregular borders of the contrast posteriorly.

cation in at least three views—the frontal, lateral, and oblique. The angiographer should also have a low threshold for performing additional views if necessary for adequate evaluation.

Unfortunately, the presence of an ulcerated plaque does not indicate that this is the cause for the patient's symptoms. We are certainly observing "asymptomatic" ulcerated plaques in a large number of cases studied for other clinical problems. Conversely, there may be distal vascular lesions that are equal in importance to the bifurcation lesion. The second most common site of carotid atherosclerotic disease is its cavernous portion. Severe stenosis and ulcerations at this site may preclude surgical repair of the cervical carotid artery. One may also see stenosis of the middle cerebral artery or proximal anterior cerebral artery that would limit surgical therapy. Careful subtraction may be necessary when the vessel is not well delineated and free from the dense bony structures at the base of the skull. The small size of these ulcers and overlapping of vessels, which occurs with arch aortography, also severely limit its use alone to evaluate patients suspected of having vascular lesions.

Others have commented on the frequency of other pathological findings in the intracranial circulation of a patient studied for clinically suspected extracranial vascular disease. With more sophisticated brain scanning techniques and ancillary tools of clinical examination in recent years, however, the incidence of this observation is certainly lower than the previous reports of 5%. We do suggest routine angiography of the intracranial as well as the extracranial circulation, therefore, but for evaluating the distal vascular bed rather than for primary evaluation of an unsuspected subdural hematoma or neoplasm.

Complete occlusion of the internal carotid artery is now considered by most surgeons to be a nonoperable condition (3). The incidence of intracranial hemorrhage following reestablishment of circulation after an acute occlusion has made this procedure hazardous, and the poor success rate in reestablishing circulation in a chronically occluded lesion has made most surgeons unwilling to attack this lesion. There are, however, cautions of which

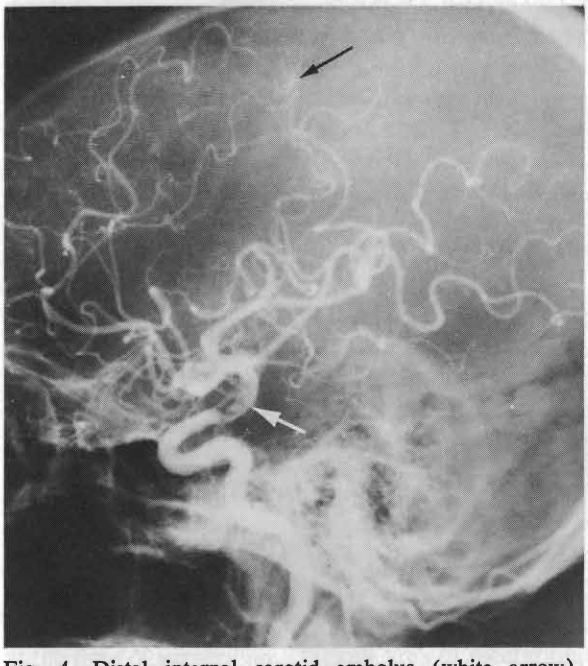


Fig. 4—Distal internal carotid embolus (white arrow). An area of infarction with arteriovenous shunting is present (black arrow). Avascular areas of branch occlusions are present in front of and behind the area of luxury perfusion.

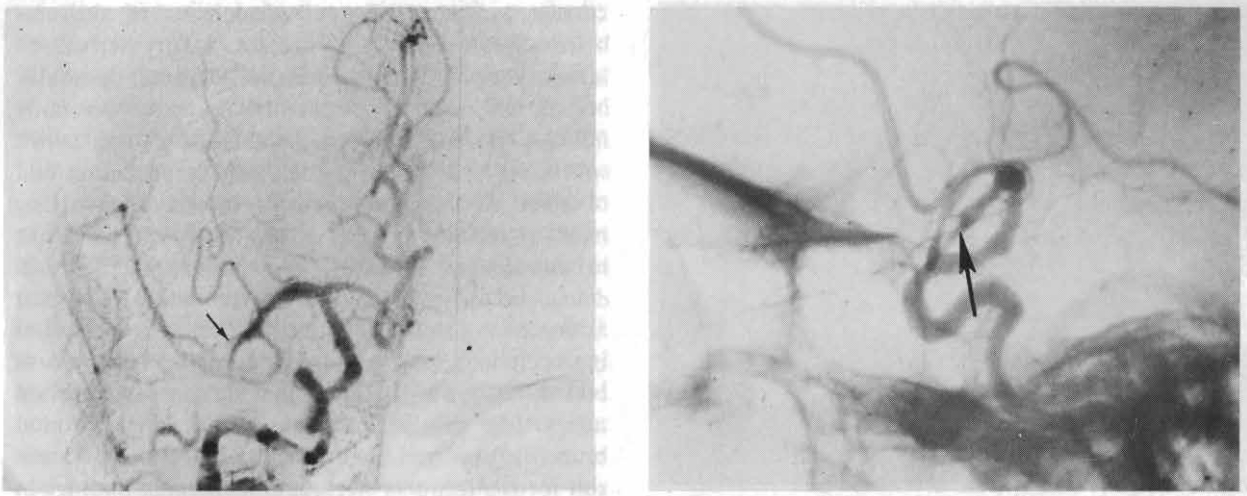


Fig. 5*A*, *B*—Frontal and lateral views of major branch occlusion of the middle cerebral artery (arrow).

one must be aware when evaluating what appears to be complete occlusion of the cervical portion of the internal carotid artery. The typical occluded internal carotid artery will obtain its intracranial filling via the opposite anterior cerebral artery or by the supraorbital branches of the ipsilateral external carotid, filling the ophthalmic artery and cavernous carotid in a retrograde manner. "Pseudo-occlusion" of the internal carotid artery may occur, however, when the stenosis is so severe that only a trickle of contrast extends beyond the obstruction, even though the internal carotid lumen immediately distal to the stenosis is normal. This faint linear accumulation of contrast may be obscured by overlying external carotid branches and may not reach the supraclinoid carotid for several seconds. Therefore, every apparent internal carotid "occlusion" should have a series prolonged for 10–15 seconds with a careful search for any patency into the skull.

The significance of cerebral emboli from other sources is also assuming increased clinical importance. Certainly most of the emboli will arise from a cardiac valve or an endocardial surface but increasing interest is developing regarding the possibility of emboli from the pulmonary veins. Large emboli may obstruct the carotid artery itself and this possibility must be carefully evaluated whenever there is obstruction other than at the bifurcation

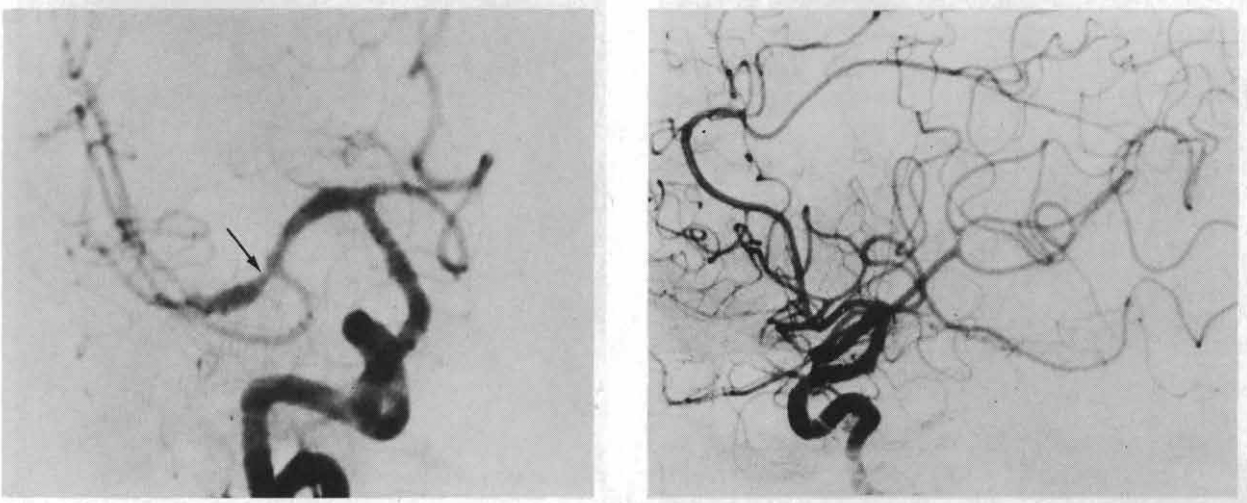


Fig. 5*C*, *D*—Frontal and lateral view of recanalization of this occlusion. Minor narrowing of the lumen is still present (arrow). An avascular area of a peripheral branch occlusion persists in frontal operculum.

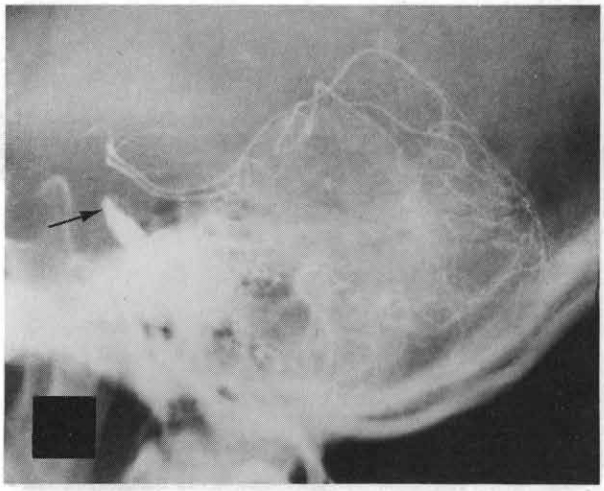


Fig. 6*A*—Basilar artery occlusion (black arrow). Collateral filling of superior cerebellar arteries has occurred via cortical anastomosis with the posterior inferior cerebellar arteries.

or in the cavernous carotid, for example, the common carotid or the midcervical carotid. These emboli may also lodge in the intracranial vascular tree, creating a flow deformity (Fig. 4) with recurrent symptomatology as fragments of the embolus migrate distally. An area of "luxury perfusion" is seen peripheral to the obstructed frontal opercular branch with a poorly defined stain and early venous filling. This patient developed further left hemisphere symptoms, and pathological confirmation was obtained of large hemorrhagic infarction involving most of the left hemisphere. Not all emboli result in this course, however. The patient in Figure 5 developed acute occlusion of the middle cerebral artery, two of the redundant trifurcation branches being occluded. Subsequent repeat angiography in several days, however, shows that this middle cerebral artery has recanalized and only a single frontal branch is now occluded. This illustrates a major reason for the frequent normal angiographic findings in the stroke syndrome. Emboli may be rapidly lysed and may migrate distally, allowing a positive angiographic diagnosis to be obtained only in the first few hours after the onset of clinical symptoms.

Basilar artery occlusive disease is a more serious problem, usually with a fatal outcome. Recent clinical data indicate, however, that some of these people survive with a reasonably minor neurological deficit. The patient in Figure 6*A* developed signs of severe upper midbrain dysfunction, with angiographic findings of complete occlusion of the basilar artery just below the origin of the superior cerebellar arteries and retrograde filling via the posterior inferior cerebellar arteries. A recent case illustrates a surgically altered course with a large basilar artery embolus (Fig. 6*B*). There is a filling defect ob-

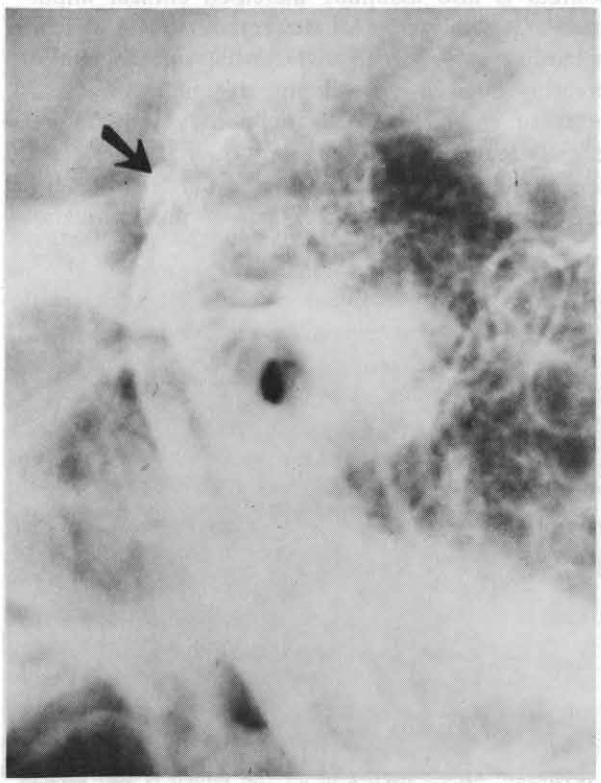


Fig. 6*B*—Embolic basilar artery occlusion (arrow).

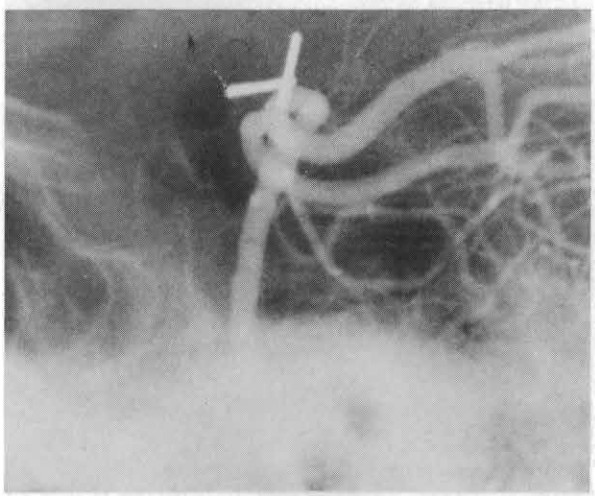


Fig. 6*C*—Postoperative patency of the basilar artery and its branches.

structing the distal basilar artery with markedly delayed flow. This view was obtained nine seconds following the injection of contrast. Collateral filling of the superior cerebellar arteries occurred via the posterior inferior cerebellar arteries. There was no filling of the posterior cerebral arteries or the dome of the basilar artery from either carotid injection or from collateral vessels. The patient underwent surgical removal of a large basilar artery embolus that was extending into both posterior cerebral arteries. The postoperative arteriogram (Fig. 6*C*) shows restoration of patency of the basilar artery and posterior cerebral arteries. This procedure did not alter the ultimate outcome of the patient but does indicate the development of surgical techniques and procedures which allow the performance of this embolectomy.

Summary. The importance of complete angiographic studies in patients suspected of extracranial vascular disease has been emphasized. Examples of a variety of lesions of the intracranial and extracranial circulation have been shown. It is important that the angiographer obtain adequate visualization of the circulation cephalad to the aortic arch with awareness of the type of lesion and technical problems that may be encountered. It is only in this way that further understanding of the "stroke syndrome" can be attained with appropriate therapy.

REFERENCES

1. HASS WK: Occlusive cerebrovascular disease. *Med Clin N Am* 56:1281, 1972.

2. CHASE N: Radiographic diagnosis of ulcerated atherosclerotic plaque. *Cerebral Vascular Diseases.* Eds. McDOWELL FH, BRENNAN RW, New York, Grune & Stratton, 1972, pp. 253–259.

3. BLAISDELL W: Extracranial arterial surgery in the treatment of stroke. *Cerebral Vascular Diseases.* Eds. McDOWELL FH, BRENNAN RW, New York, Grune & Stratton, 1972, pp. 3–15.

The Neuro-Ophthalmology of Cerebrovascular Disease*

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The neuro-ophthalmology of cerebrovascular disease is a vast plain of neuro-ophthalmic vistas, encompassing virtually all areas of disturbances of the eye-brain mechanism. This paper will be restricted to those areas of the neuro-ophthalmology of cerebrovascular disease which one might consider advances in its clinical diagnosis and treatment.

Most practitioners of medical and surgical neurology give little thought to that aspect of medicine generally accepted as the ideal approach to any disease—prevention. Usually when one is presented with an illness of the central nervous system, it seems to be a *fait accompli.* Although prevention is by no means new, certain aspects of it qualify as advances. There is one advance in cerebrovascular disease in which prevention plays a significant role. This is the recognition and surgical correction of atherosclerotic lesions of the extracranial carotid system which threaten the patient with that bane of antiquity—the "stroke."

Neuro-ophthalmology, largely by virtue of the carotid origin of the ophthalmic artery, plays a valuable role in the recognition, evaluation, therapy, and prognosis of disease of the extracranial internal carotid artery. Even this markedly restricted aspect of the neuro-ophthalmology of cerebrovascular disease is far too extensive to review adequately in this paper. I have therefore selected for discussion certain aspects of our neuro-ophthalmic approach to extracranial carotid disease. Some of these are well known; others are less obvious and frequently overlooked in our evaluation of patients. They all, however, are important pieces to the puzzle the patient may present. A wide variety of afflictions of the eye occur by virtue of its arterial dependence on the internal carotid artery. It is also logical to assume that changes in the distribution of the ophthalmic artery may reflect changes taking place in other channels of the internal carotid artery—the middle cerebral, the anterior cerebral, and depending upon anatomic variations, the posterior cerebral artery. This paper will discuss these afflictions, those common as well as rare, those well recognized, and those frequently overlooked.

Historically, the recognition of the eye as an index of cerebrovascular disease presents an interrupted course. Virchow is credited with the first autopsy correlation of ipsilateral blindness with carotid thrombosis; Gowers in 1875 demonstrated embolization as a source of central retinal artery and middle cerebral artery occlusion, resulting in monocular blindness and contralateral hemiplegia; Chiari followed in 1905 with his identification of the carotid bifurcation as a common source of atheromatous emboli to the cerebral circulation; in 1914 Ramsey Hunt emphasized the significance of transient symptoms involving the ipsilateral eye and contralateral extremities as strong evidence of ischemia. Thus by the turn of the century, the stage was set for incrimination of the extracranial internal carotid artery as a major source of "strokes." Embolization was known as a basis for ipsilateral eye and contralateral extremity symptoms and signs; the carotid bifurcation was known as a source of emboli; and transient symptoms were recognized as reflections of ischemia—a stroke prodrome or warning was discovered. Yet it was for Fisher in 1951 to rekindle interest in extracranial carotid

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disease with his emphasis on transient ipsilateral visual and contralateral extremity symptoms as precursors of future strokes. It is this reawakening which has led directly to the current advances in the medical and surgical neurologic care of extracranial internal carotid disease.

Amaurosis fugax, "fleeting blindness," has become a household phrase of those involved in the diagnosis and care of patients with carotid disease. The clinical picture of amaurosis fugax is reasonably straightforward. It consists of transient monocular painless visual loss. Much has been made of the character, duration, mode of onset, and resolution of the visual loss. Perhaps too much emphasis has been placed on such characteristic patterns as the window shade or picket fence effect. As a result, we find that many patients we see have already been "well educated" by housestaff. The potential patterns of visual loss are many. They include 1) an upper altitudinal loss of vision, "the window shade"; 2) a lower altitudinal loss of vision, "the picket fence"; 3) a generalized peripheral loss of vision; 4) a total blackout of vision; and 5) a central blurring of vision. The onset is most frequently abrupt; the curtain seldom drops or rises slowly. Occasionally, the event is associated with photopsia—crude visual hallucinations, usually in the form of showers or flecks of light but suggestions of geometric character will sometimes be seen. The key factors differentiating this photopsia from occipital disease and migraine are its clear unilaterality, the patient's age, and a detailed analysis of the history, which excludes migraine as a consideration and supports amaurosis fugax. The event need not be simply a blackout; dimming with a sensation of color may occur with green and yellow having popularity. In my experiences, color sensation has been uncommon.

The duration is generally brief, lasting two or three minutes, or rarely, five-to-ten minutes. We have found a common tendency for patients to misjudge the time sequence with frequent exaggeration of the period of visual loss. As this tendency to misjudge the duration of visual handicap may be bothersome diagnostically, we have adopted a simple time confirmation method. It consists of instructing the patient that you are going to begin to count and he is to assume that this is the onset of his visual symptomatology. We encourage the patient to "relive" the experience and with the use of our verbal clock, determine the average duration of visual loss. The rule is to find a duration of from one and one-half to two or three minutes despite the patient's initial claim of five, ten minutes, or longer of impairment. A watch second hand or stop watch could also be used; however, the vocal metronome seems helpful.

Although emphasis has been placed on the association of ipsilateral eye and contralateral extremity signs and symptoms, it should be recognized that their actual temporal association is unnecessary diagnostically and infrequent clinically. The eye symptoms and signs in isolation as evidence of cervical internal carotid disease are, in all likelihood, far more common than many practitioners realize. The work of Lubow and associates at Ohio State regarding "retinal strokes" underlines this concept. On rare occasions, transient homonymous visual impairment may be a reflection of internal carotid disease by virtue of a carotid origin of the posterior cerebral artery. Correct diagnosis will depend upon associated symptoms and signs.

The precise pathophysiology of these brief alterations of visual function continues to excite some debate. It seems certain that most are based upon emboli of either platelet aggregates or atherosclerotic debris. The exact point at which the embolus works its evil is less certain. As will be discussed, visible emboli in central retinal arterioles must play a role; whether they are the sole inciting force is less certain. Emboli to the choroid, not apparent clinically, may be important. The role of dynamic reduction of blood flow in the production of visual symptoms of carotid disease is probably small. It does, however, in selected but infrequent instances, probably play a significant role. Total carotid occlusions obviously cause some transient visual symptoms; generally, the symptoms cease following the stabilization occurring postocclusion.

Our diagnostic evaluation of patients with symptoms of transient visual loss consists of the careful analysis and integration of the specific physical signs with the presenting and elicited symptoms. Although we have defined amaurosis fugax as transient painless monocular visual loss, occasionally, residual deficits of vision remain. In addition, a number of patients with cervical internal carotid disease present not with transient ipsilateral eye symptoms but with fixed deficits.

Needless to say, the diagnostic evaluation of all patients with eye symptoms and signs suggesting ipsilateral carotid disease must begin with documentation of visual function—this includes best

corrected visual acuity, pupillary reactivity, and quantitative visual field evaluation. Although we palpate neck vessels, much less than total absence of vessel pulsation is lightly regarded. Auscultation is considered an important adjunct, with realization that bruits at sites other than the suspected symptomatic area may be significant. A bruit in isolation, however, is of dubious benefit.

The final, but perhaps most valuable, aspect of the neuro-ophthalmic diagnostic evaluation of patients suspected of harboring atherosclerotic disease is the dilated funduscopic examination with the recording of retinal artery pressures. If one is fortunate enough to be present during an amaurotic event, funduscopy may reveal white platelet emboli or bright cholesterol plaques passing through the central retinal arterioles. As this is a distinctly uncommon opportunity, one must usually be satisfied with residue which remains behind—most commonly, bright cholesterol material lodged at arteriole bifurcations. Hollenhorst, who first recognized the significance of retinal emboli in 1961, recorded a 33% incidence of these "Hollenhorst plaques" in patients with symptomatic cerebrovascular insufficiency.

Ophthalmodynamometry (ODM) should be routinely performed following a thorough funduscopic survey. The technique of ODM was first devised by Baillart in 1917 to measure central artery pressure. Svien and Hollenhorst popularized its use in 1956. One must keep in mind that ODM's are not a measurement of absolute pressures. This is, by and large, not a disadvantage as their primary benefit is a relative comparison of one eye with the other. We, as do many others, commonly record only the diastolic reading and routinely perform the ODM's in the sitting position. Before we consider the asymmetry significant, we require a 15% difference when the readings are below 40 units and a 20% difference when the readings are above 40 units. Any readings below 20 units are considered abnormal. The basic mechanism of ODM is the simple increase of intraocular pressure to levels above the central artery pressure. Needless to say, either increased or decreased intraocular tension will falsely alter the reading obtained. For this reason, tonometry—the recording of intraocular pressure—is essential in conjunction with ophthalmodynamometry. Despite great care in technique, false negative readings abound. Our experience has suggested that significant ophthalmodynamometric asymmetry indicates extreme stenosis, if not actual occlusion, of the symptomatic internal carotid artery. Ophthalmodynamometry plays a definite, though limited, role in the diagnosis of atherosclerotic cervical internal carotid disease. With the value of ODM's in perspective, we continue to use them routinely.

A discussion of amaurosis fugax is not complete without a brief review of the differential diagnosis. Although almost all transient monocular visual loss is due to internal carotid arterial disease, there are other considerations which include temporal arteritis, migraine and migraine equivalents, glaucoma, papilledema, Raynaud's disease, and other emboli. It is seldom difficult to identify these additional sources of transient monocular visual loss if they are appropriately sought.

Amaurosis fugax, although the hallmark of occlusive internal carotid disease and certainly its most common symptomatic neuro-ophthalmic presentation, is by no means the only eye manifestation encountered in internal carotid vascular disease. The following discussion will describe a number of less commonly recognized clinical syndromes caused by occlusive internal carotid disease.

Retinal stroke, although commonly an integral aspect of the syndrome of amaurosis fugax, certainly occurs in the absence of prior symptomatic transient monocular visual loss; there can be little doubt that the occurrence strongly suggests atherosclerotic disease of the cervical internal carotid artery. The work of Lubow and associates at Ohio State in 1972 has shown, angiographically, a 95% incidence of carotid bifurcation disease in patients having retinal strokes as compared to asymptomatic age-matched controls in which angiography demonstrated a 25% incidence of bifurcation abnormalities. What do retinal strokes consist of? They consist of occlusive disease of the retina, previously relegated to ophthalmic practice. It has become apparent, however, that many "retinal strokes" are of embolic origin and manifest cholesterol plaques exactly like those seen in amaurosis fugax.

Central retinal artery and artery branch occlusions, as well as more distal cholesterol emboli, producing peripheral defects frequently unappreciated by the patient, constitute the retinal stroke. Their clinical manifestation is abrupt, usually painless, persistent monocular visual loss. Blindness and optic atrophy frequently follow retinal strokes. In our brief historical review, one may recall Gowers' allusion to ipsilateral optic atrophy and blindness associated with contralateral hemiplegia. Carotid disease is obviously likely with this association. What

must not be forgotten is that isolated blindness and optic atrophy may also reflect cervical internal carotid disease. Other funduscopic alterations causally related to cervical or extracranial internal carotid disease occur. It is not commonly recognized that ipsilateral carotid occlusive disease may serve to prevent the expression of both hypertensive and diabetic retinopathy. When a patient is seen with remarkably asymmetric hypertensive or diabetic retinopathy, consideration of the possible presence of occlusive internal carotid disease should follow.

