Recently Occluded Intracranial and Extracranial Carotid Arteries

Relevance of the Unstable Atherosclerotic Plaque

G. Alistair Lammie, MD, MRCPath; Peter A.G. Sandercock, MD, FRCP; Martin S. Dennis, MD, FRCP

Background and Purpose—It is now widely accepted that thrombotic coronary artery occlusion usually follows rupture of an unstable atherosclerotic plaque. The significance of such instability in arteries supplying the brain is less well appreciated. We therefore describe the clinical and pathological features of recent, symptomatic internal carotid artery occlusion to examine the pathogenetic role of plaque instability at both extracranial and intracranial sites.

Methods—Cases were selected from a consecutive series of 188 adult neuropathology autopsies. In 90 of these, the principal neuropathological abnormality was cerebral infarction, in 14 cases due to recent occlusion of 1 or more segments of the internal carotid artery. In each case, a full systemic, cardiovascular, and neuropathological autopsy was performed. Plaque instability was assessed by the presence or absence of a large, necrotic, lipid core; a thin, fibrous cap; and superficial inflammation.

Results—Of the 14 cases, 3 showed extracranial (carotid sinus), 7 intracranial, and 4 both extracranial and intracranial carotid artery occlusion. In 6 of the 7 occluded carotid sinuses, thrombus overlay an ulcerated, unstable, atherosclerotic plaque. In 1 extracranial and all 11 intracranial occlusions, there was either no atheroma or a mildly stenotic, stable, fibrous plaque, and in these cases, the cause of occlusion was embolism (8 cases), giant-cell arteritis (1 case), and unknown (3 cases).

Conclusions—Coronary-type rupture of an unstable atherosclerotic plaque is the usual cause of fatal occlusion of the carotid sinus, but other causes usually underlie intracranial carotid artery occlusion. The nature and consequences of intracranial atherosclerosis require further study. (Stroke. 1999;30:1319-1325.)

Key Words: atherosclerosis ■ carotid artery ■ occlusion ■ pathology ■ stroke

It is now widely accepted that thrombotic occlusion of the coronary arteries usually follows rupture or endothelial erosion of an unstable, atherosclerotic plaque.1-3 Clinico-pathological study of postmortem coronary arteries has defined the unstable plaque as having a large core of extracellular lipid and/or necrotic cellular debris overlain by a thin, eccentric, fibrous cap, with evidence of inflammation.2-3 There are relatively few pathological studies of thrombosed internal carotid arteries (ICAs), and the relevance to the brain of the coronary paradigm of plaque instability remains unclear, despite the fact that occlusion of at least the cervical portion of the ICA is an important cause of stroke.6-9 We therefore describe the clinical and pathological features in 14 consecutive autopsy cases of fatal ICA occlusion to investigate its pathogenesis at both intracranial and extracranial sites and to examine the pathogenetic role of plaque instability.

Methods
Cases were selected from a consecutive series of 188 adult neuropathology autopsies referred to 1 of the authors (G.A.L.) over a 3-year period in the Neuropathology Laboratory, University of Edinburgh, beginning in October 1994. These 188 cases included referrals for a range of proven and suspected neuropathologies, with a relatively high proportion of stroke cases reflecting the authors’ research interests. In 118 cases the principal neuropathological abnormality was cerebrovascular (44, regional infarction; 39, lacunar or small cortical infarcts; 6, global or border zone ischemia; 1, venous infarction; 16, primary intracerebral hemorrhage; 11, subarachnoid hemorrhage; and 1, primary intraventricular hemorrhage).

In 14 of the 90 cases with cerebral infarction, there was recent occlusion of 1 or more segments of the carotid artery at autopsy. In all 14 cases, a full neuropathological postmortem study was performed at gross and microscopic levels, and all significant cerebrovascular pathology was documented. Occluded arteries were serially sectioned at 5-mm intervals or less. Brain infarcts were dated histologically,10 and arterial territories were defined11 according to published maps. Hypertension was defined as a documented clinical history of hypertension, either untreated or treated, or autopsy evidence of concentric left ventricular hypertrophy without other cause. Potential causes of cerebral infarction and potential cardiac sources of embolism were defined according to published criteria12 and further refined by the results of autopsy. The key features of an unstable atherosclerotic plaque were defined as being a large, \( \text{occlusion} \)
necrotic, lipid core; a thin, fibrous cap; and superficial inflammation, as in the coronary circulation.2–5

