Microscopical observations on the cerebral circulation of the blood in the cerebral cortex, by Howard Florey (BA and John Lucas Walker Student; From the Physiological Laboratory, Oxford and Pathological Laboratory, Cambridge). Brain 1925: 48; 43–64.

‘The present investigations had as their origin an observation made by Professor Sherrington while engaged in mapping out the motor area of the cerebral cortex of monkeys . . . if the superficial cortex exhibited a reddish flush the preparation was active, but if, as sometimes was the case, a somewhat yellowish colour appeared there was great difficulty in eliciting responses to electrical stimuli’. The experimental subjects are anaesthetized cats, rabbits and a monkey in whom the dura is opened, after which the pia mater with its vessels intact is then exposed. The experimental field must be dry and all bleeding points are secured with plasticine rubbed into the diploë, with cotton wool pledgets or muscle plugs applied to oozing vessels. An operating microscope with magnification up to 100 diameters is used, although 50 diameters is preferable since this results in less time out-of-focus as the brain moves with respiration and pulsation of the heartbeat. When animals are to be euthanized, the brain is perfused with blue or black Indian ink using carotid artery and jugular vein cannulation with the vertebral arteries occluded; then the animal is rapidly decapitated and the head fixed in formalin before removal of the brain. This work is relatively novel; not in the attempt to visualize the cortical surface, but through use of the microscope in a live preparation. That said, a similar methodology and set of observations were reported 59 years earlier (Schultz A., Zur Lehre von der Blutbewegung im Innern des Schädels. St Petersburg Medizinische Zeitschrift 1866; 11: 122 et seq.).

Immediately, it is clear that the surface of the cortex has a network of vessels, mainly veins. These appear flat, vary in size, follow a sinuous course and usually emerge obliquely to the surface. They combine into large channels that may narrow before receiving further input from other tributaries and form circular anastomoses. In contrast, the arteries are less numerous, have fewer arborizations and are rounder than the veins. They assume a more perpendicular orientation to the brain surface, lie superficial to the cortical veins and also may anastomose. Short segments of the arteries constrict distal to sites where they branch. Many capillaries are seen connecting the arteries and veins. The underlying brain is pink due to the contents of cortical vessels, but everything goes blue when Indian ink (Pelican brand) is infused into the carotid arteries. Flow is visibly pulsatile in the larger vessels—expansion of the arteries being matched by contraction of veins, which also oscillate in size with respiration. Observing flow in the smaller venous tributaries ‘the appearance is that of a succession of “beads” of massed corpuscles, the intervals between which are filled with clear plasma . . . when the stream from a small vein enters a larger . . . the identity of the two streams can be traced in the larger vessel for considerable distances, a zone of clear plasma separating the two columns of corpuscles’. Furthermore, flow may change direction in a venous anastomosis, lapse altogether for a few seconds, or go in both directions at a T-junction when a superficial vessel overlies a feeder entering perpendicularly from the underlying cortex.

Next Dr Florey (Fig. 1) stimulates the vessels with a fine glass needle; he observes them to contract at the point of contact, but without propagation of the annular constriction. Sometimes the constriction is limited to one side of the vessel and the opposite wall may even dilate. These alterations last between 5 s and 10 min. But after 2 h of exposure, the vessels accumulate polymorphonuclear leucocytes, start to leak and lose their reactivity. Whereas capillaries may also constrict, even to the point of complete occlusion, cortical veins are completely unresponsive to a mechanical stimulus. Concerned that these appearances may be cortex specific, Florey also studies the medulla, but those vessels behave in an identical manner. The branches of cortical (and medullary) arteries and capillaries—but not the veins—respond, within ~20 s, much in the same way and with the same variation in appearances to faradic stimulation as is seen with mechanical displacement, although the effects are often longer lasting (a few minutes to 2.5 h). Once recovered, a given vessel may be refractory to further stimulation for ~15 min. Whereas hot (45–47 °C) or cold stimuli produce arterial constriction, temperatures only slightly higher than ambient (40 °C) cause vascular dilatation.