Ischemic retinopathy, recognized as evidence of chronic retinal ischemia by Kearns and Hollenhorst in 1963, is a syndrome consisting of a retinal picture similar to diabetic retinopathy with dilated veins, some resultant blot hemorrhages and microaneurysms, low ophthalmodynamometric values, and at times, severe orbital pain. Ischemic retinopathy can be differentiated from diabetic retinopathy by the fact that it is unilateral and that there is no biochemical evidence of diabetes mellitus. Obviously, diabetes and the Kearns ischemic retinopathy may coexist. The significance of ischemic retinopathy is its reflection of severe impairment of internal carotid as well as collateral circulation to the eye and orbit. Not uncommonly, the major trunks from the aortic arch are the site of the vascular occlusion.

There are three additional presentations of eye signs reflecting occlusive vascular disease which generally indicate, as does ischemic retinopathy, a more severe and diffuse vascular embarrassment of orbital as well as central retinal circulation. These are ischemic inflammation, "pseudouveitis"; ocular hypotony; and neovascular glaucoma.

Ocular inflammation resembling uveitis may result from chronic ocular ischemia secondary to diffuse occlusive vascular disease, involving not only the internal carotid but the collateral channels as well. This syndrome is characterized by dilatation of episcleral veins, a turbid anterior chamber, iris synechiae, corneal precipitates, and edema. On occasion, vitreous hemorrhage may occur and cataracts may rapidly develop.

In circumstances where acute reduction of orbital blood flow affects more specifically the ciliary body, reduced production of aqueous humor results leading to ocular hypotony and potentially phthisis bulbi.

Chronic ischemia in the eye is also a stimulus to new vessel production. Prolonged reduction of orbital blood flow may result in proliferation of neovascular tissue on the surface and angle of the iris. This will often culminate in occlusion of the anterior chamber angle and a malignant form of secondary glaucoma referred to as neovascular or hemorrhagic glaucoma.

It is obvious that the last three syndromes reflecting eye involvement, secondary not simply to carotid stenosis but most certainly to more severe carotid occlusive disease, as well as occlusive disease of the usual orbital collateral channels, may occur either in sequence or in combination. Their incidence in reality is quite low. Ischemic retinopathy, a less severe manifestation of the same process, is reported in only 5% of unilateral carotid occlusions. It is wise, however, to realize that eye signs other than simple transient or permanent monocular visual loss may point to disease of the cervical carotid vessels.

In conclusion, one should mention the occurrence of unilateral Horner's syndrome in a not insignificant number of unilateral internal carotid occlusions. This quite likely represents involvement by edema and ischemia of the carotid sympathetic plexus in the adventitia.

BIBLIOGRAPHY

ALLEN N, MUSTIAN V: Origin and significance of vascular murmurs of the head and neck. *Medicine* 41:227, 1962.

DAVID JE, HUMPHRIES AW, YOUNG JR, BEVEN EG: A correlation of neck bruits and atherosclerotic carotid arteries. *Arch Surg* 107:729, 1973.

FISHER CM: Observation of the fundus oculi in transient monocular blindness. *Neurology* 9:333, 1959.

HOLLENHORST RW: Significance of bright plaques in the retinal arterioles. *JAMA* 178:23, 1961.

KEARNS TP, HOLLENHORST RW: Venous-stasis retinopathy of occlusive disease of the carotid artery. *Proc Staff Mtg Mayo Clinic* 38:304, 1963.

KNOX DL: Ischemic ocular inflammation. *Am J Ophthal* 60:995, 1965.

KNOX DL: Ocular aspects of cervical vascular disease. *Survey Ophthal* 13:245, 1969.

KOLLARITS CR, LUBOW M, HISSONG SL: Retinal strokes. I. Incidence of carotid atheromata. *JAMA* 222:1273, 1972.

O'DOHERTY DS, GREEN JB: Diagnostic value of Horner's syndrome in thrombosis of the carotid artery. *Neurology* 11:842, 1958.

SVIEN HJ, HOLLENHORST RW: Pressure in the retinal arteries after ligation or occlusion of the carotid artery. *Proc Staff Mtg Mayo Clinic* 31:684, 1956.

Medical Management of Cerebral Vascular Disease*

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I shall begin with two axioms and a few definitions and, subsequently, offer conclusions and a few words to the medical lexicon. Axiom #1—there is no such thing as a CVA. In the year 1974, with cerebral angiography widely available and with computerized axial transverse tomography coming into its own, CVA can only stand for "confused vascular analysis." Axiom #2—the best time to treat a stroke is before it happens or at the very least, before it significantly disables the patient.

Ultimately, there are two fundamental kinds of stroke: cerebral infarction or ischemia and cerebral hemorrhage. The first relates to a focal cerebral dysfunction due to transient or persistent insufficiency of blood in a given cerebral vascular territory. The second relates to the often massive escape of blood into the brain parenchyma, the subarachnoid space, or both locations. From a practical standpoint, a lumbar puncture which fails to reveal blood, and particularly xanthochromia, effectively rules out almost all cerebral hemorrhages and suggests the process of cerebral ischemia or infarction. The two major kinds of stroke can be differentiated clinically without too much difficulty. On the other hand, the problems of etiology, pathogenesis, and management continue to challenge the clinician. Since strokes due to cerebral ischemia and/or infarction account for 75% or more of all observed strokes, and because of the preponderance of strokes of this variety and the limits of space, we will confine our attention here entirely to the problem of cerebral ischemia and infarction.

If one is to classify strokes due to cerebral ischemia, one may do so in terms of the nature and duration of the episode, on the one hand, and the vascular territory of involvement, on the other hand. When an episode of focal cerebral dysfunction occurs which is related to a given vascular territory, persists for minutes to at most 12–24 hours, and then vanishes completely, we say that the patient has had a transient ischemic cerebral attack. If the episode involves the vision of one or the other eye (patients often state that it seemed as though a shade was drawn across the vision of the eye), we state that the patient has had a transient retinal ischemic attack or amaurosis fugax. Onset over a period of a few seconds to a few minutes characterizes these episodes. If an episode develops either quickly or over a period of minutes to hours and if the focal deficit persists for many days and then largely but not completely clears, we say that the patient has had a transient ischemic episode with incomplete recovery. From a pathogenic and treatment standpoint, the transient ischemic episodes and transient ischemic episodes with incomplete recovery are considered to be a single entity. If the focal deficit appears over minutes to hours or sometimes even days and persists, severely disabling the patient, we say that the patient has suffered from a completed stroke. In this situation, cerebral infarction, characteristically, is the underlying cerebral pathology.

Quite frankly, most neurologists in the field at this time can point to no satisfactory treatment for the completed stroke, except for good medical care with attention to cardiopulmonary function, management of blood pressure, withholding of oral intake, and treatment entirely by intravenous fluids during the acute period, particularly when the patient is mildly obtunded. These efforts have stood the test of time. More specific therapy, such as stellate ganglion block and CO_2 inhalation, as well as streptokinase and urokinase, have fallen by the wayside, some buried by their own initial advocates. Nevertheless, the search must go on. In only one area, that of stroke in evolution involving the brain stem, has a specific form of therapy, anticoagulation,

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reduced mortality and morbidity to a degree—tenfold—which causes the Mayo group to advocate its use with vigor in this specific instance.

Ischemic strokes are also defined in terms of territory of presumed blood vessel involvement. The two major territories are those of the carotid middle cerebral–anterior cerebral system and the vertebrobasilar system. Carotid territory dysfunction is characterized by one or more of the following: ipsilateral, transient or rarely persistent visual loss due to the fact that the ophthalmic artery is the first branch of the carotid artery, contralateral weakness, contralateral cortical sensory dysfunction, contralateral hemianopia, and in almost all of the right-handed individuals and in some 60% of left-handed individuals, aphasia or dysphasia—the impairment of the faculty of language when the left internal carotid artery territory and left cerebral hemisphere are involved. The words of the psalmist, "If I forget thee, O' Jerusalem, let my right hand forget its cunning and let my tongue cleave to the roof of my mouth," characterize the classic dominant carotid territory lesion.

Strokes due to vertebrobasilar involvement rarely give rise to the classic crossed syndromes so familiar in neuroanatomy texts, such as Weber's syndrome, characterized by an ipsilateral third nerve palsy and a contralateral hemiplegia. More often, one or more of the following characterize ischemia in the vertebrobasilar territory: alternating hemiparesis, ataxia, diplopia, dysarthria, hiccup, alterations in respiratory pattern, nausea and vomiting, and pupillary changes.

Many things can cause transient or persistent focal cerebral or retinal ischemia. Particularly when ischemia is encountered in younger individuals, one may suspect a primary cardiac source involving the valves as in rheumatic endocarditis or verrucous endocarditis, left atrial thrombosis in rheumatic heart disease with mitral stenosis and atrial myxoma. Changing pulses and/or chest pain should suggest a dissecting aneurysm. Atrial fibrillation should always suggest a primary cardiac source. A variety of systemic diseases including polycythemia, thrombotic thrombocytopenic purpura, idiopathic thrombocytosis, and granulomatous angiitis, as well as disseminated intravascular coagulation should be thought of in all cases; but the garden variety of transient or persistent stroke due to focal cerebral ischemia, as seen in the hospital, usually appears in a seemingly healthy male at an average age of 62. The incidence of what is still fashionably called "cerebral thrombosis" in this patient population approaches 1% per year in the age group 65–74. Almost 40% of these patients have a history of increased blood pressure, 20% a history of diabetes, and at least 50% will give a history of a previous transient cerebral ischemic episode. Hypertension, diabetes, and previous TIA's constitute the triad of the stroke-prone profile; indeed, 30–37% of patients with transient ischemic episodes will exhibit a full-blown completed stroke within five years if untreated.

Our New York University (NYU) study of the surgical treatment of transient and persistent focal cerebral ischemia revealed approximately one-third of the patients with transient ischemic attacks, one-third with transient ischemic attacks and incomplete recovery, and one-third with completed strokes. Arteriographic studies had borne out the fact, first extensively studied by Hutchinson and Yates, that the garden variety of transient or persistent focal cerebral ischemia is related more to observable extracranial atheromatous arterial disease, particularly in the carotid arteries than to *primary* intracranial occlusive disease and indeed, more to stenosis than to occlusion.

Various studies have defined the preferred sites of atheromatous disease in the surgically approachable areas of the brachiocephalic system. Predominance of the carotid bifurcation involvement is apparent with stenosis of greater than 30% being present in more than one-third of all right and one-third of all left carotid arteries. Frank occlusion is much less common. In the intracranial circulation, observable stenotic lesions in the carotid territory fall tenfold. The values for occlusion in the distal carotid artery are inflated because in many cases occlusion is taken to represent propagation of clot from the origin of the internal carotid artery. Proximal vertebral artery involvement has been seen in approximately 20% of all vertebral origins on the right and left. Considerably less often, but probably symptomatically much more important, is stenosis which is seen distally in the vertebrobasilar system.

There is no clear-cut relationship between frank carotid occlusion and the degree of neurological deficit. Another problem encountered is that patients often do not present with a single high grade stenotic lesion in the artery appropriate to their cerebral symptoms; rather they present with a complex mixture of arterial lesions which may give rise to the exact same symptomatology.

In our NYU experience with 400 patients, we tried to group all of the cases into a meaningful framework. It is understood that every patient's vascular fingerprint is individual and that there are almost as many patterns of lesions as there are symptomatic patients. It was interesting that when we classified a lesion as a lesion, if the stenosis occupied more than 30% of the vascular lumen in any x-ray plane, 17% of the patients showed no lesions which occupied 30% or more of a vessel lumen after four-vessel angiography. The existence of this pleomorphic pattern of vascular lesions, paired with the fact that 50% of all individuals over the age of 50 have a major stenosis of at least one of the four major vessels (two carotid and two vertebrals, all leading to the brain), and that only 10% ultimately become symptomatic, offered numerous roadblocks to our eventual understanding of the pathogenesis of at least most of the carotid territory transient and persistent strokes.

Until the 1960's, it had been customary to attribute the patient's symptoms to the degree of stenosis or occlusion of the vessel developing by one or more pathogenic processes, which led to marked luminal compromise and then, presumably, to symptoms which developed in proportion to the degree of collateral circulation possessed by the patient. Surgical studies compared with angiographic observations, however, began to question this stenotic theory of pathogenesis of strokes. A new concept of pathogenesis, best characterized as the embolic theory, arose.

The sources of arterial emboli from lesions, which may occupy less than 30% of the vascular lumen formerly considered to be insignificant, were as follows: necrotic plaque, clot from ulcer, and platelet emboli from ulcer. Ulcerations can easily be seen on angiography, in the initial phases associated often with high grade stenosis, and the dye can also be seen hung up in the ulcer crater. Distal propagation of thrombus, significantly compromising the internal carotid lumen, can be seen. Radiologic evidence from NYU disclosed 24 ulcerative and 22 irregular lesions at the origin of the internal carotid arteries of the neck in the cerebral angiograms of 71 patients with history of cerebral vascular occlusive disease. Further, the incidence of middle cerebral branch occlusion associated with either irregular or ulcerative lesions of the extracranial carotid arteries was 33%, compared to 16% of patients with angiographically "normal" or smoothly stenosed extracranial carotid arteries. More and more evidence, therefore, implicates the process of arterial–arterial embolization as a major one, particularly in transient and often in persistent focal cerebral ischemia.

Thus we have a process of arterial–arterial embolization as distinct from cardiac–cerebral artery embolization, which apears to be a major pathogenic factor in ischemic strokes toward which treatment should be aimed before the stroke occurs, when we are warned by the presence of a transient episode. Since the term embolus is overextended and usually implies cardiac source, muddying our thinking about cerebral ischemia, I have long felt that to require the term "cerebral embolus" to include in its embrace the widespread process of arterial embolization would be like asking a mouse to extend its amorous interests to an elephant; it would confound confusion where too much confusion already exists. I have proposed, therefore, the acronym, "artarem," to describe an embolus which arises in an artery (art-) and lodges in a distal artery (-ar-) by a process of embolization (-em). The process can be described as being artaremic. On the other hand, if the embolus, from clinical evidence, appears to arise from the heart, the term "cardiarem" will serve, and the process of heart-to-artery embolization might be described as "cardiaremic." Adjectival modifiers such as cerebral fibrinoplatelet artarem or myxomatous cerebral cardiarem could give rise to further diagnostic precision.

Having noted angiographic and operative evidence of the artaremic process, research began for a safe medication which could delay or inhibit the first step in fibrinoplatelet emboli. Surgical studies had already clearly revealed that the neck lesion often was related to visual and cerebral symptoms since these symptoms disappeared after surgery, whereas control patients who were not surgically treated with known similar lesions often developed stroke or permanent visual defect. The experience of the Cooperative Study of Extracranial Arterial Occlusion showed a tenfold reduction in the appearance of frank stroke in the territory of the operated artery in the neck. There can be no doubt, therefore, that the source of the patient's difficulty was most often in the prominent lesion at the carotid bifurcation. Surgery, however, has its drawbacks and random studies of surgery have failed to precisely define the role of arterial surgery.

Our own NYU random study reveals one rea-

son for the confusion. In patients who were not randomized, the nonsurgical patients showed a considerably smaller initial long-term survival than the surgical patients, suggesting a significant measure of surgical selection. Where the patients were randomized, long-term survival was equal in both groups; initial surgical mortality, however, was significantly greater.

Our figures show that in patients with full recovery from transient cerebral ischemic attacks, surgical mortality is down to 3% and long-term survival is greater than in the nonsurgical group (numbers too small for statistical significance). Transient ischemic attacks in patients with incomplete recovery are characterized by a greater degree of surgical mortality; but in the proportion surviving, a larger percentage survived five years. The other major point of the surgical study was that in patients with completed stroke, surgical mortality is prohibitive, particularly in patients who are obtunded, and long-term survival is significantly better in the nonsurgical group. Mortality over the long term, however, is not simply a function of cerebral vascular disease. Associated atherosclerotic disease is characteristic of this group of patients. While the major cause of death in the postoperative period after surgery is stroke, over the long term, cardiac causes account for as many deaths as stroke, and the number of deaths in the surgical and the nonsurgical series approach one another.

Since stroke surgery is prophylactic, the major question remains—will stroke surgery in selected patients significantly diminish the proportion of stroke and significantly improve survival? No data from randomized studies have yet settled this issue completely satisfactorily. Thus, the search has gone on for safe medications which will depress the tendency for fibrinoplatelet emboli to form on ulcerated or irregular plaques. Obviously nothing can be done for the initial process of disengorgement of gummatous and cholesterol material from the broken down plaque. Anticoagulants have proven to be successful in depressing the number of transient ischemic episodes; however, anticoagulants can be given only to a reliable, stable patient population, and such therapy would be much more successful in Rochester, Minnesota for Dr. Millikan's and Dr. Whisnant's patients than for our patients at Bellevue Hospital.

In the 1960's, Frasier Mustard's group in Canada (1, 2) noted inhibition of the platelet aggregation release reaction by sulfinpyrazone. Subsequent studies have shown that anti-inflammatory drugs, such as butazoladine derivatives and aspirin, the pyridopyramidine compounds such as Persantine® and the tricyclic antidepressant drugs, have an effect on platelets. The most profound inhibition of ADP or collagen-induced platelet aggregation is shown by aspirin. In the in vitro studies, 37% of serotonin is released with no aspirin, as compared to no release with aspirin. A tenfold increase in ADP reveals that aspirin can no longer be effective against aggregation, but that there is continuing inhibition of serotonin release. Similarly, aspirin inhibits connective tissue induced aggregation as well as serotonin release from platelets. This effect of aspirin is not confined only to the test tube, but it has been shown in dogs that arterial thrombus is retarded when the intimal surface of an artery is mechanically or chemically damaged and similar results have been shown after endarterectomy in patients receiving aspirin (3). While it is known that as little as 5 gr of aspirin may depress the aggregation release reaction for as long as five days in man, as judged by the epinephrine challenge to platelet rich plasma as well as with most in vitro tests, this association of inhibition of aggregation is not clearly related to observed inhibition of transient ischemic episodes. It has been noted, however, that aspirin will stop transient retinal ischemic attacks, amaurosis fugax. We have been able to follow a most instructive patient at NYU who had as many as nine attacks daily of amaurosis fugax, with response to increasing doses of aspirin in terms of attacks and effect on platelet aggregation release reaction. This unusual patient demonstrated that the optimal dose of aspirin for amaurosis fugax appears to be 5 gr qid. A retrospective study recently published in *Stroke* by Dyken (3) shows a relative diminution of transient cerebral ischemic attacks in aspirin-treated patients. It is of interest that in some of his cases the attacks responded better to four aspirin tablets per day than to two. Prospective studies of aspirin, directed toward not only the question of aspirin inhibition of transient attacks, but also to the more important question of prophylaxis against completed stroke, are in process in the United States and in Canada and no definitive statement will be made on this subject for at least another year.

The judicious mixture of surgical therapy and prophylactic therapy with a safe platelet antiag-

gregant appears at this time to be the best combination of approaches to the axiom: The best time to treat a stroke is before it happens.

REFERENCES

1. MUSTARD JF, ROWSELL HC, SMYTHE HA, SENYI A, MURPHY EA: The effect of sulfinpyrazone on platelet economy and thrombus formation in rabbits. *Blood* 29:859, 1967.

2. SMYTHE HA, OGRYZLO MA, MURPHY EA, MUSTARD JF: The effect of sulfinpyrazone (anturan) on platelet economy and blood coagulation in man. *Can Med Assoc J* 92:818, 1965.

3. DYKEN MC, KOLAR O, JONES FH: Differences in the occurrence of carotid transient ischemic attacks associated with antiplatelet aggregation therapy. *Stroke* 4:732, 1973.

Cerebral Blood Flow Studies in Stroke*

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I will discuss here some work we are doing in our laboratory on the measurement of cerebral blood flow (CBF). We are using the gamma camera, which is connected to a computer, to measure regional CBF. We inject ^{133}Xe into the carotid artery and, by using multiple probes, measure the clearance from multiple regions of the head. The advantage of the gamma camera is that it has excellent resolution and has common probe characteristics. It may be thought of in terms of multiple probes, although it has a single crystal, and it achieves the desirability of multiple regional CBF recordings confined essentially to one hemisphere because of the depth characteristics of the collimation.

The formula for height-over-area analysis in the clearance for fast and slow flow (or the first and second slopes of the curve, F1 and F2) is handled by the computer which gives an automatic write-out. In addition, having injected the xenon, which washes out fairly rapidly over an interval of 12 minutes, we then inject with a nondiffusable isotope, technetium. By use of a different formula, this gives us the regional cerebral blood volume, so that in the same patient, we have both the regional cerebral blood flow and the regional cerebral blood volume on the computer write-out. Table 1 is a typical record that comes out of the automatic print-out; it has the advantage of being rapid, taking place while the patient is being examined. It comes out objectively with a minimum amount of error, the program being highly reliable, and gives you both the regional cerebral blood flow (ROI) and the mean hemispheric flow (RCBF "H/A"), which is in good agreement with hydrogen clearance using an entirely different methodology, as well as the standard deviation. It gives you the fast or so-called gray flow (FG), the white flow (FW), the so-called weight of gray matter (WG), the weight of white matter (WW), a regional flow calculated by another method (RCBF "LOG"), and the regional cerebral blood volume (RCBF), which is of considerable use because, knowing blood flow, blood volume, and cerebrospinal fluid pressure, you can say a great deal about the amount of blood and parenchyma present in the region under study and about the various pressure-tissue-flow relationships.

For our metabolic studies, we feel that it is less traumatic and highly reliable to pass the catheter up into the lateral sinus via the brachial vein; this is done under visualization of the fluoroscope in the cardiac catheterization laboratory. I say it is highly reliable, because one can inject a little dye at the time of placement of the catheter, from which much can be learned. About 20% of patients have abnormalities of the venous system, and there is no question that, with the blind puncture or modifications of it, the needle often finishes up sampling blood that was certainly not coming from the brain, which accounts for some of the errors in methods.

To summarize some of the data—it will be found that the earlier the patient is studied after a stroke, the greater is the reduction of CBF. I would like to point out that CBF is reduced not only on the diseased side but also on the healthy side (Table 2). We called it diaschisis and supposed that it was due to the release, following stroke, bilaterally or perhaps from the brain stem, of some neurotransmitter, and it was suggested that it might be serotonin or some related substance. Judging from our current studies, it now appears that indeed there are neurotransmitter releases in a unilateral stroke and that these neurotransmitters, bilaterally, include norepinephrine, serotonin, and C-AMP; these reduce cerebral blood flow and decrease me-

* This is an edited transcription of a lecture presented by Dr. Meyer, February 7, 1974, at the Medical College of Virginia, Richmond.

TABLE 1

REGIONAL CEREBRAL BLOOD FLOW MEASUREMENTS USING GAMMA CAMERA AND INTERTECHNIQUE COMPUTER SYSTEM

		Typical Print-Out of RCBF Data					
ROI	RCBF "H/A"	FG	WG	FW	WW	RCBF "LOG"	RCBV
1,4	42.2	41.57	65.1	14.81	34.9	32.2	9.62
2,3	35.2	48.93	38.2	28.27	61.8	36.2	8.95
2,4	33.7	43.88	46.3	19.70	53.7	30.9	7.58
2,5	32.5	37.52	49.1	18.96	50.9	28.1	6.29
2,6	32.0	33.69	61.0	16.27	39.0	26.9	6.09
3,3	32.2	46.13	47.8	19.62	52.2	32.3	8.30
3,4	32.5	41.98	49.5	17.73	50.5	29.7	6.49
3,5	27.6	38.04	34.3	19.81	65.7	26.1	5.59
3,6	26.8	50.74	35.5	25.35	64.5	34.3	5.21
4,3	35.4	53.48	30.3	30.26	69.7	37.3	7.36
4,4	35.4	52.30	44.3	25.99	55.7	37.6	6.37
4,5	37.1	51.31	33.0	19.81	67.0	30.2	4.90
4,6	23.9	31.24	29.9	25.84	70.1	27.5	4.77
5,4	26.9	49.68	29.0	23.76	71.0	31.3	5.59
5,5	24.6	59.84	10.7	28.68	89.3	32.0	4.50
6,4	19.4	30.68	25.1	17.24	74.9	20.6	4.05
6,5	22.1	33.82	43.5	40.35	56.5	23.2	4.15
MEAN	30.0	41.87	39.5	23.08	60.5	30.4	6.22
S.D.	5.7	13.04	13.0	6.27	13.0	4.6	1.61

Radioisotope: ^{133}Xe

Diagnosis: Acute subarachnoid hemorrhage due to rupture of basilar artery aneurysm, diffuse vasospasm, and acute hydrocephalus

TABLE 2

HEMISPHERIC BLOOD FLOW AND METABOLIC INDEXES IN A SERIES OF PATIENTS WITH ACUTE UNILATERAL CEREBRAL ISCHEMIA

	Healthy Side	Diseased Side
HBF (ml/100 gm brain/min)	34.6 ± 3.4 (N = 30)	32.4 ± 3.3 (N = 32)
	0.01 < P < 0.02	
HMI_{O_2} (ml/100 gm brain/min)	2.28 ± 0.42 (N = 25)	2.07 ± 0.45 (N = 31)
HMI_{CO_2} (ml/100 gm brain/min)	1.84 ± 0.52 (N = 24)	1.88 ± 0.48 (N = 31)
HMI_{GI} (ml/100 gm brain/min)	3.54 ± 1.17 (N = 25)	2.87 ± 1.02 (N = 30)
	0.02 < P < 0.05	
HG:O (ml/100 gm brain/min)	1.58 ± 0.54 (N = 25)	1.46 ± 0.63 (N = 30)
HRQ	0.80 ± 0.17 (N = 24)	0.92 ± 0.23 (N = 31)
	0.02 < P < 0.05	

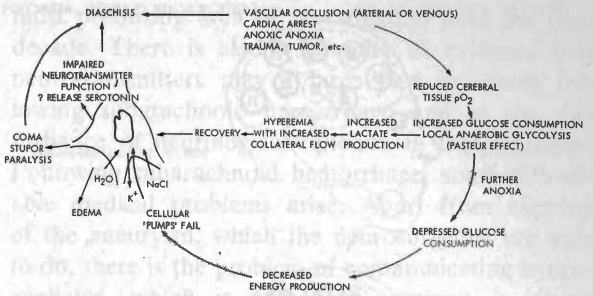
Values = mean ± standard deviation
N = number of cases
P = t test values
HBF = hemispheric blood flow
HMI_{O_2} = hemispheric oxygen consumption
HMI_{CO_2} = hemispheric carbon dioxide production
HMI_{GI} = hemispheric consumption of glucose
HG:O = hemispheric glucose:oxygen utilization ratio
HRQ = hemispheric respiratory quotient

tabolism bilaterally, despite the fact that one has only a unilateral stroke (Fig. 1).

