Cerebral Apoplexy (Stroke): Pathogenesis, Pathophysiology and Therapy as Illustrated by Regional Blood Flow Measurements in the Brain

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Abstract: Cerebral Apoplexy (Stroke): Pathogenesis, Pathophysiology and Therapy as Illustrated by Regional Blood Flow Measurements in the Brain

Pathophysiological and pathogenetic concepts, particularly in occlusive cerebrovascular disease, are reviewed and discussed with emphasis on the results of current research. Therapy is discussed in the context of these concepts.

When focal ischemia, with or without cerebral infarction, is not associated with definable arterial occlusion, studies of regional cerebral blood flow strongly support the thromboembolic theory; the arterial defect is relatively transient and is caused by an embolus or thrombus which rapidly disappears (fragments or is lysed). The treatment of transient ischemic attacks by the administration of anticoagulant or surgical reconstruction of the appropriate artery is discussed.

When cerebral infarction is caused by arterial occlusion there is vasomotor paralysis (loss of autoregulation and of reactivity to carbon dioxide). In some instances hypercapnia apparently causes only the vessels in nonaffected brain to dilate so that an increased amount of blood streams to these parts while blood pressure falls in collaterals leading to the focus and blood flow to the infarct is decreased (steal syndrome). If blood flow is decreased to nonaffected brain, by vasoconstriction caused by hyperventilation, increased amounts of blood may be shunted into the infarct (reverse steal) where autoregulation is lost. Vasoconstriction, as a treatment, might be beneficial. However, in patients with severe cerebral infarction no convincing favorable affect has been noted. The potential therapeutic action of hyperventilation in patients with mild cerebral infarction has not been studied.

Extensive (global) changes in the cerebral blood flow in cerebral infarction, certain aspects of intracerebral hemorrhage, and the role of hypertension in cerebrovascular disease are also dealt with.

Additional Key Words
- cerebral infarction
- hypertension
- hypercapnia
- thromboembolic events
- transient ischemic attacks
- hypocapnia

Tentative Division of Stroke

By cerebral apoplexy (stroke) is understood the acute occurrence of neurological symptoms caused by a vascular lesion in the brain, the brain stem or the cerebellum. Not included are subarachnoid bleedings and bleedings in tumors, nor the subdural or epidural hematomas that most often are conditioned by traumas. Hemiparesis will be the most frequent neurological symptom in cerebral apoplexy, but other symptoms are also seen, for instance, aphasia, hemianopia and sensibility disturbances.

When employing this definition, cerebrovascular diseases consist of two main groups: intracerebral hematomata and cerebral ischemic lesions. As it will appear later in this article,
these two groups apparently present enough pathogenic differences for them to be considered two different diseases. It is especially the latter group that shall be dealt with here. From a clinical point of view, the two groups of stroke have many symptoms in common, and it is sometimes not possible to make a clinical distinction between them.2,3

Various divisions of cerebral apoplexy have been attempted. Millikan, Siekert and Whisnant4 have made a clinical temporal division of stroke into “completed stroke,” “advancing stroke,” “incipient or impending stroke,” and “completed stroke with evidence of further activity of the cerebral ischemic process.” The latter group is actually only a combination of the first and the third group. A subsequent, modified division, therefore, contains only three groups as follows: “completed stroke,” “stroke in evolution,” and “transient ischemic attacks.”5,6 A completed stroke refers to a relatively stable neurological deficit; that is, little or no change in the deficit is occurring. Severe cases with massive acute symptoms followed by some progression and possibly death are, however, also included for practical reasons. A stroke in evolution refers to a patient whose neurological deficit is actively worsening during the period of observation. This aggravation of the condition may take place by steps over a period of several hours, or there may be smooth, continuous, progressive worsening of the condition. By transient ischemic attacks are understood attacks with focal neurological symptoms followed by complete remission within 24 hours.

This temporal classification is purely descriptive and does not consider the pathogenesis of the attacks.

One reason for making strokes in evolution an independent group was the possibility that they were caused by progressive thrombosis of an extracranial or intracranial artery, and that the progression of the condition might be stopped by anticoagulation treatment. The pathogenesis of stroke in evolution is, however, uncertain. A possible cause is progressive artery stenosis. Other possibilities are a recurrent embolism1 or an increasing intracerebral edema in or around an infarct with a resultant distortion of the surrounding tissue,8 or a progressing intracerebral hematoma.

The dissociation into an independent group of attacks with complete remission of the symptoms within 24 hours—the transient ischemic attacks—is rather artificial, as the various degrees of cerebral infarction merge gradually into each other, from the mild attacks with remission within a few minutes or hours, to attacks with remission within days, to attacks with moderate or severe sequelae, and to fatal attacks. Nor are there any grounds for assuming that the pathogenesis of transient ischemic attacks should differ from that of cerebral infarction proper.

However, it is practical to continue to denote these cases of apoplexy (transient ischemic attacks) because, from a clinical point of view, they differ essentially from the severe cases with permanent symptoms. The treatment of transient ischemic attacks will also differ in that it obviously will be solely prophylactic.

A traditional, more etiological division of apoplexy has been attempted with the aim of a differentiation between intracerebral hematomas, thromboses, and embolism. Large hematomas often are recognizable clinically; however, it is far more difficult to distinguish between minor hematomas and the various types of thromboembolism, especially so if angiography has not been done. The differentiation between thromboses and embolism is uncertain, and the practice most often has been that cases of stroke with auricular fibrillation, mitral stenosis, or the like have been classified as embolism, and the other cases as thromboses. It is obvious that a great many thromboses thus defined may easily be embolisms and that some cases of embolism conversely may be thromboses.

From an angiographical and pathoanatomical point of view, most strokes can be divided into intracerebral hematomas and cerebral ischemic lesions (cerebral infarction). The latter group can be subdivided into one group in which an arterial occlusion is demonstrable and another in which no arterial occlusion is demonstrable. In some ischemic lesions, the cerebral artery occluded may be so small that the occlusion is not demonstrable, whereby the stroke will be classified as nonocclusive in spite of the arterial occlusion. However, such cases will probably make up only a minor part of the nonocclusive cases (see below).
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If the ischemia is sufficient, infarction results. Infarcts are divided into white (ischemic) and red (hemorrhagic) types by pathologists. The red areas are often found in only part of the infarct. It must be assumed that the hemorrhagic infarcts occur in regions where the blood supply has been re-established (shift or disappearance of an occlusion). In many cases the hemorrhagic infarcts result in a slightly hemorrhagic cerebrospinal fluid.

Pathogenesis of Cerebral Infarction

ISCHEMIC LESIONS WITH ARTERIAL OCCLUSION
In patients in whom an arterial occlusion has been demonstrated, the cause of the ischemic lesion may be either an embolus or a thrombus. The two causes cannot be distinguished in some individual cases. The embolic cases are presumably rather frequent, as they must often be supposed to originate from the extracranial neck vessels and not from the heart. This will be further discussed under the thromboembolic theory. The most reasonable designation thus would be thromboembolic occlusions.

ISCHEMIC LESIONS WITHOUT ARTERIAL OCCLUSION
It is characteristic of this group of strokes that, at the time of examination, it is not possible to demonstrate any direct cause of the often very pronounced neurological symptoms. From a clinical temporal point of view, the group comprises all the varieties of cerebrovascular attacks from slight transient ischemic attacks with rapid remission to the most severe cases of cerebral infarction. Several theories have been advanced about the cause of the lesion in stroke without arterial occlusion: (1) the vasospasm theory, (2) the hemodynamic theory (systemic hypotension), and (3) the thromboembolic theory. These three theories as well as other rare causes will be discussed below.

The Vasospasm Theory
According to this theory, the stroke is caused by a spasm in a cerebral or extracranial artery resulting in cerebral ischemia.13-14 The theory, which was predominant for a long time, was later severely criticized by Pickering15 and Denny-Brown,16 and is now almost abandoned. While vasospasm may occur after strong mechanical irritation, or with subarachnoid hemorrhage, there are no experimental findings nor any other grounds for assuming that vasospasms frequently cause cerebral infarction. Moreover, angiographical examinations have not disclosed any cases with vasospasms, which are often seen in the case of subarachnoid hemorrhage.3, 17, 18 So, vasospasms cannot be considered a pathogenic mechanism of apoplexy without arterial occlusion.

Vasospasm is often mentioned as a pathogenic factor in hypertensive encephalopathy. However, even in this disorder the pathogenic significance of vasospasms can be questioned.

In arterial hypertension, a change in caliber occurs in the arteries of the retina, and treatment of the hypertension makes this change regress. In chronic renal hypertension, a reversible change in caliber ("spasms") of the pial arteries and arterioles has been demonstrated experimentally in rats19 and in monkeys and cats.20 At a subsequent investigation of chronic, medicamentary hypertension in mice, however, no change was found in the caliber of the pial arteries and arterioles.21 In contrast to what was found in the first-mentioned investigations, neurological symptoms did not develop in the mice, although cerebral edema did develop. In another study on acute hypertension in cats and monkeys, no change in caliber was found in the pial vessels.22 On the other hand, an investigation of the mesenteric arteries of the rat showed a change in caliber during the acute phase of the hypertension.23, 24

However, whether this change in caliber is tantamount to spasms has not been proved. A spasm must be characterized by a pronounced contraction so that the blood flow distal to the spasm is reduced below normal, resulting in a more or less pronounced tissue hypoxia. The change in caliber in the arteries may be due only to a combination of the normal autoregulation and degenerative changes in some artery segments. Deposits of plasma proteins in the vascular wall have been demonstrated in experimental examinations of arterial hypertension,23-26 and these degenerative changes were found to be localized to the dilated arterial segments.21, 24 The contracted segments, then, may be only less degenerated vascular segments, contracted in order to restrain the blood circulation to normal values. Also, an inhomogeneous distribution in the vessels of the contractile elements might
explain, to some extent, the segmental contraction. Two theories have been advanced about hypertensive encephalopathy: (1) it is caused by vasospasms with a resultant ischemia, and (2) it is caused by cerebral edema and perivascular hemorrhage owing to failing autoregulation under the high blood pressure. Based upon the above, it is reasonable to consider the second theory the more probable one.

