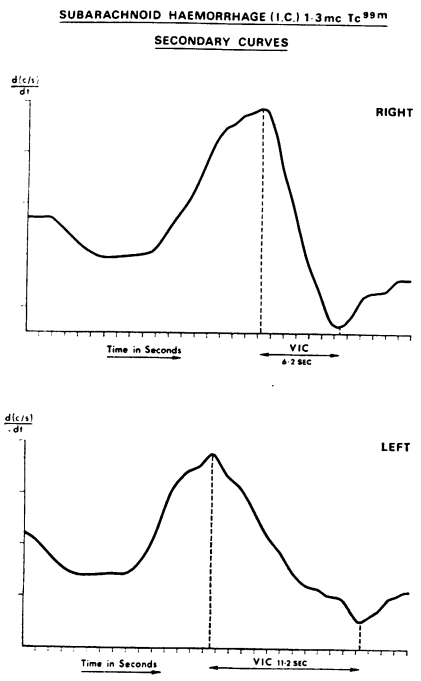

Fig 5 *Comparison of secondary curves from right and left detectors – velocity index of circulation is clearly slowed on left*

clearance time on the differentiated (secondary) curve (Fig 5); attempts to draw conclusions about the circulation from the angles of the ascending and descending slopes of the primary curve seem unlikely to yield meaningful information as so many factors can affect these parts of the curve. In the present state of knowledge it seems unwise to claim more than that this is a technique which calls for critical evaluation because its relative simplicity would make it possible to apply it in a wide variety of circumstances.

It seems likely that information about blood flow may come to form as much part of the investigation of cerebrovascular clinical problems as angiography now is. But a good deal more work must be completed in perfecting techniques and establishing criteria before these methods can provide reliable and meaningful information, and only then should they be made generally available.

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Hæmodynamic Studies of the Leptomeningeal Circulation in Primates

The superficial circulation within the distribution of the middle cerebral artery has been studied in primates by recording the intravascular pressure from branches of the middle cerebral artery. These were cannulated either downstream towards the heart, which gave a measure of the general field pressure within the middle cerebral distribution, or backwards towards the cortex, giving some measure of collateral pressure distal to the small branch catheterized (Symon 1967*a*).

Field pressure following middle cerebral occlusion was itself some measure of collateral circulation into the occluded bed as a whole. Blood flow measurements were made in the neck using electromagnetic flowmeters around the major afferent cerebral arteries (Symon, Ishikawa, Lavy & Meyer 1963) and in the brain, by small thermistor beads placed upon branches of the middle cerebral or other vessels on the surface of the hemisphere (Symon, Ishikawa & Meyer 1963). In more recent experiments, branches of the middle cerebral veins were cannulated backwards towards the cortex, and a pulsatile recording of venous pressure obtained which has been of some interest in the detection of changes in regional vascular resistance (Symon 1968). A certain number of studies, carried out some years ago, followed the transit of red cells labelled with ^{32}P through the superficial circulation with a small Geiger counter embedded beneath the pia (Symon 1960, 1961). The studies have involved detailed dissection of the circle of Willis in over

200 animals following experiments, and have also involved carmine gelatin perfusion of upwards of 50 monkey brains immediately following experimental procedures.

It has become clear from these and the experiments of other workers (Meyer *et al.* 1954, Petersen & Evans 1937) that, within the leptomeningeal distribution of the middle cerebral artery, occlusion of the main trunk does not result in cessation of flow in the distribution of the vessel. The Cohnheim theory of end arteries is not applicable to the brain, and within the leptomeningeal distribution of the middle cerebral artery of the healthy primate brisk collateral circulation is relatively easy to demonstrate. By the injection of suitably labelled radioactive cells into the carotid or vertebral circulation, it can be shown that collateral flow within the occluded segment is brought in by the leptomeningeal and anastomotic vessels (Vander Eecken 1959) from contiguous branches of the anterior and posterior cerebral vessels. These findings have been confirmed on perfusion studies, which showed good perfusion of cortical segments distal to the occlusion of a major middle cerebral branch or of the middle cerebral artery itself. There was considerable contrast, however, in the inadequacy of collateral circulation to the perforating branches of the middle cerebral artery supplying the basal ganglia, where a complete failure of perfusion of the corpus striatum, with the exception of small branches supplied by the perforating branches of the anterior cerebral artery, was demonstrated after obliteration of the striate branches of the middle cerebral artery. It has further been shown that, despite the presence of direct anastomotic channels at capillary level throughout the entire brain, the failure of function of these anastomoses in the basal ganglia can also be demonstrated at the level of the perforating branches on the surface of the brain by micro-embolization techniques (Penry & Netsky 1960).

The presence of efficient anastomoses in the leptomeninges can therefore be regarded as beyond question, as between adjacent arterial fields. Despite certain anatomical evidence to the contrary (Schmidt 1955), there is clear experimental evidence from the measurement of vascular pressure distal to areas of occlusion, that efficient anastomotic channels exist between contiguous branches of the middle cerebral artery in the primate. Thus, the effect on the vascular bed distal to an area of occlusion is considerably less if this area of occlusion is subserved by a small branch of the artery than if the entire bed is depleted.