One notices that with the passage of time, CBF improves and after about three weeks, the flow in the nonischemic hemisphere returns to normal. The quantitative reduction inflow also correlates with the size of the infarct, as assessed clinically, as well as with the degree of EEG change, particularly if it is a cortical infarct; the correlation is a little more difficult if it is a subcortical infarct. There are correlations, to some extent, with other assessments of the degree of involvement such as of the brain stem. Bilateral reduction of oxygen and glucose consumption and CO_2 production are noted, as well as blood flow reduction, although there is a greater reduction on the diseased side than on the healthy side, the respiratory quotient (RQ) is normal.

It should be noted that a hemisphere having a major infarct with hemiplegia still consumes appreciable oxygen—more than one would think, considering the neurological deficit. Also, abnormal metabolism was occurring on both sides (Table 3). There was a release of free fatty acids and inorganic phosphate, as well as serotonin and norepinephrine, from the infarcted brain; this has now been confirmed from cerebrospinal fluid. Inorganic phosphate from the infarcted brain appears only in the first 14 days of stroke and tends, with the recovery process, to revert to no essential A-V difference.

I want to mention a little about studies with



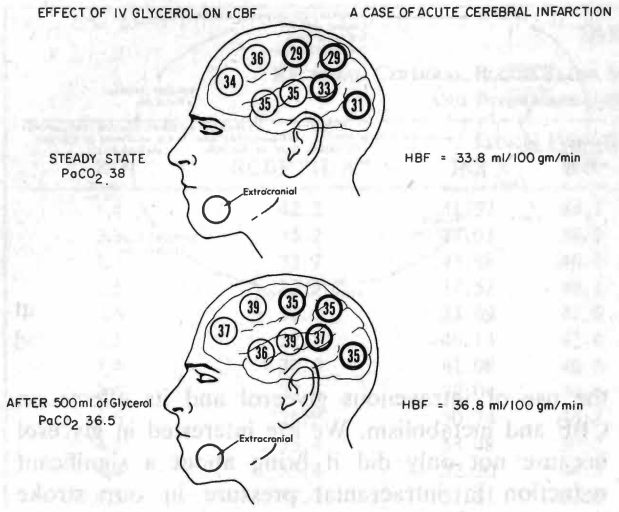
the use of intravenous glycerol and its effects on CBF and metabolism. We are interested in glycerol because not only did it bring about a significant reduction in intracranial pressure in our stroke patients, after intravenous treatment, but the patients also showed a significant clinical improvement. We were unable to show this with mannitol and, for this reason, think that perhaps glycerol had some metabolic benefits along with its hyperosmolar effect. It is a very nice investigative tool for manipulating the cerebral metabolism as well. An infusion of glycerol increases cerebral blood flow, but (and this was a big surprise to us) it decreases the oxygen consumption. We have 30 more patients now and this has become highly significant. The CO_2 production also goes down, and the glucose consumption (in a mixed group of patients) has a tendency to increase, which was

TABLE 3

HEMISPHERIC METABOLISM IN ACUTE UNILATERAL CEREBRAL ISCHEMIA

	Arterial Concentration	Arteriocerebral Venous Difference		Concentration in CSF
		Healthy Side	Diseased Side	
β-Hydroxybutyrate (mg/dl)	4.36 ± 4.47 (N = 13)	+1.04 ± 0.73* (N = 6)	+0.27 ± 0.32* (N = 13)	N.E.
		0.001 < P < 0.005		
Glutamate (mg/dl)	3.98 ± 2.21 (N = 9)	+0.25 ± 0.25* (N = 7)	+0.21 ± 0.15 (N = 8)	N.E.
Triglyceride (mg/dl)	87.5 ± 38.5 (N = 13)	+1.3 ± 10.6 (N = 9)	+1.5 ± 7.0 (N = 13)	N.E.
Free Fatty Acid (mM/L)	1.153 ± 1.765 (N = 8)	+0.121 ± 0.237 (N = 5)	−0.208 ± 0.217* (N = 8)	N.E.
Inorganic Phosphate (mg/dl)	2.34 ± 0.49 (N = 14)	−0.13 ± 0.23 (N = 6)	−0.15 ± 0.12* (N = 14)	N.E.
Serotonin (μg/dl)	12.48 ± 4.35 (N = 18)	1.92 ± 3.19 (N = 12)	−0.23 ± 1.92 (N = 18)	6.10 ± 4.86* (N = 18)
		0.02 < P < 0.05*		

* = statistically significant difference from normal
Values = mean ± standard deviation
N = number of cases
N.E. = not examined



significant in diabetics and insignificant in nondiabetics. We have postulated that we were improving metabolism other than the usual oxidative metabolism; possibly, we were recoupling uncoupled oxidative metabolism. We also considered that glycerol may provide another source of energy, which may tend to improve cerebral energy production as well as the membrane integrity and function. The EEG improves regularly and the improvement appears within two hours during continuous recording. There is an increase in central venous pressure, as might be anticipated, due to the hyperosmolar effect of an infusion of 500 cc of a substance that is drawing fluid into the circulating blood volume. Since the intracranial venous pressure is a mean between the central venous pressure and the cerebrospinal fluid (CSF) pressure, then essentially, there is an increase followed by a decrease in the intracranial venous pressure. The mean arterial pressure is increased also by a substance that increases a circulating blood volume. Regional CBF and blood volume studies of the effects of glycerol on the ischemic area of the middle cerebral artery occlusion show redistribution of blood with an increase in blood flow and blood volume in the infarcted zone (Fig. 2). Often, if there is a marked hyperemia on the border zone, there is a redistribution of blood in the infarcted zone, with reduction on the bordering zone. The mean hemispheric flow goes up regularly. Our data show a significant reduction, after the use of glycerol, in the release of free fatty acids and/or inorganic phosphates from the infarcted brain. We believe that glycerol is combining with free fatty acids to form triglycerides. Inorganic phosphate may be taken up by ADP to form ATP. It could also be that the phospholipids are being resynthesized.

Norepinephrine and serotonin in the CSF of patients with acute stroke are elevated; it seemed likely that, in cerebral ischemia, the reduced tissue P_{O2} might be interfering with the synthesis of neurotransmitters, such as norepinephrine and serotonin and that the release of these might interfere with neuronal function. We measured C-AMP in the cerebrospinal fluid of these patients and found that it was significantly increased, actually much more significantly than serotonin and norepinephrine. If these neurotransmitters were disordered in the brain and were causing trouble, we wondered whether, with the use of adrenergic blockades such as propranolol or phenoxybenzamine, one could show an effect similar to that of glycerol, and indeed, this is what happened. The introduction of propranolol shows the same reduction of oxygen consumption, CO_2 production, and glucose utilization. This reaction makes sense because norepinephrine is known to stimulate glycolysis and oxidative consumption and has been shown to be released in infarcted brain and to stimulate the release of free fatty acid. This finding supported our view that the release of these neurotransmitters is very important in cerebral infarction and may enhance the symptoms. We found also that the release of fatty acids was improved by the infusion of propranolol, which makes sense because norepinephrine stimulates the release of free fatty acids from fat stores and lipids. Inorganic phosphate, likewise, tended to be reduced and the consumption of triglyceride, increased. Phenoxybenzamine, which is another α-adrenergic blocker and blocks serotonin as well as norepinephrine without having any effect whatsoever on hemispheric blood flow, reduced oxygen consumption and CO_2 production in the same pattern that we found with both propranolol and glycerol. The use of phenoxybenzamine tended to reduce the release of free fatty acids and enhance the uptake of inorganic phosphate and triglycerides by the brain.

After about the 14th day, the serotonin disappears, as does the C-AMP, from the cerebrospinal fluid in patients with acute cerebral infarction; the serotonin change can be correlated with the cerebral blood flow. As the serotonin disappears, CBF increases, which supports the view that serotonin is important in diaschisis and the bilateral reduction

of CBF. Other vasoconstrictive substances, such as epinephrine or norepinephrine, angiotensin, or prostaglandins may exist, which we have not measured yet.

C-AMP is the second messenger for virtually all the neurotransmitters of the central nervous system, certainly for serotonin and norepinephrine. We found that there was similar elevation of C-AMP in cerebral venous blood when compared to the arterial blood in the steady state before glycerol. After giving glycerol, there was a reduction in the cerebral venous C-AMP, an inhibition of the release of C-AMP from the infarcted brain. An elevation of C-AMP in the steady state was noted in the cerebrospinal fluid of patients with cerebral infarction as well. When glycerol is given intravenously, there is a reduction of the C-AMP in the cerebrospinal fluid.

This consideration of the relationship of neurotransmitters not only to cerebral infarction but also to subarachnoid hemorrhage is, to my mind, the most promising area of investigation over the next decade. There is also a quantity of evidence that neurotransmitters play a large part in spasm following subarachnoid hemorrhage and in the disturbance of neurological function in that situation. Following subarachnoid hemorrhage, some remediable medical problems arise. Apart from clipping of the aneurysm, which the neurosurgeons are able to do, there is the problem of communicating hydrocephalus, which is extremely common in about 40% of patients. It can be discerned by the method of determining regional CBF and doing a spinal tap. If you note an increase in cerebral blood flow with removal of 25 cc of spinal fluid, you know you have a problem with communicating hydrocephalus. This is because autoregulation is disturbed. This increase will not occur when a spinal tap is done on a normal person who does not have communicating hydrocephalus. Finally, one can give glycerol and reduce the brain edema in patients with subarachnoid hemorrhage and brain swelling.

Advances in the Surgical Treatment of Patients with Extracranial Cerebral Vascular Disease* **

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Introduction. Since the subject of surgery for carotid artery occlusive disease is too broad to be covered in its entirety, we will dwell primarily on some results of cerebral blood flow measurements and electroencephalograms performed during this procedure, their meaning and relationship to states of cerebral ischemia, and some controversial aspects of the surgery. An understanding of cerebral hemodynamics and the tolerance of neural tissue to ischemia is of major importance to any surgeon or physician dealing with this illness.

Cerebral Blood Flow Measurements during Carotid Endarterectomy. Cerebral blood flow (CBF) measurements, determined from intra-arterially injected ^{133}Xe have been performed routinely on all patients on the author's service undergoing carotid endarterectomy over the past four years, and therefore, flow data are available from 279 cases of carotid stenosis and 13 cases of carotid occlusion. These measurements have been determined prior to carotid occlusion, during occlusion, with a shunt in place (when used), and following restoration of flow. Analyses of results of these measurements have indicated an increase in CBF, determined by the initial slope technique from 58–73 ml/100 gm/min when carotid artery stenosis exceeds 90% (1). When carotid artery stenosis is less than 90%, analysis of these measurements has indicated no essential change in CBF. These measurements have been recorded with the patient under general halothane anesthesia with moderate induced hypertension and with a constant Pa_{CO_2} of 42 torr. Therefore, these anesthetic CBF measurements are higher than those found in normal awake patients, where a normal CBF approximates 54 ml/100 gm/min. I do not wish to imply that an increase of CBF in this setting, of this magnitude, is necessarily lasting or of clinical significance other than an area's susceptibility to symptomatic emboli.

It is necessary to distinguish between the change in absolute regional CBF and alteration in relative contribution to that flow from the internal carotid artery before and after endarterectomy. Even in instances where no true alteration in CBF could be determined by these types of measurements, Boysen (2) found an increase in internal carotid artery flow following endarterectomy, and therefore an increase in the relative contribution to CBF from the vessel operated upon, when a significant stenosis was present.

Electroencephalographic Measurements during Carotid Surgery. In addition to CBF measurements, all patients undergoing endarterectomy now have a constant electroencephalogram (EEG) recorded from the time of induction-of-to-arousal-from anesthesia. It has been found that the EEG is a valuable monitor for evaluating cerebral function during this surgery with a properly maintained level of anesthesia (3). It is noninvasive, has no risk, and has proven to be highly accurate in correlating cerebral metabolic function during surgery with the neurological function postoperatively. The EEG offers a continuous technique for monitoring cerebral function throughout the entire procedure, something that is not possible by any other technique unless

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the patient is operated upon under local anesthesia. The very close correlation between the EEG and the CBF measurements below 17–18 ml/100 gm/min at a Pa_{CO_2} of 40 torr is most impressive. In our series to date, we have not had a single CBF measurement during carotid occlusion below this level that did not have an associated EEG abnormality. The lower the occlusion flow, the more rapid the EEG changes. A typical EEG demonstrating the changes with occlusion and resolution with a shunt in place is illustrated in Figure 1.

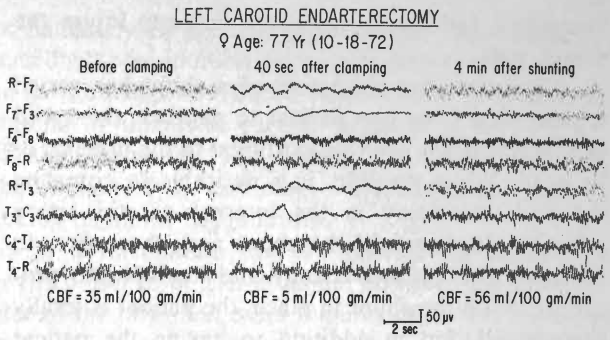

Fig. 1—A typical EEG demonstrating the changes seen with occlusion for endarterectomy when cerebral blood flow falls to 10 ml/100 gm/min. Changes include both generalized slowing and loss of background activity. In this patient with opposite carotid artery occlusion, the changes were seen bilaterally. Most commonly, changes occur only on the side of occlusion. The EEG improves following placement of the shunt and improvement in CBF values doubles that seen prior to occlusion. (Reprinted by permission from *J Neurosurg* 41:315, 1974.)

CBF-Ischemic Tolerance Ratio. The ischemic tolerance of neural tissue is directly proportional to the relative decrease in CBF. A decrease in CBF to between 20 and 30 ml/100 gm/min can be tolerated quite well for limited periods of time. When the CBF falls to below 18 ml/100 gm/min, cerebral metabolic function changes and a physiological paralysis follows (1, 3). This is, however, to be distinguished from infarction. It is probable that this degree of ischemia can be tolerated for a period of hours, rather than minutes, without major infarction, whereas flow reductions below 10 ml/100 gm/min produce infarction in a much shorter time.

This hypothesis cannot be tested in its entirety clinically, but it has been extensively investigated in the laboratory. In squirrel monkeys, a degree of ischemia approximating 20 ml/100 gm/min can be tolerated for up to two hours without the uniform development of a cerebral infarction (4). In these animals cerebral adenosine triphosphate (ATP) falls to 55% of normal and cerebral lactate rises to seven times normal following two hours of occlusion (5). During the period of occlusion, the EEG shows changes similar to those seen in patients with severe flow reductions during carotid occlusion. Following restoration of flow in the laboratory preparation, there is a gradual rise in ATP, fall in lactate, and normalization of the EEG. An infarction is not uniformly seen in this animal unless occlusion is maintained for four hours. The degree of ischemia and metabolic alteration which follows this single major vessel occlusion must be distinguished from the situation which follows cardiac arrest when there is zero blood flow. In this setting, ATP falls to 25% of normal in only four minutes, and there is the rapid production of cerebral infarction with the probability of the "no-reflow phenomenon" (6).

We had previously doubted the necessity for a shunt in any case undergoing carotid endarterectomy, on the basis that flow values seldom if ever fell to extremely low levels (7). It is now apparent that this hypothesis was incorrect and that, indeed, a great many patients have CBF measurements with unilateral carotid artery occlusion that fall to appallingly low levels, and in some instances, to values too low to measure, approximating cardiac arrest. Furthermore, unfortunately, we have found that the degree of backflow is proportional to the cerebral vascular resistance which varies quite a bit from one patient to another; that is, it is an unreliable indicator of CBF and collateral flow. In contrast to our previous position, we now readily agree that there are definite indications for a shunt during carotid endarterectomy.

Use of a Shunt during Carotid Endarterectomy. A shunt has been employed in approximately one-third of the patients operated upon in this series. EEG changes, along with occlusion values below the critical perfusion level, occurred in 56 of these patients; shunts were used in the remaining cases because of borderline perfusion values that could conceivably produce a critical perfusion flow in the internal capsule area, which might be missed both by a CBF measurement and an EEG change.

Shunts are not used routinely because there are several disadvantages in using them. A shunt interferes with a precise endarterectomy, can serve as a source of emboli when in place, and requires constriction of the proximal carotid artery in a

tourniquet fashion, a maneuver that can injure the vessel wall.

The time for placement of a shunt has varied a great deal from one patient to another; the speed of placement has been proportional to the urgency of its need. When possible, it is desirable to complete the endarterectomy in the internal carotid artery prior to placement of the shunt and, thereafter, to complete the endarterectomy and angioplastic procedure. With the shunt in place, the patient is totally heparinized, but in addition to having the patient totally heparinized, the shunts we are using are impregnated with heparin to avoid or minimize the possibility of emboli. Using this new type of heparin coating, provided for us by Battelle Laboratories of Columbus, Ohio, we have seen no platelet material at the mouth of the shunt following its removal. Prior to this added measure, even with total heparinization of the patient, we routinely found platelet material at the mouth of the shunt.

To this date, none of our patients has developed an abnormal EEG with carotid occlusion that did not revert with prompt placement of a shunt; however, one patient in the group did develop EEG alterations with the shunt in place, proven to be related to microembolism through the shunt, and this patient sustained a permanent neurological deficit. Since that occasion, we have been using only heparinized shunts and have had no recurrent problems of that nature. This patient represented the only embolic complication from the group in which a shunt was employed.

CBF, Ischemic Tolerance, and Pa_{CO_2}. We have not routinely employed hypercapnia during the period of carotid occlusion. Under halothane general anesthesia, hypercapnia predisposes to cardiac arrhythmias, giving problems not justified by proven beneficial effect. Boysen (2) found, during carotid endarterectomy, the expected increase in CBF prior to carotid clamping from hypercapnia as a result of maximal vasodilatation. With carotid clamping, however, there was a greater relative reduction in CBF in comparison to the group studied at normocapnia, and furthermore, a paradoxical reaction was occasionally demonstrated. In this paradoxical reaction, hypercapnia did not improve regional CBF but rather resulted in an intracerebral "steal." We have demonstrated this in our patients also and it therefore seems safe to conclude that hypercapnia cannot be relied upon invariably to increase regional perfusion in the areas of severe ischemia.

The use of hypocapnia, to produce a reverse steal and hence increase cerebral perfusion to areas of ischemia, has been suggested by Lassen (8); however, a careful analysis of their patient group with proven cerebral ischemia, treated with hypocapnia, indicated no clinical effect from hypocapnia, although they were able to produce a reverse steal with its use.

Laboratory studies support the clinical findings of Lassen and his group (9) and have indicated that although a reverse steal can be produced with the use of hypocapnia, the effect of hypocapnia in areas of focal ischemia is definitely detrimental. In a group of animals with focal ischemia in which hypocapnia was induced, the cerebral ATP was significantly less and the cerebral lactate significantly higher than corresponding values in hypercapnic and spontaneously breathing animals. One must conclude that the Pa_{CO_2} should be maintained at as near a normal level as possible during carotid endarterectomy and that it should not be raised to produce hypercapnia or lowered to produce hypocapnia.

Surgical and Nonsurgical Lesions. I should now like to refer to some of the clinical and surgical aspects of this illness. The majority of patients upon whom we operated in this series have had a severe stenosis or a deep ulceration at the origin of the internal carotid artery from the common carotid artery. Minor degrees of ulceration at the origin of the internal carotid artery from the common carotid artery are not considered surgical lesions unless the patient is quite young. It has been our judgment that such small ulcers frequently heal spontaneously, and this is supported by a recent study designed to determine the frequency of strokes from such lesions. Minor degrees of ulceration or stenosis at the origin of the internal carotid artery are not uncommon in the elderly population, and even when associated with a bruit, are not necessarily an indication for surgery. Loops of the internal carotid artery are rarely symptomatic—notwithstanding a recent report to the contrary.

Correlation of Angiographic Findings with Symptom Complexes of Carotid Arterial Disease. A correlation, retrospectively, of the angiographic findings, cerebral blood flow measurements, and clinical symptomatology in patients suffering from carotid ulcerative stenosis has permitted a judgment regarding the etiology of the various forms of symptomatology. In general, the focal symptom complexes are felt to be most commonly the result of

cerebral embolization (10), but we have noted that focal regions of the brain, and to a lesser extent the retina, are particularly vulnerable to emboli if that region is under a low perfusion pressure; this is an angiographic finding—space does not permit us to discuss it in detail. In such instances, regions of marginal perfusion are dependent in part on collateral circulation, so that any embolus to a collateral vessel is likely to be of major significance symptomatically. Obviously, such regions of marginal perfusion are also particularly vulnerable to periods of hypotension. In general, amaurosis fugax, transient ischemic attacks (TIA's), and small completed infarcts represent manifestations of cerebral embolization (11). A progressing stroke—that is, a neurological deficit which is progressive over a period of hours—quite often is the result of multiple embolization into a region of very marginal perfusion. The temporal profile of this type of progressing stroke must be distinguished from a massive infarction that reaches its zenith two or three days later from severe cerebral edema. The progressing stroke which begins with a minor neurological deficit and progresses through intermittent stages of deterioration can be helped by emergency surgery in many instances, whereas the massive infarction with immediate profound hemiplegia is often a contraindication to surgery.

Generalized cerebral ischemia represents an uncommon, nonembolic, symptom complex that may be the patient's only complaint or may coexist with symptomatology of focal cerebral ischemia (12). An individual with generalized cerebral ischemia must be differentiated from the patient with vertebrobasilar insufficiency; these patients are suffering from severe bilateral carotid arterial stenosis or a high-grade stenosis in association with a contralateral occlusion. Upon assuming the erect posture, there is a rather dramatic fall in the retinal artery pressures, although the peripheral blood pressure does not fall proportionately. At this time, the patient may complain of light-headedness or a sensation that he may faint. This is not true vertigo. He may complain of dimness of vision or difficulty in balance. The family usually reports changes in behavior or memory. CBF measurements have indicated a very significant increase in CBF following endarterectomy in these patients, and there has been a rather gratifying improvement following surgery. Approximately 10% of our patients have had symptomatology of this type. I would like to reemphasize that these are not patients with presenile dementia or vague lightheadedness. In addition to the symptoms, there are the hard findings of reduced retinal artery pressures, bilateral or unilateral carotid bruits of a very significant character, and subsequent angiographic confirmation of the pathology—severe disease—not kinking or minor irregularities.

It is uncommon that we operate on patients for the presence of a bruit alone; however, the character of the bruit and other features of the examination, such as the presence or absence of retinal emboli, the patient's age, and the presence or absence of vascular disease elsewhere, enter into the decision regarding the method of treatment.

Preoperative Risk Factors in Carotid Endarterectomy. Space does not permit details of our system for grading a patient's risk for surgery and the morbidity and mortality related to these risk factors, which include obesity, advanced age, coronary artery disease, progressing neurological deficits, frequent daily transient ischemic attacks, contralateral arterial occlusion, high bifurcations, long plaques, and soft thrombi. This system is graded from I through IV for carotid stenosis, acute internal carotid occlusion being considered grade V and analyzed separately. The combined morbidity and mortality in this series has ranged from 1% in low-risk, or grade I, patients for surgery to 8% in high-risk grade IV patients for surgery (12).

Vessel Patency. Patency in all vessels on which we have operated for ulcerative stenotic disease was 99.3% at the time of discharge from the hospital as determined by retinal artery pressure (RAP) measurements, angiography, or both; however, four vessels were reopened prior to discharge with insertion of a vein graft because of occlusion in the immediate period following surgery. All of these occurred earlier in the group in which grafts were not employed; all were symptomatic with TIA's; all occurred in relatively small vessels; and all were detected or confirmed by finding a reduction in the RAP which in each case returned to normal after restoration of flow and patency. In the first patient, reopening was delayed and a permanent upper monoparesis and mild expressive aphasia resulted. In the other three patients, the vessels were immediately reopened, and there was no delay in discharge from the hospital and no morbidity. One vessel in a grade IV candidate occluded simultaneously with a myocardial infarction; flow was

not restored and hemiplegia resulted; this has been our only permanently occluded artery.

To Patch or Not To Patch. Admittedly one can perform this surgery without the use of a patch and have the vessel remain patent in most instances. There is little question in my mind at this time, however, that the use of a patch improves the prognosis for both acute and chronic patency. The use of a patch prolongs the procedure, but with careful monitoring, this is of no great importance. We frequently reinforce the portion of the graft in the common carotid artery with a thin teflon sheath to prevent an aneurysmal dilatation and excessive stress on the graft in patients who are hypertensive.

Hemorrhagic Infarction. The final controversial subject I would like to discuss is that related to the risk of hemorrhagic infarction. This risk has led some surgeons to consider the presence of any recent neurological deficit and certainly a progressing deficit as a relative contraindication to surgery (13). The controversy is not easily resolved. Our group of patients who were neurologically unstable at the time of surgery, considered as grade IV risks, embraces a group of 56 patients in whom we have had an 8% combined morbidity and mortality; the risks of not operating are obviously considerably higher. This group includes progressing strokes, frequent daily TIA's, impending occlusion with ischemic carotid pain, and recent minor fixed deficits in association with severe degrees of ulceration.

Hemorrhagic cerebral infarction can result from cerebral embolization with or without surgery (14). A very high risk of surgery in these unstable neurological patients is related to a soft thrombus that is frequently present at the bifurcation of the carotid artery and is superimposed upon an ulcerated plaque. In these patients, extra care must be exercised in preventing a recurrence of cerebral embolization. It would seem likely that hemorrhagic infarction has often resulted from embolization rather than restoration of perfusion pressure to an ischemic region of brain.

The combination of a reduced retinal artery pressure on the side of intended surgery, and a major branch occlusion intracranially with a region of severe ischemia represents, in our judgment, a contraindication to surgery.

