THE FIRST OBSERVATIONS of cerebral autoregulation were made by Fog around 1930.1,2 Fog, observing the cat's pial vessels through a cranial window and varying the way of manipulating blood pressure, was able to conclude that pial autoregulatory vasomotor responses are independent of neurogenic stimuli—a notion that still stands with only minor modification. The concept of cerebral autoregulation in terms of blood flow constancy during perfusion pressure changes was finally established by Lassen in his review from 1959,3 based on studies of controlled hypotension in man where cerebral blood flow (CBF) was measured with the Kety-Schmidt technique. In Lassen's review it was shown that there is a lower blood pressure limit of CBF autoregulation. Hypertensive forced vasodilatation had been implied in the literature for many years,4 but it was as late as 1971 that an upper blood pressure limit of autoregulation was demonstrated.6 The influence of disease states on CBF autoregulation has been the subject of a host of clinical and experimental studies in the last 20 years.

The mechanism of autoregulation of blood flow in the brain and elsewhere remains obscure. The rapidity of the autoregulatory response, which is initiated within a few seconds after a change in resistance vessel transmural pressure,4 and largely completed in 15–30 seconds, suggests a myogenic response. Possibly, however, changing periarteriolar concentrations of vasodilator metabolites influence or even control CBF autoregulation. Adenosine has been proposed as such a regulator. Thus, brain adenosine levels rise with only moderate blood pressure reductions,9 and this might mediate autoregulatory vasodilatation. It should be noted, though, that the adenosine hypothesis has not yet accounted for the immediate autoregulatory vasoconstriction that follows blood pressure elevation. Perivascular nerves play a limited role in CBF autoregulation. During hemorrhagic hypotension, however, alpha-adrenergic sympathetic vasoconstriction shifts the lower limit of autoregulation towards higher pressure,7 a weak analogue of the intense vasoconstriction occurring in the renal and mesenteric vascular beds.

Further, alpha-adrenergic activity during hemorrhagic hypotension causes inhomogeneity of CBF, an effect that can be abolished by an alpha-blocker such as phenoxybenzamine.8 During blood pressure changes a difference in response seems to be present between larger and smaller resistance vessels.10 The sympathetic nerves, when stimulated, constrict the larger vessels,11 whereas autoregulation predominantly is a function of the smaller resistance vessels.12

It is sometimes claimed that cerebral autoregulatory vasodilatation is maximal at the lower limit of autoregulation, i.e., at the pressure level below which CBF decreases. That this is not so was shown by Hägendorf and co-workers,13 who demonstrated that hypercapnia may increase CBF even if the blood pressure is below the lower limit of autoregulation. Similar observations were made in a study by MacKenzie and co-workers14 where pial arteriolar diameters and cortical blood flow measured by hydrogen clearance in the anesthetized cat were followed during controlled hypotension. Cortical or fast component blood flow was constant until the mean blood pressure was around 70 mm Hg; at lower pressures, the flow fell progressively. Pial arteriolar dilatation, however, continued as the pressure fell further, and reached a maximum around 40 mm Hg; at lower pressures the vessels collapsed. Thus, at pressures moderately below the lower limit of autoregulation, drug-induced vasodilatation might normalize CBF. The cerebral vasodilating properties of hypertensive drugs will be discussed in detail below. It may be mentioned already here, though, that cerebral vasodilatation during hypotension carries the risk of inducing uneven, "patchy" perfusion.15

In chronic hypertension CBF autoregulation is adapted to high blood pressure. Thus, both in hypertensive man16 baboon,17 and rat,18 the lower end of the autoregulation curve is shifted towards high pressure. Presumably this is a consequence of hypertensive structural vascular adaptation with vessel wall thickening and luminal narrowing limiting the resistance vessels' capacity for dilatation. A similar shift in the upper limit of CBF autoregulation has been found in the baboon with experimental renovascular hypertension.19 With chronic antihypertensive treatment in young hypertensive patients, a shift back to normal CBF autoregulation can be anticipated. Such a normalization of the lower end of the autoregulation curve has been shown in young rats with treated renal hypertension.20 In elderly hypertensive patients, only limited
readaptation of CBF autoregulation can be expected during antihypertensive treatment.