It was demonstrated as long ago as 1954 by Meyer *et al.* that, following occlusion of a major cerebral artery, adjustment in the collateral circulation began promptly. Further experiments carried out by Symon, Ishikawa & Meyer in 1963 showed that the adjustments in contiguous vascular beds seemed to be evoked by the establishment of a pressure differential between the area of occlusion and the contiguous beds. Further, the evidence of collateral dilatation appeared within 4 seconds of the establishment of an ischæmic area. These findings have made it unlikely that metabolic factors are the major ones in the immediate adaptation to vascular occlusion within the cerebral circulation. The distribution of the zones of hyperæmia is further evidence against their primarily metabolic origin, since the metabolic changes are most intense near the centre of the area of ischæmia, and the collateral changes are more evident on the periphery. In regard to cerebral collateral function, it emerged during these experiments that, in the primate, differential pressures between the contiguous vascular fields were set up in the leptomeningeal circulation on the surface of the brain following carotid or vertebral occlusion, indicating that the circle of Willis did not completely eliminate inequalities of blood flow produced by occlusion of one or more of the major afferent vessels and demonstrating that, following occlusion of vessels in the neck, the leptomeningeal anastomoses might well have an important part to play in the re-distribution of blood throughout the hemisphere, as suggested by Potter (1959).

Studies of blood flow in the major neck vessels to the primate brain indicated that like immediate compensatory responses in flow were evoked in surviving intact vessels by occlusion of a major afferent artery. In the neck vessels the responses were susceptible to detection by methods with rather shorter latency than thermocouple estimations on the cortical surface, and the immediacy and adequacy of the response was quite striking (Symon, Ishikawa, Lavy & Meyer 1963).

It is therefore fairly clear that immediate collateral responses are evoked in the primate cerebral circulation both at the level of the vessels in the neck and at the level of the vessels in the leptomeningeal distribution of the major cerebral arteries, and that these responses are of quite surprising efficiency. The initiation of these responses is a direct result of the establishment of differential pressures between contiguous vascular beds and not the result of impaired metabolism in areas of brain subject to ischæmia, although doubtless metabolic factors play an important sustaining role with the passage of time. It is clear as demonstrated by Lowe (1962) in the rabbit, and by Symon, Ross Russell & du Boulay (unpublished) in the primate, that the chronic adaptation to ischæmia results in the extensive hypertrophy of collateral channels at all levels from the neck to

the brain. The notable exception to this picture of remarkable facility in collateral supply appears to be the deep structures within the substance of the cerebral hemispheres, and this accords well with the experiences of neurosurgeons for whom the perforating vessels to brain stem or striatum have recognizably spelt hazard and morbidity for many years.

The presence of reactive hyperæmia within the cerebral circulation has clearly been shown in the course of these studies. It was found by Symon, Ishikawa & Meyer (1963) that, following a severe ischæmic episode to the whole brain, occasioned by the temporary obstruction of all four afferent vessels, a considerable transient hyperperfusion in the cerebral cortex could be demonstrated. This was subsequently confirmed by Ishikawa *et al.* (1965) by electromagnetic flowmeter techniques, and it has been investigated in detail in a study of regional resistance changes in the cortical distribution of the middle cerebral artery. The method of production of reactive hyperæmia in the cerebral circulation is far from fully established. It was suggested by Penfield (1938) that hyperperfusion in an area of an epileptic focus could be demonstrated by the presence of red veins observed at the time of surgery, and Feindel & Perot (1965), in a series of beautiful photographic studies, have shown the presence of arteriovenous shunts in the region of tumours, but it is on the whole accepted that arteriovenous shunts in the normal cerebral circulation are of little significance. The origin of hyperæmia appears to be twofold. In the first place the reaction of the cerebral vessels themselves to sudden severe falls in intraluminal pressure has been known for many years (Fog 1938, Bayliss 1902) to be one of dilatation. The effect of the restoration of perfusion pressure to a maximally dilated bed is, of course, considerable overswing in flow until readjustment takes place. A further possible factor is the contribution of accumulated metabolites, although here the uncertainty of paralysis of metabolism following ischæmia has to be taken into account. It has, however, been shown by Meyer & Gotoh (1961) that secondary metabolic changes within an area of ischæmia would all tend to the accumulation of products of a vasodilator character and it is therefore reasonable to suppose some place for a metabolic factor in the production of hyperæmia.

The responses of the collateral circulation to an ischæmic area is of interest beyond cerebrovascular physiology and recent physiological results have thrown some light upon this pressing clinical problem. It has become clear that the effect of CO_2, first shown by Symon (1963) to reduce the perfusion pressure distal to an area of cerebral arterial occlusion, is frequently associated not only with reduction in perfusion pressure but also flow (Brawley *et al.* 1967). An analysis of the effects of CO_2 on the damaged primate vascular bed (Symon 1967*b*) has suggested that an imbalance between the arterial inflow and the outflow through the intensely dilated peripheral vascular resistance results in effect in a bleeding out of the ischæmic zone directly into the venous circulation. Paralysis of autoregulatory mechanisms at high levels of arterial P_{CO_2} has been reported by Harper (1966), and it has also been recently shown that the hyperæmic response to middle cerebral occlusion in the primate is considerably altered by elevation of the arterial P_{CO_2}.

It seems likely that failure of autoregulation or vasomotor paralysis in an ischæmic vascular bed with the maximal dilatation of arterial and arteriolar vessels secondary to vastly lowered intraluminal tension results in a bed which cannot respond by the normal compensatory processes to further elevation in the arterial P_{CO_2}. It may also be that acid products of metabolism in the ischæmic area are further acting upon the dilated vessels, and it would therefore seem unreasonable to attempt to increase the arterial P_{CO_2} as, for example, by the inhalation of 5% CO_2 mixtures. Certain confirmatory evidence is already available from the work of Hoedt-Rasmussen *et al.* (1967) in man that these primate studies are of direct relevance in the human cerebral circulation.

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