The Hemodynamic Theory (Transient Systemic Hypotension)

This theory was originally advanced by Denny-Brown as an alternative to the vasospasm theory. According to the theory, there exists in the brain a focal region with marginal blood supply resulting from a stenosis in an artery. A fall in the arterial blood pressure will result in a decrease in the blood flow through the focal region, thereby causing a focal cerebral ischemic lesion. Denny-Brown assumed that hemodynamic crises (transient systemic hypotension) were the cause of approximately 80% of the transient ischemic attacks. Zülch and Romanul and Abramowicz believed that the infarcts occurred in most peripheral parts of the region supplied by the arteries, as the diffuse arteriosclerosis here affected the blood flow most. The infarcts, therefore, should occur where the supply regions of two major arteries bordered, by what Zülch called “Die letzte Wiese,” and Romanul and Abramowicz called “watershed infarction.”

Thompson and Smith and Denny-Brown and Meyer observed that if the arterial blood pressure was reduced in monkeys, infarcts occurred on ligation of the middle cerebral artery. In these experiments infarcts did not develop if the blood pressure was kept normal. In patients who had had several transient ischemic attacks, the degree of stenosis in the neck vessels was often less than 40% of lumen, which means that the stenosis was insignificant from a hemodynamic point of view. Only in a few exceptional cases has it been possible to produce transient ischemic attacks by lowering the blood pressure. Kendell and Marshall examined 37 patients with transient ischemic attacks and arterial hypertension. While the patients were lying on a tilt table, the arterial blood pressure was lowered until there were signs of focal cerebral ischemia (transient ischemic attack) or global cerebral ischemia (incipient syncope). The signs of focal ischemia preceded those of global ischemia in only one of the 37 patients.

From a clinical point of view, there is no strong evidence either that suggests that cerebral infarction commonly occurs in connection with a fall in blood pressure. Cerebral infarction occurring during sleep has been explained by a decrease in blood pressure. A subsequent large clinical study, however, demonstrated no connection between a fall in blood pressure and the occurrence of cerebral infarction. Furthermore, in a few patients with transient ischemic attacks, it has been possible to measure the blood pressure at the beginning of the attack, and it was found to be increased.

Regional cerebral blood flow examinations have further weakened the theory that hemodynamic changes are a frequent cause of apoplexy without arterial occlusion. Only two
patients in a series of 44* were found to have changes in the regional cerebral blood flow that might indicate chronic affection of the cerebral vasomotor function possibly leading to a fall of the regional cerebral blood flow during a decrease in systemic blood pressure. In one of them there was a region where the cerebral vessels could not be further dilated, but where contraction was possible. In another patient, the autoregulation was chronically slightly affected. Regional cerebral blood flow determinations during the acute phase of the cerebral infarction (within the first few days) often disclose hyperemic foci in patients without arterial occlusion. This finding also makes the hemodynamic theory unlikely, as hyperemia in these regions suggests that the cerebral vessels cannot have been maximally dilated in the resting condition, and that only a very great fall in blood pressure, therefore, could have produced the ischemic lesion. The hemodynamic theory also seems to be strongly disfavored in a recently completed study of regional cerebral blood flow measurements during 21 operations for carotid stenosis in patients with previous cerebrovascular symptoms. The blood pressure gradient over the carotid stenosis was only small in these patients. During clamping of the carotid artery, the blood pressure in the distal part of the artery fell in all the cases, but in most of them the cerebral blood flow was either unchanged or showed only a moderate fall. A marked fall in the cerebral blood flow was seen only in a few cases and occurred especially if the fall in blood pressure in the distal part of the carotid artery was very marked. More distal in the hemisphere there was apparently not any essential hemodynamic hindrance present either, as no regions with selective loss of autoregulation were observed.

As a result of the observations mentioned, the hemodynamic theory (transient systemic hypotension) has been abandoned as the most common cause of transient ischemic attacks and cerebral infarction without demonstrated arterial occlusion.

The Thromboembolic Theory

According to this theory, cerebral infarction is caused by an acute arterial occlusion or a severe stenosis resulting from a local thrombus or from an embolus coming from the intracranial and extracranial arteries, aorta or the heart. By a subsequent thrombolysis, the lumen is restored. If the occlusion persists at the time of examination, the case will be classified as an ischemic lesion with arterial occlusion. The theory is particularly attractive, as it can explain cases of cerebral infarction with and without demonstrable arterial occlusion. The degree of severity, then, will depend on the size of the occluded artery, on the duration of the arterial occlusion, and on the collateral supply to the ischemic region.

The thromboembolic theory is classic and goes back to the last century. In modern times it was again advanced as an alternative to the spasm theory. The thromboembolic theory was not generally accepted, however, until it had been demonstrated that anticoagulation may reduce the frequency of transient ischemic attacks. The observation of retinal microemboli in patients with attacks of transient blindness has also strongly supported the theory. Symptom-free retinal emboli have also been observed. At autopsy examinations, microemboli have been found consisting of agglutinated thrombocytes, of cholesterol, and of neutral fat. The origins of these emboli have recently been discussed by Ross Russell, who considered the extracranial neck vessels as well as the heart to be the most common origins of emboli. This agrees with a high frequency of arteriosclerotic changes in these vessels and of heart diseases in apoplectics (see below). The aorta, too, may be the origin of distal emboli.

Furthermore, indirect support of the thromboembolic theory has been given by the many observations and investigations that tell against the spasm theory and the hemodynamic theory.

There are some additional clinical conditions to be pointed out in the discussion. The occurrence of heart disorders is increased in patients with cerebral apoplexy.
thromboembolic theory is thereby substantiated, as these patients are more inclined to get emboli coming from the heart, because they have either cardiac rhythm disturbances or endocardial defects, for instance in cases of coronary thrombosis. This is strongly supported by examinations in patients with rheumatic heart diseases. It was found that in a series of 323 patients, 60 had suffered from classic apoplexy with rather pronounced symptoms, and 38 had had transient ischemic attacks.

Patients with cerebrovascular diseases often have arteriosclerotic changes in the extracranial neck vessels which may cause the distal emboli. This is supported by the fact that in cases with murmur over the carotid artery, the murmur has been observed to change its character in connection with transient ischemic attacks. The fact that not all patients with lesions in the neck vessels get cerebral symptoms is probably due to the fact that in some cases the surface of the lesion is smooth and covered by endothelium, while in other cases it is ulcerated and affected by recent thrombosis, which may cause distal emboli to develop. Gunning and co-workers endarterectomized the carotid artery and found recent thrombi on the surface of arteriosclerotic changes in the internal carotid artery in six patients who had had moderate apoplectic attacks within the last seven weeks before operation. On the other hand, such thrombi were not found in six patients in whom no attacks had occurred within the last seven weeks before operation. It must be assumed that the surface structure of such arterial lesions vary from time to time, which agrees with the clinical finding that transient ischemic attacks may cease spontaneously.

In the majority of patients with cerebral infarction, there are symptoms from the middle cerebral artery region. This also supports the thromboembolic theory. Since the middle cerebral artery is the largest terminal branch from the internal carotid artery, a distal embolus will have the greatest possibility of arriving in this artery. It is also well known that occlusions of the anterior or posterior cerebral arteries are rare compared with occlusions of the middle cerebral artery. Transient ischemic attacks are relatively stereotyped in that patients with attacks often have the same symptoms at each attack. This fact has also been adduced in support of the hemodynamic theory, but it is consistent with the thromboembolic theory too, since retinal emboli have been demonstrated in patients with numerous recurrent attacks of monocular blindness.

An angiogram made soon after cerebral infarction may show an arterial occlusion, whereas a later one may show that the occlusion has moved to a more distal part of the artery or that the lumen is now normal. In such cases, the thromboembolic mechanism is well proved. It was found in one of the investigations that the occlusion was most often located in the main stem of the middle cerebral artery when the angiogram was performed early, whereas occlusion of the branches of the middle cerebral artery was more frequent on later angiograms.

Finally, patients with transient ischemic attacks and a stenosis of an extracranial neck artery became symptom-free after thromboendarterectomy that failed and resulted in total occlusion of the artery. These findings obviously indicate that in these patients the cause of the attacks was thromboembolic rather than hemodynamic.

It must be concluded that the vast majority of cerebral infarction is due to a thromboembolic occlusion, irrespective of whether the occlusion is demonstrable or not at the time of examination. This is also the common opinion of several other investigators.

Ran Causes of Apoplexy With Ischemic Lesion But Without Arterial Occlusion

A brief mention shall be made of various pathogenic conditions that in rare cases may cause apoplexy with moderate or severe symptoms.

