Hypertensive Cerebral Small Vessel Disease and Stroke

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Lacunar infarcts and "hypertensive" primary intracerebral hemorrhages, collectively often referred to as hypertensive small vessel strokes, constitute about one third of all strokes. However, despite their public health importance, their etiopathogenesis remains ill-understood. Like all strokes, they are a heterogeneous entity, but the autopsy pathology evidence suggests that the majority are caused by a limited number of cerebral small vessel lesions. Small vessel atherosclerosis is causally implicated in a proportion of lacunar infarcts, although modern concepts of atherosclerotic plaque biology and natural history have yet to be applied to small cerebral vessels. A lesion characterized in its acute form by fibrinoid necrosis appears to be important in causing both lacunar infarcts and primary intracerebral bleeds. Advances in molecular genetics may prove instrumental in understanding the cause of this lesion and therefore in designing its targeted prevention.

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Introduction–Terminology

Hypertension mediates brain damage in a variety of ways—it is associated with an increase in the extent and severity of large vessel atheroma (29, 39, 81), with "malignant" hypertensive encephalopathy (28) and eclampsia (87), with expansion and rupture of berry aneurysms (16, 113), and with diffuse white matter changes or leukoaraiosis (99). By convention, however, the term "hypertensive small vessel stroke" is commonly used to refer to 2 common, pathologically distinct entities, namely lacunar infarction and so-called "hypertensive" primary (or non-traumatic) intracerebral hemorrhage (PICH). This review will focus on these stroke subtypes, their importance, pathological features and pathogenesis.

At the outset, it will be clear that terminological confusion in this field is rife and has been a real obstacle to progress in understanding—physicians, radiologists, and pathologists often use the same term to describe subtly or completely different lesions. This confusion is best avoided by clear reference to specific, clearly-defined brain and vessel pathologies.

Epidemiology

Stroke is a major cause of death and disability in both the developed and developing world; about 25% of men and 20% of women can expect to suffer a stroke if they live to 85 years (17). It is the third most common cause of death in Europe and the United States, after coronary heart disease and cancer, and caring for its victims in the United Kingdom consumes some 6% of the total National Health Service and Social Services budget (110). As lacunar strokes comprise approximately 25% of first-in-a-lifetime ischemic strokes (7), and PICH some 10% of all strokes, at least in the West (6), it is clear that small vessel stroke is of considerable global and socio-economic importance.

Next to increasing age, raised blood pressure is the most prevalent, important and treatable risk factor for stroke in general, both ischemic and hemorrhagic (120, 129). The risk of stroke doubles for every 7.5 mmHg increase in usual diastolic pressure, and antihypertensives have been shown to reduce stroke risk by some 38% (84). Further, there is no evidence of a diastolic blood pressure threshold below which risk becomes stable. The specific risk factor profiles of lacunar and hemorrhagic strokes are still being developed, but are broadly similar to the risk factor profile of large vessel ischemic stroke, differing mainly in terms of emphasis of individual factors. Whilst hypertension has traditionally been regarded as the cardinal risk factor for both lacunar stroke and PICH, this association is likely to have been overemphasized in the past. Thus, evidence of prior hypertension has been found in only 45 to 59% of recent series of patients with PICH (3, 18, 51). The term "hypertensive" small vessel stroke is therefore a potentially misleading simplification—not all hypertensives suffer these stroke subtypes, and they are also prone to develop other types of stroke. A significant proportion of patients with lacunes and PICHs appear to always have been normotensive. Hypertension, it would seem, is neither necessary nor sufficient to explain every case of small vessel stroke. On the other hand, "normotensive" PICH patients *may* have had mild undetected degrees of hypertension—for any disorder "high risk" patients

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constitute only a small fraction of sufferers, most being at only moderate risk (106).

Nonetheless, the overall body of evidence *does* perhaps suggest that hypertension is significantly more prevalent among patients with lacunar strokes than with other forms of ischemic stroke (14), and hypertension remains the most important risk factor for, and shows a dose–response relationship with, PICH (55, 78, 97). Perhaps more importantly, and what justifies small vessel strokes being viewed as a clinicopathologic entity, is the assumption that they are usually caused by the same, or a limited number of similar, small vessel lesions.

Autopsy Pathology

Human autopsy-based pathology studies, imperfect though they are, remain the cornerstone of our current understanding and classification of small vessel stroke. As one stroke physician wrote recently in this context, "Attempts to infer the underlying disease by the analysis of clinical risk factors… is at best an approximation of what would be learned by microscopy" (92).

Brain lesions. The controversial term "lacune" refers to a small cavity located deep within the brain. It was originally described at the beginning of the 20th century by Durand Fardell and Marie (102), and their compatriots Poirier and Derouesne have more recently provided a useful neuropathological classification of lacunes (101). Numerically and clinically, the most significant is the Type I lacune—an irregular cavity 1 to 20 mm in diameter, reported in 6 to 11% of autopsy brains (40, 123), and most commonly found in the putamen, caudate, thalamus, pons, internal capsule, and hemispheric white matter (Figure 1A). The consensus view that these cavities represent old, small infarcts is based on their histologic similarity to developing and established large-vessel and cortical infarcts, and the demonstration in some instances of an obstructed feeding artery. A variant (Type 1b) lacune mirrors this classic lesion in terms of its size, shape and distribution, but is characterized by loss only of selectively vulnerable cellular elements, falling short of pan-necrotic cavitation (Figure 1B) (72). Although it has been suggested that such rarefied brain lesions represent the local effects of oedema rather than ischemia (82), it is perhaps more useful to regard them as "incomplete" small infarcts, caused by transient or less severe ischemia than their fully cavitated counterparts (69).