The local application of adrenaline (from 1:1000 to 1:10000) to cortical vessels or those in the floor of the fourth ventricle has no effect whatsoever on their calibre other than occasionally to cause slight dilatation of arteries, and pre-conditioning with adrenaline may inhibit subsequent responses to mechanical stimulation. Intravascular injection also does not constrict the vessels, but merely increases blood flow due to systemic cardiovascular responses, resulting in minor cortical swelling. Nor is any response observed with pituitrin, 5% barium chloride or 3% sodium nitrite, whereas amyl nitrite and 2% strychine sulphate or 1% strychine hydrochloride cause marked dilatation. The effect of asphyxia is to
raise venous pressure transiently, resulting in dilatation of those vessels and the capillaries, but with no arterial responses. Eventually flow ceases altogether in the veins, pulsations stop and ‘long lengths of arteries and veins could be seen to be filled with plasma only, while short lengths showed a close packing together of the corpuscles’.

In order to investigate the neural regulation of blood vessel size, experimental animals undergo stimulation of the stellate ganglion. Although the pupils dilate, confirming adequate stimulation, the blood vessels remain unchanged. Direct vagal stimulation in the floor of the fourth ventricle leads to cardiac slowing and stagnation in the cerebral veins, but no change in their calibre. Intravenous injection of 50% thujone, the active ingredient of absinthe, in alcohol causes violent generalized convulsions, but these are not preceded by changes in the cortical blood vessels nor does direct application of thujone to the cortical surface affect the local vasculature. However, as a direct consequence of these seizures, there is massive venous dilatation and cortical bulging.

Prolonged experimentation leads to additional changes in the preparation: ‘small opaque perfectly white rounded bodies began to form in the veins … these bodies adhered to the wall of the vein and visibly increased in size until they suddenly became detached and shot off into the blood-stream … [eventually] the growth was of sufficient size to block the vein; but complete blockage did not immediately ensue, for a slow tortuous stream could be observed for some time forcing its way through the white mass’. This effect of local thrombus formation—shown to consist of leucocytes, platelets and fibrin entangling a few red corpuscles—is observed both in veins and arteries. Irritation by heat or iodine leads to localized arterial constriction and subsequent dilatation, with passive effects on the adjoining veins and capillaries both of which become more visible—flow oscillating and then coming to a complete stop, the capillaries leaking and the brain swelling as the inflammation evolves. Examined by histology, the brain shows extravasation of leucocytes and monocytes into the pia and superficial cortical layers, but not penetrating neighbouring brain parenchyma.

The results using adrenaline clarify a previously discordant literature in which constriction and dilatation are variously reported—Dr Florey finds neither—and they correct the erroneous interpretation that adrenaline-induced apnoea results from constriction of vessels supplying the brainstem respiratory centre. Only the dilatatory effect of amyl nitrite is consistently reported in the literature. If vasomotor nerves exist along the walls of cortical arteries, their stimulation does not alter the calibre of these vessels. They are apparently uninfluenced by major events such as asphyxia and exposure to convulsants; and the effects of inflammation are strictly localized. It seems that the cerebral vessels are not subject to the controls that act upon the systemic vasculature elsewhere: ‘the evidence given is, therefore, emphatically against the recognition of any effective intracranial vasomotor control, in spite of the fact that the vessels are capable, with appropriate methods of stimulation, of entering into strong contraction’. Of the stimuli that are shown to produce a response in cortical blood vessels, only cold might have a practical application in arresting cerebral haemorrhage. Working with Dr Albert Leyton (formerly ASF Grünbaum), Dr Florey’s mentor, Professor Sherrington has shown that a cold compress on the head cools the cortex. Straying further into the field of clinical neurology, Dr Florey speculates that arterial spasm may affect cerebral vessels in response to some abnormal metabolic product: ‘that such a transient spasm does occur is rendered probable by the comparatively rare but well recognized fact that transient paralyses do occur, similar in all respects to those produced by haemorrhage, from which the patient makes a remarkably rapid and complete recovery’.

It is in the context of local vascular changes affecting cortical vessels, the factors on which they depend and the interplay with electrical brain activity that Joshua Chang and colleagues from Los Angeles (USA) now report the effects of cortical spreading depression on cerebral arterial constriction in the mouse cortex (page 996).

Alastair Compston
Cambridge