Polycythemia is predisposing to transient ischemic attacks as demonstrated by Millikan, Sickert and Whisnant. These authors assumed that an increased tendency to thrombosis in polycythemia patients caused the transient ischemic attacks. Hemodynamic change (transient systemic hypotension) resulting from the increased viscosity of the blood is an unconvincing explanation, particularly since the blood pressure in a patient did not fall during an attack. Thus, it must be assumed that the transient ischemic attacks in polycythemia are connected with the thrombocytosis and thereby form a subgroup of the
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thromboembolic cases. Transient ischemic attacks have been observed in primary thrombocytosis too, and in these cases the mechanism must be supposed to be similar to that in polycythemia.30, 94

Transient ischemic attacks induced by coughing have been described in a few cases.56 It is most likely that these cases are due to a hemodynamic mechanism (transient systemic hypotension), which is strongly supported by the fact that the only patient in whom Kendell and Marshall could induce transient ischemic attacks during hypotension had his attacks when coughing hard.

In very rare cases, anemic patients may get transient ischemic attacks that end if the anemia is corrected.95 In even more rare cases, transient ischemic attacks or severe neurological symptoms have been observed in connection with hypoglycemia. The pathogenesis of these attacks is not quite clear, but a hemodynamic mechanism (transient systemic hypotension) must be assumed to be of importance.

Some rare cases of transient ischemic attacks are caused by compression of a carotid artery owing to coiling or kinking, or of a vertebral artery owing to rotation of the head.98-105 The mechanism involved in these cases is obvious.

A certain kind of transient attack is found in the case of the "subclavian-steal syndrome."106-112 In these cases there exists a stenosis or an occlusion of the subclavian artery, and the brachial artery is supplied with blood via the vertebral artery, in which the direction of the blood stream thus is reversed. When the arm is used, the blood supply to the arm is increased, which results in more blood streaming from the vertebral to the brachial artery; the blood pressure in the basilar artery consequently falls, and neurological symptoms may occur.

INTRACEREBRAL HEMAtoMAS

Intracerebral hematoma is closely connected with arterial hypertension. The majority of the patients with intracerebral hematomas have hypertension,90, 118-117 and intracerebral hematomas are a frequent cause of death in patients with malignant hypertension.118-120 Some hemorrhages are due to vascular malformations or bleeding tumors,118, 119 but these cases shall not be dealt with here.

Hemorrhagic infaracts, that is, infarcts in which the blood by diapedesis has extravasated into the tissue without formation of a hematoma, shall be considered in this work—as in most others—an infarct and not a hematoma.

Two main theories have been advanced about the cause of an intracerebral hematoma. According to one theory, the cerebral tissue is damaged by a minor ischemic lesion (arterial occlusion) resulting in a small necrosis which includes the artery; the subsequent re-establishment of the blood supply—and thereby of the local blood pressure—causes hemorrhage. According to the other theory, the hemorrhage is caused by a primary rupture of an artery that is weak due to chronic degenerative changes. The latter is probably correct.

In experimental hypertension, deposits of plasma protein in the wall of minor arteries might result in degeneration and necrosis.23-26 At postmortem examinations of patients with arterial hypertension, multiple microaneurysms repeatedly have been found in the small arteries and arterioles in the brain.121-125 Such microaneurysms also occurred in normal, older people, but were significantly less pronounced than in patients with arterial hypertension. Furthermore, it was found at postmortem examinations of patients who had died from different causes that there were often small hemorrhages in the brains of hypertensive patients.125 Such hemorrhages were only found in those hypertensive patients who had microaneurysms (approximately 50%) and they were located in the same cerebral region as were the microaneurysms. In a few cases of intracerebral hematomas it has been possible to demonstrate that they originated from burst microaneurysms.128, 129

Though it is rare, it is probable that intracerebral hematomas also may occur if an occluded vessel has the lumen opened. This is suggested by the fact that following acute surgical recanalization of an occluded carotid artery, not only a hemorrhagic infarct but also a large, coherent hematoma have been described several times.126-128

The conclusion of these considerations is that most, though not all, hemorrhages presumably are caused by a primary vascular rupture in vessels with hypertensive, degenerative changes including microaneurysms.
Pathophysiological Conditions in Cerebral Infarction Illustrated By Regional Cerebral Blood Flow Determinations

NORMAL CIRCULATORY CONTROL IN THE BRAIN

In young healthy persons, the cerebral blood flow is approximately 50 ml/100 gm/min. Normally, the blood flow in the brain is effectively controlled by homeostatic mechanisms.

The term “autoregulation” refers to the stability of cerebral blood flow in spite of changes in blood pressure. Thus, the cerebral blood flow is independent of the blood pressure when this is not abnormally low (mean blood pressure above approximately 70 mm Hg). This regulation agrees with the observations made by Fog and co-workers that the pial arteries contract when the blood pressure is increased and dilate when it is reduced.

Also important in autoregulation is the intracranial pressure, as the intracranial venous pressure on the whole is equal to the intracranial pressure. The arteriovenous pressure difference thus corresponds to the arterial pressure minus the intracranial pressure. When the intracranial pressure is altered (though not to extremely high values), the arterial blood flow will be autoregulated and kept fairly constant, as is the case when the blood pressure is altered. This corresponds to a dilatation of the pial vessels at increased intracranial pressure. A primary change in the extracranial venous pressure will not alter the cerebral blood flow either.

Another important factor in the circulatory regulation is the arterial Pco2, especially the arterial Pco2. Hypercapnia thus induces a strong cerebral vasodilatation and hypocapnia induces a strong vasoconstriction. The Pco2 regulation is closely related to the local vascular segment and is not directed by any center in the brain stem. This has been demonstrated by altering locally the arterial Pco2 in the carotid and the vertebral region, respectively. Moreover, it has been shown that the Pco2 regulation mechanism is closely connected with the arterial Pco2, but not with the cerebral venous Pco2. The regulation mechanism, therefore, must be local and closely related to the arterial part of the circulation.

Carbon dioxide in itself is not assumed to change the contraction of the vessels, but to act by changing the pH of the tissue; actually, the pH in the arteriolar wall is assumed to be the regulating factor. The fact is that carbon dioxide can diffuse freely across the blood-brain-barrier which, on the other hand, is impermeable to bicarbonate. The blood-brain-barrier is presumably located in the endothelium of the vessels. This means that the vascular wall in the arterioles acts as a “Severinghaus electrode,” as pH in the vascular wall is determined by the bicarbonate concentration in the tissue and by the Pco2 of the arteriolar blood. This explains why the cerebral blood flow regulation is closely connected to the arterial Pco2. The tissue Pco2, however, can also influence the pH in the arteriolar wall by changing the gradients across the arteriolar wall.

The arterial Pco2 also influences the cerebral blood flow. A slight fall in the cerebral blood flow is seen at increased arterial Pco2 and, conversely, a small rise is observed at moderately decreased arterial Pco2. A pronounced increase in the cerebral blood flow occurs, however, if the arterial Pco2 is critically low. Also changes in the cerebral metabolism influence the cerebral blood flow, as the latter rises with a higher metabolic rate. According to the pH regulation theory, these regulatory mechanisms of CBF might be explained by a change in the tissue Pco2 and/or lactic acid concentration.

Whether the autoregulation induced by changes in the blood pressure also can be explained by this pH mechanism is not known. Perhaps an independent myogenous regulation mechanism also forms part of the autoregulation response.

Several investigations have been carried out to examine whether a neurogenic sympathetic control of the cerebral blood flow exists. The results, which to some extent have been conflicting, seem to indicate that such a control is only minimal and probably insignificant from a physiological point of view and that sympathetic tonus does not seem to be present.

Most drugs will not influence the cerebral circulation. Here it shall only be mentioned that papaverine causes cerebral vasodilation and aminophylline vasoconstriction.
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DISTURBANCES IN THE CEREBRAL CIRCULATORY CONTROL IN ACUTE CEREBRAL DISEASES

The homeostatic regulation of the cerebral circulation is disturbed in a number of conditions, such as cerebral infarction, intracranial tumors, head traumas, hypoxia, compression of the brain, and highly increased intracranial pressure. Under such conditions, vasomotor paralysis occurs in the affected tissue with the result that the autoregulation and the responses to $P_{CO_2}$ changes to aminophylline and to papaverine are impaired (the latter two responses have only been examined in a few of the said conditions). Apparently, vasomotor paralysis is a rather nonspecific phenomenon. However, some degree of tissue hypoxia must be assumed in all the conditions mentioned. The vasomotor paralysis, therefore, is probably due to a lactic acid acidosis and in some of the conditions also to a carbon dioxide acidosis. Acidosis has previously been demonstrated in experiments where occlusion of the middle cerebral artery resulted in a low pH in the ischemic region. It has been demonstrated during experimental hypoxia that the bicarbonate concentration and the pH in the cerebrospinal fluid are reduced, that the lactate content in the cerebral tissue is increased, and that the bicarbonate concentration is reduced compared to the tissue $P_{CO_2}$. Direct demonstration of acidosis in the form of a low content of bicarbonate has recently been reported in brain biopsies frozen in situ in patients operated on for intracranial tumors or for intracerebral hematomas.

The cerebral blood flow in regions with vasomotor paralysis depends on the local blood pressure gradient and on the local cerebrovascular resistance. Both of these factors may be abnormal. The local arterial blood pressure thus may differ from the systemic one and be abnormally low owing to a severe arterial stenosis or occlusion, or the arteriovenous blood pressure difference may be abnormally low owing to a much increased intracranial pressure. The local cerebrovascular resistance either may be abnormally low if the paralytic (dilated) vessels are not more than normally compressed by the surrounding tissue, or it may be abnormally high owing to a local or general cerebral edema or to occlusive changes in the arterioles and capillaries.