The type II lacunar cavity is characterized by numerous haemosiderin-laden macrophages (Figure 1C), and is usually assumed to represent an old, small hemorrhage (101), although at least some are as likely to represent old, hemorrhagic microinfarcts. Microbleeds are unlikely to be more than a rare cause of a lacunar syndrome; more clinically important appears to be the fact

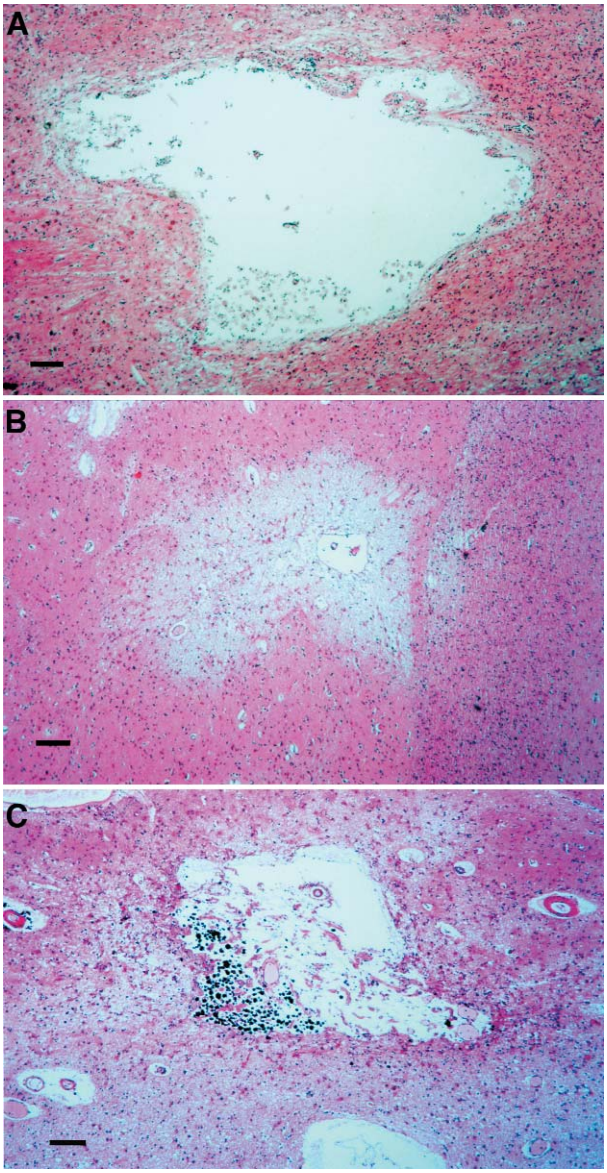

Figure 1. *Histological classification of lacunes.* **a.** Type 1a lacune—a small old, deep infarct consisting of a small cavity containing occasional small vessels and scattered macrophages. **b.** Type 1b lacune—an incomplete lacunar infarct, comprising an area of perivascular rarefaction with loss of all neurones and some oligodendroglia, with patchy astrogliosis. **c.** Type II lacune—a presumed small deep hemorrhage, in which the cavity contains numerous hemosiderin-laden macrophages. Note the area of surrounding incomplete infarction.
(All H&E. Bar = 200 μm)

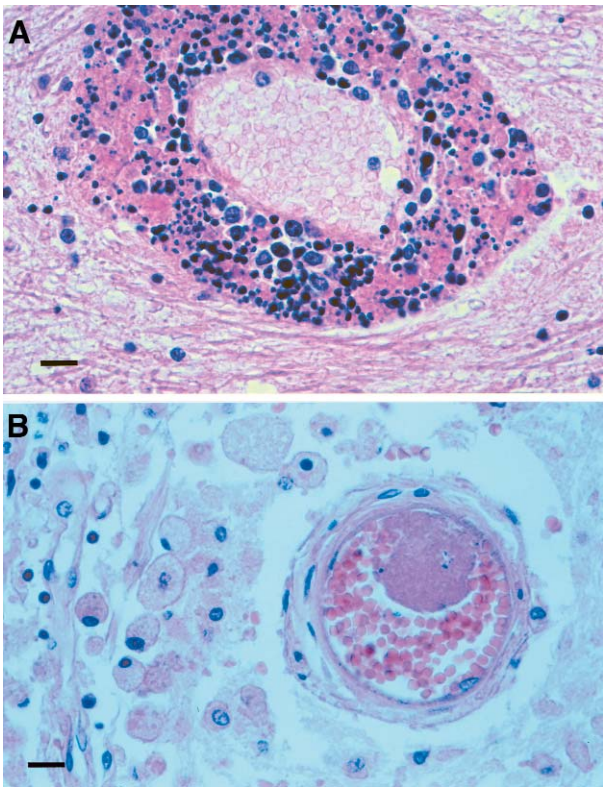

Figure 2. *Rare causes of small vessel stroke.* **A.** Necrotizing small vessel vasculitis—from a 9 year old girl with systemic lupus erythematosus. **B.** Platelet-rich embolus in a small cerebral vessel supplying a small area of acute infarction. (Both H&E. Bar = 20 μm)