Conclusion. The use of intraoperative CBF measurements, continuous EEG's, postoperative RAP's, vein patches, and intraoperative shunting when indicated, has aided materially in reducing morbidity and mortality in this surgery.

REFERENCES

1. SUNDT TM JR, SHARBROUGH FW, ANDERSON RE, MICHENFELDER JD: Cerebral blood flow measurements and electroencephalograms in neurovascular surgery. *J Neurosurg* (in press).

2. BOYSEN G: Cerebral hemodynamics in carotid surgery. *Acta Neurol Scand* (Suppl) 52:1, 1973.

3. SHARBROUGH FW, MESSICK JM JR, SUNDT TM JR: Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. *Stroke* 4:674, 1973.

4. SUNDT TM JR, WALTZ AG: Cerebral ischemia and reactive hyperemia: Studies of cortical blood flow and microcirculation before, during, and after temporary occlusion of middle cerebral artery of squirrel monkeys. *Circ Res* 28:426, 1971.

5. SUNDT TM JR, MICHENFELDER JD: Focal transient cerebral ischemia in the squirrel monkey: Effect on brain adenosine triphosphate and lactate levels with electrocorticographic and pathologic correlation. *Circ Res* 39:703, 1972.

6. AMES A III, WRIGHT RL, KOWADA M, THURSTON JM, MAJNO G: Cerebral ischemia. II. The no-reflow phenomenon. *Am J Pathol* 52:437, 1968.

7. WALTZ AG, SUNDT TM JR, MICHENFELDER JD: Cerebral blood flow during carotid endarterectomy. *Circulation* 45:1091, 1972.

8. CHRISTENSEN MS, PAULSON OB, OLESEN J, ALESANDER SC, SKINHØJ E, DAM WH, LASSEN NA: Cerebral apoplexy (stroke) treated with or without prolonged artificial hyperventilation. I. Cerebral circulation, clinical course, and cause of death. *Stroke* 4:568, 1973.

9. MICHENFELDER JD, SUNDT TM JR: The effect of Pa_{CO_2} on the metabolism of ischemic brain in squirrel monkeys. *Anesthesiology* 38:445, 1973.

10. MILLIKAN CH, SIEKERT RG: Studies in cerebrovascular disease. IV. The syndrome of intermittent insufficiency of the carotid arterial system. *Proc Staff Mtg Mayo Clinic* 30:186, 1955.

11. HOUSER OW, SUNDT TM JR, HOLMAN CB, SANDOK BA, BURTON RC: Atheromatous disease of the carotid artery: Correlation of angiographic, clinical, and surgical findings. *J Neurosurg* (in press).

12. SUNDT TM JR: Surgical therapy of occlusive vascular diseases of the brain. *Surg Annual* VI, Appleton-Century-Crofts Meredith Corporation, New York (in press).

13. WYLIE EJ, HEIN MF, ADAMS JE: Intracranial hemorrhage following surgical revascularization for treatment of acute strokes. *J Neurosurg* 21:212, 1964.

14. FISHER M, ADAMS RD: Observations on brain embolism with special reference to the mechanism of hemorrhagic infarction. *J Neuropathol Exp Neurol* (abstract) 10:92, 1951.

Clinical Advances in the Diagnosis of Cerebral Vascular Disease*

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I have chosen some thoughts about recent clinical advances in the diagnosis of cerebral vascular disease, which I feel are appropriate for this paper, confining my discussion to the signs, symptoms, natural history, and risk factors of cerebral vascular disease.

Atherosclerosis and stenosis of the cerebral vessels result in occlusion and embolization of the brain parenchymatous vessels, particularly if the atherosclerotic lesions of the vessels not only stenose but cause ulcerated lesions as well, which will give rise to fibrinoplatelet emboli and even large, red emboli. This process results in slow blood flow, turbulence, erythrocyte and platelet aggregation—with local anoxia resulting in endothelial damage, the loss of plasma fluid—resulting in brain edema, and compression of capillaries and venules. This vicious cycle is depicted in Figure 1, showing a worsening of the ischemic and hemorrhagic infarction. In the area of circulation around the ischemia, hyperproteinemia and hemoconcentration occur, which tend to cause deposition of the platelets. One can easily see these platelets under direct examination of the microcirculation of the brain, showing increased viscosity and the tendency toward thrombosis and further infarction.

Hypertension will promote atherosclerosis, and certain other systemic factors such as hypotension or lowered blood pressure, particularly much below 80–90 mm Hg (systolic), will worsen the situation because of distorted autoregulation. Associated polycythemia or sickle cell disease will be aggravated by the situation.

Conversely, anticoagulants and platelet inhibitors tend to prevent the aggregation of these platelets and erythrocytes as well as preventing the development of thrombosis. Systemic dehydration will have an adverse effect while collateral blood flow enhancement will tend to improve the situation. Hyperlipidemia and hyperlipemia will cause aggravation for several reasons—they promote atherosclerosis and they enhance the tendency toward platelet aggregation and changes in the properties of the blood. Hypothermia will tend to protect the patient by decreasing brain metabolism; systemic anoxia will make him worse. Neurotransmitters are released, probably as a result of the deleterious changes.

Let me summarize the risk factors with which the American Heart Association Committee concerned itself in 1971 (1), which we now agree are reasonably well established (Table 1). A hypertension of 160/95 mm Hg is present in at least 85% of cases—a significant risk factor, the control of which is one of the great advances in prevention of stroke. EKG abnormalities occur in 60–70% of our patients with stroke, consisting of left ventricular hypertrophy (LVH), myocardial infarction (MI), or a recent or old dysrhythmia. Clinical angina, myocardial infarction, claudication, diminished pulses, bruits—all are associated with a stroke patient and should be sought. Diabetes mellitus occurs, depending upon how you evaluate it, in at least 30–40% of these patients. Certainly, an elevated fasting blood sugar and an abnormal glucose tolerance test or a two-hour postprandial blood sugar exceeding 160 mg% should be considered sig-

* This is an edited transcription of a lecture presented by Dr. Meyer at the 27th Annual Stoneburner Lecture Series, February 7, 1974, at the Medical College of Virginia, Richmond.

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nificant. Recently, we have been studying the blood lipid profile, another important factor, with Dr. Gotto at our institution. Type IV lipidemia, particularly, is a risk factor that occurs in approximately 30% of these patients. Other factors—smoking, polycythemia, erythrocytosis, gout, and hyperuricemia should be evaluated. Of our patients with cerebral vascular symptoms and extracranial occlusive disease, 43% had hyperlipoproteinemia, and almost all of these were type IV. Of our patients with intracranial small and large vessel lesions, 20% had hyperlipoproteinemia, but of those with intracranial small vessel disease, only 3% had hyperlipoproteinemia. As might be expected, of those with combined extra- and intracranial lesions, there is an incidence of 25%. Those with a normal angiogram have, essentially, a normal lipoprotein pattern. In summary, one can say that hyperlipoproteinemia type IV is a significant aspect of extracranial occlusive disease.

It is wise in evaluating your patients, particularly the young patients with hypotension and extracranial occlusive cerebral vascular disease, to look for fibromuscular dysplasia. Acute myocardial infarction is seen in 10% of patients with acute stroke and in 60% of those with chronic arteriosclerotic heart disease. As illustrated in Table 2, a stroke-prone individual is one who has not yet had a stroke but is likely to because of the risk factors present in his profile. Thus, a patient with hypotension, diabetes, hyperlipidemia, and/or arteriosclerotic heart disease, who is obese or a heavy smoker, is extremely apt, on a prospective clinical trial period, to have a stroke and is at great risk.

Similarly, patients having transient ischemic attacks (TIA's) or reversible ischemic neurological deficits (RIND's) will proceed to a stroke 30–50% of the time within a five-year period. Transient ischemic attack is a neurological deficit existing, due to cerebral vascular disease, for 24 hours or less; whereas reversible ischemic neurological deficit is a little stroke lasting longer than 24 hours but with recovery in about three weeks. A patient who has had a neurological deficit for longer than 24 hours, progressing in the acute stage is said to have a stroke in evolution. A stabilized neurological deficit appears in a patient who has a stroke in the past and comes in sometime later in a stable condition. Table 3 represents a summary of several natural history studies of cerebral vascular disease, which indicates that of those undergoing TIA's,

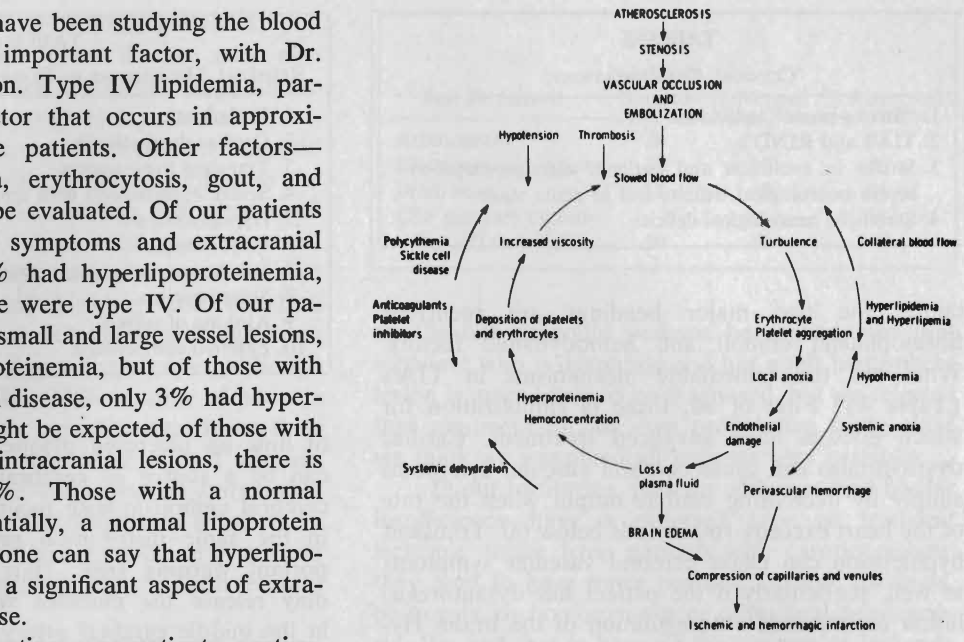

Fig. 1.

one-third progress within five years to irreversible cerebral infarction; one-third continue to have TIA's and therefore continue to be at risk of cerebral infarction; and one-third seem to cease having TIA's spontaneously within five years, without further neurological disorder, but they are at great risk of suffering other complications of atherosclerosis such as myocardial infarction.

The mechanism of TIA's is still under consideration by many scientists and physicians. Cer-

TABLE 1

RISK FACTORS IN STROKE*

1. *Hypertension* of 160/95 mm Hg (present in 85% of cases)
2. Cardiac Enlargement by X-ray
3. EKG Abnormalities, LVH, MI, and Dysrhythmia
4. Clinical Angina, MI, Claudication, Diminished Pulses, and Bruits
5. Diabetes Mellitus (2 hr pp 160 mg% or more; FBS 120 mg% or more)
6. Elevated Blood Lipids (cholesterol, β-lipoproteins, triglycerides)
7. Smoking
8. Erythrocytosis
9. Gout—Hyperuricemia

* Reprinted by permission of the American Heart Association, Inc. (1)

TABLE 2

CLINICAL CLASSIFICATIONS

1. "Stroke-prone" individual
2. TIA's and RIND's
3. Stroke in evolution and patients with moderate-to-severe neurological deficits still in acute stage
4. Stabilized neurological deficits

tainly, the two major headings are recurrent fibrinoplatelet emboli and hemodynamic factors. What are the remediable mechanisms in TIA's (Table 4)? First of all, there is embolization for which doctors have advanced treatment. Cardiac dysrhythmias can cause cerebral vascular symptoms simply by decreasing cardiac output when the rate of the heart exceeds 160 or falls below 60. Transient hypotension can cause cerebral vascular symptoms as well, particularly if the patient has dysautoregulation or impaired autoregulation of the brain. Hypertension with spasm of cerebral vessels, first described many years ago and then abandoned, is now well established as a significant factor. Hypoglycemia, a relatively rare factor, can cause localized neurological deficits but will respond to the administration of glucose. Likewise, polycythemia, the subclavian innominate steal syndrome, severe anemia, kinking of vessels in the neck, and external compression may, by such things as osteophytes and cervical spondylosis, give rise to TIA's.

While it was considered dangerous at one point to lower elevated blood pressure in patients with stroke or cerebral vascular symptoms, it now seems clear that controlling the hypertension improves the prognosis. In a series of hypertensive stroke patients treated with Aldomet® for one-to-two weeks, we noted that cerebral blood flow actually increased as the mean arterial blood pressure was decreased significantly and thereby decreased cerebral vascular resistance.

Figure 2 is a sketch of a very important concept

TABLE 3

TRANSIENT ISCHEMIC ATTACKS*

1/3 → Irreversible cerebral infarctions
1/3 → Continue to have TIA's
1/3 → Cease in five years

* It is impossible to predict into which category an individual patient with TIA's will fall.

TABLE 4

REMEDIAL MECHANISMS IN TRANSIENT ISCHEMIC ATTACKS

1. Embolization
2. Cardiac dysrhythmia
3. Transient hypotension
4. Severe hypertension with spasm of cerebral vessels
5. Hypoglycemia
6. Polycythemia
7. Subclavian, innominate steal
8. Severe anemia
9. Kinking of vessels
10. External compression

of how an ulcerated plaque in the carotid artery can be a source of cerebral embolism. Recurrent cerebral embolism with recurrent TIA's may occur in the same distribution repeatedly—a very important warning sign. Thus the ulcerated plaque may release the embolus which may then lodge in the middle cerebral artery territory, causing turbulent flow. Circulating fibrinolysin, apparently present in the body normally but probably decreased in these patients, tends to dissolve the fibrinoplatelet deposition. Platelet aggregate inhibitors, such as aspirin, Persantine®, sulfinpyrazone, along with anticoagulants, tend to inhibit emboli. Today, there is a greater tendency to use platelet inhibitors rather than anticoagulants.

We studied cerebral embolization in 42 cases prospectively. In our patients, prosthetic heart valves

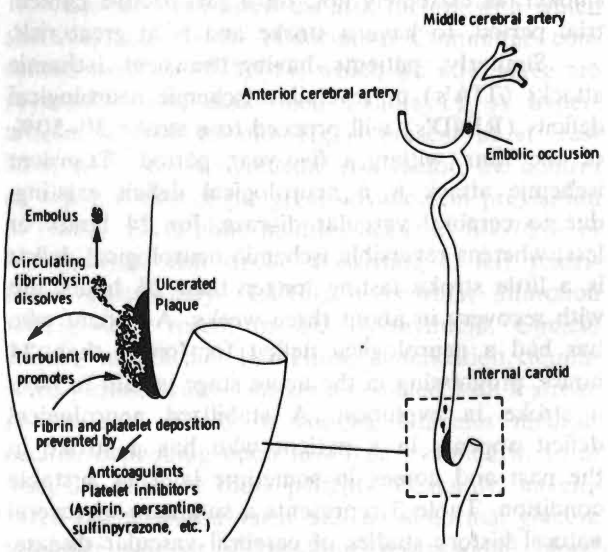

Fig. 2.

were important as a source of fibrinoplatelet emboli to the brain. Rheumatic heart disease may also cause emboli formation; arteriosclerotic heart disease may cause emboli as a result of myocardial infarction, pacemaker failure, or dysrhythmias. Carotid plaques emerge along with cardiac disorders as the most common causes, accounting for almost all emboli. There are rare causes such as aortic aneurysms with mural thrombi, carotid stenosis without ulcerated plaque, carotid kinking, and vertebral thrombosis. Two types of embolism can result from the justifiable insertion of prosthetic valves, although it must be emphasized that 90% or more of patients receiving them show no complications from their use, and they should be considered a great advance in surgical treatment. The fibrinoplatelet emboli that arise from the valve, particularly if it is a ball valve with a rough surface, can be seen and can be treated with Persantine®. The larger types of emboli respond to anticoagulants.

Although we never used to think that seizures occurred with cerebral vascular disease, it is now quite apparent that they commonly occur in cerebral embolization. Neurological findings show that abnormal tendon jerks and motor deficits are common and cranial nerve involvement is a frequent physical finding; hemianopsia is relatively frequent as well. Regarding the work-up, the arteriogram is by far the most valuable test and will usually show the occluded vessel early in the course of disease. We were able to show the occluded vessel in 93% of our cases. In 90% of cerebral embolisms, the EEG is abnormal. The brain scan is abnormal in 91% of the cases and the cerebrospinal fluid (CSF) pressure is increased in about 50% of the cases (Table 5). The left hemisphere is involved more often than the right in cerebral embolisms; the incidence was about twice as high in our study. Sixty-five percent of emboli of cardiac origin and 64% of carotid plaque origin lodge in the left hemisphere. This tendency can probably be explained by the anatomical distribution of the aorta and the great vessels in the neck. The innominate artery tends to go against the vector of force or the thrust of the cardiac output; it is somewhat protected and emboli would tend to go to the right arm rather than into the carotid or vertebral artery. The left common carotid artery, however, is particularly prone to receive the emboli, since it lies directly in the direction of the thrust of the cardiac output. Also, I believe the incidence of plaques is greater on the left. It could perhaps be argued also that a patient who is dysphasic and has a left hemisphere lesion is more likely to be diagnosed, but we rejected that argument in our own prospective study since we think we examined all patients very carefully.

TABLE 5

Test Performed	No. Cases Studied	% Normal	% Abnormal
Arteriogram	28	7	93
Electroencephalogram	30	10	90
Brain scan	11	9	91
CSF pressure exceeding 180 mm H_2O	20	50	50

In our institution, patients with vertebral basilar insufficiency have a different type of transient ischemic attack from patients with carotid emboli; they tend to have more postural vertigo, dizziness, photopsia, or homonymous or altitudinal hemianopsia. We feel that is because the process of ischemia of the brain stem itself involves those centers that are concerned with autoregulation. There is evidence now from many laboratories showing that autoregulation, the property of the brain enabling it to maintain a constant blood flow despite changes in the perfusion pressure, is due, in part, to the neurogenic innervation; this property has a brain stem or diencephalic-brain stem origin. Ischemia in this area will damage the autoregulation process. A fall in cerebral perfusion pressure will cause a decrease in cerebral blood flow (CBF), and the patient will become dizzy and symptomatic. Data from analysis of the sites of lesions in acute and in chronic strokes correlated with the delta CBF over the delta cerebral perfusion pressure (which happens to be called the autoregulation index) indicate that the effects are more severe in the acute stages, especially in those patients with brain stem and subcortical infarction as compared to patients with cortical infarction. Increased intracranial pressure is relevant in cerebral infarction.

Cerebral edema can be lethal. We have tried to combat this with hyperosmolar agents; glycerol seems to be the best agent that we have evaluated in cerebral vascular disease. We find that it is better to treat the patient with 10% glycerol intravenously for six days rather than four. Glycerol (one should not use more than 10%) seems to benefit metabolism as well as lower intracranial pressure; it is another source of energy for the brain.

Finally, I would like to make a few remarks about transient global amnesia and dementia as a result of vertebral basilar insufficiency. Transient global amnesia and dementia effect persons of middle age; they have attacks of loss of memory for a period of 24 hours and then make a more or less complete recovery. During the attacks, they do not lose personal identity and knowledge of self, but they have loss of memory for just about everything of recent occurrence. They are able to carry out routine behavior; they can respond when spoken to; they may be rather pale and sweaty. The origin of this interesting syndrome being unknown, epilepsy, migraine and various equivalents, and also cerebral vascular disease were considered as possibilities. We have studied a fairly large series of these patients, having followed them now for an interval of two-to-three years. They actually have vertebral basilar insufficiency symptoms in addition to the attacks of transient global amnesia. They have drop attacks, ataxia, vertigo and nausea, vomiting, nystagmus, dizziness, light-headedness, syncope, diplopia, oscillopsia, paresthesias alternating from side to side, circumoral paresthesias, tremor, cortical blindness, episodic bilateral blurred vision, occipital headaches—all of which are symptoms of vertebral basilar insufficiency. When we analyzed them in terms of their age, the youngest was 48 years of age and the oldest was 95 with a mean of about 70; so it is a disease of late-middle-to-early-elderly aged individuals. We noted that the cerebral blood flow measured in these patients was reduced; the major reduction was in the occipital area, in the distribution of the posterior cerebral arteries. We then analyzed the patients for the risk factors for cerebral vascular disease mentioned previously; it is apparent that these patients do have a high incidence of hypertension, hyperlipidemia, coronary artery disease of one sort or another, and diabetes mellitus.

A study of their natural histories, prospectively, indicates that they frequently have had recurrent attacks of transient global amnesia, often resulting in dementia; this leads to amnesic stroke with permanent loss of memory and gross dementia in a vast number of cases. These patients usually have abnormal EEG's. Bitemporal EEG's showing occipital slow waves are found most often; occasionally, bifrontal slow waves are seen as well. Angiograms of 12 patients revealed vertebral basilar arterial disease in the majority of them. Occlusion or stenosis of the posterior cerebral artery was extremely common. Thus, clearly, this disease is due to vertebral basilar insufficiency, and it is probable that the posterior cerebral artery is responsible for loss of memory.

I have tried to summarize what I consider to be recent and, I think, relevant and important clinical findings contributed by neurologists, neurosurgeons, and internists in the past few years on the subject of cerebral vascular disease.

REFERENCES

1. Executive Committee of the Council on Cerebral Vascular Disease of the American Heart Association, Inc: Risk factors in stroke due to cerebral infarction. *Stroke* 2:423, 1971.

Reconstructive Intracranial Vascular Surgery*

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It is scarcely less than two decades since the initial cautious explorations of reconstructive surgery for the prevention of cerebral infarction caused by extracranial vascular disease began. The next years recorded an accumulative experience in the field of vascular surgery. Early clinical investigations led to the discovery that extracranial vascular disease is a major cause of cerebral infarction or stroke. Estimates indicate, however, that only 30–40% of the patients with cerebrovascular insufficiency have significant extracranial occlusive disease. For this larger group of patients, previous surgical methods offer no hope. It is the purpose of this report to review the current status of our clinical explorations in the area of reconstructive intracranial vascular surgery.

This is not a new venture for as early as 1944, Henschen (1) transplanted a pedicle of temporalis muscle and artery over the surface of the brain in a type of encephalomyosynangiosis. This procedure, performed in a patient with bilateral carotid stenosis, was similar in concept to the Vineberg-Jewett operation for revascularization of the myocardium, first published in 1947 (2). The patient is reported to have improved, but angiographic confirmation of graft function was not accomplished. The procedure apparently was not explored further until the work of Donaghy and Yasargil (3) in 1966.

Direct reconstruction of the middle cerebral artery was successfully performed by Welch (4) in 1956, an amazing feat achieved without the aid of a surgical microscope and many other refined techniques which today are regarded as essential; subsequent reports by Shillito (5), Scheibert (6), Driesen (7), and Chou (8) followed. Jacobson, Donaghy, and colleagues (9) first reported that the microsurgical technique was of considerable value in performing this procedure. Subsequently several centers (10, 11) have reported their results with surgical treatment of occlusions of the middle cerebral artery. Yasargil (12) tabulated eleven cases in 1969, of which he operated on nine, more than one week following the onset of symptoms. One case, on which he operated within two hours of occlusion, failed to improve although the artery remained patent. A second case, on which he operated twelve hours following occlusion, developed a hemorrhagic infarction. All cases studied by postoperative angiography were patent.

In our personal experience, we operated on only five cases two days-to-two weeks following occlusion. Patency was reestablished in each case although, in one case, the embolus had already passed on to a more distant site. One patient worsened as a result of the procedure probably due to hemorrhagic infarction and the other four improved, but their improvement was similar to that expected in the natural history of this disorder.

Recorded experience certainly indicates that reconstruction of flow through the embolically occluded middle cerebral artery is technically feasible; yet, experimental evidence indicates that if restoration of flow is to be of value, it must be accomplished in less than four-to-eight hours in order to reverse hypoxia. It must also be remembered that it is in this period that one incurs the greatest risk of hemorrhagic infarction if the flow is restored. Finally, it is rare, indeed, that the patient reaches the surgeon in the allotted time. In conclusion, it seems that this procedure, although technically successful, has few indications in practice. Hopefully with the advent of less thrombogenic cardiac valves,

* Presented by Dr. Tew at the 27th Annual Stoneburner Lecture Series, February 7, 1974, at the Medical College of Virginia, Richmond.

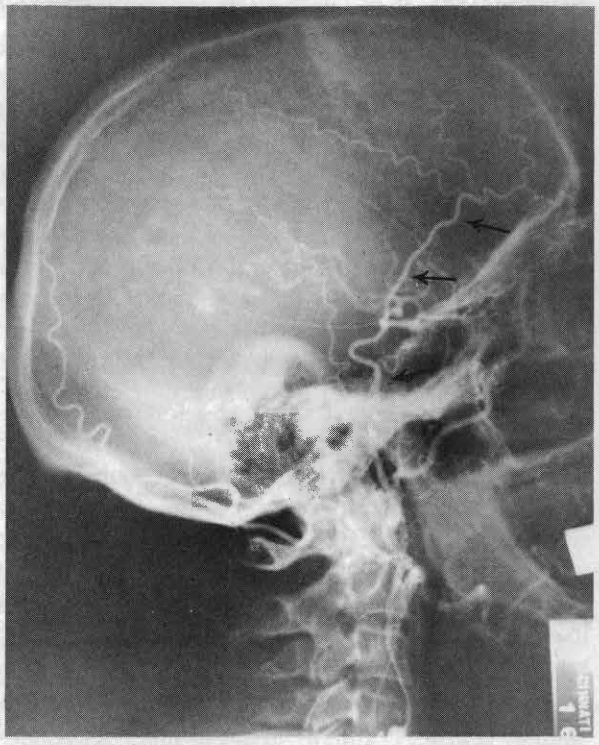

Fig. 1—Preoperative angiogram demonstrates occlusion of internal carotid artery, collateral circulation through ophthalmic artery, and the course of the superficial temporal artery (arrows).

the temptation to consider the procedure will disappear.