Despite hypertensive adaptation of CBF autoregulation, antihypertensive treatment generally is not associated with a risk of inducing cerebral ischaemia. On the contrary, the brain is the organ that has benefited most from modern antihypertensive treatment. It is now universally agreed that even moderate degrees of hypertension should be treated, in order to protect a substantial proportion of the patients against the disaster of stroke. The reasons why cerebral ischaemia is so seldom caused by antihypertensive treatment are at least three: First, despite hypertensive adaptation of CBF autoregulation, there is still in most patients considerable room for therapeutic blood pressure lowering before CBF is jeopardized. Typically, in acute, controlled hypotension the pressure can be lowered around 25% before the lower limit of autoregulation is reached and around 50% before symptoms of brain hypoperfusion are encountered. Second, during long-term treatment, as mentioned above, some hypertensive patients readapt their CBF autoregulation towards normal. And third, even though the blood pressure falls somewhat below the lower limit of autoregulation, the brain can compensate for the fall in flow by increasing the oxygen extraction from the blood. Thus, in the internal jugular venous blood, oxygen saturation typically is around 60% whereas e.g. in the coronary sinus it is 20–30%. This difference may well explain why antihypertensive treatment has been so successful in preventing ischaemic stroke, but has failed to prevent myocardial infarction. The risk of provoking cerebral ischaemia by overzealous antihypertensive treatment can largely be limited to four clinical settings: First, in the initial treatment of patients with accelerated hypertension. Second, in the elderly hypertensive. Third in very rare patients with transient cerebral ischemic symptoms of hemodynamic origin with occlusion of major arteries (candidates for extra-intracranial arterial bypass surgery), and fourth, in acute stroke patients with transient hypertension.

When the blood pressure is lowered acutely by drug intervention, two kinds of effects on the cerebral circulation can be anticipated. First, if the blood pressure is brought below the lower limit of autoregulation, CBF will fall. And second, there may be a pharmacologic effect of the drug on the cerebral vessels. Until the latest years, there have been few studies on how hypertensive drugs influence CBF, and this question has largely been ignored in reviews on emergency treatment of hypertension. Now, however, a pattern is emerging. Thus, drugs used for emergency blood pressure lowering may be classified into three, and perhaps four groups from the point of view of the cerebral circulation.

First, drugs with no vasodilatory or other effect upon the cerebral resistance vessels. Diazoxide is one such drug. When given in the favored bolus dose of 5 mg/kg i.v., this drug causes an abrupt fall in blood pressure of 50% or more. In the hypertensive rat this results in on the average a 30% fall in CBF as the blood pressure goes below the lower limit of autoregulation. Limited observations in man suggests a similar CBF response after diazoxide.

Second, cerebral vasodilators such as dihydralazine which in man may cause a rise in CBF along with the fall induced in blood pressure. This may be associated with a rise in intracranial pressure, which can be dangerous in neurological patients or in patients with malignant hypertension who often have a high intracranial pressure before treatment is started. In the hypertensive rat dihydralazine maintains a normal CBF well below the lower limit of autoregulation, with a tendency for CBF to rise with high doses. Sodium nitroprusside is another drug which at low pressure may dilate cerebral vessels, at least in anesthetized patients. This drug also has an undesirable increasing effect on intracranial pressure, but this tends to wear off as hypotension becomes more profound. The untoward effects of hypertensive drugs that dilate cerebral resistance vessels include not only a rise in intracranial pressure, but also the possibility of uneven, "patchy" perfusion where areas of high and low flow coexist. Metabolic derangement suggestive of such a pattern of flow is induced when cerebral vessels are dilated with hypercapnia or papaverine during hypotension. Studies of both cerebral metabolism and electrocortical activity during sodium nitroprusside induced hypotension, do, however, suggest that patchy ischaemia is not present, and the drug is considered superior to trimetaphan for profound hypotensive anaesthesia. Thus the effect of sodium nitroprusside on the cerebral vessels seems more complex than that of simple vasodilatation.