### Results

#### Clinical and Autopsy Findings

All 14 patients were white, whose age at death ranged from 32 to 87 years. In 13 of the 14 cases, carotid occlusion was associated with clinical features consistent with carotid territory stroke, and in the remaining case (case 11), the patient presented with a brain stem stroke caused by simultaneous basilar artery occlusion. Poststroke survival ranged from <1 day to 12 weeks, and the cause of death in each case was attributed, either directly or indirectly, to the stroke. Thus, 5 patients died as a result of brain swelling secondary to cerebral infarction, and in 1, death was due to brain stem infarction. The remaining 8 patients died from complications of stroke; in 5 cases, bronchopneumonia; and in 3, deep venous thrombosis and subsequent pulmonary embolus. Therefore, all 14 cases could reasonably be classified as fatal stroke.

Of the 14 cases, 3 showed only extracranial carotid occlusion (cases 1 through 3); 7, only intracranial occlusion (cases 8 through 14); and 4, both extracranial and intracranial occlusion (cases 4 through 7). In all 7 cases with extracranial carotid occlusion, this involved the carotid sinus; in 6 cases, occlusion extended a short distance up the proximal internal carotid artery (ICA), and in 2 cases (cases 4 and 7), involvement of the distal segment of the common carotid artery was noted. Of the 11 intracranial carotid occlusions, 1 involved the siphon alone (case 5); 4, the supraclinoid segment (cases 7, 9, 11, and 12); and 6, both segments. There was extension into contiguous branches of the circle of Willis in 8 of the 11 cases; in 6 cases this involved the middle cerebral artery, in 1 case the middle and anterior cerebral arteries, and in 1 case the middle and posterior cerebral arteries.

The resulting pattern of brain infarction corresponded to all or part of the combined middle and anterior cerebral artery territories (cases 1, 2, 3, 7, and 13), the middle cerebral artery territory alone (cases 4, 9, 10, and 14), the anterior/middle cerebral artery border zone territory (case 5), the anterior choroidal artery territory (case 8), and multiple anterior circulatory loci (cases 6, 11, and 12). The histological age of each infarct corresponded, at least focally, with the clinical stroke onset. Relevant clinical and autopsy findings are summarized in Table 1.

#### Underlying Vessel Wall Pathology

In 6 of the 7 occluded extracranial carotid segments (cases 1 through 6), thrombus focally overlay ulcerated, unstable, atherosclerotic plaque (Figure 1). In each, there was a large necrotic, lipid core that occupied at least 80% of the plaque cross-sectional area, which was covered by a uniformly or focally thin, fibrous cap (Figure 1A). Superficial plaque monocytes and foam cells were present in each of these 6 plaques but in varying proportions and numbers (Figure 1B). The underlying plaque was between 50% and 95% stenotic. In 2 cases, there was evidence of intraplaque hemorrhage comprising a relatively pure population of red blood cells, and in 5, of intraplaque thrombus, with evidence of a fibrin “scaffold” and enmeshed platelets as well as red blood cells. In the 1 remaining occluded extracranial carotid artery (case 7) and in 7 of the 11 occluded intracranial segments (cases 4 through 10), there was underlying atherosclerosis, which was <50% stenotic and either fibrous or fibrocalcific (Figure 2). In none of the 11 occluded intracranial carotids

### Table 1. Clinical and Autopsy Features

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Interval From Stroke Onset to Death, d</th>
<th>Site, Side of Occlusion</th>
<th>Vascular Risk Factors</th>
<th>Autopsy-Verified Sources of Emboli</th>
<th>Other Relevant Disease/Autopsy Findings</th>
<th>Cause of Death</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>M</td>
<td>62</td>
<td>L</td>
<td>HT</td>
<td>LV AA</td>
<td>Pneumonia</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>M</td>
<td>14</td>
<td>L</td>
<td>HT</td>
<td>Carotid sinus</td>
<td>PE</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>M</td>
<td>3</td>
<td>R</td>
<td>HT, DM</td>
<td>AA</td>
<td>Brain swelling</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>F</td>
<td>1</td>
<td>R</td>
<td>HT</td>
<td>LV</td>
<td>Brain swelling</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
<td>M</td>
<td>40</td>
<td>R</td>
<td>HT</td>
<td>LV AA</td>
<td>Pneumonia</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>M</td>
<td>28</td>
<td>R</td>
<td>HT</td>
<td>AA</td>
<td>Pneumonia</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>7</td>
<td>81</td>
<td>F</td>
<td>14</td>
<td>R</td>
<td>HT</td>
<td>PFO/DVT</td>
<td>PE</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>F</td>
<td>26</td>
<td>R</td>
<td>HT</td>
<td>LA</td>
<td>Pneumonia</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>M</td>
<td>14</td>
<td>R</td>
<td>HT</td>
<td>AA carotid sinus</td>
<td>PE</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>F</td>
<td>4</td>
<td>R</td>
<td>HT</td>
<td>ASD/DVT/PE</td>
<td>Brain swelling</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>11</td>
<td>74</td>
<td>M</td>
<td>2</td>
<td>R</td>
<td>HT</td>
<td>Carotid sinus</td>
<td>Brain stem infarction</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>F</td>
<td>Multiple</td>
<td>L and R</td>
<td>HT</td>
<td>LV</td>
<td>Oxalosis</td>
<td>Pneumonia</td>
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<tr>
<td>13</td>
<td>32</td>
<td>M</td>
<td>6</td>
<td>L</td>
<td>...</td>
<td>...</td>
<td>Bilateral EC VA dissection</td>
<td>Brain swelling</td>
</tr>
<tr>
<td>14</td>
<td>40</td>
<td>M</td>
<td>1</td>
<td>L</td>
<td>DM</td>
<td>...</td>
<td>...</td>
<td>Brain swelling</td>
</tr>
</tbody>
</table>