Having removed the acutely occluded middle cerebral artery from consideration for reconstruction, what other lesions and indications for intracranial vascular reconstruction exist? A recent study from UCLA (13) indicates that 19% of a series of patients with symptoms of transient cerebral ischemia had a completely occluded internal carotid artery as a principle hemodynamic factor in their angiographic study. Other studies (14, 15) indicate that 30–35% of the patients presenting with transient cerebral ischemia or mild infarction have obstructive lesions inoperable by general vascular techniques. Accordingly, any effective surgical procedure must either extract the obstructing lesion or bypass the area of obstruction. Since a major cause of cerebral insufficiency is unsuspected carotid occlusion, extending from the cervical to the cavernous portion, extraction of the thrombosis rarely is practical. Bypass procedures then become important in the creation of compensatory vascular channels.

What then are the indications for these vascular augmentation procedures? In a collaborative attempt to answer this question, investigators from four centers have pooled a hundred cases for retrospective analysis (16). As a result of this study, the following general indications are suggested:

Generalized Low Perfusion Syndromes

Symptoms:

1. impaired mentation
2. syncopal episodes
3. transient motor, speech or sensory deficit
4. transient or progressive visual loss
5. ataxia and postural vertigo

Etiology:

1. multiple vessel occlusion
2. multiple stenosis of intracranial vessels
3. unilateral vessel occlusion with inadequate collateral circulation or congenital anomalies which interfere with collateral circulation

Lateralized Low Perfusion Syndromes

Symptoms:

1. transient or progressive motor, sensory, or speech deficit

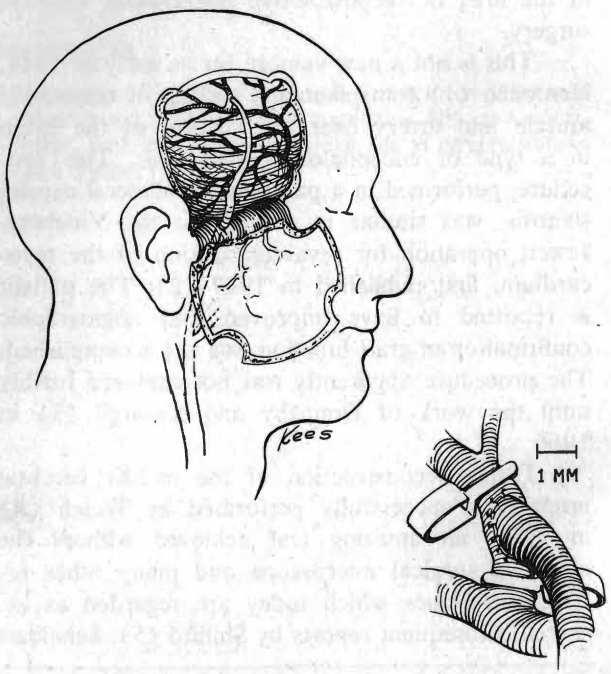

Fig. 2—Illustration for technique of anastomosis of superficial temporal artery to a cortical branch of the middle cerebral artery (MCA).

Etiology:

1. middle cerebral stenosis or occlusion with inadequate collateral circulation
2. cervical carotid occlusion or intracranial carotid occlusion with inadequate circle of Willis
3. inoperable carotid aneurysms or tumors such as meningiomas which produce carotid occlusion

Having agreed on these general indications, a prospective study is now underway to determine the merits of this approach to cerebral vascular disease (17). This report will be conducted during the next three years. Presently, I will review with you the techniques currently employed for cerebral vascular reconstruction and the findings in eighteen cases which have been under my personal care.

Donaghy and Yasargil (3) jointly devised the concept of performing an arterial graft; perhaps they remembered the initial explorations of Henschen. A satisfactory superficial temporal artery is required for this procedure; in this angiogram, a complete occlusion of the internal carotid artery is demonstrated (Fig. 1, see arrows). Delayed filling is noted through the ophthalmic and dural communicating arteries. The illustration (Fig. 2) demonstrates the technique: the superficial artery is dissected free from the scalp and a small skull flap is turned to expose the sylvian fissure and a portion of the temporal and frontal lobes. An oblique end-to-side anastomosis is created between the temporal artery and a carefully selected branch of the middle cerebral artery. A segment of the superficial temporal artery is first freed from its muscular branches for 7–8 cm. The artery remains in situ while the craniotomy flap is turned and the sylvian fissure is explored. A cortical artery of 1.5 mm in diameter or greater is selected as it

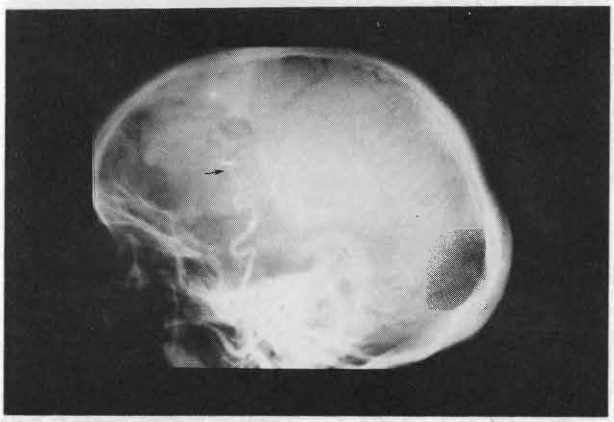

Fig. 3*A*—Common carotid angiogram with total occlusion of internal carotid artery; superficial temporal artery (STA) has been anastomosed to MCA branch at arrow.

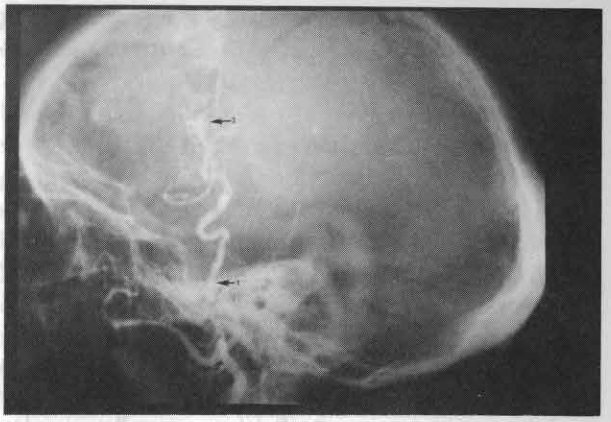

Fig. 3*B*—Later sequence in angiogram (Fig. 3*A*). 1 = site of STA entrance into cranial cavity and 2 = site of anastomosis. Note retrograde reflex toward proximal MCA trunk.

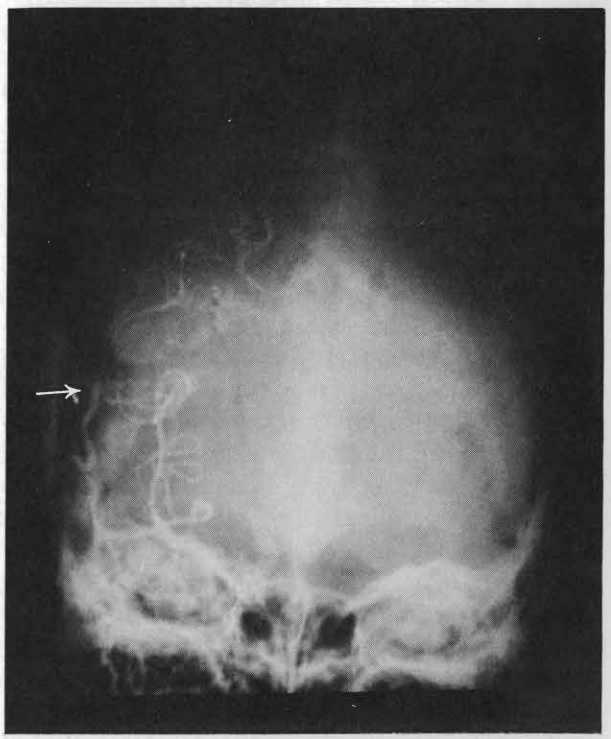

Fig. 3*C*—Anterior view of later sequence (Fig. 3*A*) showing site of anastomosis (arrow) and reflex to proximal MCA and subsequent filling of distal cortical MCA branches indicating that the graft is a major source of perfusion for this isolated hemisphere. Note absence of cross-fill phenomenon.

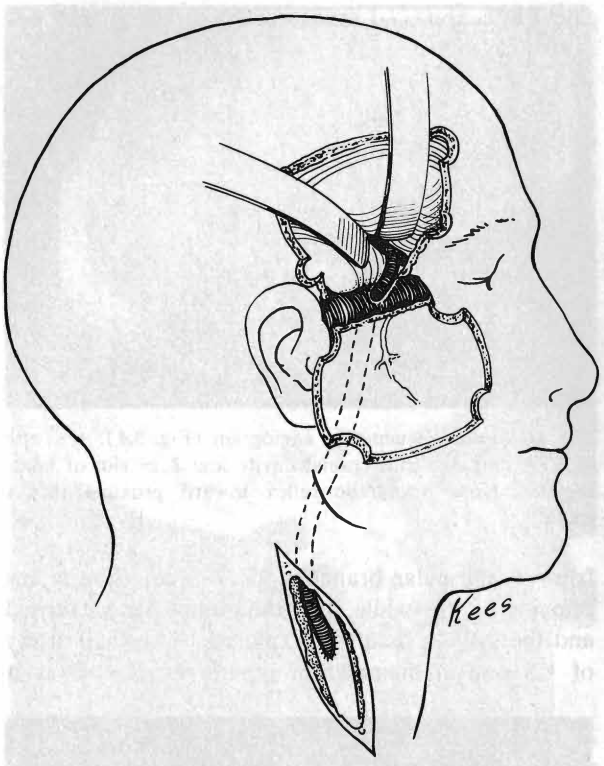

Fig. 4*A*—Vein bypass graft. Reversed vein graft is passed beneath the zygoma and joined to the proximal internal carotid artery.

leaves the sylvian fissure. Using 20–30 magnification, the cortical artery is prepared to receive the transplant. Minute penetrating branches are coagulated and incised. The cortical artery is lifted from the surface of the brain and a slip of latex is placed underneath it. The temporal artery is incised obliquely and brought into the field. The adventitia and other tissues are stripped from the terminal centimeter of the temporal vessel. The artery is dilated with pressure injection of heparinized saline and bathed in a dilute papaverine solution to reduce spasm. A longitudinal arteriotomy is made in the thin wall of the middle cerebral artery branch by a fragment of sharp razor blade. An incision is made the precise length to accommodate the oblique cut of the temporal artery. A polyethylene stint, 1.2 mm in diameter, is placed in the cortical artery after it is irrigated with heparinized saline. Interrupted sutures of 10.0 monofilament nylon are placed at either end of the suture line. The remaining portion is closed with similar interrupted sutures leaving the final three to be placed. The stint is then removed and the final sutures are secured. The artery is flushed to remove all air and particles of thrombus.

This technique has been employed in 14 cases, there being twelve males and two females with an average age of 50. Twelve have had symptoms of transient ischemia, indicating a lateralized low perfusion syndrome. Eight cases have had previous significant cerebral infarctions; two have had symptoms of progressive dementia indicating generalized low perfusion syndromes. Angiography demonstrated that twelve patients had occlusion of the ipsilateral

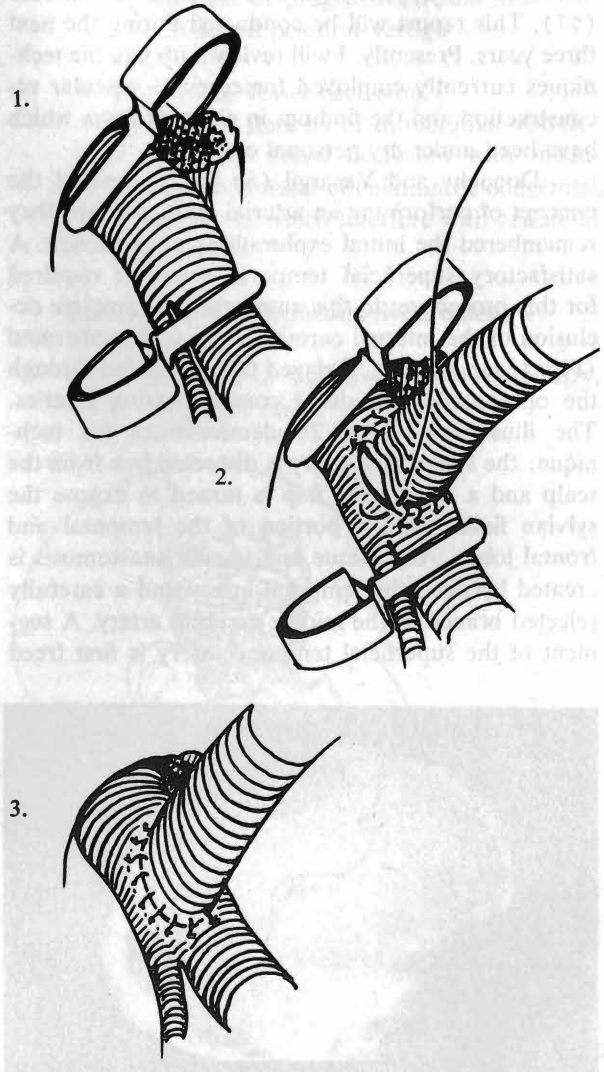

Fig. 4*B*—Technique for intracranial anastomosis of vein graft to internal carotid. 1 = anterior clinoid excised; note that clamps exclude ophthalmic and posterior communicating artery collateral supply; 2 = end-to-side anastomosis; 3 = completed graft.

internal carotid artery; three had bilateral carotid artery occlusion; five had marked stenosis of the contralateral internal carotid artery; and three had unilateral vertebral artery occlusion.

Results. Angiography was performed in all cases, postoperatively, usually one or two weeks following the procedure (Fig. 3). Nine grafts were patent; one, not patent on an earlier angiogram, was opened when the study was repeated two months later. We have recognized that spasm may interfere with early visualization of the graft. Four patients had symptoms of recurrent cerebral ischemia, one of whom had a patent graft. Two patients who had occluded grafts have not had recurrent attacks of ischemia. Both patients with dementia seem improved. Two patients have had recurrent cerebral infarction; both had had occluded grafts. One patient suffered a postoperative intracerebral hemorrhage presumably due to hemorrhagic infarction. One patient died of myocardial infarction. Complications consisted (one case each) of scalp necrosis, intracranial hemorrhage, subgaleal infection, and myocardial infarction; graft occlusion occurred in five cases.

The results of analyzing my personal cases and those of my colleagues (16) previously mentioned, suggest that the following contraindications to bypass graft procedures be considered: 1) major long-standing neurologic deficit; 2) severe recent cerebral infarction less than six weeks; 3) marked cardiovascular disease; 4) advanced diabetes mellitus; 5) inadequate donor artery—that is, a superficial temporal artery less than one millimeter in diameter. As noted in number five, inadequate donor artery has posed a serious problem in this technique; this inadequacy was the reason that Lougheed (18), in 1970, suggested the vein bypass procedure. As initially proposed by Lougheed, a saphenous vein graft was taken from the leg, the valves were stripped, and the small end was anastomosed to the supraclinoid portion of the internal carotid artery. The graft was brought out over the zygomatic arch. We have subsequently revised this procedure somewhat, simply reversing the

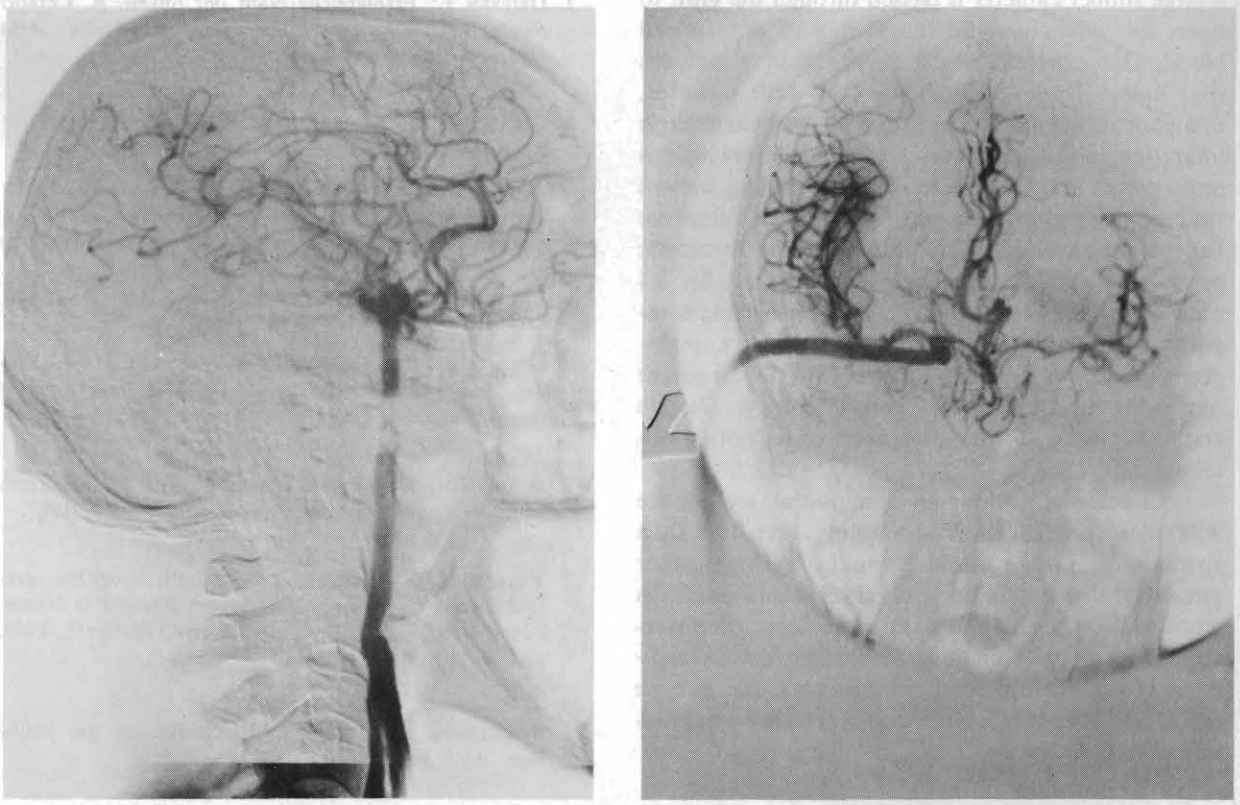

Fig. 5*A, B*—Postoperative angiograms of a patient who had generalized low perfusion due to occlusion of all major cerebral vessels. Lateral angiogram demonstrates course of draft (*A*). Anterior view illustrates bilateral filling of distal circulation (*B*).

graft and suturing the larger end to the internal carotid artery (Fig. 4). Flow is restored through this segment as soon as possible, since the hemisphere may be dependent on the collateral supply reaching it through the ophthalmic and posterior communicating arteries, which must, by necessity, be occluded during the cranial anastomosis. We have not yet developed a satisfactory shunt system to perfuse the hemisphere during the 10–15 minutes required for this portion of the procedure. Technically, this is a relatively simple procedure; yet the lack of a satisfactory internal bypass prohibits its performance in some of the most worthy candidates. The next major obstacle to bypassing the internal carotid artery is severe plaque formation in the carotid siphon above the anterior clinoid. Frequently, endarterectomy is required in opening a segment to receive the vein graft. Impaired runoff may be a problem in spite of careful attention to this maneuver.

The artery is led from the cranium beneath the zygoma into the neck. Prior to completion of the proximal anastomosis to the common carotid artery, a large rubber catheter is passed through the graft to open the valves and fill the vein with heparinized blood. Our experience with this technique includes four cases. Three grafts functioned well; however, one patient, our first, died of a massive hemorrhagic infarction, although it was six weeks following his most recent cerebral infarction. Our second patient suffered delayed thrombosis of the graft, a failure we believe to be related to compression at the zygomatic process. A third graft has functioned well for 14 months and the patient remains free of ischemic complications. Figure 5 shows the postoperative angiograms. A fourth graft was unsuccessful due to severe narrowing of the internal carotid artery. Despite endarterectomy, satisfactory runoff could not be obtained.

Conclusion. Although our initial experience with these procedures has certainly been less than spectacular, it does seem to indicate that further pursuit of the project of cerebral revascularization is worthwhile. Careful selection of patients, improvement of surgical technique (including the development of an internal shunt for bypass), and precise tabulation of results remain essential to the continuation of this study.

REFERENCES

1. HENSCHEN C: Operative Revascularization des zirkulatorisch geschädigten Gehirns durch Auflage gestielter Muskellappen (Encephelo-Myo-Syngangiose). *Langenbecks Arch Klin Chir* 264:392, 1950.
2. VINEBERG A, JEWETT BL: Anastomosis between coronary vessels and internal mammary artery. *Canad Med Assoc J* 56:609, 1947.
3. DONAGHY, RMP: Patch and bypass in microangiorsal surgery. In: *Microvascular Surgery* (ed.) RMP Donaghy, MG Yasargil. Thieme, Stuttgart, 1967, pp. 75–86.
4. WELCH K: Excision of occlusive lesions of the middle cerebral artery. *J Neurosurg* 13:73, 1956.
5. SHILLITO J: Intracranial arteriotomy in three children, four adults. In: *Microvascular Surgery* (ed.) RMP Donaghy, MG Yasargil, Thieme, Stuttgart, 1967, pp. 138–142.
6. SCHEIBERT CD: Middle cerebral artery surgery for obstructive lesions. Presented at the meeting of Harvey Cushing Society, New Orleans, La., May 2, 1962.
7. DRIESEN E: Erfolgreiche Naht der linken. A. Cerebri media nach Verletzung bei Tumorresektion. *Acta Neurochir* 10:462, 1962.
8. CHOU SN: Embolectomy of middle cerebral artery: Report of a case. *J Neurosurg* 20:161, 1963.
9. JACOBSON JH, WALLMAN LJ, SCHUMACHER GA, FLANAGAN M, SUAREZ FL, DONAGHY RMP: Microsurgery as an aid to middle cerebral artery endarterectomy. *J Neurosurg* 19:108, 1962.
10. LOUGHEED WM, GUNTON RW, BARNETT HJM: Embolectomy of internal carotid, middle, and anterior cerebral arteries. *J Neurosurg* 22:607, 1965.
11. SUNDT TM, NOFZINGER JD: Clip-grafts for aneurysm and small vessel surgery. *J Neurosurg* 27:477, 1967.
12. YASARGIL MG: Reconstructive operations on the cerebral blood vessels. In: *Microsurgery Applied to Neurosurgery* (ed.) MG Yasargil, Thieme, Stuttgart, 1969, pp. 96–119.
13. MACHLEDER HI, BARKER WF: Stroke on the wrong side. *Arch Surg* 105:943, 1972.
14. MARSHALL J: Angiography in the investigation of ischemic episodes in the territory of the internal carotid artery. *Lancet* 1:719, 1971.

15. BLAISDELL WF, HALL AD, THOMAS AM, ROSS SJ: Cerebrovascular disease, experience with panarteriography in 300 consecutive cases. *Cal Med* 103:321, 1965.

16. REICHMAN H, CHATER N, YASARGIL MG, TEW J: Recent advances in treatment of cerebrovascular disease. Exhibit presented at American Association of Neurological Surgeons, April 8, 1973.

17. REICHMAN H: Personal communication. December, 1973.

18. LOUGHEED WM, MARSHALL BM, HUNTER M, MICHEL ER, SANDWITH-SMYTH H: Common carotid to intracranial internal carotid bypass venous graft. Technical note. *J Neurosurg* 34:114, 1971.

Advances in the Management and Surgical Treatment of Intracranial Aneurysms* **

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Introduction. Patients who have sustained a spontaneous subarachnoid hemorrhage are victims of a very serious illness. Not only are they subject at all times to the potentially catastrophic results of a recurrent bleed, but they are faced with the manifestations of the irritative effects of blood in the subarachnoid space where the blood may function as a poison to the vessel wall. These acutely ill individuals may suffer a composite of secondary effects from a bleed which may include a communicating hydrocephalus, cerebral edema (ischemic or chemically induced), sterile meningitis, inappropriate ADH syndrome (osmotic effects of blood in the cerebrospinal fluid), spasm, and the likelihood of a recurrent bleed.

Physiology and Pathogenesis. Both the physiology and the anatomy of the cerebral blood vessels differ from those of comparable size elsewhere in the body (1). Unlike most organs and muscles, the brain maintains a relatively constant blood flow throughout a wide range of cardiac output and activity. The flow is approximately 700–900 milliliters per minute, whether the cardiac output is five liters per minute, as during rest, or four or five times that volume, as in strenuous exercise (2). Cerebral blood flow apparently is not directly sensitive to circulating epinephrine or norepinephrine, as these catecholamines do not cross the intact blood-brain barrier (3). Furthermore, it is common knowledge that these catecholamines in physiological doses do not produce marked vasoconstriction, even when applied topically to relatively normal cortical vessels. The cerebral circulation seems to be governed by its own autoregulation, a mechanism at present poorly understood (4). In health, this mechanism is not directly sensitive to the peripheral blood pressure within reasonable extremes. In cases of acute head injury, subarachnoid hemorrhage or cerebral ischemia, however, the autoregulatory mechanism is no longer functional and cerebral circulation becomes pressure and volume dependent (5).

The presence of a great abundance of autonomic nerves in the conducting vessels in the subarachnoid space has been the subject of recent intensive investigation directed toward identifying a physiological role for this system. Because conflicting data are reported from a variety of highly respected groups, one might maintain almost any role for this system today and find laboratory data to substantiate his position. It is our judgment that the autonomic nervous system provides a modulating and buffer action for the conducting vessels in the subarachnoid space, and we will direct our attention to this aspect of the problem a little later in this discussion.

Intracranial vessels have a characteristic and unique design (1). Perhaps this is because vessels inside the head are protected by a rigid skull and are not subject to the moving stresses and angulations of vessels in the body. They have a thin intima and adventitia. The media is also quite thin and not heavily endowed with elastic tissue. There is, however, a thick internal elastic membrane of considerable importance in providing the wall with strength. Defects in the media occur so frequently that they can hardly be termed pathological.

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* Presented by Dr. Sundt at the 27th Annual Stoneburner Lecture Series, February 8, 1974, at the Medical College of Virginia, Richmond.

** From the Cerebrovascular Clinical Research Center and the Department of Neurologic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901; this study was supported in part by Research Grant NS 6663 from the National Institutes of Health, Public Health Service.

