When I was a medical student in the 1950s we were taught about two main kinds of stroke – cerebral thrombosis, caused by blockage of one of the three main arteries supplying the brain, and cerebral haemorrhage (usually fatal) caused by rupture of an intracerebral artery. There was also a third and less common variety, cerebral embolism, which tended to affect younger patients and was caused by the sudden dislodgement of intracardiac thrombus. Minor strokes, which lasted a few minutes or hours and the patients recovered fully, were recognized and thought to be due to temporary spasm of a small artery within the brain. Textbooks of neuropathology described in detail the severity and distribution of ischaemic changes in neurones and glia but little was said about the cerebral blood vessels.

The carotid arteries (which we were told to palpate to determine the character of the pulse) were regarded as inert conduits taking blood from the heart to the brain. They had a complicated embryological derivation from the branchial arches and were linked at the top by the circle of Willis to ensure that all regions of the brain were perfused at the same pressure. There were no autonomic nerves in cerebral arteries and brain blood supply was passive, depending entirely on perfusion pressure. In practice, all completed strokes were called CVAs – cerebrovascular accidents. Patients were under the care of general physicians and it was not thought that a neurologist would be helpful, or even interested.

HOW HAVE THINGS CHANGED?
The medical student in the 21st century certainly knows more about cerebral vascular physiology, that the resistance arteries auto-regulate to pressure changes, that this is largely independent of innervation, and that regional blood flow also changes in response to metabolic requirements. He, or now more often she, knows that there is no evidence that cerebral arteries go repeatedly into spasm without any local stimulus. She also knows a great deal more about thrombosis, about the factors, cellular and humoral, influencing platelet aggregation and adhesion to the vessel wall. Modern imaging has spared her the impossible task of trying to decide for certain whether a small stroke is ischaemic or haemorrhagic, or even not a stroke at all.

In spite of all this knowledge she must quickly come to realize that there are many different kinds of stroke, that strokes occur and recur at unpredictable times and for no obvious reason, even in patients taking preventative treatment, and that there is still much to be learned about the vascular factors governing the onset both of ischaemic and haemorrhagic stroke.
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I have selected three topics in cerebrovascular
disease where ideas on pathogenesis have altered radically in my working lifetime.

CEREBRAL EMBOLISM
- A NEW LOOK AT AN OLD PROBLEM

The proportion of strokes caused by cerebral embolism is much higher than was previously thought. It was not difficult to diagnose cerebral embolism when a young women with rheumatic heart disease and atrial fibrillation had a sudden hemiplegia, but not easy to predict whether she was going to make a rapid recovery within a few minutes or be left with permanent disability. We were taught that this depended on the size and composition of the embolus and on the site of impaction in the distal arterial tree. Emboli were thought of as stable plugs originating in the left atrium and causing permanent arterial blockage. What we now realize is not only are there many more intracardiac embolic sources than we used to think, but also that the majority of emboli to the brain are newly formed friable bodies released not from the heart but from the walls of major arteries and they are capable of being broken up or dissolved in the circulation, or moving distally to smaller vessels. The old teaching that cerebral embolism (as distinct from cerebral thrombosis) did not cause stereotyped transient ischaemic attacks preceding the major event has also proved to be untrue.

The impetus behind the changing views on the behaviour and importance of emboli was CM Fisher. In a series of papers in the 1950s, and employing the traditional techniques of clinico-pathological correlation, he confirmed earlier observations that the internal carotid artery was a frequent site of atherosclerosis and thrombosis (much more so than the major cerebral arteries). And he showed for the first time that portions of thrombus of similar composition could be found in distal small arteries within the brain. He also noted that in life such patients with carotid disease had frequently experienced repeated transient ischaemic attacks (TIAs) affecting the hemisphere or the retina on the side of the affected artery. He followed this a few years later by ophthalmoscopic observations on a patient with frequent attacks of transient monocular blindness in which white granular bodies were seen traversing the retinal circulation during attacks (see fig. 1). The composition of the white bodies was unknown but they were shown in a later publication from Oxford to be newly formed fibrin-platelet thrombus originating in the carotid artery.

Microembolism has proved to be surprisingly common and a wide variety of particles of varying composition have been described in the retinal and cerebral circulation, including
fragments of atheroma and cholesterol crystals, fat globules, air bubbles and small foreign bodies such as starch grains. The passage of small emboli up the internal carotid artery can now be detected and monitored by ultrasonography. The concept of artery-to-artery embolism gives a rational explanation for repeated TIAs affecting the same territory. In practice, the most frequent source is atherosclerosis at the origin of the internal carotid artery, and should be suspected when repeated brief attacks of hemiparesis or monocular blindness affect (at different times) the retina and hemisphere on the same side. There may be clinical signs of carotid stenosis, with a bruit in the neck, and the attacks often stop when the carotid artery becomes completely blocked, or is ligated. The

Figure 1  Diagrams of observations in a patient with an attack of transient monocular blindness in the left eye (except the upper temporal quadrant); the attack had started at 8.55 am, 20 min before the beginning of the observations. The column of blood in the retinal arteries was in some places interrupted by white segments, initially at the stems of the superior and inferior retinal arteries (A): also the column of blood in at least six venous branches of the superior half of the retina was broken into transverse bands. The white segments in the retinal arteries slowly passed through the superior temporal artery (B–H). At (C), the vision in the upper half of the visual field had returned. At (D), a fine trickle of erythrocytes moved slowly along one side of white segment AB to the superior nasal artery, and at (E), vision had also returned in the inferior temporal quadrant. After (H), when the column of blood had been completely restored, vision returned to normal (with permission from CM Fisher 1959). Figure 2.7 From Warlow CP et al. (2000) Stroke, Blackwell Science, Oxford.
attacks may cease spontaneously and there may be a dramatic response to antiplatelet drugs.