EC indicates extracranial; IC, intracranial; L, left; HT, hypertension; LV, left ventricle; AA, aortic arch; PE, pulmonary embolism; PFO, patent foramen ovale; DVT, deep vein thrombosis; R, right; DM, diabetes mellitus; ASD, atrial septal defect; and VA, vertebral artery.
nor in the occluded sinus in case 7 was there evidence of hemorrhage, ulceration, or fissuring, and none had a significant lipid, necrotic core or superficial plaque inflammation.

In case 11 there was focal segmental giant-cell arteritis on multiple segments of the circle of Willis and intracranial ICAs. In case 12, both intracranial ICAs and proximal middle cerebral arteries were occluded by a mixture of vascularized fibrous tissue and recent organizing and organized thrombus. The occluded intracranial vessel walls in cases 13 and 14 appeared histologically normal. These pathological findings are summarized in Table 2.

Mechanism of Occlusion

The mechanism of occlusion in 6 of the 7 occluded extracranial carotids (cases 1 through 6) was ulceration of unstable carotid sinus atherosclerotic plaque with subsequent thrombosis. In cases 3 and 5, this event appeared to have been coincident with and was possibly precipitated by postoperative hypotension. In each of these 6 cases, the thrombus was of mixed type histologically (platelets, fibrin, and red blood cells), in 3 with a distally propagating red blood cell–rich “tail.” In 3 cases with extracranial carotid occlusion, there was also ipsilateral siphon occlusion (cases 4 through 6) by...
thrombus, histologically similar to the main stem or tail of the sinus thrombus, and in these cases, siphon occlusion was assumed to be embolic from the ipsilateral sinus.

In the 1 remaining case with sinus occlusion (case 7), there was simultaneous contralateral siphon occlusion, both presumed to be due to paradoxical embolism from autopsy-verified deep leg vein thrombosis through a large patent foramen ovale. In this and all other cases with intracranial carotid occlusion, the occluded segment was either histologically normal or <50% stenosed by fibrous or fibrocalcific stable, atherosclerotic plaque.

Of the 7 cases with solely intracranial carotid occlusion, a probable mechanism was determined in 3: cardiac embolism (case 8, histologically verified left atrial thrombus), artery-to-artery embolus (case 9, ulcerated unstable aortic arch and carotid sinus atherosclerosis), and paradoxical embolus (case 10, atrial septal defect, deep venous thrombosis, and multiple pulmonary emboli). In 4 of the total of 8 cases assumed to be embolic, there was a pattern of multiple cortical microinfarcts elsewhere in the brain, which provided further evidence in support of this mechanism.

In case 11 there were multiple intracranial thromboses in the circle of Willis due to giant-cell arteritis, which had been unsuspected during life, and death followed brain stem infarction due to basilar artery occlusion. The etiopathogenesis of bilateral intracranial carotid occlusions in case 12, giving a radiological and pathological picture characteristic of the so-called moyamoya syndrome, is obscure. The details of this case and the possible contribution of the underlying primary oxalosis are discussed elsewhere.13