Quite different, however, is the occurrence of defects in the internal elastic membrane. When this membrane fragments and bulges through a defect in the media, an aneurysm forms. Controversy continues over the cause of this fragmentation—whether it is congenital or degenerative—and also over the importance of a preexisting medial defect. The point of importance concerning the necessity and technique for repair is that the elastic lamella ceases to exist in the aneurysm itself. Furthermore, as the aneurysm grows in size, although there is no increase in the pressure per unit of area, the total force on the aneurysm increases. This subjects the base of the aneurysm to increased tension and tends to cause progressive growth of the lesion.

The weakest points in an aneurysm are usually in the dome itself or at its base where it arises from the vessel. The wall consists of collagenous tissue, which is continuous with the adventitia and intima of the parent vessel. There is a marked difference in the thickness from one aneurysm to another. Frequently through the operating microscope one can actually see the blood swirling in eddying currents through the walls of a thin aneurysm. In other instances, the aneurysmal wall does not seem different in consistency or thickness from the parent vessel; in the special case of giant aneurysms, the wall is quite thick. There is, of course, no way to predict from arteriography alone what the case is in each patient. In those patients who survive a subarachnoid hemorrhage from an aneurysm, a blood clot forms around the aneurysmal membrane, and along with the surrounding arachnoid, seals the vessel temporarily.

Surgery of Aneurysms. Most surgery for aneurysms today is performed through the operating microscope. A description of the procedure for repair of an aneurysm might be of interest to those of you who are not surgeons.

We will discuss four aneurysms, two internal carotid artery aneurysms and two anterior communicating artery aneurysms, the location of most aneurysms upon which we operate. Space does not permit us to cover middle cerebral and basilar aneurysms; their appearance is not greatly different.

The first case is of a left internal carotid artery aneurysm. Looking through the microscope, you expose the operative field, revealing the white structure of the optic nerve. Initially, with the point of an eleven blade knife, the arachnoid overlying the optic nerve is severed and the dissection is carried laterally to identify the internal carotid artery, the aneurysm arising and projecting laterally from that structure. (We prefer the tip of an eleven blade knife to a predesigned surgical instrument for this purpose; we have used the latter and found that they dull all too rapidly; the #11 blade can easily be replaced with a new, sharp blade.) There is a noticeable difference in the texture of the wall of the aneurysm and the carotid artery. The carotid artery is whitish by comparison to the aneurysm. A careful look at the aneurysm should permit you to see that the blood is swirling in eddying currents through the very thin-walled lesion. The clip we would use to repair this aneurysm is known as a clip-graft; in this case it would be applied with a right angle applier and the clip would circumferentially surround the internal carotid artery and seal the aneurysm at its base. We prefer this type of clip for repair of carotid artery aneurysms, because these aneurysms arise from a relatively wide portion in a relatively large vessel and repair with a straight clip does not reinforce the base or prevent the redevelopment of an aneurysm in the future, and furthermore, should the base tear with application, the clip seals the vessel. This is in direct contrast to middle cerebral aneurysms, for instance, in which ordinarily speaking one is able to find a relatively thick base in the aneurysm to accept a straight clip.

The second case is also an internal carotid artery aneurysm, but this aneurysm arises not only from the internal carotid artery but from the posterior communicating artery as well, which in the individual served as the sole source of blood supply to the posterior cerebral artery on the side of surgery. We could not use a clip-graft for fear of occlusion of the posterior communicating artery; the aneurysm must, therefore, be repaired with a Scoville clip, a type of straight spring clip. Following clipping of this aneurysm, a search made anteriorly to be certain of the patency of the posterior communicating artery showed it to be patent in this patient, and he made an uncomplicated postoperative recovery.

The third case is that of an anterior communicating artery aneurysm. Viewed through the operating microscope in an approach along the floor of the frontal fossa, the optic nerve would initially be identified and the dissection would be carried medially to the location of the anterior communicating artery and the aneurysm. Examination of the angiograms prior to surgery revealed that this aneurysm projected anteriorly, and comforted by this knowledge, the arachnoid overlying this lesion could be dissected

from between the two frontal lobes at their base, just anterior to the anatomical site of the vessel. Initially, the aneurysm would be difficult to see, being surrounded by some thick fibrinous material, which in turn was overlayed by arachnoid; these structures served to seal the aneurysm when it bled. The aneurysm having been dissected anteriorly away from the knee of the A-1 segment of the right anterior cerebral artery and the anterior communicating artery, a clip would be placed tangentially at this point, and following clipping, a search would be made posteriorly to be certain of patency of the major vessels.

The final case relates to an anterior communicating artery aneurysm repaired with a clip-graft. Both anterior cerebral arteries filled from the right A-1 segment—a not uncommon configuration in this type of aneurysm; that is, all too frequently both anterior cerebral arteries derive their blood supply from one side or the other through an enlarged A-1 segment. Therefore in this instance it would be particularly important to be certain that the anterior communicating artery remained patent, and therefore, the clip-graft would be placed with the right angle clip holder circumferentially around the anterior communicating artery sealing the small aneurysm projecting posteriorly at its base. The small aneurysms are often much more treacherous than the large aneurysms, because they do not offer a large enough sac to accept dissection and occlusion by a straight clip should they bleed.

Clinical Features and Diagnosis of Ruptured Aneurysms. The sudden onset of an excruciating headache, with or without the loss of consciousness, indicates a subarachnoid hemorrhage until proven otherwise. The patient describes an "explosion" in the head or a feeling of being struck behind the head with a hammer. Some patients complain of pain on one side, but more commonly the headache is primarily suboccipital in nature.

Often, the patient will have a seizure with his first hemorrhage, but repeated seizures thereafter are infrequent and anticonvulsants are usually not necessary. Patients may vary in their level of consciousness from alert to comatose following recovery of the bleed.

Most patients appear acutely ill and in pain. They complain chiefly of headache and commonly of nuchal rigidity, which incidentally increases after 24–48 hours. Blood pressure is commonly elevated. The patients who have suffered more severe hemorrhages are confused, stuporous, semicomatosed, or even comatosed. In this group, lateralizing signs such as hemiplegia, hemiparesis, or aphasia may be present. On the basis of the neurological symptomatology, Botterell (6) described a system of classification from grades I through V based upon the presence or absence of findings indicated above. A grade I patient is one with only minimal symptomatology, primarily headache; a grade V patient is preterminal and seldom considered a surgical candidate. Between grades I and V the classification is based upon a level of consciousness and the presence or absence of focal findings. This grading classification has proved to be of immense help in considering results of both operative and conservative management.

Natural History of Subarachnoid Hemorrhage. Various studies in the epidemiology of subarachnoid hemorrhage from a ruptured intracranial aneurysm have indicated the catastrophic nature of this illness. If a patient remains moribund for more than 24 hours after his initial bleed, his likelihood of a one-year survival is 8% with rather a severe morbidity; if he recovers from the bleed with only minor symptoms present or a clouding of consciousness, his chances for a one-year survival are approximately 50% (7, 8). Furthermore, approximately 70% of the patients with an aneurysm demonstrated on angiography will have a second hemorrhage, the peak incidence of which is in the second or third week following the initial bleed (9). The second occurrence is usually more severe than the first, frequently leaving the patient in a state of unconsciousness or coma.

Timing of Surgery. Although it would seem optimal to operate on the patient within the first few days after the bleed in order to prevent a recurrent hemorrhage, experience in early surgery from a variety of outstanding institutions has indicated the high morbidity of such a course of action. Accordingly, almost all patients initially are managed conservatively.

Initial Management by Clinician. The most important step in the care of a subarachnoid hemorrhage is the early diagnosis of a warning bleed by the family physician. All too frequently the warning bleed is unrecognized and only after a subsequent and more severe bleed is the patient referred for definitive management. A sudden, excruciating headache with or without the loss of consciousness is a subarachnoid hemorrhage until proven otherwise. A careful atraumatic spinal puncture is necessary in the diagnosis of this illness.

As soon as the patient recovers from the insult of his first hemorrhage, he should be transported by ambulance or air ambulance to a center where such problems are handled in volume. These patients rarely represent acute surgical emergencies, and except in instances of an associated large intracerebral or subdural hematoma, benefit from conservative management for the first several days following hemorrhage. This period of bedrest is perhaps even better for the patient in the setting of the local facility than at the referral center. It is disquieting for the clinician to have a patient with a subarachnoid hemorrhage die prior to referral or prior to obtaining a neurological consultation, but he can be comforted to know that bedrest with light sedation and analgesic medication would have been recommended for the first four or five days or perhaps even longer at most major centers and little could have been done by others that was not done by himself.

One is tempted to lower the blood pressure moderately in such patients with the hope of preventing a recurrence of bleeding while awaiting surgery or diagnostic studies. There are currently conflicting reports, however, regarding the usefulness of this measure and certainly it is not without risk. As mentioned above, patients with a subarachnoid hemorrhage become pressure dependent for cerebral perfusion; if a significant degree of intracranial vasospasm is present, lowering the blood pressure can result in cerebral ischemia and even infarction. This is not to say that hypotensive treatment is not indicated in selected instances, but the criteria are so complex for hypotensive management that definite rules cannot be developed at present.

The use of dexamethasone or some other steroid has been advocated by many experienced workers in this field; others feel that the risk of a stress ulcer is aggravated by an unproven beneficial effect from this drug and have cautioned against its use as a routine procedure. My personal experience with the use of dexamethasone in this setting, in marked contrast to its dramatic effect on the edema of gliomas, has not been very encouraging.

Final data regarding the ability of ϵ-aminocaproic acid to prevent a rebleed is not available. My experience with this drug has not been good, but admittedly we have not used it in the large dosages currently recommended.

Patients who have had a subarachnoid hemorrhage are particularly vulnerable to develop a type of inappropriate antidiuretic hormone (ADH) syndrome; therefore, moderate restriction of fluids is recommended, so that the patient's total fluid intake is between 1500 and 2000 ml daily. Serum sodium should be drawn every 48 hours and if the patient has a fall in the serum sodium, indicating extracellular volume expansion, fluids should be restricted to 1000–1200 ml daily.

Spasm. Early surgery in this illness is risky primarily because it accentuates and aggravates a state of arterial spasm, a reaction to the vasoconstrictive effects of blood and its breakdown products in the subarachnoid space (10). It is a diagnosis based upon the caliber of intracranial vessels seen on angiography; it may be focal or generalized, minimal or severe, unilateral or bilateral. Symptomatically it may produce evidence of both generalized and focal cerebral ischemia, the former manifested by an alteration in the level of consciousness and confusion, the latter by a focal neurological deficit. Although blood related, its etiology and pathogenesis are far from being elucidated.

In general terms, the more severe and widespread the spasm, the worse the patient's clinical condition. Extrapolating from our cerebral blood flow data, it seems likely that spasm can be tolerated until a critical reduction in cerebral blood flow occurs—probably somewhere in the level of 20–30 ml/100 gm/min. Often, prior to this reduction in cerebral blood flow, an angiographic appearance of spasm will not be matched by the clinical appearance of the patient; some individuals look amazingly well considering the angiographic picture. The reverse is not true; patients who show the severe symptomatology of ischemia in this illness usually have angiographic correlation not only with evidence of focal vessel constriction but also of slowing of flow.

Recently, we have employed a combination of isoproterenol (Isuprel®) and lidocaine hydrochloride (Xylocaine®) in the treatment of cerebral vasospasm (11). Isuprel® is given for its beta-adrenergic function and the Xylocaine® is used to counteract cardiac arrhythmias that might result from the intravenous administration of Isuprel®. All patients have had continuous EKG monitoring and special nursing care. Both drugs are administered intravenously on a continuous basis and should cardiac arrhythmias result, the Isuprel® is decreased in its strength and rate of administration or the Xylocaine® is increased in its strength and rate of administration.

There is a wealth of experimental evidence to indicate that the conducting vessels in the subarachnoid space have a rich adrenergic nerve supply which, after sympathectomy or subarachnoid hemorrhage, loses its fluorescence, indicating inactivation of the granulated vesicles at the nerve endings. These granulated vesicles are important not only for metabolism, production, storage, and release of norepinephrine but also for the control of function. In contrast with cholinergic endings in which an enzyme functions to destroy the freed acetylcholine, the limited duration of action of the adrenergic endings is thought to be related to the prompt reuptake of norepinephrine by the granulated vesicles. It is possible that some of the adverse effect of blood on a vessel is the result of this type of end-organ sympathectomy obliterating the function of the granulated vesicles and their buffer action. Alpha and beta sites are pharmacological concepts, not anatomical structures, and there is evidence that between various vasoconstrictive amines there is a competition for a type of membrane response. Isoproterenol is given not so much as a vasodilator but in an attempt to introduce a non-vasoconstrictive drug to compete at the end-organ for the membrane response and hopefully thereby to ameliorate the effects of vasoconstrictor substances such as serotonin. Our laboratory studies indicate that Isuprel® definitely does shorten the period of basilar artery constriction from the topical application of blood.

Table 1 illustrates the author's experience with the use of these drugs in operating on 159 patients over the past four years. This table is primarily intended to demonstrate the distribution of patients with this problem as a major complication and treated patients are identified in parentheses. The result columns indicate the final clinical state of the patient and not necessarily the response of the patient to the administration of these drugs. Most patients treated in the grade I and grade II categories were treated following surgery for the onset of a progressive neurological deficit. Most patients treated in the grade III and IV categories were treated prior to surgery in an attempt to arrest a progressive neurological deficit or improve their condition to a point where surgery could be tolerated. Patients who did not undergo surgery are not illustrated and not included.

TABLE 1

DISTRIBUTION OF TREATED* CASES AMONG ALL PATIENTS OPERATED ON ACCORDING TO GRADE AND FINAL CLINICAL RESULT

	Final Clinical Result			
Grade	Excellent	Good	Poor	Death
I	63 (7)	3		1
II	32 (6)	1 (1)	2	2 (1)
III	14 (5)	13 (3)	8 (2)	4
IV	2	1	8 (4)	5 (1)
Total	111	18	18	12

* No. of treated patients is in parentheses.

A retrospective analysis of the results of the use of these drugs indicates that no improvement has been noted, if the drugs have been used after a period of two hours from the time of the onset of the neurological deficit. Obviously, the more severe the deficit, the more important it is that therapy be instituted early. Although an occasional dramatic response has been noted, most commonly a progressive deficit is halted with a rather major recovery in the first 48 hours, and recovery thereafter related only to the predicted improvement and recovery pattern seen in patients with regions of focal ischemia. The drugs are, however, with careful monitoring, safe, and we have had no mortality from their use. It now remains for others to judge the merits and demerits of this program. Thirty patients treated in this group are shown; treatment was discontinued in another five because of arrhythmias.

In considering and analyzing the results of any medications, it is necessary that they be evaluated in properly selected patients. Spasm, as a major complication, was not uniformly seen in the patient group and although most morbidity and mortality is noted in the high-risk patients, grades III and IV, death and morbidity in these patients was not always a result of their preoperative state. Poor results and death in this group include one patient who bled in the hall prior to entering the operating room, one who bled during the induction of anesthesia, two who sustained a recurrent hemorrhage—the result of poor aneurysmal repair, and two who had occlusion of a major parent vessel from which a giant aneurysm arose. A permanent Korsakoff's syndrome accounted for a poor result in two patients (one of whom had a giant aneurysm and predated surgery). This syndrome, although occasionally the

result of spasm, is more commonly a complication of surgical trauma in the septal or preseptal area.

Conclusion. Improved neuroanesthesia and surgical techniques, especially including magnification of vision and an intense light source, have drastically lowered the operative mortality and morbidity in aneurysm surgery; however, because of a delay in surgery to avoid major vasospasm, many patients are lost from rebleeding. Until a solution to the complication of vasospasm is obtained, most major institutions still prefer to delay surgery. Isoproterenol and lidocaine seemingly ameliorate this dreaded complication but are certainly no panacea and we are still looking forward to a final miracle drug from one of our sister institutions (12).

REFERENCES

1. SAHS AL: Observations on the pathology of saccular aneurysms. *J Neurosurg* 24:792, 1966.

2. GUYTON AC: *Textbook of Medical Physiology*. Philadelphia, W. B. Saunders Company, 1966.

3. WURTMAN RJ: Catecholamines. *N Engl J Med* 273: 693, 1965.

4. LASSEN NA: Autoregulation of cerebral blood flow. *Circ Res* (Suppl) 15:201, 1964.

5. SUNDT TM JR, WALTZ AG: Cerebral ischemia and reactive hyperemia: Studies of cortical blood flow and microcirculation before, during, and after temporary occlusion of middle cerebral artery of squirrel monkeys. *Circ Res* 28:426, 1971.

6. BOTTERELL EH, LOUGHEED WM, SCOTT JW, VANDEWATER SL: Hypothermia, and interruption of carotid, or carotid and vertebral circulation in the surgical management of intracranial aneurysms. *J Neurosurg* 13:1, 1956.

7. LOCKSLEY HB: Natural history of subarachnoid hemorrhage, intracranial aneurysms, and arteriovenous malformations: Based on 6,368 cases in the cooperative study. *J Neurosurg* 25:321, 1966.

8. MCKISSOCK W, PAINE KW, WALSH LS: An analysis of the results of treatment of ruptured intracranial aneurysms: Report of 772 consecutive cases. *J Neurosurg* 17:762, 1960.

9. TRUMPY JH: Subarachnoid haemorrhage: Time sequence of recurrences and their prognosis. *Acta Neurol Scand* 43:48, 1967.

10. ALLCOCK JM, DRAKE CG: Ruptured intracranial aneurysms. The role of arterial spasm. *J Neurosurg* 22:21, 1955

11. SUNDT TM JR, ONOFRIO BM, MERIDETH J: Treatment of cerebral vasospasm from subarachnoid hemorrhage with isoproterenol and lidocaine hydrochloride. *J Neurosurg* 38:557, 1973.

12. WURTMAN RJ, ZERVAS NT: Monoamine neurotransmitters and the pathophysiology of stroke and central nervous system trauma. *J Neurosurg* 40:34, 1974.

Clinical Advances in the Evaluation of Deep Coma* **

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Today, 1974, in large medical centers, evaluation of the patient in coma is almost a daily necessity, and the need to evaluate the patient in deep coma arises once or twice every week. Even in smaller hospitals the problem is not uncommon. This has come about because many laymen and most medical personnel are now well trained in methods of cardiorespiratory resuscitation (1, 2). Persons are not allowed to die easily and once resuscitated, are moved to intensive care units where life is maintained. Fortunately, if they do not die of their underlying disease, such as trauma or myocardial infarction, many patients thus rescued recover completely; that more do not is due to the fact that the brain is such a tender organ—only a few minutes without oxygen and neurons die or are damaged—only a short while without blood flow and, apparently, the cerebral blood does not flow again. On the other hand, neurons, silenced completely by drugs for hours or even days, may recover and soon be alive and well.

A proper decision as to the cause and degree of brain damage may lead to useful treatment and recovery or, if the brain is dead, may allow other organs to be used for transplantation and relieve the family, as well, of hours of anguish and added expense. In 1966, Plum and Posner (3) outlined in an orderly fashion the various clinical observations necessary for the evaluation of the ordinary comatose patient. They did not, however, give special attention to the patient in deep coma or the problem of possible brain death. The problem of diagnosing deep coma and determining brain or cerebral death became more urgent with the advent of widespread organ transplantation. Although at first, the problem of evaluation of deep coma was approached by each specialist from his own area of expertise, a combination of clinical examination and laboratory tests has now been developed which promises to allow routine and relatively rapid diagnosis and prognosis. Impetus for such an approach in the United States first came in 1968 from the report of the ad hoc committee of the Harvard Medical School (4) to examine the definition of brain death. These so-called "Harvard Criteria" were primarily a combination of clinical examination and electroencephalogram recording. Standards for acceptable electroencephalographic recording were further studied and summarized by an ad hoc committee on "EEG Criteria for a Demonstration of Cerebral Death" (5) of the American Electroencephalographic Society published in 1970. While these and other studies (6, 7) emphasized the usefulness of the EEG in the evaluation of deep coma, investigators in Europe demonstrated the usefulness of cerebral arteriography and the assessment of cerebral blood flow as prime criteria for the determination of brain death (8–10). Further refinements of the clinical and EEG evaluation of deep coma will soon be available in the report of the National Institutes of Health Collaborative Study on Cerebral Survival (11). This study of over 500 patients also emphasizes the clinical examination and the electroencephalographic study; however, it will include the report of an ancillary study on a rapid bedside method of assessing cerebral blood flow by the injection of radio isotopes—the Bolus technique (12).

At the Medical College of Virginia, we became interested in the problem of acute bedside recording in the mid-1960's, particularly in relationship to patients with seizures and strokes. We were espe-

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cially interested in changes in patients with cerebral emboli who often presented with continuous focal seizures (13). This interest was expanded to include patients in deep coma, primarily for the purpose of making decisions related to organ transplant. For over five years, we have maintained regular 24-hour EEG coverage in the Medical College of Virginia Hospitals. Beginning in 1971, we took part in the National Institutes of Health Collaborative Study on Cerebral Survival (11). From this experience, and a survey of recent literature, comes the following assessment of our present approach to the diagnosis of the patient in deep coma. The main items of importance in the process are presented below.

Clinical Examination. Responsiveness to stimuli is basic to the definition of coma. Persons in deep coma do not respond to the spoken word at all; they do not respond in any purposeful manner but only by reflex movement to other stimulation. With deep pain, they may respond not at all or respond by reflex movement such as decorticate or decerebrate posturing. In some cases, eye blinks, either spontaneous or to stimulation, may occur and occasionally chewing movements. Any easily elicited response, particularly of a purposeful nature to any stimuli, suggests that the patient is not in deep coma.

The presence or absence of spontaneous respiration is, of course, a critical point in the evaluation of deep coma. With brain death, including the cerebral cortex as well as the brain stem, there will be no spontaneous respiration. With cerebral cortex damage alone, but with brain stem function intact, respiration may be nearly normal. This accounts for the rare situation of a patient showing electrocerebral silence on EEG with some loss of other cranial reflexes who surprisingly breathes spontaneously after the mechanical respirator is disconnected. These are the patients who may survive for months or years with an EEG showing electrocerebral silence. This also indicates the necessity of carefully testing all cranial reflexes before cerebral death is pronounced. In general, the absence of spontaneous respiration is a bad prognostic sign in patients with structural lesions, such as cerebral hemorrhage or trauma, and to a considerable degree in patients with cerebral anoxia. Patients in coma from overdose, however, may not have spontaneous respiration for a considerable period of time and still completely recover.

The Harvard criteria emphasize the absence of all reflexes, both cranial and spinal, and the lack of spontaneous respiration as the prime elements in the clinical examination. Experience in the Collaborative Study on Cerebral Survival (11) has confirmed the importance of cerebral reflexes. In this regard, the pupillary reflexes are the most important since fixed dilated pupils (not necessarily maximally dilated) and absence of respiration are the most common clinical accompaniment of brain death. The presence of oculocephalic reflexes indicates that brain stem structures are still alive. The presence of oculovestibular reflexes also suggests the presence of functioning brain stem structures, but this reflex seems to persist longer than the oculocephalic reflex. The response of eye blinks, either as a reflex or spontaneously, also indicates some brain stem function and since this is routinely recorded in the electroencephalogram, it serves as a reminder to the electroencephalographer that brain stem function persists, even though the recording may show electrocerebral silence otherwise (Fig. 1).

It may be noted that the examination of the optic fundi is not included as an important factor in determination of cerebral death. Although examination of the optic fundi may help in the etiological diagnosis of coma, it is of little direct help in prediction of the level of coma or its outcome. Information of the presence or absence of blood flow in the retinal vessels is not sufficiently accurate to serve as a criterion of brain death.

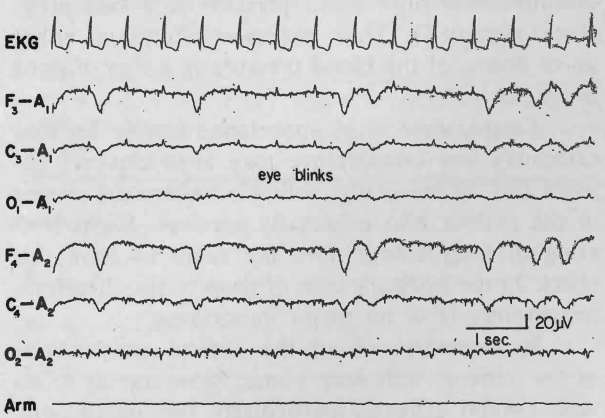

Fig. 1—This record shows eye blink, muscle, and EKG artifacts. After succinylcholine injection the muscle and eye blink artifacts were abolished and no evidence of cerebral activity remained. Despite this fact, the patient is still alive, nine months after cardiorespiratory arrest. The patient still remains in coma but breathes spontaneously.

One result of our experience in the cerebral survival study is the understanding that spinal reflexes are completely unreliable in the prediction of brain death or of the outcome of coma. Although the paper outlining the Harvard criteria is not exactly clear on this point, it suggests the absence of spinal reflexes as part of the criteria; this is one part of the Harvard criteria that may definitely be discarded. Although spinal reflexes are often absent, patients in deep coma may show some degree of reflex movement as well as actual muscle stretch reflexes and even Babinski signs. Such reflexes, of course, may be suppressed in patients with drug overdose, and yet the patient may still recover completely.

Convulsions or myoclonic jerks are common during the 12–24 hours immediately following cerebral damage from anoxia due to cardiac arrest. During this time, the EEG may indeed show no clear activity except the artifacts produced by such movements. With the use of succinylcholine or Valium®, the cerebral discharges alone can be recorded. The occurrence of convulsions or diffuse rhythmic myoclonic jerks can be taken as proof of some brain function.

Blood pressure, as such, is of little value in the evaluation of the patient in deep coma. It is true, however, that a sudden fall of blood pressure is often a terminal event in a patient with brain death maintained on a respirator for a long period. It is also apparently true that in patients with cerebral trauma or cerebral hemorrhage, the presence of excessively high blood pressure is a bad prognostic sign (14). Thus, excessive alteration, either up or down, of the blood pressure is a sign of poor prognosis (15).

Temperature is of importance mainly because extremely low temperature may alter cerebral activity and be associated with electrocerebral silence in the patient who eventually survives. Slight lowering of temperature does not seem to have this effect. In the ordinary case of deep coma, therefore, temperature is of no major importance.

In summary, of all the clinical observations of the patients with deep coma, those having to do with cranial reflexes, particularly the pupils, and with respiration, are the most important.