that MRI-detected "microbleeds" may be a significant risk factor for subsequent PICH (105, 119). Similarly, dilated perivascular spaces (Type III lacunes) are rarely clinically significant. They can, however, be confused radiologically with small infarcts and on rare occasion they may evolve into "expanding" space-occupying lesions (10, 34, 100). Their pathogenesis is disputed, having at various times been ascribed to arterial permeability or interstitial fluid drainage disorders (34, 103), to perivascular inflammatory (85) or "lytic" (95) factors and to the mechanical effects of pulsating arterioles (63).

The pathological features of hypertensive PICH, in contrast to lacunes, are stereotyped and well-documented (2, 43, 54, 64, 112). The acute lesion is a variably-sized hematoma which compresses and distorts surrounding brain, and the healing and resolved lesion is a blood-stained, compressed cavity with a gliotic, neovascularised and ultimately fibrotic peripheral zone (117). In terms of understanding the cause of hypertensive PICHs, the key pathological feature is their striking co-localisation with lacunar infarcts.

Vessel lesions. A variety of small vessel pathologies are routinely encountered in hypertensive brains, only some of which appear to be causally related to stroke, at least directly (70). It was Miller Fisher, by serial section reconstructions of the blood supply to a total of 68 lacunar infarcts in 18 human autopsy brains, who made the fundamental observation that most lacunar infarcts lie distal to, and are presumably therefore caused by, occlusive lesions of small perforating arteries (40, 41, 44, 45, 46, 48, 49). He observed two main culprit vessel lesions, namely intracranial atherosclerosis and so-called "lipohyalinosis." These were responsible for the large majority of infarcts, whilst in a small minority he found no occlusive lesion and assumed embolism. Pathologically his data remain unchallenged, and subsequent clinical and epidemiological data have been largely supportive of his so-called "lacunar hypothesis." Thus, lacunar stroke patients have a relatively low frequency of cardiac and large vessel atheromatous embolic causes compared to those with cortical infarcts (80), and appear also to have a low risk of early recurrence. Although not universally accepted (91), the lacunar hypothesis has achieved widespread support, and importantly, has proved useful in patient management.

The heterogeneity of small vessel stroke. Before describing the vessel pathology underlying small vessel stroke, it should be remembered that there are a large number of potential causes of small vessel occlusion and rupture, most of which have been postulated or proven at some time as a rare cause of lacunar infarcts or PICHs (Figure 2). Thus, infective or immune vasculitis, cardiac and large vessel emboli, arterial dissection, thrombosis in, or compression by, micro- or saccular aneurysms and in situ thrombosis due to a variety of hypercoaguable states have all been implicated as causes of lacunar infarction (104). This heterogeneity of lacunar stroke applies not only to the underlying vessel lesions but also to brain lesions—there is, for example, both pathological (75) and clinical (15, 33, 57, 128) evidence that small infarcts in the centrum ovale, probably lying in arterial borderzone territories, are more commonly the consequence of cardiac and carotid disease than the classical deep-seated grey matter lesions. Similarly, the list of possible and documented causes of spontaneous ICH is long—any pathology which weakens the vessel wall, particularly in the face of raised blood pressure or cerebral blood flow, may lead to vessel rupture and brain hemorrhage. Nonetheless, despite

the notorious heterogeneity of stroke in general, the bulk of small vessel stroke appears to be a consequence of either atherosclerosis or a destructive lesion characterized by fibrinoid necrosis.

Small vessel atherosclerosis. Hypertension appears to "drive" atherosclerosis into smaller, more distal reaches of the cerebrovascular bed (Figure 3A). Fisher identified lacunes, particularly larger symptomatic lesions, which were due to atherosclerotic plaques in 200 to 800 μm diameter vessels. The plaques were either in the proximal perforating arteries ("microatheroma"), at their origin ("junctional atheroma"), or in the parent artery on the circle of Willis ("mural atheroma") (47), perhaps particularly in the basilar artery and its pontine perforating branches (44, 48). The mechanism of infarction he thought was related to either occlusive thrombosis (perhaps exacerbated by the hypercoaguable state associated with essential hypertension) (79), or to a non-occlusive post-stenotic hypoperfusion (23, 104). However, this work predated modern concepts of atherosclerotic plaque "instability" derived from autopsy study of coronary artery disease (32), according to which end-organ damage usually follows ulceration or erosion of vulnerable lipid-rich, fragile and inflamed plaques. This concept is likely to be relevant to large vessel stroke (1, 74), but the issue of plaque instability in small cerebral vessels has not been studied.

Morphologically, proximal perforating artery atheroma resembles common larger vessel disease, but Fisher and others (25, 41, 46) also saw an unusual lesion in smaller perforating vessels which was characterised by stenotic or occlusive (subintimal) foam cell accumulation (Figure 3B). Such lesions are still encountered, albeit rarely, in relation to lacunar infarcts but their significance is uncertain. It is possible that they may represent an early atherosclerotic lesion akin to the "fatty streak" or "intimal xanthoma" (125), a lesion which in larger calibre vessels is innocuous, but in small caliber vessels becomes severely stenosing or frankly occlusive. Alternatively they may conceivably represent a response to, rather than a cause of, brain injury. Clearly, more autopsy-based pathological study of small vessel atherosclerosis is required to assess its significance as a cause of lacunar infarction in the current era of treated hypertension.