Ganglionic blockers and alpha blockers are a third group of hypertensive drugs. They abolish the weak alpha-adrenergic constriction of the larger cerebral resistance vessels which occurs during haemorrhagic hypotension. Trimetaphan is recommended for moderate hypotension during anaesthesia in neurological patients, as it does not increase intracranial pressure.

Whereas ganglionic blockers and alpha-blockers can be said to shift the lower limit of CBF autoregulation towards lower pressure, i.e. to improve autoregulation, this terminology should not be used to describe the effects of the vasodilators. Hence, if blood pressure is first lowered with e.g. dihydralazine and global CBF maintained normal below the lower limit of autoregulation in a hypertensive rat, and then blood pressure is raised with angiotensin infusion, gross cerebral hyperemia will result as autoregulation is evidently lost.

Very recent observations in our laboratory have suggested that the converting enzyme inhibitor captopril may belong to a fourth category of drugs which actually improve autoregulation at low blood pressure. Thus, in patients with congestive heart failure, and a history of hypertension, captopril brought the mean blood pressure down to 55 mm Hg without any fall in CBF. These observations might be caused by the drug’s ability to block the angiotensin induced amplification of sympathetic vasoconstriction. In hypertensive rats,
However, where the sympathetic nervous system was almost completely blocked during anesthesia, captopril shifted both the lower and upper limit of autoregulation significantly to the left on the blood pressure axis, i.e., towards low blood pressure. The mechanism of captopril's modulating effect on the cerebral autoregulation thus remains to be investigated.

Cerebral autoregulation protects the brain against changes in systemic blood pressure. If autoregulation were not present, an otherwise trivial fall in the pressure e.g. during sleep might cause tissue ischaemia and possibly cell damage. Likewise a sudden rise in arterial pressure, e.g. during isometric muscular work or coitus, would in the absence of autoregulation lead to passive vasodilatation of arterioles and capillaries and a potential for development of brain oedema. This oedema might be caused by blood-brain barrier dysfunction with plasma protein extravasation as well as by hydrostatic filtration of plasma water across the wall of the microvessels. That is actually what seems to happen if the blood pressure exceeds the upper limit of autoregulation for a prolonged period, and probably is the pathogenetic mechanism behind acute hypertensive encephalopathy. Endogenous blood pressure rises such as those mentioned above are associated with high alpha-adrenergic activity which by causing some vasoconstriction of the larger cerebral resistance vessels shifts the upper limit of CBF autoregulation towards higher pressure. This explains why e.g. coitus does not usually precipitate a hypertensive cerebral crisis.

In acute cerebral lesions, e.g. ischemia or trauma, the cerebral vasomotor functions are disturbed. Autoregulation is no longer present, and changes of the arterial blood pressure are now followed by similar changes of the CBF. In very severe lesions it has been observed that autoregulation apparently may be preserved in spite of marked disturbances of other regulatory mechanisms. This "false" preserved autoregulation may be due to several interacting mechanisms including changes in cerebral tissue pressure along with changes in blood flow. The reason for loss of autoregulation in acute cerebral lesions seems most often to be some degree of tissue ischaemia and/or acidosis. These factors dilate the cerebral resistance vessels in an attempt to increase blood flow, and in these dilated vessels the normal vasomotor regulatory function including the autoregulation will be impaired. The actual level of the blood flow in such regions not only depends on the degree of vasodilation, but also on other factors such as intracranial pressure, local cerebral oedema and vascular obstruction. Flow may well be low therefore despite the vasodilator stimuli. In regions surrounding an acute lesion, and even in the hemisphere contralateral to the lesion, autoregulation may be impaired despite a normal response to changes in arterial carbon dioxide tension, and despite a level of the blood flow which corresponds to the metabolic demand. In these regions autoregulation may be restored by moderate hypocapnia which constricts the cerebral vessels and reduces the flow. These rather complicated aspects of disturbed autoregulation have formed the basis of several therapeutic considerations for the treatment of acute head trauma and stroke.

In conclusion, autoregulation of cerebral blood flow is a physiological regulatory mechanism of major importance for the daily regulation of the cerebral perfusion, and an important function to take into account when lowering the blood pressure, in hypertensive diseases, and in acute cerebral lesions.

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