Tests for Drugs and Metabolic Abnormalities. Since recovery from deep coma in patients with electrocerebral silence on the EEG is seen almost exclusively in patients whose coma is due to drug overdose or metabolic derangement, the diagnosis of toxic and metabolic factors in coma is of great importance. Experience in this regard suggests that tests for metabolic derangement, at least ordinary metabolic derangement, are rapidly and easily obtained. The same is not true of toxicology. Even in large medical centers, it is often difficult to obtain rapid, reliable, quantitative tests for drugs and toxic substances. While it is true that drug levels are not important in cases of clear trauma or of anoxia secondary to cardiac disease, occasionally the two conditions may coincide. For this reason and because of the legal implications, improvement of our services in this area is urgent (16). Even though rapid toxicology reports may become available in large medical centers, it will remain a difficulty for some time in smaller hospitals. Fortunately, evidence at this point suggests that usually the patient in deep coma can have an adequate evaluation without knowing the actual drug levels. For instance, in our experience, no patient with dilated pupils and electrocerebral silence on the electroencephalogram has survived. Since such a case might exist, however, due to drug overdose, this is an area in which the use of a rapid simple test of cerebral blood flow would help give a final answer concerning cerebral death without reference to drug levels (10).

Another recurring problem of patients in deep coma, particularly with anoxic coma, has to do with the fact that many present with convulsive or myoclonic seizures. Such patients are often treated with rather large doses of anticonvulsant drugs which are also sedatives. Obviously, it is not appropriate to accept clinical and EEG evidence of brain death in the patient who has just been given large doses of such drugs. Quantitative drug levels are necessary before final decisions can be made.

Electroencephalogram. The importance of the electroencephalogram in the evaluation of coma has escalated in direct proportion to the 24-hour availability of such recordings, the excellence of the recording technique, and the experience of the electroencephalographer. When these criteria are met, the electroencephalogram is indispensable in the diagnosis and prognosis of deep coma.

Meticulous technique is the mark of the excellent EEG technician and the true electroencephalographer. The model of such meticulous technique was established by Hans Berger (17) in his extensive studies to prove that the oscillations

of his recorders were due to cerebral activity and not to artifact. Modern electroencephalographers have retraced Berger's steps with the opposite intent, namely to prove that the oscillations *are* artifact and not cerebral activity.

Fortunately, with present equipment, excellent artifact-free records may be obtained in even the most chaotic intensive care unit. Adequate technical recording requires that records be made at a very high amplification with portions of the record being recorded with an amplification of two microvolts per millimeter. It is then necessary that all deflections of the recording be clearly identified either as artifact or as cerebral activity. Common artifacts come from the electrocardiogram, from mechanical respirators, from cardiac monitors, and from other monitoring equipment. Any slight movement of the bed or patient may present a problem. When these artifacts cannot be eliminated, they can at least be monitored as a part of the actual recording. Figure 2 shows respirator artifact and electrocerebral silence when the respirator is briefly stopped. Figure 3 shows the monitoring of the respirator cycle by an accelerometer actually attached to the respirator instrument.

The most consistently bothersome artifact is that of muscle activity. Even in deeply comatose patients and even in patients without brain stem function, some muscle activity may remain. Fortunately, since such patients are on respiratory support, the use of succinylcholine given intravenously to abolish muscle artifact is an extremely useful procedure. This is particularly true since in a review of our records on patients in deep coma, the type of record which was most consistently thought to be technically inadequate was the record with muscle artifact. Particularly records with low amplitude artifact due to muscle alone may be thought to show low-fast brain activity. Figure 4*A* shows such a record and the recording after succinylcholine (Fig. 4*B*).

As regards the Harvard criteria (4), our studies have shown that all patients with a single record of thirty minutes of electrocerebral silence with no spontaneous respiration and with dilated fixed pupils have died. A recent report of Jorgensen (18, 19) from Copenhagen reaches this same conclusion, except that he adds to the criteria the loss of spontaneous maintenance of systemic blood pressure.

Aside from the usefulness of the electroencephalogram in the recording of electrocerebral silence in cases of brain death, experience in a great variety of patients with lesser degrees of coma has given a new appreciation of certain distinct EEG patterns (13, 20–27). Such distinctive EEG

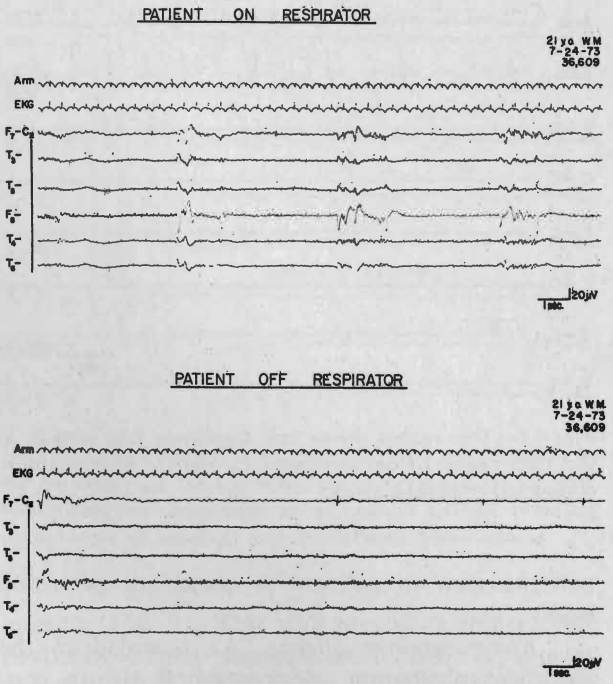

Fig. 2—The first record shows regular, recurring respirator artifact. The second record shows the disappearance of this artifact when the respirator is stopped. Though some very slight muscle artifact remains, the record after the respirator is stopped is essentially that of cerebral silence.

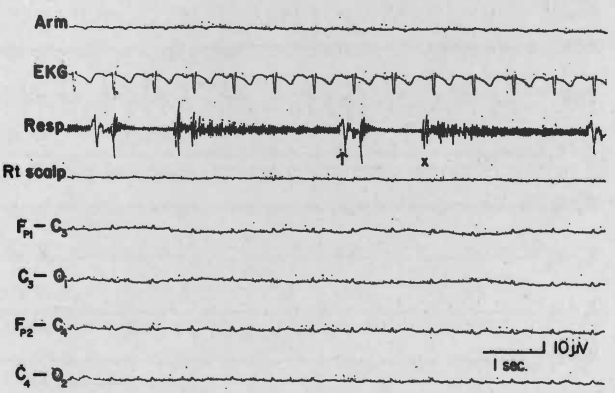

Fig. 3—Monitoring of the respirator cycle by an accelerometer is demonstrated in Channel 3. Although the recording is that of electrocerebral silence and no marked respirator artifact appears, a slight swaying of the baseline in time with the respiration can be detected in Channels 5 & 6.

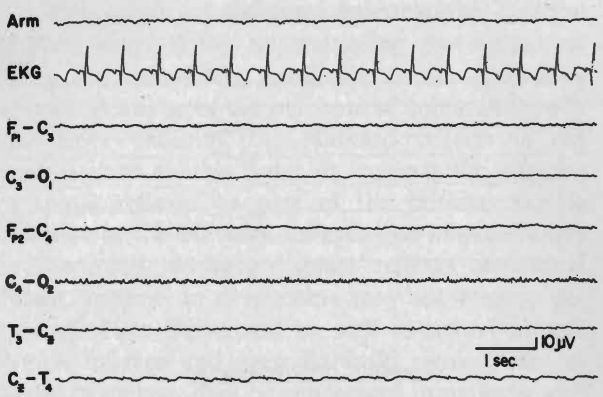

Fig. 4*A*—This record shows low amplitude fast activity in the sixth channel from electrodes C_4 and O_2. This might be considered cerebral activity.

patterns seen in patients in coma are presented below.

Electrocerebral Silence. As recorded in the electroencephalogram, electrocerebral silence consists of no deflections above a millimeter with the machine set at an amplification of two microvolts per millimeter. Actually, some older machines have a background noise level of two-to-three microvolts, and in this situation, some leeway will have to be given for determination of electrocerebral silence. In the newer machine with everything in order, a record without deflections beyond a one-millimeter range should be obtainable. Nevertheless, it is usually impossible, except by special subtraction or computer techniques, to remove all of the EKG artifact from the record (28). This usually appears as a regular deflection which can be monitored and determined to be directly synchronous with the EKG (Fig. 5).

Low Amplitude-Fast Activity (Muscle) Abolished by Succinylcholine. Low and high amplitude muscle artifact is seen in many recordings, even in patients with severe damage of the brain stem. It occurs in patients who already have dilated fixed pupils and no spontaneous respiration. If these patients are continued on respiratory support, eventually all muscle activity ceases. The muscle activity may be the only remaining artifact that makes it impossible to be sure the record is that of electrocerebral silence. Also, the muscle artifact may appear actually as beta activity. Since beta activity is often seen in patients with overdose who will survive, it is extremely important that this differential be made. This can be done by a single injection of 30–60 mg of succinylcholine intravenously or, better yet, by a slow constant drip of succinylcholine (29–31). This is done, of course, only on patients with respiratory support (Fig. 4*B*).

Electrocerebral Silence Except for Myoclonic Jerks. We have observed, particularly early in the course of deep coma and especially in coma due to cerebral anoxia, that the patient may present with repeated myoclonic jerks, but the recording, except for these jerks, shows no cerebral activity (Fig. 6). Succinylcholine given in this situation has to be given in very large amounts to block the myoclonic jerks. Drugs such as diazepam may block the myoclonic jerks but then raise the question as to whether the drug might also suppress

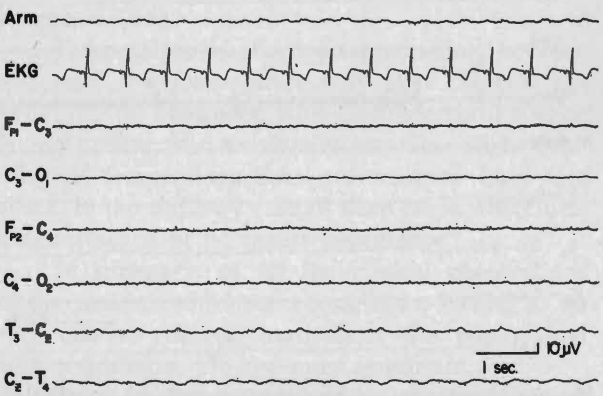

Fig. 4*B*—After succinylcholine the low amplitude fast activity seen in Channel 6 disappeared and therefore was due to muscle artifact. The recording is now that of electrocerebral silence.

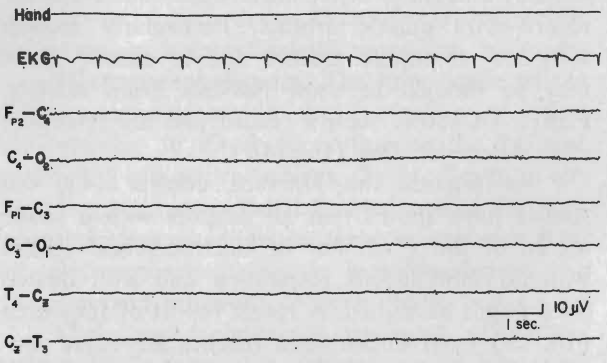

Fig. 5—At a recording amplitude of 2 μV/mm, no discernible cerebral activity appears and this is a typical record of electrocerebral silence. Very slight EKG artifact is seen.

other cerebral activity. In general, this type of record is usually, but not always, a very poor prognostic sign. The fact that myoclonic jerks exist, particularly as they are bilateral and symmetrical, indicates that some brain function remains.

Burst Suppression Pattern. In many records of deep coma, particularly due to cerebral anoxia and often following a few hours of records which show only myoclonic jerks, there may occur a burst suppression pattern. In this situation, fairly high amplitude complexes, either singly or in paroxysmal episodes, occur with intervening periods of electrocerebral silence. The intervening period may vary from one or two seconds up to a minute or more. Such a burst suppression pattern, in general, is a bad prognostic sign (Fig. 7).

PLED's and "Bilateral" PLED's. In a great number of patients with cerebral emboli or other lesions, particularly associated with some metabolic disturbance, bilateral, semirhythmic, periodic discharges are seen but these discharges are definitely greater on one side. Often associated with these discharges, there are brief but continuous myoclonic jerks. In our laboratory at the Medical College of Virginia, these were observed in the early 1960's and designated "acute spikes" (13). They also have been described and usually called "PLED's" (periodic lateralized epileptiform discharges) in the literature (32). Most patients with this pattern are stuporous but may be conscious; depending upon the lesion involved, they may proceed with it and die or they may recover completely. It is thought that the cerebral ischemia, resulting from embolization which has produced a temporary anoxia, causes the unilateral discharges. In any case, a similar pattern, bilaterally symmetrical, is seen following severe cerebral anoxia of a diffused nature such as that due to cardiac standstill. In this situation, the bilateral PLED's have a much more serious prognosis (Fig. 8*A, B*).

Continuous Spike or Spike Waves. Certain patients who are stuporous or in coma present with continuous diffuse spike or spike wave discharges. Some of these patients have a chronic form of convulsive disorder and are in a type of convulsive state. Such patients are not usually confused with deep coma, since reflexes remain and pupils react, and the patient breathes spontaneously. Following a reasonably severe anoxic insult, however, certain patients also go into a period of one, two, or three days of continuous diffuse spike and spike wave

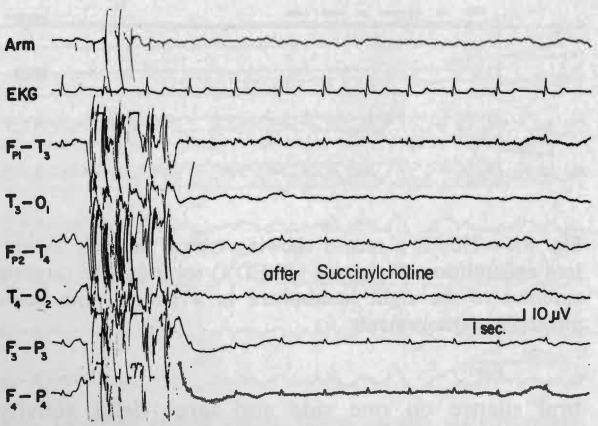

Fig. 6—In this record myoclonic seizures such as seen in the beginning of the recording occur every 10–30 seconds. Succinylcholine suppressed other muscle artifact revealing no evidence of cerebral activity between these attacks.

activity (Fig. 9). This may precede a more severe continuous burst suppression record, or it may precede a longer period when the patient simply has a theta coma. A few of these patients recover, usually with some degree of neurological damage. Control of such activity with anticonvulsant drugs usually does not produce an electrocerebral silence record but tends to produce a record with either delta or theta activity, so that there is no problem concerning decision as to electrocerebral silence.

Severe Asymmetry. A record with severe asymmetry, particularly showing essentially electrocere-

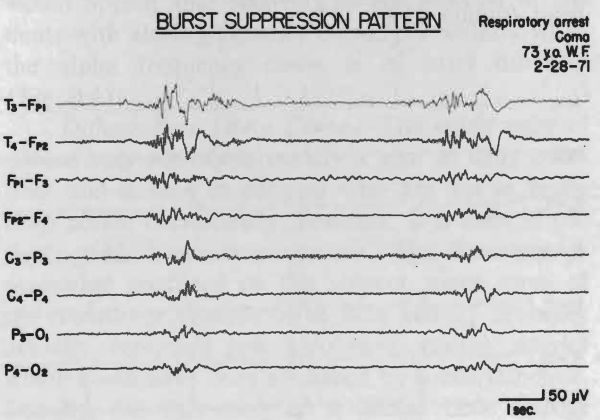

Fig. 7—This record shows relatively high amplitude discharges occurring in a rhythmic fashion with only low amplitude activity between. Such discharges appearing over a period of time in general have a bad prognostic significance.

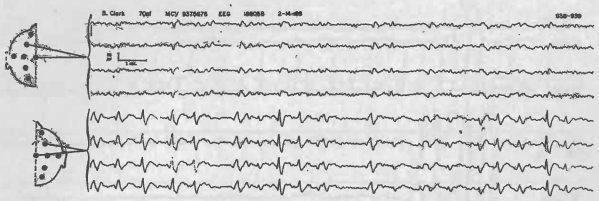

Fig. 8*A*—This is a record showing typical periodic lateralized epileptiform discharges (PLED's) secondary to cerebral embolus to the right hemisphere in a patient with some metabolic derangements.

bral silence on one side and large delta activity on the other, is seen primarily in cerebral trauma but occasionally in intracerebral hemorrhage. Such a record indicates a poor prognosis for complete recovery, though dependent upon the treatment carried out and the nature of the illness, the patient may survive (Fig. 10). Lesser degrees of asymmetry seen in ordinary subdural hematoma, of course, may be followed by complete recovery of the patient and normality of the EEG.

Diffuse Delta. Classically, diffuse delta activity has been associated with coma or diffuse brain damage or disease. Actually, this is not a very frequent pattern in the patient in deep coma. The presence of diffuse delta may indicate any of a great number of relatively acute cerebral disturbances which may be transitory. Thus, many patients who show diffuse delta and periods of coma or confusion recover completely. This is particularly true following metabolic happenings and following closed head trauma (Fig. 11).

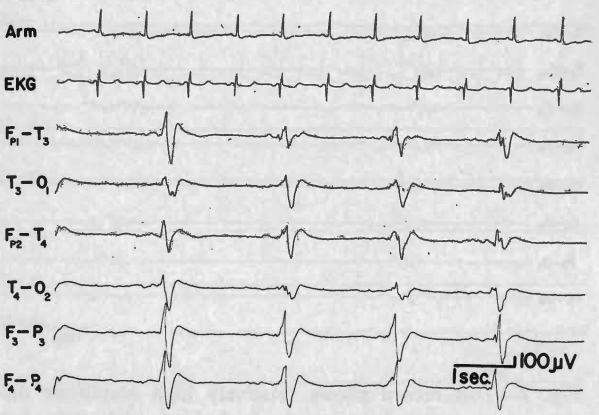

Fig. 8*B*—This is a recording showing periodic generalized discharges or so-called bilateral PLED's in a patient with diffuse cerebral anoxia secondary to cardiorespiratory arrest.

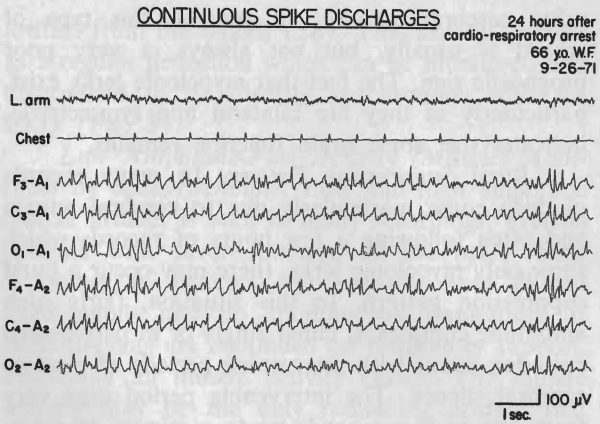

Fig. 9—This record shows continuous spikes and spike waves in a diffuse fashion due to an acute cerebral anoxia.

Diffuse Theta (Theta Coma). We have observed a number of patients with a fairly regular diffuse theta activity in the electroencephalogram (25). This activity is often seen during a recovery stage following cerebral anoxia of a severe degree. At this point the patient may deteriorate and revert to burst suppression and eventually to electrocerebral silence but more often shows a tendency toward recovery. This finding of theta coma is of importance directly in proportion to how long it occurs. As a transient happening, it has a good prognosis in general; if theta coma pattern persists for days or weeks, however, it is usually in association with a patient who has received rather severe diffused cerebral damage as well as some brain stem damage. Such patients usually breathe spontaneously, have some pupillary reflexes, but do not respond in purposeful fashion

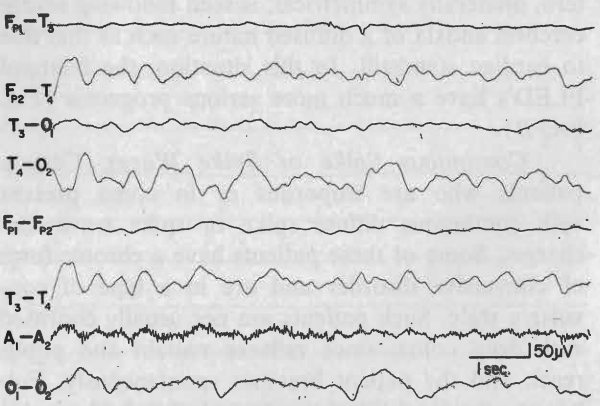

Fig. 10—This record shows marked asymmetry with severe depression over the left hemisphere secondary to a large subdural following trauma in the so-called "battered child."

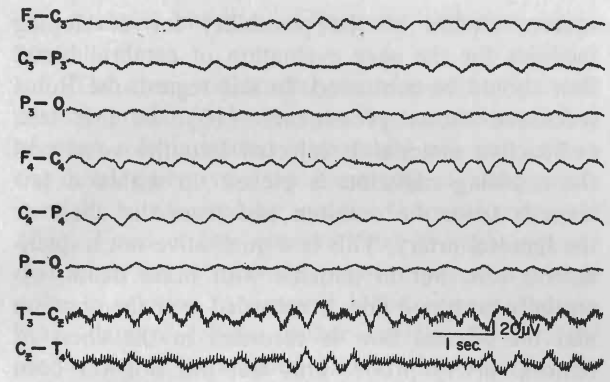

Fig. 11—This record shows diffuse delta in a patient comatose following a hypoglycemic episode.

to stimuli. They may stay in this state for long periods of time (Fig. 12).

Diffused "Sleep Spindle" Activity. Reports have appeared concerning sleep spindle activity in coma associated with brain stem lesions (24), particularly in pontine lesions. We have seen one particularly impressive case with a cerebellar hemorrhage and brain stem compression. This type of record may be confused with records in drug overdose which may also show sleep spindles. The presence of such a record in a deeply comatose patient, however, should always raise the possibility of a brain stem lesion and compression by a cerebellar lesion, particularly since this may be a treatable situation (Fig. 13).

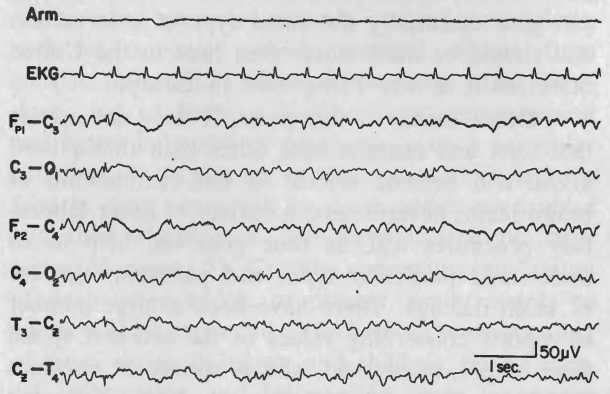

Fig. 12—This record shows so-called theta coma with predominant discharges in the 4–8 c/sec range in a diffuse fashion. This patient had severe diffuse cerebral damage following cerebral anoxia but, though comatose, was still breathing spontaneously and making nonpurposeful movements to stimuli two months following the injury.

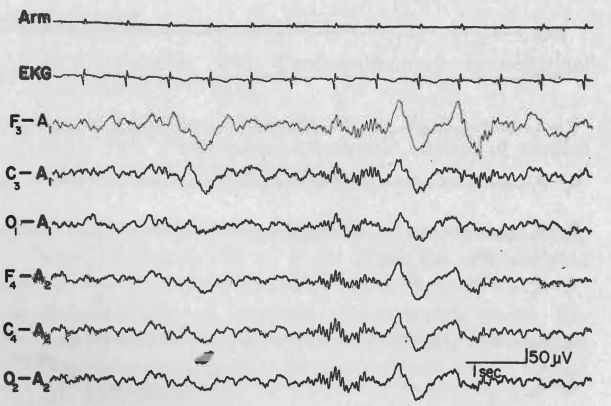

FIG. 13—This record shows diffuse spindle activity resembling sleep in a patient with a cerebellar hematoma and compression of the brain stem. Removal of the hematoma resulted in nearly complete recovery of the patient.

Diffuse Alpha Frequency (Alpha Coma). Reports of normal electroencephalograms in patients in coma have appeared (26, 27). What is usually meant by this is that the patient has an alpha frequency discharge which occurs in a diffuse fashion. Actually, such a diffuse alpha frequency discharge is quite abnormal and is indeed usually associated with coma secondary to pontine or brain stem lesions or damage. Most such patients have died; however, we have recently recorded such alpha frequency coma in several patients who survived (33). Two of these had coma following severe accidental electroshock and one had coma following cerebral vascular insufficiency attack. It would appear that recovery is not unusual in patients with alpha frequency coma, particularly when the alpha frequency coma is of brief duration (Fig. 14).

Diffuse Beta (Beta Coma). The occurrence of diffuse beta activity is usually a sign of drug overdose and is seen in patients who are not in really deep coma; occasionally, however, it is seen in patients with brain stem lesions. The literature is somewhat confused on this subject, since some of the recordings thought to be beta activity probably actually represent low amplitude muscle activity which could have been abolished by succinylcholine. Usually, the recording of a diffuse beta activity record is a good prognostic sign, because it is usually related to drug overdose (Fig. 15).

These are some of the characteristic patterns with which we have become familiar in the study of coma. As time goes on, and larger numbers of

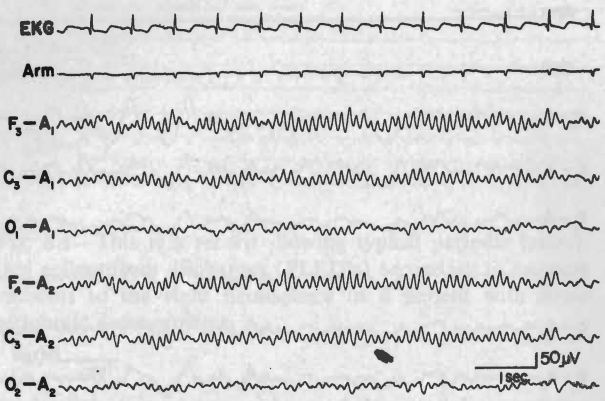

Fig. 14—This record shows so-called alpha frequency coma in a patient comatose following cardiorespiratory arrest from a severe electric shock. The patient remained comatose for nearly three weeks but then slowly regained consciousness and is still living with a large degree of recovery but with some slight memory and learning defect.

cases are collected, more definite prognostic attributes can be given to each type of finding.