Lipohyalinosis (fibrinoid necrosis). The second small vessel lesion of pathologically-proven relevance to lacune formation is a destructive lesion of smaller (40-300 μm diameter) perforating vessels than those involved by atherosclerosis. It causes corresponding

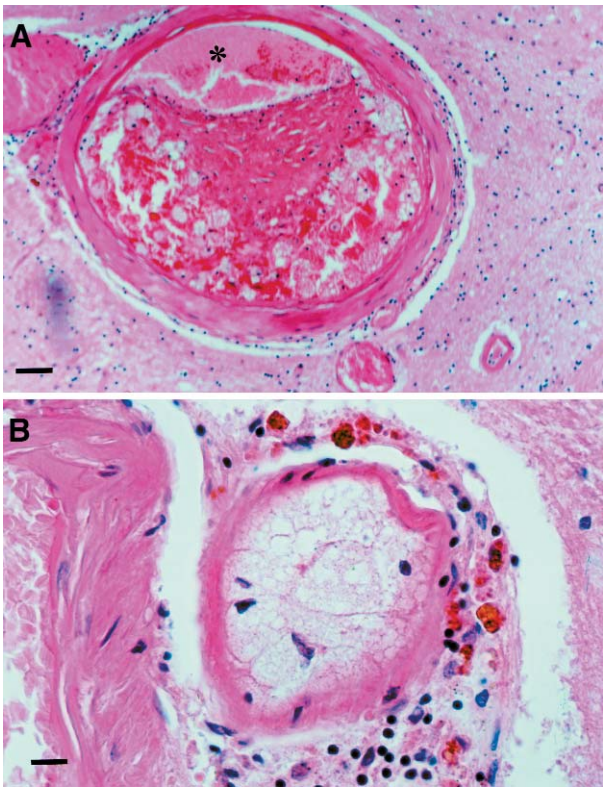

Figure 3. *Small vessel atherosclerosis.* **A.** Eccentric atherosclerotic plaque in a perforating vessel in the putamen, causing significant narrowing of the lumen (asterisk). **B.** Occlusion due to foam cell accumulation in a small perforating vessel leading into an acute lacunar infarct in the putamen.
(Both H&E. Bar **A** = 80 μm, **B** = 20 μm)

smaller (3-7 mm diameter), less commonly symptomatic, infarcts than atherosclerosis, particularly in the striatocapsule and thalamus (41, 45). This "segmental arterial disorganization" or "lipohyalinosis" was responsible for 46 of the 68 lacunes studied by Fisher. Due to the low mortality rate of lacunar infarction (7), most lipohyalinotic lesions seen at autopsy are old, healed lesions, characterized by a loss of normal wall architecture, collagenous sclerosis and mural foam cells, usually with evidence of aneurysmal dilatation and red cell extravasation (Figure 4B). These old healed lesions may cause stroke either by thrombosis (Figure 4C) or via a post-stenosis low-flow mechanism. This latter is exacerbated by the hypertensive brain's vulnerability to hypotension associated with autoregulatory resetting. Despite the presence of mural foam cells, there is little reason to suppose this lesion is a variant of atherosclerosis, and in the rare examples visualized in autopsy brains, the cardinal feature of the acute lesion appears to be non-inflammatory fibrinoid vessel wall necrosis