THE CAUSES OF TRANSIENT CEREBRAL ISCHAEMIA

Occlusion of the carotid artery in the neck or near its termination within the skull had been known since the 17th century and was noted by Willis himself in his description of the anastamotic arterial circle that bears his name. He pointed out that the anterior and posterior communicating vessels afforded some protection against occlusion of any one of the four main arteries and this explained why surgical ligation of the cervical carotid artery (sometimes performed in those days to arrest haemorrhage or in the course of operations on cervical lymph-nodes) was not usually followed by signs of brain damage.

The first successful reconstruction of the proximal internal carotid for arterial stenosis was performed in 1952 and shortly afterwards the operation of carotid endarterectomy was introduced. In the ensuing enthusiasm for a new surgical treatment for stroke – which has now been shown to be effective in reducing the incidence of future stroke – an important paradox was sometimes forgotten. Why do some patients tolerate complete occlusion without symptoms while others with a stenosis suffer a major stroke?

The term cerebrovascular insufficiency as an explanation for transient cerebral ischaemia (previously ascribed to vasospasm) was introduced by Denny-Brown following a series of experimental studies with JS Meyer on the cerebral circulation of the monkey. By measuring oxygen availability with a polarograph of the surface of the exposed cortex, they showed the extent of collateral blood flow following occlusion of the internal carotid or the middle cerebral artery and were able to demonstrate the critical importance of systemic blood-pressure in maintaining viability of the cerebral region.
at risk. Denny-Brown proposed that TIs in patients were caused not by vasospasm but by ‘haemodynamic crises’, usually periods of systemic hypotension of postural or cardiac origin, causing failure in collateral blood flow to part of the brain in the territory of a damaged artery.

This proposal was one that could be put to the test and attempts were made by a number of groups to induce ischaemic attacks in susceptible patients by deliberately lowering blood pressure, using a tilt-table and ganglion-blocking drugs. Although Denny-Brown himself claimed to be able to induce regional EEG changes by titling, others were unable to confirm this. Patients might lose consciousness if their blood pressure was severely reduced, but only rarely did symptoms of focal ischaemia occur.

It is now accepted that haemodynamic TIs, although important to recognize, make up only a small proportion of TIs and are largely confined to patients with severe proximal occlusions in multiple extracranial arteries. The underlying pathology is usually atheromatous but may be arteritic, such as in Takayasu’s disease or granulomatous arteritis. The symptomatology is often distinctive, with a slower onset related to posture or exercise and focal limb jerking as a prominent feature. Visual symptoms are common, often with visual blurring on exposure to bright light. Permanent cerebral damage may result if the period of ischaemia is prolonged and the resulting infarct may be confined to the territories of the major cerebral arteries.

**CAROTID OCCLUSION – DELAYED TIs AND STROKE, MALE AGED 62**

- 1918: Penetrating missile injury left side of neck, ligation of artery (common and internal carotid)
- 1960: Repeated right-sided TIs usually on standing or beginning to walk. Duration, a few minutes. Mild right completed stroke. Left carotid arteriogram: complete occlusion common carotid artery.

In this case, surgical occlusion of the common carotid artery at the age of 20 was symptomless for over 40 years when focal repeated TIs began in the territory of the ligated artery. Sometimes related to standing, intermittent failure of the collateral circulation to compensate after such a prolonged period strongly suggests that systemic factors such as intermittent hypotension were responsible for the attacks.
LACUNAR STROKES
Small, deep, multiple infarcts (état lacunaire) were well recognized by French neuropathologists in the 19th century and were thought to cause dementia with bilateral pyramidal and extrapyramidal signs. The lesions are mainly found in the distribution of the paramedian penetrating arteries, arising from the basilar artery and from the proximal segments of the three main cerebral arteries. The study of single lacunar infarcts was a further contribution from Fisher who, as well as correlating the physical signs with the site of the lesion, showed that the causative arterial disease of each lacune was blockage of a single penetrating artery. The pathological changes in the artery wall were of an unusual kind, differing from atherosclerosis or thrombosis, but resembling the appearances found in chronic hypertension. Fisher called this lipohyalinosis. Following on the disruption of the wall by this process, there was in some cases thrombosis of the small affected artery. Lacunar strokes particularly affect elderly and hypertensive subjects. The same arterial pathology is probably responsible for rupture of small intracerebral arteries which gives rise to cerebral haemorrhage.

The recognition of lacunar strokes has been a major advance in the understanding of cerebrovascular disease in the past two decades and in an elderly population this type of infarction has become the most common variety of stroke. Because it is not primarily a thrombotic disorder but an arterial reaction to chronic hypertension, the antithrombotic and fibrinolytic drugs used to treat or prevent other varieties of stroke may not be appropriate for lacunar infarction. It is tempting to suggest that long-term antihypertensive treatment would be more effective but although this has been shown to reduce the overall risk of secondary stroke, a trial confined to hypertensive patients with lacunar infarcts has never been carried out.

IN CONCLUSION
To summarize, conceptual changes have occurred in at least three important varieties of cerebral arterial disease. Firstly, the concept of cerebral embolism has become much wider to include not only large emboli derived from the heart but smaller emboli arising from the walls of the aorta or carotid arteries. Such emboli can cause repetitive TIAs as well as completed strokes. Secondly, there is now a clearer understanding of the way in which carotid stenosis and occlusion affects the cerebral circulation and that the benefits of carotid endarterectomy are in many cases the elimination of a source of embolism rather than the relief of an obstruction to flow. Thirdly, a new pathological process affecting the intracerebral arteries has been recognized - lipohyalinosis - with strong links to age and high blood pressure, and which causes lacunar infarction and probably primary intracerebral haemorrhage as well.

FURTHER READING