Hyperemia as well as ischemia thus may be found in regions with focal vasomotor paralysis. A special condition arises in focal hyperemia, or rather where focal blood flow surpasses the metabolic demands of the tissue. This condition, denoted "luxury perfusion," is characterized by a high oxygen content in the venous blood, and in the extremes by red venous blood. Red venous blood has been observed at surgery on patients with cerebral tumors and also at experimental occlusion of the middle cerebral artery.

THE CEREBRAL RESPONSE TO HYPOXIA AT DIFFERENT LEVELS OF THE ARTERIAL CARBON DIOXIDE TENSION

Several experiments have shown that the cerebral tissue is more vulnerable to hypoxia at higher than at lower levels of the arterial $P_{CO_2}$. In animal experiments, analysis of cerebral tissue metabolites thus demonstrated that tissue hypoxia occurred in hypercapnic animals when the arterial blood pressure was reduced in order to obtain the same cerebral blood flow as during the normocapnic control condition. Other experiments have shown that increase in the cerebral or spinal cord blood flow in response to hypoxia occurred at a higher oxygen tension during hypercapnia than during normocapnia or hypocapnia.

CEREBRAL CIRCULATORY DISTURBANCES IN APOPLEXY

The focal symptoms in apoplexy without hematomas are presumably always caused by a primary tissue ischemia, regardless of the pathogenic mechanism mentioned previously. As mentioned above, the cerebral circulation in stroke is characterized by focal vasomotor paralysis.

Cerebral Infarction with Arterial Occlusion

In experimental occlusion of the middle cerebral artery with infarction, the blood flow is reduced in the infarct. The blood flow is likewise reduced through the region of infarction in patients with occlusion of the middle cerebral artery. In animals with experimental arterial occlusions, it has been found, furthermore, that the blood pressure is reduced in the pial arteries of the infarction. The oxygen tension also is much reduced in the infarction.

In the outer zone of the infarction, on the other hand, the oxygen tension is increased and the metabolic activity continued. This was demonstrated by the fact that the oxygen tension increased further following administration of cyanide. At autoradiographical examinations, a hyperemic region in the outer zone...
of the infarction has been demonstrated signifying a perifocal hyperemia corresponding to the regions with increased oxygen tension.\textsuperscript{186, 187} In experimental middle cerebral artery occlusion, red veins have been observed in regions of infarction,\textsuperscript{176–178, 179} and it must be assumed that these red veins drain the perifocal hyperemic zone. In patients with occlusion of the middle cerebral artery, perifocal hyperemia has been demonstrated by determining the regional cerebral blood flow (Xenon-133 method).\textsuperscript{88} In patients, as distinct from experimental animals, it is uncertain, however, whether the perifocal hyperemia observed is due to the narrow hyperemic zone surrounding the infarct or whether it is due to a small shift of the occlusion with the result that previously occluded arterial branches have been opened. Thus, in the above investigation, there were signs of the occlusion having shifted in one of the patients with especially pronounced perifocal hyperemia.

The perifocal hyperemia must be a result of the metabolic changes in the ischemic focus. The ischemic focus is acidotic, and the acidosis is most probably due to an accumulation of lactic acid and carbon dioxide.\textsuperscript{188} It is assumed that the acidosis induces the perifocal hyperemia by spreading to the surrounding regions where the perfusion pressure is normal.\textsuperscript{168}

The infarction region is affected by vasomotor paralysis (loss of autoregulation, of reactivity to CO\textsubscript{2}, and of reactivity to papaverine and aminophylline). This has been observed in animal experiments\textsuperscript{188, 189–191} as well as in examinations of patients with arterial occlusion.\textsuperscript{88, 186, 185–187, 188, 192–194} In earlier experimental investigations it has been observed, furthermore, that the oxygen tension falls in the infarction when the blood pressure is lowered\textsuperscript{188} and that the normal increase in oxygen tension during hypercapnia, and the decrease during hypocapnia, respectively, are lost.\textsuperscript{195}

By occluding the middle cerebral artery in experimental animals infarction will develop more easily and be more pronounced during hypotension than during normotension.\textsuperscript{40, 41, 196}

In the focal ischemic region the normal reactions to \textit{Paco}\textsubscript{2} changes, to aminophylline and to papaverine do not operate as mentioned, and paradoxical reactions may even be seen in the form of a focal flow reduction at vasodilation (hypercapnia or papaverine injection) concomitant with a normal flow increase in the nonaffected regions—"the steal syndrome"—or in the form of a focal flow increase at vasoconstriction (hypocapnia or aminophylline injection) concomitant with a normal flow decrease in the nonaffected regions—"the inverse steal syndrome."\textsuperscript{95, 100, 187, 188, 186, 190, 192, 193} Such a focal paradoxical reactivity to \textit{Paco}\textsubscript{2} changes has also been observed in cerebral oxygen tension in experimental animals with occlusion of the middle cerebral artery.\textsuperscript{185} In patients with occlusion of the middle cerebral artery examined with the Xenon-133 clearance method, the steal syndrome and the inverse steal syndrome were not a predominant feature.\textsuperscript{88} This may be explained to some extent by the fact that the blood pressure rises during hypercapnia and, owing to the lost autoregulation, the blood flow through the focal region increases and thereby conceals the steal phenomenon. Furthermore, detectors over the middle of the infarction also count over some of the nonaffected tissue, which is comparatively better supplied with the isotope than are the ischemic regions, and this tends to erase the focal abnormalities on the clearance curves. Thus, it is probable that steal and inverse steal syndromes actually occur far more frequently and markedly than it was observed.

The explanation of the steal syndrome must be that the hypercapnia causes only the vessels in the nonaffected parts of the brain to be dilated, so that an increased amount of blood is streaming to these parts, whereby the blood pressure falls in the vessels (the collaterals) leading to the focus. The blood pressure in the pial arteries in the region of infarction has been measured and shows a fall during hypercapnia.\textsuperscript{182–184} The intercranial pressure rises during hypercapnia owing to the increased blood flow through the nonaffected parts of the brain. This may contribute to the steal syndrome, as autoregulation in the focal region is lost. In the animal experiments mentioned, the cranium was open.

Focal blood flow increase in the inverse steal syndrome which is associated with vasoconstriction in nonaffected regions is explained by the blood being shunted into the area of ischemia where autoregulation is lost. In animal experiments with occlusion of the middle cerebral artery, the infarcts are smaller.

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in hyperventilated animals than in nonhyperventilated controls. This observation is consistent with the theory of the inverse steal syndrome.

Vasomotor paralysis has also been observed in the perifocal hyperemic region as well as in the focal region. Thus, perifocal vasomotor paralysis was clearly demonstrated in a patient in whom the arterial occlusion presumably had shifted distally. The oxygen tension in the perifocal hyperemic region also has been found to vary with the blood pressure.

It has to be added that in a few studies, focal vasomotor paralysis has not been observed. Thus, in a nine-year-old girl with occlusion of the middle cerebral artery no focal flow abnormalities were observed in the resting state, but during hypocapnia the blood flow fell more in the focus than outside. The patient later recovered completely. Such a flow pattern has not been observed in other patients. The explanation of this strange finding might be that the ischemic lesion had not been severe enough to produce significant acidosis and total vasoparalysis, but only a condition with so-called "dissociated vasoparalysis" with loss of autoregulation but preserved reaction to PaCO₂ changes (autoregulation was not tested in this patient). In cases of dissociated vasoparalysis the regional cerebral blood flow may be abnormally high compared to the metabolic rate during normocapnia, and normal conditions with preserved autoregulation may be restored by hypocapnia.

In some experimental studies with occlusion of distal branches of the middle cerebral artery in dogs only partial paralysis (dissociated) or no vasoparalysis was observed. However, it is well known that cerebral infarction only seldom occurs in distal occlusion of the middle cerebral artery in contrast to what is the case in proximal occlusion. Therefore, it seems reasonable to assume that cerebral infarction had not occurred in these studies and that ischemia only was so slight that minimal or no acidosis occurred.

At experimental occlusions of the middle cerebral artery, the microcirculation in the region of infarction shows paleness of cortex, dark venous blood, reduced perfusion rate in the pial vessels, and agglutination of the platelets with some adhesion to the vascular wall in the veins. In severe ischemia, change in caliber of the arterioles has also been found as well as thrombosis of the veins, venous stasis, vascular collapse, perivascular hemorrhages, and edema in the infarction region. Wall and Sundt observed red venous blood as well. Cerebral edema has also been found in experimental studies with arterial occlusion and in patients who had died from cerebral infarction with arterial occlusion.

The blood-brain-barrier is destroyed in the region of infarction. Following experimental air embolism, extravasation of Iodine-131-labeled albumin and of trypan blue from the vessels shows that the capillary permeability is increased. An increased uptake of Iodine-131-labeled serum protein or trypan blue and an increased water content have been observed in the ischemic hemisphere in rats in which hypoxia was induced following occlusion of one of the carotid arteries. Protein and other substances thus escape into the tissue and develop an edema that primarily must be extracellular. The development of edemas will be furthered if the arterial occlusion disappears and normal blood pressure is re-established in the distal arterial branches. Under such conditions there may be an increased occurrence of small perivascular hemorrhages or hemorrhagic infarcts. It is possible that the tissue acidosis in itself can produce edema. The acidosis will in fact depress the normal metabolic processes, among those the Na⁺ and K⁺ exchange across the plasma membranes. This may cause intracellular edema. Finally, the metabolic breakdown products in the destroyed tissue, including lactate, may further the development of intracellular as well as extracellular edemas by increasing the number of osmotically active particles.