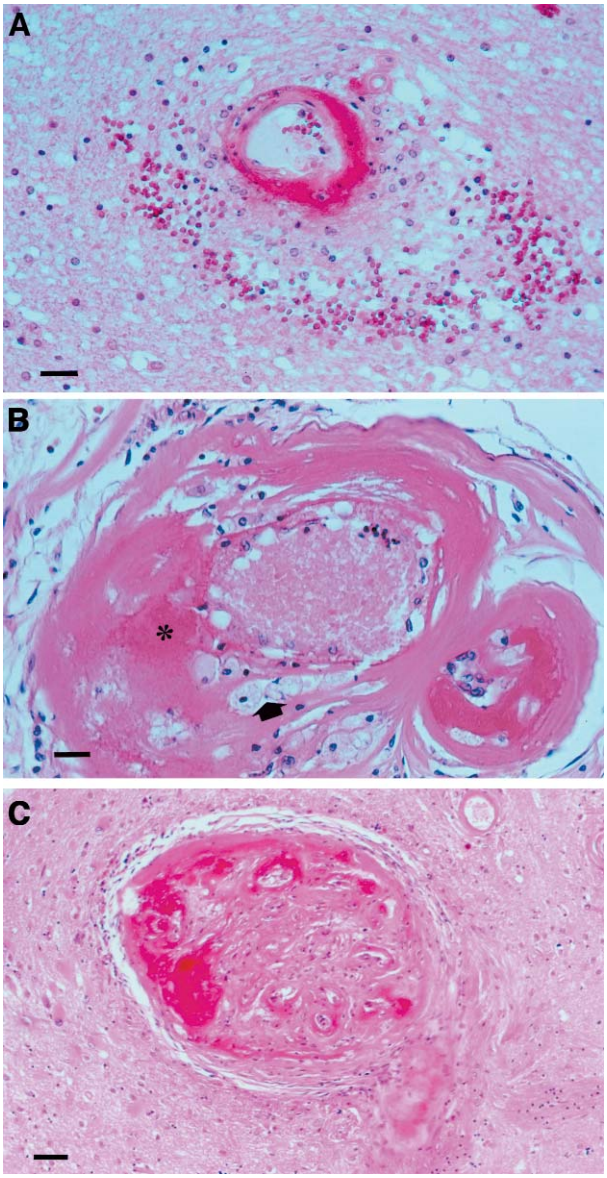

Figure 4. *Proposed stages in the development of lipohyalinosis (complex small vessel disease).* **A.** Acute –focal segmental, necrotising vessel wall changes (fibrinoid necrosis), with red cell extravasation. **B.** Healing lesion within a Type Ia lacune—an asymmetrically thickened, focally dilated and disorganised vessel segment with focal fibrosis, fibrinoid degeneration (asterisk) and mural foam cell infiltration (arrow). This is the lesion which Fisher called "lipohyalinosis." **C.** Healed—a variant complex sclerosed lesion with focal dilatation, sclerosis and neovascularisation, probably representing an organized, thrombosed lesion.
(All H&E. Bar **A, B** = 40 μm, **C** = 80 μm)

(Figure 4A). Originally viewed as a complication of severe hypertension, lipohyalinosis is still seen in relation to lacunar infarcts in the modern era of controlled hypertension, albeit perhaps less frequently (47, 71, 88). However, due to the paucity of modern autopsy data, the relative importance of atherosclerosis and lipohyalinosis in causing lacunar infarcts is unclear.

The observations that hypertensive PICHs and lacunar infarcts show striking co-localisation, are often found in the same brains, and share similar risk factor profiles, suggest that they may share a common or related causal vessel lesion (11, 30, 31, 38, 43, 88, 97, 119). Although post mortem study of PICH is hampered by the fact that vessel wall rupture destroys, or at least modifies, the causal vessel lesion, the bulk of pathological evidence suggests that lipohyalinosis, usually in its acute form characterized by fibrinoid necrosis, is the causal vessel lesion most commonly associated with hypertensive PICH (38, 43, 88, 107, 108, 118). Such fibrinoid vessel lesions are only reliably detected using special stains (38, 107, 108), may be circumferential or focal and segmental (38, 107), are particularly prevalent perhaps in the basal ganglia of moderate hypertensives (38, 88) and in the pons in severe hypertensives, and are seen not only at vessel rupture sites, but also adjacent to and distant from hematomas (38, 43, 107).

Fibrinoid necrosis, and its healed form of lipohyalinosis, are often associated with aneurysmal vessel wall dilatation (38, 42, 107, 109, 112, 118), so it is in retrospect unsurprising that so-called Charcot-Bouchard microaneurysms were found to co-localise with hypertensive PICHs (30, 31, 60, 109). However, the assumption that they were the source of bleeding is now considered less likely, particularly as some at least were likely to have been illusions of the relatively crude original injection studies, mimicked by complex arteriolar coils and perivascular clots (26). Moreover, as Caplan has pointed out, the Charcot-Bouchard aneurysm has never been unambiguously identified as the definite cause of even a single hematoma (24). Microaneurysms *do* occur in the brain and *do* tend to co-localise with sites of small vessel stroke, but, paradoxically perhaps, they are the legacy of those healed fibrinoid lesions which have *not* ruptured, rather than themselves being the cause of rupture.

How the same or a similar vessel lesion (lipohyalinosis) may cause both infarction and hemorrhage is unclear; perhaps the acute fibrinoid lesion is prone to rupture and therefore to PICH , but if it heals is less likely to rupture and becomes more prone to thrombosis and low-flow ischemic stroke. There is clearly potential for a complex interplay of acute haemodynamic and acquired structural vessel wall changes in the pathogenesis of these stroke subtypes.

Arteriolosclerosis. Since its introduction, the term "lipohyalinosis" has been consistently misused to describe a variety of unrelated small vessel pathologies, in particular the concentric hyaline wall thickening of small arteries and arterioles (hyaline arteriolosclerosis) that is perhaps the most common of the cerebral vasculopathies (Figure 5A). To some degree this lesion is seen in most aged brains. It begins in the fourth decade (56), increases in severity with increasing age thereafter (4, 5, 56), and is exacerbated principally by hypertension and diabetes. Its severity, often defined in terms of the "sclerotic index" or wall thickness-to-lumen ration (56, 71), correlates reasonably well with systemic blood pressure (56). Pathologically, tunica media smooth muscle cells and the internal elastic lamina degenerate and are replaced by fibroblasts, and by deposits of collagens I, III, V, VI and the basement membrane proteins laminin and collagen IV (131). In hypertensives, this may be preceded by an onion-skin concentric smooth muscle cell proliferation (66). Ultimately, the vessel becomes an elongated, tortuous and paucicellular hyaline tube, with a variable degree of stenosis, which is compounded by a "remodelled" reduction in external wall diameter (9). However, it is rarely completely occlusive. The evolution of arteriolosclerosis has been followed in hypertensive rat models (52, 53), in which a key early feature appears to be increased vessel wall permeability, associated with plasma protein extravasation and organisation (66). Certain systemic conditions in humans which are associated with cerebral vessel leak may be related to the development of arteriolosclerosis, suggesting that enhanced permeability may also be of pathogenetic significance in humans (71).