The underlying mechanisms of occlusion in cases 13 and 14 are unknown. In neither was there an obvious cardiac or arterial source of embolus detected during life or at autopsy. In case 13, autopsy revealed bilateral extracranial vertebral artery dissections and evidence of fibromuscular dysplasia, but neither was present in the occluded intracranial arteries. In case 14, there was a history of insulin-dependent diabetes mellitus. In neither case was there significant atherosclerosis. Both patients had a prior history of migraine, an exacerbation of which appeared to herald the onset of the fatal stroke. A possible relation between stroke and migraine in these 2 patients is therefore intriguing, although neither case fulfilled strict criteria for migrainous stroke.14

Discussion

Occlusion of the cervical ICA, while sometimes asymptomatic,15 is an important cause of stroke.6–9 However, in contrast to coronary artery occlusion, there has been a relative paucity of necropsy data regarding carotid sinus thrombosis. Fisher6,7 suggested that atherosclerosis was the likely pathological cause of occlusive carotid sinus thrombosis, and he confirmed Chiari’s earlier observation that thrombosis at this site is often preceded by plaque ulceration.7 This concept has subsequently been confirmed by others, and carotid sinus plaque rupture has been associated with sites at which a thin, fibrous cap overlies a large necrotic core16 as in the coronary circulation. There are rather more data, although much conflicting, concerning nonocclusive carotid plaque morphology and its prognostic value regarding the development of neurological symptoms. These data are based mainly on pathology studies of carotid endarterectomy specimens, in some of which neurological symptoms have been correlated with lipid, necrosis-rich plaques17 or with thin, fibrous caps, foam cell cap infiltration, and plaque rupture.18 Such observations clearly support the potential relevance of coronary-type plaque instability in the carotid sinus, and aspects of this literature have been the subject of recent review.19 However, there remain very few autopsy studies of thrombotic occlusion of the cervical ICA: most predate the modern concept of the unstable atherosclerotic plaque, and in some, the importance of intimal rupture is disputed.20 Our observations suggest that fatal carotid sinus occlusion almost always follows rupture of an unstable atherosclerotic plaque, in a manner directly analogous to coronary artery occlusion.1–5

It has become increasingly apparent in the coronary circulation that the degree of stenosis per se is a poor predictor of the propensity of the plaque to rupture.21 Similarly, whereas high-grade stenosis is widely held to be closely related to stroke and transient ischemic attacks,22 it has been argued that the nature of the plaque in this situation may also be at least as important.23 Thus, although thrombotic sinus occlusion is often reported in relation to tight stenosis,9,16,24 1 serial-section study of 11 cases of recent thrombotic ICA occlusion
TABLE 2. Pathology of Thrombosed Carotid Artery and Proposed Mechanism of Occlusion

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Approximate % Stenosis</th>
<th>Fibrous Cap</th>
<th>Necrotic/Lipid Core, %*</th>
<th>Superficial Inflammation†</th>
<th>Ulceration</th>
<th>Stable/Unstable</th>
<th>Other Features</th>
<th>Proposed Mechanism of Occlusion</th>
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<tr>
<td>Extracranial</td>
<td>1</td>
<td>60</td>
<td>Thin</td>
<td>90</td>
<td>++</td>
<td>+</td>
<td>Unstable</td>
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<tr>
<td></td>
<td>2</td>
<td>50</td>
<td>Thin</td>
<td>80</td>
<td>+</td>
<td>+</td>
<td>Unstable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>90</td>
<td>Thin</td>
<td>90</td>
<td>+++</td>
<td>+</td>
<td>Unstable</td>
<td></td>
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<tr>
<td></td>
<td>4</td>
<td>90</td>
<td>Thin</td>
<td>90</td>
<td>+++</td>
<td>+</td>
<td>Unstable</td>
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<td></td>
<td>5</td>
<td>90</td>
<td>Thin</td>
<td>80</td>
<td>+</td>
<td>+</td>
<td>Unstable</td>
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<td></td>
<td>6</td>
<td>95</td>
<td>Thin</td>
<td>90</td>
<td>+</td>
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<tr>
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<td>5</td>
<td>...</td>
<td>...</td>
<td>-</td>
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<td>4</td>
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<td></td>
<td>11</td>
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<tr>
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<td>...</td>
<td>-</td>
<td>...</td>
<td>Normal</td>
<td></td>
</tr>
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</table>

*Maximal percent area of plaque occupied by the core.
†† indicates occasional cells; *, mild; ++, moderate; ++++, severe; and ulceration present (+) or absent (−).

suggested that in nearly half, there was only moderate (<60%) stenosis.\(^{20}\) In our cases, the preexisting degree of stenosis ranged from 50% to 95%, suggesting that it is plaque instability, often but not necessarily in association with a tight stenosis, that is the essential precursor to thrombotic occlusion.