Cerebral Infarction with Ischemic Lesion but Without Arterial Occlusion

While cerebral infarction with arterial occlusion is characterized by vasomotor paralysis and by a region with reduced blood pressure in the distal arterial branches, the latter phenomenon does not occur in cerebral infarction without arterial occlusion. As mentioned previously, the absence of arterial occlusion in cerebral infarction is presumably due to a primary thromboembolic occlusion which has been dissolved. The blood pressure in the arterial branches to the infarction, therefore, will have been re-established.

In these cases it is to be expected, therefore, that there is a pronounced hypereemia in a vasomotor paralytic region. There is a high frequency of hyperemic foci during the first
days after the acute attack. In many of these patients a simultaneous angiographical examination showed early filling of regional veins and also a capillary blush. A rapid passage of the contrast media and short venous filling time have also been observed in cerebral infarction in other investigations. Short regional venous filling time was seen, however, in patients without as well as in patients with arterial occlusion. In the latter cases, the explanation is that the occlusion has shifted distally, so that some of the arterial branches have been re-opened; but in some cases the perifocal hyperemia may—as mentioned above—be the cause of the early filling of the veins.

In principle, the changes in the regional cerebral circulation in cerebral infarction without persistent arterial occlusion are the same as those found in arterial occlusion (focal hyperemia, focal ischemia, and focal vasomotor paralysis); however, the frequency of the various circulatory disturbances differs. Hyperemic foci thus were more frequent in the nonocclusive cases, while ischemic foci, sometimes with hyperemic perifocal regions, were predominant in arterial occlusion. Furthermore, in some patients with cerebral infarction without arterial occlusion, the response to hypertension may be paradoxical with unchanged or even reduced blood flow through focus simultaneously with a rise in the blood flow through the other parts of the hemisphere. It is, however, most probable that this response will also be observed in cerebral infarction with arterial occlusion if larger series are examined. The paradoxical response to hypertension will be treated in detail later under "extensive (global) changes in the cerebral blood flow in cerebral infarction."

After the re-opening of an experimentally occluded middle cerebral artery, the blood flow has been found to rise to supranormal values. An increase to supranormal values may likewise be seen in the oxygen availability of the tissue, and direct observations of the pial vessels show that they are dilated, have a fast blood flow, and have red blood in the efferent veins. This experimental hyperemia corresponds to the above-mentioned observations in patients with cerebral infarction without arterial occlusion.

Examination of patients with cerebral infarction without arterial occlusion some days after an acute attack reveals focal vasomotor paralysis but no longer combined with a hyperemic focus; on the contrary, there was either no focal change or the vasomotor paralysis was combined with an ischemic focus during rest (normocapnia). In this situation other factors must be taken into account. The normal vasomotor function may be re-established gradually so that there is a phase with partial vasomotor paralysis. Focal edema may have developed in the same way as mentioned above under cerebral infarction with arterial occlusion. Focal edema would account for low blood flow and a low tissue pH with vasomotor paralysis corresponding to the conditions in experimental examinations of anoxia. Later on the focal flow abnormalities disappear, as will be discussed below.

Hemorrhagic infarcts are probably due to the disappearance or shifting of an arterial occlusion. Hemorrhagic infarcts are characterized by numerous small perivascular hemorrhages in the gray matter of the brain. The hemorrhages may possibly become confluent, but there is no major bleeding or hematoma. There is often simultaneous ischemic infarction in the white matter and possibly in other parts of the gray matter. Hemorrhagic infarcts, which are caused by tiny diffuse bleedings in the ischemic region, are essentially different from intracerebral hematomas, which normally are caused by a primary rupture of a vessel (see above).

Hemorrhagic infarcts most often occur in tissues that primarily have been severely ischemic and where the blood supply has been wholly or partially re-established. Thus, Fisher and Adams found that of 66 patients with hemorrhagic infarcts, the greater part showed signs of an embolic occlusion which had been dissolved or had shifted to more distal arterial branches. On the other hand, in the case of anemic infarcts, the authors as a rule could demonstrate an arterial occlusion. In the last ten patients with hemorrhagic infarcts examined, Fisher and Adams succeeded in demonstrating embolic occlusions in more distal arterial branches of the infarction and that the corresponding parts of the infarcts were ischemic. Similar observations of re-established
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blood flow to areas of hemorrhagic infarction have been made by other investigators. It has been reported, furthermore, that hemorrhagic infarcts may occur in cerebral infarction where an acutely occluded carotid artery has been surgically reconstructed.

Similar observations have been made in animal experiments. Thus, it has been possible to induce hemorrhagic infarcts by air embolism followed by acute arterial hypertension. In experimental occlusion of the middle cerebral artery in cats hemorrhagic infarcts have been difficult to induce but, when it was possible, it was always following re-opening of the occluded artery. In the latter investigation no observation was made of an abnormally high perfusion. However, such a phase may have existed prior to the blood flow determination, which was performed after the animals were killed. An autoradiographical technique was employed.

Hemorrhagic infarcts have also been associated with arterial occlusions, though it is possible that the occlusion shifted to more distal arterial branches. Fisher and Adams reported an arterial occlusion in a few instances. In animal experiments, hemorrhagic infarcts have also been found associated with arterial occlusion. Thus, experimental occlusion of the middle cerebral artery combined with hypertension produced hemorrhagic areas in the peripheral parts of the infarct. Earlier experiments had also shown that hemorrhagic infarcts might occur with arterial occlusion; however, the blood pressure was not recorded. In some cases of experimental occlusion of the middle cerebral artery, Waltz and Sundt found perivascular hemorrhages and in all these cases there was a slight rise in blood pressure.

Probably the pathogenesis of hemorrhagic infarcts combined with arterial occlusion is the same as those not combined with arterial occlusion. In both instances the hemorrhagic reaction occurs in regions with severe ischemic damage where the blood supply and the blood pressure in the distal vessels have been wholly or partially re-established.

Venous stasis is also of some importance in the development of hemorrhagic infarcts. Hemorrhagic infarcts occur in sinus thrombosis. In the investigations of air embolism, the hemorrhagic infarcts were more severe if the animal experiment included venous stasis. A sudden, marked increase in the cerebral venous pressure has produced hemorrhagic infarcts experimentally. In severe ischemic lesions produced by occlusion of the middle cerebral artery, agglutination of thrombocytes and venous stasis occur. These changes may be of some importance to the pathogenesis of the hemorrhagic infarcts following re-establishment of the blood supply to the region of infarction.

Extensive (Global) Changes in the Cerebral Blood Flow in Cerebral Infarction

In some patients with cerebral infarction, the blood flow is low not only in an ischemic focus but also in the whole hemisphere. In the investigations of air embolism, the cerebral blood flow was always following re-opening of the occluded artery. In the latter investigation no observation was made of an abnormally high perfusion. However, such a phase may have existed prior to the blood flow determination, which was performed after the animals were killed. An autoradiographical technique was employed.

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A focal paradoxical response to hypertension with a fall in the focal blood flow has been found in some cases with global loss of autoregulation. The focal responses to changes in $P_{\text{a}CO_2}$ and to aminophylline were abolished. It must be assumed that a rise in the intracranial pressure is of importance here, and the syndrome resembles to some extent the "steal syndrome" seen in hypercapnia, as the less-affected regions steal from the affected ones. Such a focal paradoxical response to changes in blood pressure is frequently found in patients with intracranial tumors. It is possible that in cases of cerebral infarction a similar paradoxical blood pressure response occurs owing to the mass of the infarct.

Duration of Circulatory Changes in Apoplexy (Strokes)
Due to Focal Ischemia

To the practical clinician, the duration of significant focal cerebral ischemia is in a general way related to the severity and duration of the focal neurological deficit. Thus, a patient with a transient ischemic attack consisting of left hemiplegia coming on in a few seconds, persisting 15 minutes, and disappearing completely has had transient focal ischemia for only a few minutes; and since the patient is normal it is presumed that infarction has not occurred or had only occurred in "silent" areas of the brain. Focal acidosis with accumulation of lactic acid developing during the period of ischemia may persist some time (hours?), however, after normal neurological function has been regained. In a study of patients with transient ischemic attacks, definite disturbances of the regional cerebral blood flow and its regulation thus were observed only within the first hours after the attack. However, in another recent study where calculation was made of the regional cerebral blood flow in gray and white matter separately and of the weight distribution between white and gray matter, focal disturbances were often observed in these flow parameters several weeks after the patient's latest transient ischemic attack. The cerebral vascular reactivity to hypocapnia was only focally abnormal in a few cases. In most cases the flow abnormalities were observed only in one single region (with one of 16 scintillation detectors used). Presence of reduced flow or of reduced weight of the gray or white matter was attributed to small infarction (clinically silent). However, increased flow values were recorded even as frequently, a finding which is difficult to explain; these interesting results therefore need confirmation.

Disturbances of the regional cerebral blood flow and its regulation have been observed during the first two weeks after the attack in patients with apoplexy without arterial occlusion. In patients with occlusion of the middle cerebral artery such flow abnormalities may persist for months.

Other investigations of the regional cerebral blood flow have also shown that the autoregulation is seldom affected longer than two weeks after the acute attack. On the other hand, in quite a number of patients an abnormal response to hypercapnia was observed more than two weeks after the attack. The cause of the different results is not apparent.

Regional Cerebral Blood Flow in Apoplexy (Strokes)
with Intracerebral Hematoma

Determinations of the regional cerebral blood flow have shown that the intracerebral hematomas may be surrounded by hyperemic regions. Vasomotor paralysis has been found located not only in the regions surrounding a hematoma but also in the entire hemisphere. Biopsies from patients with intracerebral hematomas have demonstrated acidosis in the tissues around the hematomas.