Arteriolosclerosis is a consistent feature in brains with diffuse white matter disease or leukoaraiosis (19, 37, 56, 77, 99, 131), an association which is often assumed to be causal, ischemic in nature and due to luminal narrowing. However, it is also possible that this co-localization may merely reflect a common insult, such as abnormal vessel wall permeability. Furthermore, while the severity of arteriolosclerosis *does* appear to correlate with the presence and number of lacunar infarcts (35), there is no evidence that this association is directly causal. Indeed, the hyaline thickened vessel is often considered to be a structural modification designed to protect against rupture or damage in the face of high pressure. Overall, arteriolosclerosis itself seems unlikely to be a cause of either ischemic or hemorrhagic small vessel stroke. It may indirectly predispose to such strokes in that the hyaline resistance vessel, devoid of smooth muscle, is likely to be an ineffective autoregulatory organ and may render the distal, unprotected, vessel bed vulnerable to the injurious effects of high pressure, as well as to low pressure and low-flow states.

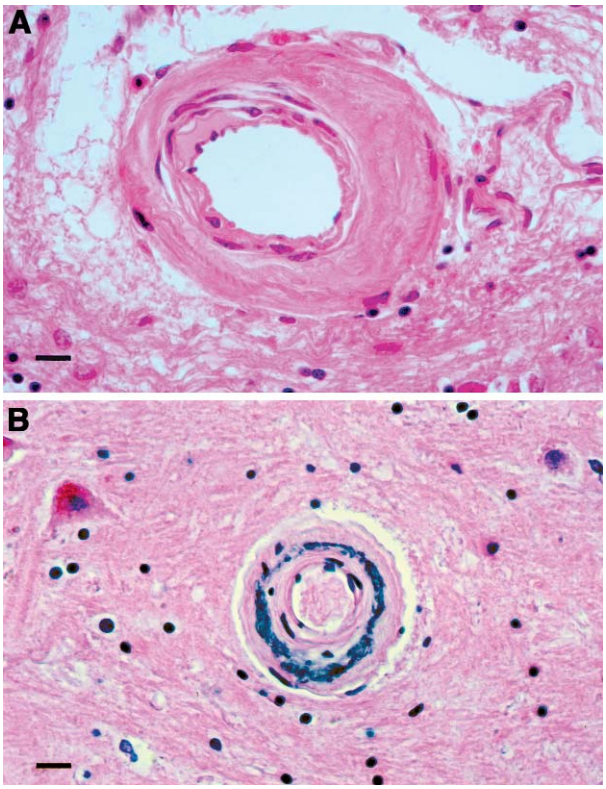

Figure 5. *Arteriolosclerosis ("simple small vessel disease").* **A.** Arteriolosclerosis, characterized by approximately concentric hyaline wall thickening, loss of smooth muscle cells and mild lumen narrowing. **B.** Concentric tunica media mineralisation—a common age-related finding, particularly in the globus pallidus. (Both H&E. Bar = 20 μm)

Molecular Pathophysiology of Fibrinoid Necrosis

Although central to our current understanding, human autopsy studies are inherently limited in scope. The low case fatality rate of lacunar stroke (7), the destructive nature of PICH, the heterogeneity of both (13, 58), and the technical difficulty of tracing a lesion's vascular supply are all compounded by the current decline in autopsy rates. The necessarily static nature of autopsy observations means we can often only speculate upon the causal dynamics of stroke. Most importantly perhaps, descriptive pathology studies of the lesions underlying small vessel stroke shed no light on the *underlying* mechanisms of vessel wall damage, and have not translated into rational prevention or treatment. However, the molecular genetic pathogenesis of

the key small vessel lesion, fibrinoid necrosis, is perhaps more amenable to the new tools of the experimental pathologist. How such an approach could in future complement traditional pathological research is now discussed.

Fibrinoid vessel wall necrosis is a lesion familiar to pathologists in a variety of contexts—immune and infective vasculitis, irradiation damage, certain tumours, adjacent to intracerebral bleeds and in the rostral midline hemorrhages of the herniating brainstem. It is, importantly in this context, a pathologic hallmark of acute hypertensive brain damage, and may be seen in the brain as well as in other organs, in "malignant" or "accelerated" hypertension, both naturally occurring and experimentally induced (61). Its occurrence in the brain, and not apparently in other vascular beds, in less severe or "benign" hypertension (38, 107), has led to the idea that brain vessels are in some way uniquely susceptible to its development (108). In a novel inbred rat model of inducible hypertension, in which the degree and duration of hypertension are tightly regulated in a dose-dependent and reversible manner, there is indeed differential susceptibility of organs to the hypertensive stimulus, mediated perhaps by the local renin-angiotensin system (RAS) (67). However, in this model the brain appears to be, paradoxically perhaps, relatively resistant to vascular injury compared to heart, mesentery, and kidney. Clearly, much remains to be learned of the hierarchy of susceptibility of different vascular beds to hypertension, but these new models of hypertension offer novel experimental insights.