Determination of Cerebral Blood Flow. Although our experience indicates that a careful clinical examination and excellent electroencephalographic recording give enough information, even within 30–90 minutes, to make a decision as to the presence of brain death (dilated fixed pupils, no spontaneous respiration, and electrocerebral silence EEG for thirty minutes equal brain death), the addition of information about cerebral blood flow might increase ones sense of confidence in cases where drugs or metabolic abnormalities might be active. For this reason, studies of the possibility for developing facilities for the easy evaluation of cerebral blood flow should be continued. In this regard, the Bolus technique shows prominence (10). In this test, radioactive material is injected into the veins and the resulting radiation is picked up within a few seconds from the cranium and from the chest or the femoral artery. This is a qualitative not a quantitative test, but in patients with brain death, essentially no blood flow is recorded over the cranium and the normal flow is recorded in the chest or femoral artery probe. This test has not yet been firmly authenticated with contrast cerebral arteriography, but so far its correspondence with other studies is excellent. Because it represents a relatively simple bedside test, could be available in a large number of hospitals, and offers confirmation of brain death from a different parameter, it may indeed have widespread application.

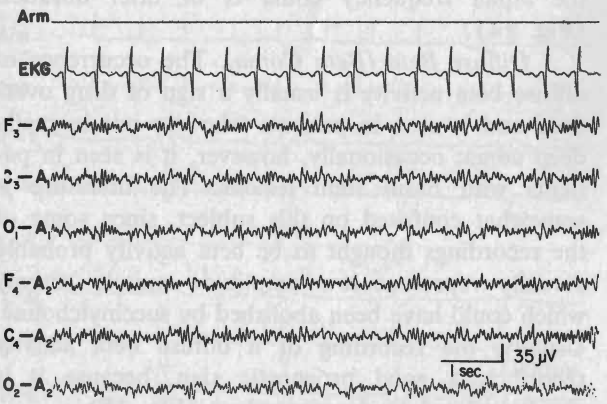

Fig. 15—This is so-called beta coma seen in a patient with a drug overdose who was comatose but who recovered rapidly and completely.

It is assumed that in a case of severe drug overdose without cerebral anoxic damage or cerebral infarction, the cerebral blood flow would be present and, if not normal, at least not severely depressed. For this reason this test would become an ideal test on a patient with drug overdose who had remained comatose with electrocerebral silence for a period of 12–24 hours. In similar cases, where ordinary contrast cerebral arteriography has been performed, it has shown no cerebral blood flow in patients even with overdose after 24 hours. This is almost certainly due to the fact that these patients have also suffered anoxic damage. Even now, when doubt exists, ordinary contrast cerebral angiography can give essentially the same type of information and should be used more often here in the United States as it is now being used in Europe.

Other Tests. At this point, it does not appear that tests and examinations other than those listed above will become critical in the examination of brain death; nevertheless, a variety of other laboratory procdures will, as time goes on, help us to understand particular types and particular degrees of brain damage. There have been a large number of reports concerning values in the cerebral spinal fluid of pH, lactic acid, and a variety of enzymes related to the stage and degree of brain damage (34, 35). In general, we have not carried out lumbar puncture or cerebral spinal fluid examination routinely in patients with deep coma, since in some cases this might be contraindicated because

of increased intracranial pressure or other intracranial lesions.

The more widespread use of monitoring intracranial pressure assures our better understanding of what role increased intracranial pressure has in the development of deep coma and at what points it might be reversed by various forms of treatment (36). From a few observations, it might appear that when the intracranial pressure passes a critical point in relation to systemic blood pressure, severe brain damage follows rather rapidly. So far, the monitoring of intracranial pressure has been largely in patients with trauma or hemorrhage, but it would appear to be a reasonable procedure in most patients in deep coma.

What of the Future? As the assessment of the patient in deep coma becomes more exact and routine, it is reasonable to expect continued progress in both diagnosis and treatment, particularly in the following areas: 1) The routine collection and correlation of data concerning the clinical examination, drug and metabolic levels, electroencephalogram, and cerebral blood flow will allow dependable decisions concerning cerebral brain death to be made at any point in the patient's course in a matter of one or two hours. As outlined previously, some combinations of these findings will supplant the Harvard criteria (4) as a dependable basis for determining cerebral or brain death. 2) Complete assessment of the patient in coma will occur earlier and nearer the time of the original insult to the brain, thus allowing a better understanding of the patterns of evolving brain damage or recovery. 3) An understanding of the usual course of coma in particular situations, such as cerebral trauma, cerebral anoxia from cardiac standstill, cerebral hemorrhage, drug overdose, and so forth, will allow better management and better judgment of prognosis in each particular situation. 4) A number of distinctive EEG patterns seen in deep coma will be more widely recognized and their significance will be validated by large series of cases. 5) Criteria concerning evaluation of deep coma which, at present, apply mainly to adults will be expanded to include an understanding of the situation in infants and children. 6) As clinical information and information from laboratory work accumulate, useful means of altering the course of severe brain damage by the application of a variety of medical and surgical treatments will be found.

REFERENCES

1. Kouwenkoven WB, Cardiopulmonary resuscitation. *JAMA* 226:877, 1973.
2. Zoll PM: Development of electric control of cardiac rhythm. *JAMA* 226:881, 1973.
3. Plum F, Posner JB: Diagnosis of stupor and coma. *Contemp Neurol Ser* 1: F. A. Davis Co., Philadelphia
4. Beecher HK: A definition of irreversible coma: Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. *JAMA* 205:337, 1968.
5. Silverman D, Masland RL, Saunders MG, Schwab RS: Irreversible coma associated with electrocerebral silence. *Neurology* 20:525, 1970.
6. Korein J, Maccario M: On the diagnosis of the cerebral death: A prospective study of 55 patients with definite irreversible coma. *Clin EEG* 2:178, 1971.
7. Brain death: A bibliography with key words and author indexes. *NINDS Biblio Ser* 1:1, 1972.
8. Toennis W, Frowein RA: Wie lange ist Wiederbelebung bei schweren Hirnverletzungen möglich? *Mschr Unfallheilk* 66:169, 1963.
9. Gros D, Vlahovitch B, Frèrebeau P, Kuhner A, Billet M, Sahut G, Gavand G: Critères artériographiques des comas dépassés en Neuro-Chirurgie. *Neuro-Chirurgie* 15:477, 1969.
10. Bücheler E, Käufer, C, Düx A: Zerebrale Angiographie zur Bestimmung des Hirntodes. *Fortschr Roentgenstr* 113:278, 1970.
11. Boshes G: A report for the collaborative study of cerebral death. *NIH* (In press).
12. Braunstein P, Korein J, Kricheff I, Corey K, Chase N: A simple bedside evaluation of cerebral blood flow in the study of cerebral death: A prospective study on 34 deeply comatose patients. *Am J Roentg* 118:757, 1973.
13. Suter C, Creveling JG: A report of 20 cases with periodic lateralized epileptiform discharges (acute spikes) in the electroencephalogram. *Neurology* (abstract) 16:304, 1966.
14. Overgaard J, Hvid-Hansen O, Land AM, Pederson KK, Christensen S, Haase J, Hein O, Tweed WA: Prognosis after head injury based on early clinical examination. *Lancet* 2:631, 1973.

15. AFIFI AA, SACHS ST, LIU VY, WEIL MH, SHUBIN H: Accumulative prognostic index for patients with barbiturate, glutethimide, and meprobamate intoxication. *N Engl J Med* 285:1497, 1971.

16. BENJAMIN PS, WILLIS CE, TYTKO S, MIDLICH P: The coma profile. *Cleveland Clin Qtrly* 40:57, 1973.

17. GLOOR P: Hans Berger on the electroencephalogram of man. *Electroencephalogr Clin Neurophysiol* (Suppl) 28:1, 1969

18. JORGENSEN EO: Requirements for recording the EEG at high sensitivity in suspected brain death. *Electroencephalogr Clin Neurophysiol* 36:65, 1974.

19. JORGENSEN EO: EEG without detectable cortical activity and cranial nerve arflexia as parameters of brain edath. *Electroencephalogr Clin Neurophysiol* 36:70, 1974.

20. PRIOR PF: The EEG in acute cerebral anoxia. *Excerpta Medica* Amsterdam, 1973.

21. BICKFORD RG, BUTT HR: Hepatic coma: The electroencephalographic pattern. *J Clin Invest* 34:790, 1955.

22. SILVERMAN D: Some observations on the EEG in hepatic coma. *Electroencephalogr Clin Neurophysiol* 14:53, 1962.

23. SILVERMAN D: Retrospective study of the EEG in coma. *Electroencephalogr Clin Neurophysiol* 15:486, 1963.

24. CHATRAIN GE, WHITE LE, DALY E: Electroencephalographic patterns resembling those of sleep in certain comatose states after injuries to the head. *Electroencephalogr Clin Neurophysiol* 15:272, 1963.

25. SUTER C: Theta coma. *Neurology* (abstract) 23:445, 1973.

26. LOEB C, ROSADINI G, POGGIO GF: Electroencephalography during coma: Normal and borderline records in five patients. *Neurology* 9:610, 1959.

27. JONES BN, BINNIE O, FUNG D, HAMBLIN JJ: Reversible coma with an EEG pattern normally associated with wakefulness. *Electroencephalogr Clin Neurophysiol* 33:107, 1972.

28. BICKFORD RG, SIMS JK, BILLINGER TW, AUNG ML: Problems in EEG estimation of brain death and use of computer techniques for their solutions. *Trauma* 12:61, 1971.

29. MOSIER JM: The use of succinylcholine in EEG. *Electroencephalogr Clin Neurophysiol* 24:394, 1968.

30. VOURC'H P: Utilisation de la succinylcholine dans le diagnoistic des comas. *Anesth Analg Réanim* 30:988, 1973.

31. WOOD-SMITH FG, STEWART HC, VICKERS MD: Muscle relaxants. *Drugs in Anesthetic Practice*. Third Ed., New York, Appleton-Century, Crofts; London, Butterworths, 1968, pp. 243–267.

32. CHATRAIN GE, SHAW CM, LEFFMAN H: The significance of electrographic clinical and pathological study. *Electroencephalogr Clin Neurophysiol* 17:177, 1964.

33. GRINDAL AB, SUTER C: EEG showing alpha-pattern coma in high voltage electrical injury: Two patients after injury. (Personal observation)

34. PAULSON GW, WISE G, CONKLE R: Cerebrospinal fluid lactic acid in death and in brain death. *Neurology* 22: 505, 1972.

35. PAULSON GW, STICKNEY D: Cerebrospinal fluid after death. *Confin Neurol* 33:149, 1971.

36. VRIES JK, BECKER DP, YOUNG HF: A subarachnoid screw for monitoring intracranial pressure: Technical note. *J Neurosurg* 39:416, 1973.

Chromosome Abnormalities and Repeated Abortion: A Preliminary Report

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The role of chromosome aberrations in the etiology of early spontaneous abortions has been well established (1). Various investigators have found that 25–35% of all such abortions are the result of cytogenetic abnormalities (2, 3). The great majority of these aberrations are believed to be the result of *de novo* errors in meiosis and only rarely can early mitotic mistakes account for these events (3). In a minority of cases, one of the parents may harbor a transmissible chromosome anomaly. The carrier is apparently physically normal and has a balanced genetic make-up compatible with life. During gametogenesis, however, unequal gametes may be formed, resulting in development of a nonviable zygote. This may predispose the carrier to recurrent early abortion of his or her offspring.

Recently, a number of studies have attempted to find such a correlation between recurrent pregnancy loss and parental chromosome anomalies (3, 4, 5, 6). An investigation of this type was initiated at the Medical College of Virginia in the fall of 1973. Letters were sent to obstetricians in eastern Virginia requesting referrals of patients with histories of two or more spontaneous abortions. Blood was drawn from both the husband and wife and karyotype analysis was performed according to conventional methods. Five anomalies have been ascertained in the 25 couples studied so far. A discussion of the significance of these findings is considered below.

A 28-year-old white female was found to have a modal chromosome number of 47. The patient was intelligent and physically normal with a history of two spontaneous abortions and no live births. Karyotype analysis, banding studies, and buccal smears showing two sex chromatin bodies in 31% of 800 cells analyzed confirmed that the patient was a triplo-X female. The incidence of 47,XXX females is believed to be about one per 1000 in the normal population (7). Due to wide phenotypic variability, a clearly defined triplo-X syndrome has not been established. Fertility is thought to be unimpaired (8). There is, however, a slightly increased risk of sex chromosome anomalies in the offspring.

Chromosome polymorphism was detected in a 30-year-old white female with a history of two early spontaneous abortions. Satellites on chromosome 17 were seen consistently in all preparations. A polymorphism of this type is not believed to contribute to repeated fetal wastage (4), although the possibility cannot be ruled out until prospective studies are done. The patient was in the seventh month of an uneventful pregnancy when the study was done.

Another structural polymorphism was discovered in a husband whose wife had experienced three spontaneous abortions and no live births. The husband's karyotype was 46,XY with an enlarged #16 chromosome. The clinical significance of this finding is not known at present, and the patient's chromosomes are being studied with banding techniques.

One of the most interesting findings was the ascertainment of two families with balanced D/D

(Continued on page 167)

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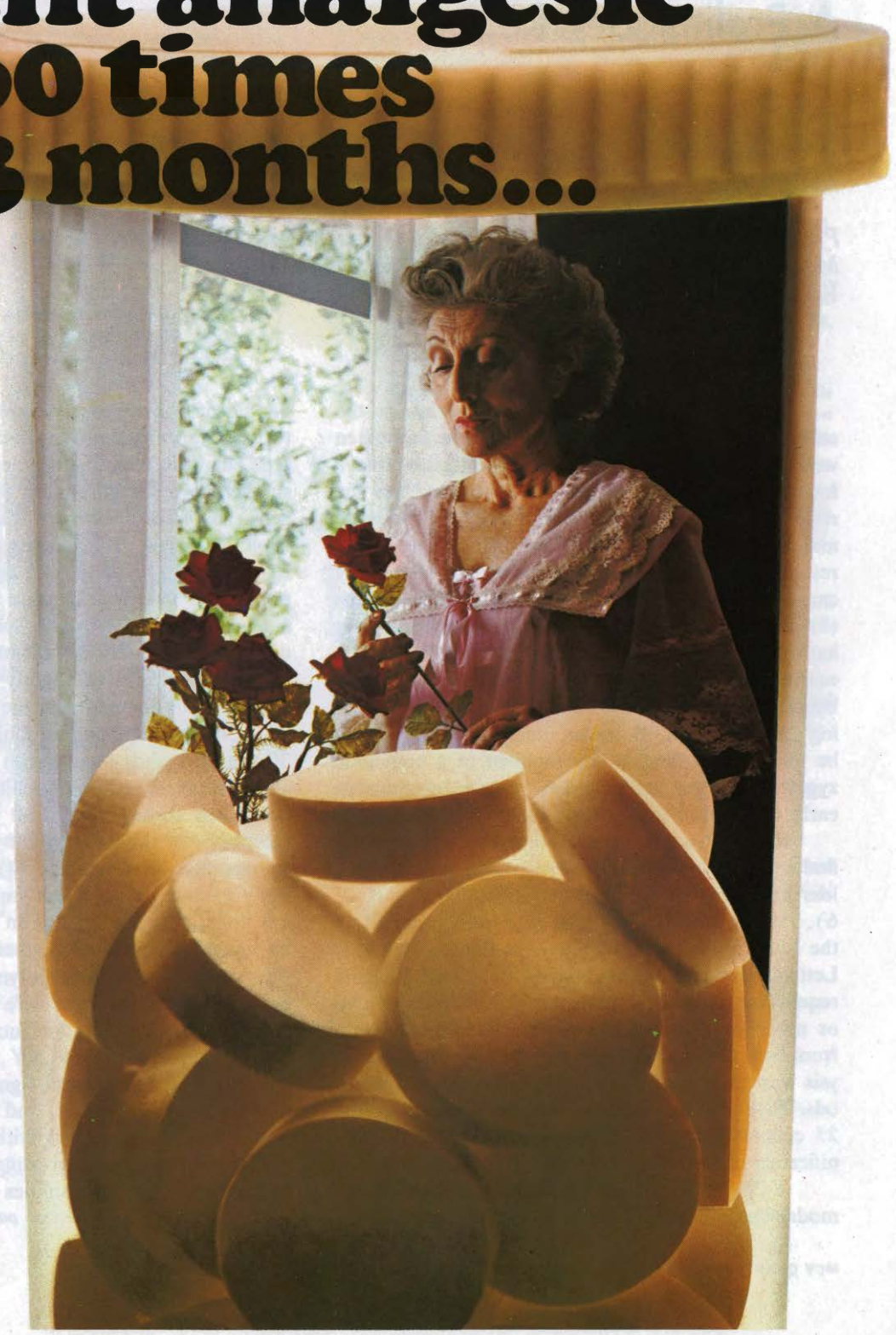

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1. Sadove, M. S.: A look at narcotic and non-narcotic analgesics, *Postgrad. Med.* 49:102, June 1971.

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Chances are, the same 50 mg. Talwin Tablet you prescribe originally will continue to provide good pain relief. Talwin can be compared to codeine in analgesic efficacy: one 50 mg. tablet appears equivalent in analgesic effect to 60 mg. (1 gr.) of codeine. However, patients receiving Talwin Tablets for prolonged periods face fewer of the consequences you've come to expect with narcotics. There should be fewer "adverse effects" on her way of life.

Tolerance rare: Tolerance to the analgesic effect of Talwin Tablets is rare.

Dependence rare: *During three years of wide clinical use, there have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.*

*In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.**

Generally well tolerated by most patients*: Infrequently causes decrease in blood pressure or tachycardia; rarely causes respiratory depression or urinary retention; seldom causes diarrhea or constipation. Acute, transient CNS effects, described in product information, have occurred in rare instances following the use of Talwin Tablets. If dizziness, lightheadedness, nausea, or vomiting is encountered, these effects may decrease or disappear after the first few doses.

*See important product information for adverse reactions, patient selection, prescribing and precautionary recommendations.

in chronic pain of moderate to severe intensity

Talwin® 50 mg. Tablets

brand of

pentazocine

(as hydrochloride)

Talwin® Tablets brand of pentazocine (as hydrochloride)

Analgesic for Oral Use—

Indication: For the relief of moderate to severe pain.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.*
In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.
Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.
Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.
Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.
Usage in Children. Because clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.
Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* Although respiratory depression has rarely been reported after oral administration of Talwin, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.
Impaired Renal or Hepatic Function. Decreased metabolism of the drug by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.
Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.
Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.
Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.
CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations (see *Acute CNS Manifestations* under **WARNINGS**); and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, toxic epidermal necrolysis.

Dosage and Administration: *Adults.* The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg.
When antiinflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with Talwin.
Children Under 12 Years of Age. Since clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.
Duration of Therapy. Patients with chronic pain who have received Talwin orally for prolonged periods have not experienced withdrawal symptoms even when administration was abruptly discontinued (see WARNINGS). No tolerance to the analgesic effect has been observed. Laboratory tests of blood and urine and of liver and kidney function have revealed no significant abnormalities after prolonged administration of Talwin.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.
Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

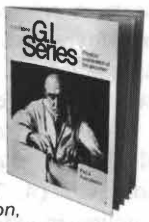
How Supplied: Tablets, peach color, scored. Each tablet contains Talwin (brand of pentazocine) as hydrochloride equivalent to 50 mg. base. Bottles of 100.

(1623A)

Winthrop Laboratories, New York, N.Y. 10016 Winthrop

A service to medical education from A. H. Robins:

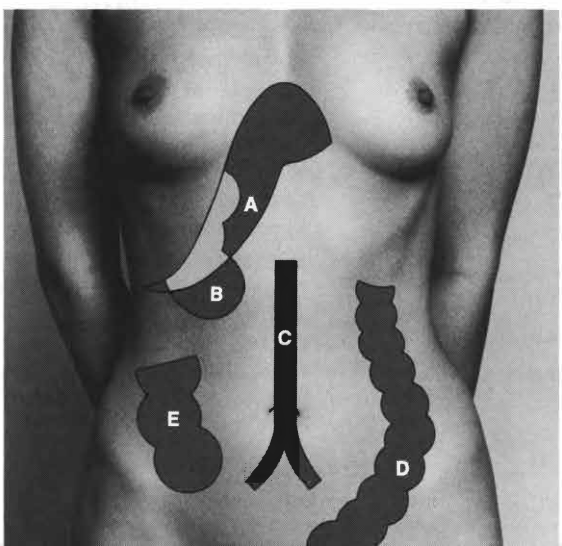
Excerpted from Volume 2 of the **G.I. Series** on physical examination of the abdomen:

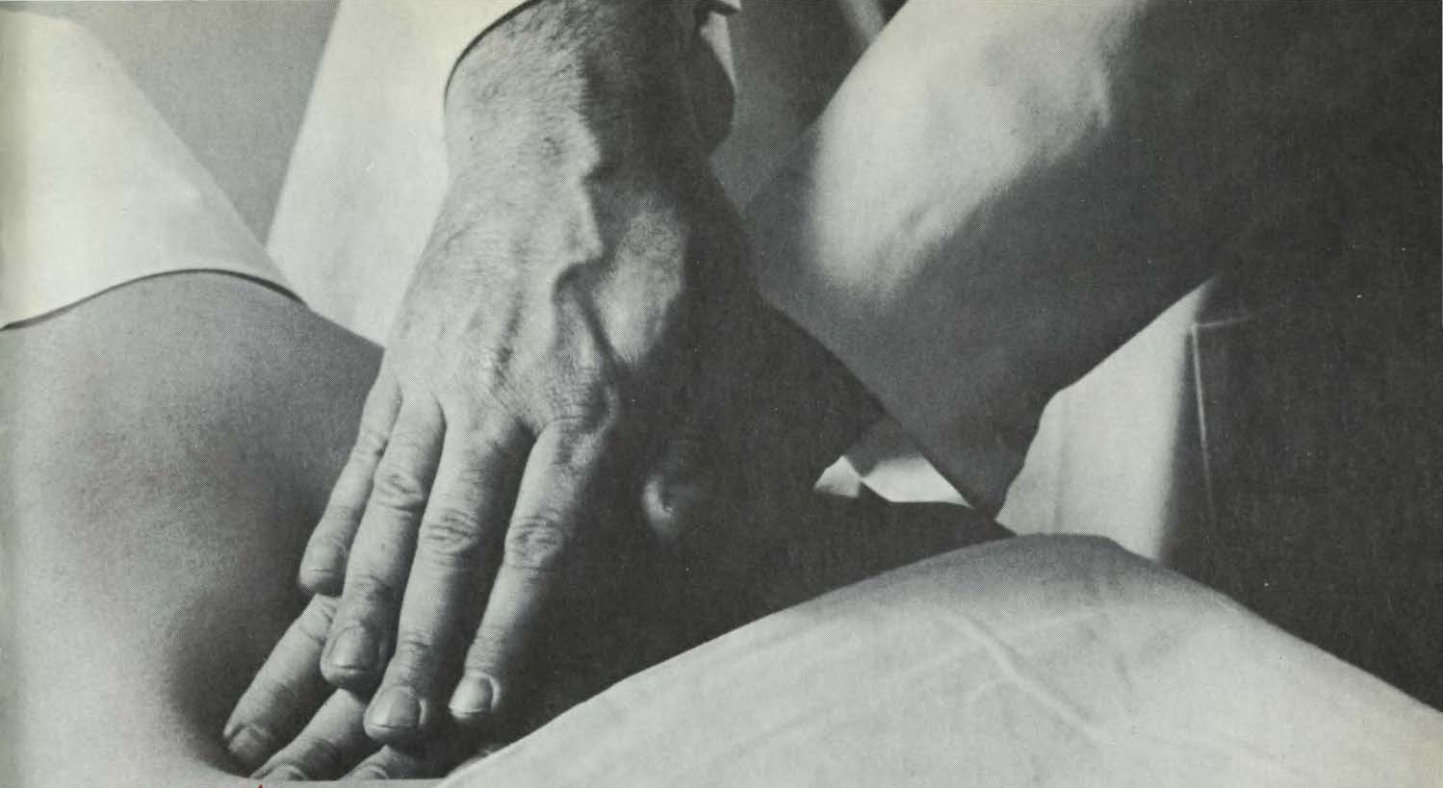


The A. H. Robins G.I. Series consists of six booklets, designed to provide a quick, yet comprehensive review of basic procedures and practices in G.I. medicine—with particular emphasis on the physical examination as performed in the office or at bedside. If you have teaching responsibilities, limited quantities are available: Part 1—*Inspection*, Part 2—*Palpation*, Part 3—*Percussion*, Part 4—*Auscultation*, Part 5—*Abdominal Pain* and Part 6—*Differential Diagnosis of Abdominal Disorders*. Write to: The Medical Department, A. H. Robins Company, 1407 Cummings Drive, Richmond, Virginia 23220.

Normally palpable organs: the edge of the liver descending, on inspiration, below the costal margin (A); the lower pole of the right kidney (B); the abdominal aorta (C); the descending colon and the sigmoid (D); the ascending colon (E); and occasionally the bladder (though rising of this organ beyond the pubis does not necessarily indicate disease).

Impossible to outline, unless diseased, distended or enlarged: the gallbladder, pancreas, stomach, small intestine, transverse colon and spleen.





Spasm reactor?

Donnatal®!

	each tablet, capsule or 5 cc. teaspoonful of elixir (23% alcohol)	each Donnatal No. 2	each Extentab
hyoscyamine sulfate	0.1037 mg.	0.1037 mg.	0.3111 mg.
atropine sulfate	0.0194 mg.	0.0194 mg.	0.0582 mg.
hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
phenobarbital	(¼ gr.) 16.2 mg.	(½ gr.) 32.4 mg.	(¾ gr.) 48.6 mg.

(warning: may be habit forming)

Brief summary. Adverse Reactions: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Contraindications: Glaucoma; renal or hepatic disease; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); or hypersensitivity to any of the ingredients.

A·H·ROBINS A. H. Robins Company, Richmond, Virginia 23220

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

If there's good reason to prescribe for psychic tension...

When, for example, reassurance and counseling on repeated visits are not enough

Effectiveness is a good reason to consider Valium®

(diazepam)

2-mg, 5-mg,
10-mg tablets