Knowledge of cerebral blood flow in patients with intracerebral hematoma is limited; however, examinations of intracranial tumors provide rather reliable information. The predominant effect of intracerebral hematomas, like that of intracranial tumors, is in exerting a pressure on and causing a distortion of the surrounding cerebral tissue, often with a resultant rise in the intracranial pressure. The disturbances found in regional cerebral blood flow in patients with intracranial tumors are of the same nature as those found in patients with stroke, but are often more pronounced. Especially in increased intracranial pressure, the regional cerebral circulation and its regulation will often be globally disturbed.

This similarity between intracerebral hematomas and intracranial tumors—and, moreover, to some extent also severe brain traumas—means that in the case of general anesthesia in connection with arteriography or...
surgery, care should be taken to avoid accumulation of carbon dioxide and employment of vasodilating anesthetics. Fall in the blood flow through critically perfused regions should be prevented as should further rise in a possibly increased intracranial pressure. These problems have been discussed in detail in a recent survey by Alexander and Lassen.238

Discussion of Therapeutic Measures in Cerebral Infarction Based on Pathophysiological Conditions and Clinical Observations

TREATMENT DURING THE ACUTE PHASE OF CEREBRAL INFARCTION
Ischemic Lesions with Arterial Occlusion

In these cases there is an ischemic region distal to an occlusion or a severe stenosis. It can be foreseen that an effective therapy must either (1) increase the blood flow through the ischemic region, increase the blood pressure or induce vasoconstriction in the nonaffected vascular regions (hyperventilation or amino-

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carbonyl. The amount of cerebral tissue which can be saved will therefore vary between patients even if they have the same type of arterial occlusion. Owing to this variation in the spontaneous course, it is difficult to evaluate the results of a therapy, and it is therefore necessary to compare the results between treated and untreated patients in controlled studies where the two groups have been selected according to the same criteria.

Increasing blood pressure. If an artery supplying the brain is occluded, there will exist an ischemic region with vasomotor paralysis and consequently without autoregulation. The blood supply to the ischemic region can be increased by increasing the blood pressure. In experimental occlusion of the middle cerebral artery it has thus been observed that infarctions were more pronounced and sometimes developed only if the animals were exposed to hypertension.40, 41, 154 Favorable results have been reported from increasing the blood pressure in the small series of patients with cerebral infarction.235, 236 In some patients the severity of the symptoms varied with the blood pressure.236 The treatment has never been adequately evaluated. In neither of the above clinical studies were the results compared with those from a control group.

When patients with acute apoplexy are treated with hypertension, it should be borne in mind that in certain patients with acute cerebral infarction there is global loss of autoregulation. A paradoxical focal reduction of the blood flow may occur during hypertension in some of these patients. In such rare instances, treatment with hypertension might aggravate the condition. An increase in the blood pressure may provoke a hemorrhagic infarction or a hemorrhage. Therefore, the blood pressure probably should not be changed in most stroke patients with arterial occlusion. However, if patients with severe hypertension, a slight reduction of the blood pressure might be induced carefully, and in patients with an extremely low blood pressure, it might be increased. Further controlled investigations would be highly interesting.

Hyperventilation. Therapeutic use of hypop-
capnia, which normally reduces the cerebral blood flow, might be beneficial for several reasons. As discussed above under pathophysiological considerations in cerebral infarctions, hypocapnia may induce on "inverse steal syndrome" and thereby increase
the blood supply to the ischemic region. The use of a low PaCO₂ will render the cerebral tissue less vulnerable to hypoxia. The induction of a respiratory alkalosis will reduce a focal cerebral acidosis and might thereby tend to normalize the metabolic processes and counteract the formation of a focal edema. If global loss of autoregulation is present, hyperventilation restores the autoregulation and thereby counteracts the formation of global cerebral edema. In addition to the effect of hypocapnia already mentioned, the production rate of the cerebrospinal fluid will be reduced. This, in connection with the vasoconstrictor effect in the nonfocally diseased brain tissue, will tend to reduce the intracranial pressure.

In patients with apoplexy, the focal neurological symptoms might not necessarily be influenced by hypocapnia since the focal damage may be irreversible at the onset of treatment. This has been suggested by observations in experimental brain infarction with occlusion of the middle cerebral artery. When hyperventilation was started before the arterial occlusion, the infarction was reduced to less than a tenth compared to the normocapnic controls. In another study where hyperventilation was started half an hour after the arterial occlusion, the infarction was reduced to about a third in the hypocapnic animals which were normotensive, but not in hypertensive animals. In a study where hyperventilation was started one hour after the arterial occlusion and in another where it was not started until four to six hours after the occlusion, no reduction of the size of the infarction was observed in hypocapnic animals. The skull was open in all these studies, so an effect induced via the intracranial pressure was eliminated or partly eliminated. In a recent controlled study of patients with severe apoplexy, prolonged artificial hyperventilation did not seem to influence the clinical neurological deficit, but the mortality appeared to be somewhat, though not significantly, reduced in the hypocapnic group. In patients with less severe apoplexy and cerebral lesion therapeutic hyperventilation might give better results; however, this has not been studied at the present time.

Based upon the same considerations, the use of slight hypocapnic anesthesia for surgery on the neck vessels must be expected to be favorable from the point of view of reducing a disabling effect of any kind of cerebral ischemia during the operation. This concept has been strongly supported recently by studies of the regional cerebral blood flow and of the distal pressure in the internal carotid artery during preoperative clamping of the internal carotid artery.

Aminophylline. As aminophylline acts as a vasoconstrictor in the normal brain, it is able to increase the blood supply to an ischemic region by inducing an "inverse steal syndrome" in the same way as hypocapnia does. Aminophylline, moreover, produces a slight hyperventilation. Clinical claims have been made that in certain cases intravenously injected aminophylline has instantaneously a pronouncedly improving effect on cerebral infarction; a severe hemiparesis thus may disappear almost completely, but the effect lasts as a rule only a few hours or less. None of these investigations were controlled. In a clinical study which included a control group, although it was not quite comparable to the treated group, no sure effect of aminophylline could be observed. At present, the value of treatment with aminophylline is quite uncertain.

Thrombolytic agents. The purpose of this treatment is a dissolution of the thrombus. However, there is a considerable risk involved in employing this therapy, as hemorrhagic infarcts and possibly hemorrhages may develop, and as arterial puncture in connection with angiography may cause large hematomas to occur. In a controlled investigation, where streptokinase was administered, the prognosis was poorer in the treated patients than in the nontreated ones, irrespective of dosage. There is consequently no practical fibrinolytic treatment using the existing methods. However, investigation of new agents continues.

Vascular surgery. When vascular surgery is performed, the purpose is to reconstruct a narrowed or occluded artery, to increase the blood supply to the ischemic focus, or, in the case of a "progressive stroke," to stop a progressing arterial occlusion.

There are numerous publications on reconstructive surgery of the extracranial neck vessels (thromboendarterectomy). The time at which thromboendarterectomy was performed varied from a few hours or days
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after the acute attack to several weeks after the attack. Few of these investigations included a conservatively treated control group.

An operation performed within the first hours or days after the occurrence of the symptoms will involve an essential risk of the infarct becoming hemorrhagic and edematous, and also of the development of hematomas in the infarct.126-128 The mortality in these operations is higher during the acute phase than during the chronic phase.90, 260, 261, 266

Neither have the results from a controlled examination of acute carotid surgery (37 operated and 39 nonoperated patients) shown any positive effect, and the higher mortality was even found in the group of operated patients.90 Arterial surgery thus seems contraindicated in patients with acute cerebral infarction.

If the operation is performed several weeks after the attack, it is hardly possible that there still remains any functional capacity in the damaged cerebral tissue, so a positive result of the operation cannot be expected in this case either. This is also compatible with the results from a controlled investigation (27 operated and 34 nonoperated patients), where the higher mortality was found in the operated patients.90

Hyperbaric oxygenation. In a series comprising a small number of patients, this therapy has been found to improve the condition of the patients.257-260 However, the patients cannot stand hyperbaric oxygenation for more than a limited time owing to pulmonary complications, especially, and on return to respiration of normal atmospheric air the symptoms most often recurred.

It is unlikely that hyperbaric oxygenation will be of great importance in the treatment of acute cerebral infarction.

Barbiturates and hypothermia. A barbiturate anesthesia and intoxication will reduce the cerebral oxygen consumption and blood flow.192, 161 Animal experiments have proved that barbiturates may increase the resistance to anoxia.260-262 The neurological signs were fewer in the animals treated with barbiturates.262 Neurological symptoms and signs seldom occur in survivors of severe barbiturate intoxication with respiratory insufficiency.266 Consequently, it is possible that barbiturate anesthesia might improve the course of cerebral infarction by reducing the oxygen demand in the ischemic region. However, this has not been examined.

Hypothermia is another way of reducing the oxygen demand in the ischemic region. It has been shown in animal experiments that following occlusion of the middle cerebral artery, the infarcts were smaller in the hypothermic animals than in the normothermic controls (the arterial blood pressure and $P_{acO_2}$ were not stated, however).264 Whether treatment with hypothermia has any clinical value in patients with acute cerebral infarction is unknown as yet.