Whatever the basis of its selective vulnerability (or resistance), two hypotheses have been advanced to explain the occurrence of acute hypertensive vascular injury in the brain. Each invokes abnormal mechanical forces on the arterial wall, and each may have direct relevance to small vessel stroke, both ischemic and hemorrhagic. The first, and prevailing, hypothesis links high arterial pressure directly to blood-brain barrier breakdown, edema and plasma protein (including fibrin) deposition in small artery walls, the latter accompanied by smooth muscle cell destruction (53). Thus, "forced dilatation" of resistance vessels follows breakthrough of the autoregulatory mechanism that normally protects small distal vessels from high blood pressure and blood flow (76, 83), and it has been shown experimentally that high arterial blood pressure per se may induce fibrinoid necrosis (62). Such a mechanism is most obviously of potential relevance to hypertensive PICH, and Caplan has reviewed a variety of unusual instances of human PICH in which the common feature was acute elevation of blood pressure or cerebral blood flow (22, 24). The scenarios included emotional stress, extreme cold weather, severe dental pain, sympathomimetic drug use or abuse, and trigeminal stimulation (22, 24). Subsequently, stress-related PICH has been linked with autopsy-proven cerebral vessel fibrinoid necrosis (73). Clearly, such a mechanism is of potential relevance to hypertensive PICH, and as emphasised by Caplan, may affect normotensive, as well as chronically hypertensive, individuals. The characteristic distribution of hypertensive PICH in the brain may reflect, at least in part, those regions (brain stem and probably basal ganglia) in which arteriolar pressures have been shown, in rats at least, to be highest (8).

The second, or "vasospasm," hypothesis concerning acute hypertensive brain injury proposes an excessive autoregulatory vasoconstriction leading to focal ischemia. Such a mechanism may be invoked to link hypertension, fibrinoid necrosis, and small vessel stroke, perhaps particularly lacunar infarction. Thus, as the severity of hypertension in the community lessens, there is current interest not so much in the direct effects of high pressure but in the possible role of underlying hypertension-associated endothelial dysfunction and neurohumoural mechanisms in mediating vessel and brain damage. To this end, various lines of evidence implicate disordered small vessel tone in lacunar infarction in particular. For example, directly visualised pial arterioles in experimental hypertension undergo fibrinoid necrosis only in very localised segments which show alternating vasoconstriction and dilatation (21, 83). It has long been known that necrotising, fibrinoid arterial changes can be produced in rats by repeated injection of vasoconstrictors, such as vasopressin (20). The new generation of hypertensive laboratory animals have the potential to further our insight (115); for example normotensive rats transgenic for the prorenin gene develop classical hypertensive end-organ damage, including fibrinoid necrosis (124). The significance of this observation is that fibrinoid necrosis, the hallmark of acute hypertensive injury, can be dissociated from raised blood pressure and its molecular pathogenesis dissected. In this model damage is thought to be mediated by local generation of angiotensin II, which is both a potent vasoconstrictor and also influences cell growth and matrix deposition, which are important in vascular wall remodeling (59). Further evidence of a role for local RAS components is that the angiotensin I converting enzyme (ACE) gene is associated with malignant vascular injury in a transgenic rat model of malignant hypertension (68), and this injury is prevented by pharmacolog-

ical ACE inhibition (94). The role of other vasoconstrictors in hypertensive vessel injury clearly needs to be investigated. Meanwhile, disordered vasodilatation may also be involved, and preliminary data linking abnormal nitric oxide vasodilatory tone with vessel wall injury are emerging. For example, hypoperfused "penumbral" brain tissue around experimental "ICHs" develop striking fibrinoid necrosis small vessel lesions in diabetic, but not in non-diabetic, rats (Figure 6). Pharmacological manipulation of this model suggests that the peri-lesional ischemia and fibrinoid vessel lesions are due to vasospasm, which is itself linked to a lack of cerebral nitric oxide-mediated vasodilatory reserve in diabetes (50). Diabetes is a well recognised risk factor for stroke, including lacunar infarction and also, contrary to a widely held belief, PICH (65). A clinical observation which supports these experimentally observed links between fibrinoid necrosis and abnormal vessel tone, is that cerebrovascular reactivity (a measure of the dilatory capacity of brain arterioles) is impaired in hypertensive and diabetic individuals, and may itself be an independent risk factor for lacunar infarction (93).