Low molecular dextran (Rheomacrodex®). Besides expanding the blood volume, Rheomacrodex also has proved capable of reducing the intravascular aggregation that occurs in experimental occlusion of the middle cerebral artery.265, 266 The opposite effect, where the aggregation is increased, is found after hemococoncentration and after infusion of high molecular dextran (Macrodex®).267

Rheomacrodex may increase the cerebral blood flow.268, 269 This increase corresponds to a reduction in the oxygen-binding capacity and seems not to be a result of a change in the viscosity.268 This is in accordance with the fact that no increase is found in the cisternal oxygen tension following administration of Rheomacrodex, unless the patient is simultaneously treated for shock.270

In an experimental study with occlusion of the middle cerebral artery, treatment with Rheomacrodex resulted in essentially smaller infarcts in the treated than in the nontreated animals.271 It is a great defect of these examinations, however, that neither the arterial blood pressure nor the arterial $P_{acO_2}$ is reported, as both factors highly influence the size of the infarcts. It is possible that the administration of Rheomacrodex increased the blood pressure. This might wholly or in part explain the observed effect. In a recent study of temporary or permanent experimental occlusion of the middle cerebral artery in which the blood pressure was controlled, no beneficial effect was observed in the animals treated with Rheomacrodex and/or albumin as compared to those not receiving such treatment.177a In another investigation no beneficial effect of Rheomacrodex was observed either, as no essential reduction of the size of the infarcts occurred. But simultaneous treatment with albumin, Rheomacrodex, and urea reduced the
size of the infarcts, whereas the size was increased by administration of isotonic saline. However, these authors do not state the arterial $P_{\text{CO}_2}$ and blood pressure. A recent controlled clinical trial has shown some beneficial effect of treatment with Rheomacrodex in patients with apoplexy.

The knowledge of the effect of low molecular dextran (Rheomacrodex) on cerebral infarction thus seems still too limited for any therapeutic conclusion to be drawn. Hyperosmolar solutions (urea, mannitol, sorbitol, etc.). A reduction in the intracranial pressure and in the volume of the brain will take place following administration of hyperosmolar solutions of substances that do not pass the blood-brain-barrier or that pass it only slowly. The cerebral blood flow is normally not changed by the administration of such agents. It is possible, though unestablished, that treatment with hyperosmolar solutions might increase the blood flow through an ischemic infarct by reducing the intracranial pressure and thereby increasing the arteriovenous blood pressure difference.

The focal edema that develops in acute stroke may be diminished by administration of osmotically active agents. In rats exposed to anoxia following ligation of one of the carotid arteries, the edema in the ischemic hemisphere was less in those animals that had been given an intravenous injection of urea. Where experimental infarcts were induced by small plastic emboli, the edema was likewise less in animals treated with urea than in the controls. These studies do not state the arterial $P_{\text{CO}_2}$ or the arterial blood pressure.

As the blood-brain-barrier in the focal region is destroyed, treatment with hyperosmolar solutions cannot directly be expected to have any effect on the focal edema. However, the blood-brain-barrier may only be partially destroyed, or there may be a concentration gradient across the capillary wall, which is suggested in the study by Spector. He found the protein content in the extracellular fluid in cerebral edema to be only one-twentieth of that in the blood. It is possible that destruction of the blood-brain-barrier proceeds gradually, so that part of the function remains during the initial phase and that treatment with osmotically active agents then might be effective; later, when the destruction is complete, such agents would have no effect. It is impossible to decide whether this theory holds good, but there are several findings in support hereof. Thus, in experimental animals, a reduction in the size of the infarcts was noted when a combined treatment with albumin, Rheomacrodex, and urea was given before the middle cerebral artery was occluded, whereas in one case, where treatment was not given until 12 hours after the arterial occlusion, an aggravation of the infarct with increased edema was observed. Additional support of the theory that the blood-brain-barrier is gradually destroyed is the finding that a brain scanning is negative during the first days after an apoplectic attack and not positive until later—if at all.

The value of treatment of cerebral infarction with hyperosmolar solutions is uncertain. Owing to the above considerations, no conclusions can be drawn from experimental observations in animals either.

The influence of glucocorticoids on the cerebral edema in cerebral infarction. It is well known that glucocorticoids have an improving effect on cerebral edema in patients with intracranial tumors. At experimental examinations of brain injuries, a reduction of a cerebral edema often has been demonstrable following glucocorticoid treatment.

At controlled examinations of ischemia in connection with anoxia, no positive effect of treatment with glucocorticoids has been shown. At these examinations, the higher mortality was found in the animals treated with glucocorticoids; the edema did not differ between the treated and the nontreated groups. Glucocorticoid treatment also has been examined in a controlled series of patients with cerebral apoplexy and was found not to have any effect.

Anticoagulation. Only treatment of the acute attack will be discussed here; prophylactic treatment will be dealt with later. A differential diagnosis between intracerebral hematomas and ischemic lesions is of great importance, when treatment with anticoagulants is applied to acute attacks, because, in the case of intracerebral hematomas, this treatment involves the risk of aggravating the bleeding. It is well known that this differential diagnosis is not always easily arrived at. By investigating 378 apoplectic patients on whom autopsy had been performed, Dalsgaard-Nielsen found that 31% of the clinically diagnosed thromboses turned out to
be hematomas, and 26% of the clinically diagnosed intracerebral hematomas were thromboses. It should be mentioned also that hypertension is considered a contraindication to long-term anticoagulant treatment owing to the increased frequency of intracerebral bleedings in these patients.

With regard to anticoagulation, a division of the apoplexies into "strokes in evolution" and "completed strokes" will be an advantage, as anticoagulant treatment could be expected to be effective only in cases with "stroke in evolution" with a progressing arterial thrombosis. Thus, Fisher found that "strokes in evolution" often stopped progressing when treated with anticoagulants. Controlled examinations later have proved that some effect is obtainable by treating these patients with anticoagulants. In this connection it should be borne in mind that from a clinical point of view the course of a "stroke in evolution" is seen not only in the case of progressing arterial thrombosis and perhaps of recurrent cerebral embolisms, but also in the case of an increasing intracerebral hematoma, or of increasing focal or global edema with possible hemorrhagic infarction, or of a subdural hematoma, or of an intracranial tumor. A critical evaluation of the individual case, therefore, is always necessary.

In a "completed stroke," the damage has already reached its maximum at the time of examination, so no effect can be expected from treatment with anticoagulants. This is in accordance with the results from several controlled investigations. The mortality was even higher in the treated group as well as to a lower frequency of venous thromboembolic diseases and of new emboli from the heart in the treated group.

It can be concluded that anticoagulant treatment of acute cerebral infarction is indicated in those cases where the course is a "stroke in evolution," and where the latter is due to a gradually occluding arterial thrombosis.

Stellate ganglion block and sympathectomy. As the sympathetic has but a very small and uncertain physiological influence on the cerebral blood flow, no effect can be expected from stellate ganglion block or sympathectomy in the treatment of cerebral infarction. At experimental examinations in monkeys with occlusion of the middle cerebral artery, it was demonstrated that the region with a low oxygen tension remained unchanged after cervical sympathectomy. Yet, sympathetic block has been rather widely used clinically as a possible way of dilating the collaterals to the ischemic region. However, as it might have been expected, controlled examinations showed that sympathetic block did not have any effect on the course of apoplexy. Millikan and co-workers found the poorer prognosis in the treated patients (in this examination, the selection of treated and nontreated patients was not quite a random one).

Vasodilators. Such agents may be contraindicated, as they may reduce the blood flow in the ischemic region by inducing a "steal syndrome." Vasodilators probably will not increase the blood circulation in the ischemic region. The clinical effect of the vasodilating agents has been the object of only very limited, poorly controlled investigation. A controlled investigation showed that the course of cerebral infarction in patients treated with papaverine and in nontreated patients did not differ significantly—though there was some indication of a better course in the treated patients.

Ischemic Lesions Without Arterial Occlusion.

The vast majority of this type of cerebral infarction is caused by a thromboembolic occlusion that has disappeared by the time of examination. Therefore, the blood supply to
much of the ischemic region has been re-established. However, there may be hyperemia, altered metabolic processes, or focal edema with a resultant secondary ischemia. These changes are associated with a lactate acidosis in the injured tissue; but other factors, including disruption of the blood-brain-barrier, may be important.

The general purpose of the treatments dealt with under ischemic lesions with arterial occlusion was to increase the blood supply and/or the oxygen supply to the ischemic region distal to the occlusion. This therapeutic principle cannot be expected to be directly effective in ischemic lesions without arterial occlusion.

The theoretical purposes of a treatment for cerebral infarction without arterial occlusion are to decrease the focal acidosis (by reducing the arterial $P_{\text{CO}_2}$) and thereby restore normal focal metabolic processes; or to diminish the focal edema (by reducing the arterial $P_{\text{CO}_2}$ by administration of hyperosmolar solutions); or to reduce the oxygen consumption in this region (with barbiturate anesthesia, hypothermia); or, in the case of a secondary ischemia due to a focal edema, to increase the blood supply to the focal region (by increasing the blood pressure, by inducing vasoconstriction in the nonaffected tissues of the brain). In the last instance, it should be noted that an increase in the blood supply may easily aggravate the focal edema. The therapeutic principles outlined above do not differ fundamentally from the principles of treatment of cerebral infarction with arterial occlusion.

In cerebral infarction without arterial occlusion, our knowledge of the most effective treatment is even less than in the case of cerebral infarction with arterial occlusion.

PROPHYLAXIS AGAINST NEW CEREBROVASCULAR EVENTS

Natural History After Previous Cerebrovascular Events. In cerebrovascular diseases, the natural history of each category is important when evaluating a prophylactic therapy. In patients with previous transient ischemic attacks there is a mortality of about 5% each year of follow-up, cardiovascular diseases being the most common cause of death. A similar number of patients have cerebral infarction with more severe symptoms.$^{80, 288-300}$ The frequency of new transient ischemic attacks was essentially higher, and about 50% of the patients had fresh attacks within the first year. Patients who previously have had a more severe cerebral infarction (nontransient) have an annual mortality rate of approximately 10%, and a slightly smaller number of patients get new cerebral infarcts with severe symptoms; the figures vary from study to study.$^{301-309}$ Also for these patients, the most common cause of death is cardiac disease.

Statements about the natural history of each category show considerable variability from patient to patient, and as the prophylactic therapies applicable have a marginal or uncertain effect, a comparison between a treated group and a control group, selected according to the same criteria, is of the utmost importance.

Vascular surgery. Vascular surgery is performed prophylactically, especially on patients with transient ischemic attacks, in order to reduce the frequency of transient ischemic attacks and to diminish the risk of cerebral infarction with chronic focal symptoms or of death. A problem of special interest is whether the risk of a subsequent severe cerebral infarction or of death can be diminished, as the frequency of transient ischemic attacks can be reduced with anticoagulant treatment.

Cerebral infarcts associated with stenosis of the carotid artery most often are caused by emboli coming from the diseased artery. Even mild stenoses may produce emboli and possibly indicate surgery.

No evaluation of prophylactic vascular surgery based on a controlled series has been made until recently. In a large cooperative study the selection of operated and nonoperated patients was made according to exactly the same criteria, namely by lot.$^{258, 810}$ A report from this study deals with the cumulative survival rates in 1,225 patients who were followed during 42 months.$^{261}$ The mortality was significantly reduced following surgery on patients with previous transient ischemic attacks or minor cerebral infarction with the only vascular lesion was a unilateral stenosis of one internal carotid artery. Patients of the same clinical category with one carotid artery occluded and the other stenosed had a slight, but not significant, reduction in mortality. On the other hand, no beneficial effect of surgery was seen if there was a unilateral occlusion or a bilateral stenosis of the internal carotid artery. Mortality was significantly increased in
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the operated patients with permanent symp-
toms after cerebral infarction. Higher mortality
following surgery was noted in such patients
who had unilateral stenosis of the carotid
artery or where one carotid artery was
occluded and the other stenosed. Another
report dealt with the prognosis of new
cerebrovascular attacks and death in 316
patients with previous transient ischemic at-
tacks. The recurrence of transient ischemic
attacks was not reduced among operated
patients with bilateral carotid artery stenosis
and with stenosis of one and occlusion of the
other carotid artery, but was reduced in those
with unilateral carotid stenosis. The follow-up
also showed that the occurrence of nonfatal
and fatal strokes was reduced in the operated
groups. However, the operative mortality was
not included and if one adds this figure, no
difference between operated and nonoperated
patients was demonstrable.

As the disease picture is mild in the
patients whose prognosis can be improved by
prophylactic vascular surgery and as the
patients have a normal neurological examina-
tion at the time of operation it is very
important that the risk of operation be kept at
a minimum. It must be taken into
account that angiography of the extracranial
neck vessels is necessary to select those who
can be treated by surgery and that this
procedure may involve some risk.

Finally, it is possible that improved
surgical technique may better the results. If so,
vascular surgery may become an applicable
therapy in other subdivisions of cerebrovascu-
lar disease.

Anticoagulation. The purpose of prophylactic
anticoagulant treatment is to reduce the fre-
cuency of transient ischemic attacks and to
diminish the risk of serious cerebral infarction.
Hypertension is a contraindication to long-term
anticoagulant treatment because of the risk of
cerebral hemorrhages. Dementia and old age to
some degree must also be considered a
contraindication of long-term anticoagulant
treatment.

In patients with transient ischemic at-
tacks, Millikan, Siekert and Shick observed
that the attacks decreased or could be stopped
by anticoagulant treatment. This finding subse-
quently has been confirmed by several investi-
gations, most of which include a comparable
control group. In two investiga-
tions, the same frequency of transient ischemic
attacks was found in treated and in nontreated
patients with a previous history of apoplexy and
transient ischemic attacks, respectively.

Some investigations showed that antico-
agulation may reduce the risk of cerebral
infarction in patients with transient ischemic
attacks. Subsequently, critically con-
trolled investigation did not confirm such a
reduction of cerebral infarction in patients
treated with anticoagulation. However, in
other controlled studies, a significant reduc-
tion of the occurrence of cerebral infarction
was found in the patients treated with anti-
coagulation; there were also some instances of
cerebral hemorrhage in these patients.

Patients who previously had cerebral
infarction associated with rheumatic heart
disease (mitral stenosis, auricular fibrillation)
have the frequency of recurrence 50% reduced
by long-term treatment with anticoagulant.

Patients who have completed cerebral
infarction do not benefit from long-term
anticoagulant treatment. The risk of
cerebral hemorrhage increased somewhat in
the treated patients. In another study, however,
the risk of recurrent cerebral infarction was
found to be smaller in patients treated with
anticoagulants, even if the occurrence of
hemorrhages here also was somewhat in-
creased in the treated patients. When these
investigations are considered collectively, it
appears that anticoagulant treatment does not
seem effective in reducing the frequency of
reurrence in patients with a history of cerebral
infarction, unless it can be assumed that the
cerebral infarction was caused by rheumatic
heart disease.

The conclusion that can be drawn on the
basis of these investigations is that anticoagu-
lant treatment improves the prognosis in
patients with transient ischemic attacks and
reduces the frequency of attacks. In patients
with rheumatic heart disease who previously
have suffered from cerebral infarction caused
by an embolus originating from the heart,
treatment with anticoagulants may reduce the
frequency of recurrence.

Antiplatelet agglutination. Dipyridamole (Per-
santin®) has been demonstrated in vitro to
hinder platelet aggregation and in vivo to
hinder the development of thrombi in the injured vessels of the rabbit. Dipyridamole recently has been employed in a
controlled study of thromboembolic complications in patients who had undergone surgery for cardiac-valve replacement: the treated group, which was given dipyridamole as well as anticoagulants, showed no thromboembolic complications in contrast to 17% in the control group which was given anticoagulants only.828

In patients who had previously suffered from cerebral infarction, a controlled investigation of treatment with dipyridamole did not show any effect on the mortality or the occurrence of new cerebrovascular events.824 This investigation did not include simultaneous administration of anticoagulants which might have been of interest considering the above positive results with this combination.

**Antihypertensive treatment.** Several investigations indicate that treatment of hypertension will diminish the risk of subsequent severe cerebrovascular attacks.119 825-827 This has recently been confirmed in a randomized controlled clinical trial of antihypertensive treatment of patients with previous cerebrovascular attacks.828 In this connection it has to be mentioned that the occurrence of coronary infarction does not seem to be influenced by the antihypertensive treatment. As mentioned previously, hypertension will be present in most patients with intracerebral hematomas (congenital malformations being excluded). Thus, it has been discussed whether antihypertensive treatment will diminish only the risk of intracerebral hematomas or also the risk of ischemic cerebrovascular lesions. The controlled trial mentioned seems to indicate that the occurrence of both types of cerebrovascular lesions is reduced.828 Independently hereof it must be stated that treatment of hypertension has a clearcut beneficial effect. For the use of antihypertensive treatment it is also important to recognize that the vast majority of cerebral ischemic lesions are due to thromboembolic arterial occlusion often with subsequent rapid thrombolysis. Hemodynamic mechanism involving systemic arterial hypertension is only seldom responsible for the apoplectic attack. This has been discussed in detail above under the pathogenesis of cerebral infarction.

**Summary**
The aim of this survey has been to discuss pathogenic, pathophysiological and therapeutic aspects of cerebral apoplexy with special regard to recent experimental and clinical research on the regional cerebral circulation. Ischemic cerebral lesions are discussed extensively, whereas intracerebral hematomas are only shortly commented on. The whole survey shall not be summarized here but some major points will be mentioned.

In apoplexy with ischemic lesion an arterial occlusion may or may not be demonstrated. In those patients where no arterial occlusion is present, recent studies of the regional cerebral blood flow strongly support the thromboembolic theory according to which the ischemic lesion is due to a thromboembolic arterial occlusion with rapid subsequent thrombolysis. It is concluded, not only on the basis of these studies but even more on the basis of the large amount of studies in the literature, that these short-lasting thromboembolic occlusions must be responsible for the majority of apoplexy without arterial occlusion and of transient ischemic attacks.

The studies on the regional cerebral circulation have provided new essential pathophysiological information; among other things, a characteristic finding is focal vasomotor paralysis with loss of the normal ability of vasoconstriction and of vasodilation. The focal flow may even show paradoxical reactions with flow decrease during stimuli normally causing flow increase—"steal syndrome"—or with focal flow increase during stimuli normally causing flow decrease—"inverse steal syndrome."

Therapeutic measures in apoplexy at the present time have been of rather limited value. Only prophylactic treatment of selected cases with anticoagulation or carotid surgery, prophylactic antihypertensive treatment, and acute treatment of selected cases with anticoagulation seem to have shown some effect. In the acute phase the outlined new pathophysiological knowledge may be of significant importance for a rational treatment. Thus, vasodilators should be avoided as they may be harmful, whereas vasoconstrictor treatment might be beneficial by inducing an inverted steal. Animal experiments have shown a beneficial effect of hyperventilation, but the time interval from the onset of cerebral ischemia until hyperventilation was started was critical. No convincing effect was observed in patients with severe apoplexy where hyper-
ventilatory treatment was started as soon as possible but several hours after the onset of symptoms. Probably the infarction was completely irreversible in these severe cases when hyperventilation treatment was undertaken. Treatment with hyperventilation may be of value in less severe cases; however, it has not yet been studied.

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