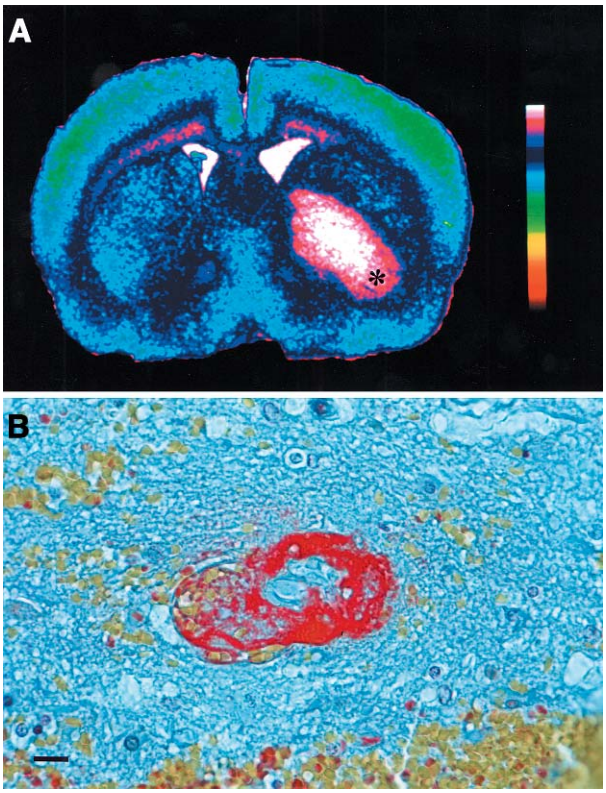

Figure 6. *Experimental fibrinoid necrosis.* **A.** Color-coded blood flow (14C iodoantipyrine) autoradiogram from a coronal section of rat brain into the caudate nucleus of which arterial blood (50 μl) had been stereotactically injected 24 hours previously. The dense caudate ischemia (white color) corresponding to the hematoma, is surrounded by a zone of significant oligemia (purple and dark blue—asterisk) (~35 ml × 100 g^{-1} × min^{-1}). The color scale on the right represents optical densities that can be converted to blood flow with knowledge of the isotope concentration at the time of the experiment. **B.** The oligemic "penumbral zone" in diabetic animals contained small vessel fibrinoid necrosis lesions. In this human autopsy example of peri-PICH fibrinoid necrosis Martius Scarlet Blue (MSB) is used to stain fibrin bright red.
(MSB. Bar = 20 μm)

Genetics of Small Vessel Stroke

The links between small vessel pathology, disordered autoregulation, and vessel reactivity may not only reflect acquired structural and functional vessel abnormalities, in particular those caused by aging, hypertension, and diabetes, but also genetic susceptibility. Stroke, like most multifactorial diseases, is likely to reflect a combination of both genetic and environmental risk factors, and genotypic differences may explain why only some at risk individuals suffer strokes, with all the implications for targeted prevention this entails. The considerable variability in terms of end-organ damage between races and individuals with comparable blood pressures strongly suggests that genetic factors to some extent determine target end-organ damage. Transgenic and gene knock-out animals (27) have potential to model specific stroke-associated vessel lesions, complementing our recently improved understanding of the genetic basis of established animal stroke models. Thus, in the stroke-prone spontaneously hypertensive rat (SHRSP), which does suffer cerebral hemorrhages and small infarcts (52, 53, 130) and in which stroke appears to associate and co-segregate with impaired endothelium-dependent vasorelaxation (126), chromosomal loci have been identified which contain blood pressure-independent factors predisposing to stroke (111). Such studies may prove important in the search for biologically plausible candidate genes in human stroke and illustrate the usefulness of working with intermediate phenotypes (such as fibrinoid necrosis) rather than the generality of strokes. Not only will such intermediate phenotypes be necessarily influenced by fewer genes than stroke itself, but they may also shed light on the mechanisms underlying any putative genetic associations (12).

Early genetic studies of human small vessel and other subtypes of stroke have been difficult to interpret for several reasons—small sample sizes, inadequate controls, and a lack of biological data or validity (122). However, it is intriguing that provisional genetic polymorphism data in human small vessel stroke have

implicated specifically some of the genes alluded to above. Thus, a weak but significant association has been shown between the deletion (DD) genotype of the angiotensin-converting enzyme gene with ischemic stroke in general (114) and perhaps with lacunar stroke in particular (86). The insertion/deletion (I/D) ACE gene polymorphism is associated with variance in both plasma and tissue concentrations of ACE, being highest in the DD genotype (121). Other studies in humans have shown an association of at least one copy of the D allele with malignant vascular injury, at least in the kidney (89) and retina (116). There are therefore genetic markers emerging of individuals who are at risk of developing target end-organ damage in hypertension, offering the possibilities of specific and targetted preventive treatment. Lacunar strokes specifically have also been associated with the GG phenotype of the Glu298Asp endothelial nitric oxide synthase gene polymorphism (36). Perhaps it is not coincidental that, as discussed above, nitric oxide and angiotensin have been 2 of the mediators of vessel tone linked experimentally to fibrinoid necrosis.

By comparison with ischemic stroke, genetic association studies in human PICH have been relatively few, but some also make use of pathological intermediate phenotypes. For example, the $\epsilon 2$ allele of the ApoE gene predisposes to cerebral amyloid angiopathy-related hemorrhage (96), an association which may reflect a link with fibrinoid necrosis (90, 127). Such associations, however, lack an obvious biologic rationale, and studies are now needed to assess the relevance to human hemorrhagic stroke of genes linked experimentally to malignant vessel injury.

Conclusion

Despite their socio-economic importance, small vessel strokes remain under-researched and their pathogenesis ill-understood, although to some extent, heterogenous, descriptive human autopsy studies suggest that small vessel strokes are caused by a limited number of cerebral small vessel lesions. They are, it is hoped, not merely stochastic events caused by the unfortunate concurrence of multiple acquired risk factors but, at least to some degree, genetically predictable and therefore preventable. Understanding and prevention will require a long term, coherent, and multi-disciplinary research strategy.

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