It should be emphasised that whereas our observations do suggest that similar plaque features may promote plaque ulceration and thrombosis in carotid and coronary arteries, the clinical significance may well be different at the 2 sites, and in the carotid, this phenomenon remains ill understood. It is possible, for example, that asymptomatic plaque complications may be more frequent in the carotid than in the coronary circulation. This subject merits further study.

In contrast to the carotid sinus, atherosclerotic narrowing and occlusive thrombosis of the intracranial ICA are considered relatively rare, at least in whites. The intracranial portion of the ICA is by convention divided into petrous, cavernous (together constituting the siphon), and supraclinoid or T segments. Although the intracranial ICA commonly harbors some atherosclerosis, particularly in its cavernous and supraclinoid segments,\(^{25–26}\) this is more often calcific\(^{25–28}\) and less often severely stenotic\(^{24–27,29}\) than in the sinus. Perhaps in large part due to this phenomenon, intracranial ICA thrombosis is considered to be significantly less common than in the neck, its frequency in autopsy studies of carotid occlusion ranging from 0% to 30%.\(^{7,9,24,26,27,30}\) Furthermore, whereas intracranial carotid thrombosis has been attributed to atherosclerosis,\(^{9}\) it has also been suggested that thrombus in this region is more likely to be embolic,\(^{5,9,24,31–34}\) perhaps due to clotting abnormalities,\(^{35}\) or, by implication, nonatherosclerotic vessel disease.\(^{36}\) Thrombi also appear to develop in less severely stenosed lumens in the distal compared with the proximal ICA.\(^{9}\)

Despite these various claims, intracranial atherosclerosis and occlusion remain underresearched, both in the carotid siphon and in other intracranial arteries. Understanding the nature and consequences of intracranial atherosclerosis is, however, potentially important, not the least because it may be a marker of severe cerebrovascular and systemic atherosclerosis elsewhere. Furthermore, it has an unexplained tendency to be more severe in blacks, Asians, and Orientals,\(^{37–39}\) and some have suggested it has a worse prognosis than extracranial disease.\(^{40–42}\)

Our findings suggest that fatal thrombotic occlusion of the intracranial ICA is usually not due directly to underlying atherosclerosis. The same may also be true for contiguous arteries on the circle of Willis. Thus, in 1 careful autopsy study of middle cerebral artery occlusion, only 2 of a series of 47 infarcts were considered to be caused by in situ thrombosis due to underlying atherosclerosis.\(^{43}\) In the occluded intracranial carotid artery, we suggest that where there is underlying atheroma, it is usually fibrous or fibrocalcific and lacks any of the hallmarks of plaque instability. Similarly, whereas cases of “atherosclerotic” circle of Willis thrombus are recorded, they are more commonly related to less severely stenotic...
fibrous, or nonruptured plaques, thus casting doubt on a causal role for atheroma in these cases also. Some authors have suggested that thrombosis in arteries on the circle of Willis may complicate ulceration of fibrous plaques or may even be a consequence of intramural hemorrhage, while in others, in situ thrombus could be seen without either plaque rupture or intraplaque hemorrhage. Finally, it should be emphasised that the posterior circulation may not necessarily conform to this pattern. In 1 thorough autopsy study of vertebrobasilar occlusions, a high proportion were associated with and presumed to be caused by tightly stenotic atherosclerotic plaques, although the nature of the underlying plaques was not detailed. Differing frequencies of cardiac emboli, as well as discrepancies in the severity of atherosclerosis between anterior and posterior circulations, may underlie such observations.

We confirm that the majority of fatal occlusive intracranial ICA thrombi are likely embolic and emphasise that these emboli may arise not only in the heart and aorta but also in the ipsilateral carotid sinus or paradoxically, in the venous circulation. However, it should be emphasised that this selected autopsy series is unlikely to be representative of the entire spectrum of carotid disease and may underestimate other common sources of emboli, such as atrial fibrillation.

In a significant proportion of patients with intracranial carotid artery occlusion, careful clinical work-up may fail to identify a possible cause during life. This study illustrates how subsequent autopsy may reveal an unexpected predisposing factor or vasculopathy, for example, intracranial giant-cell arteritis. Nevertheless, a relatively high proportion of intracranial occlusion cases remains in the "cause unknown" category even after autopsy, particularly in the "cause unknown" category even after thorough postmortem examination. Indeed, in the 3 comparatively young cases in this series (cases 12 through 14), the cause remained uncertain even after thorough postmortem examination.

In conclusion, our observations suggest that coronary-type plaque instability usually underlies fatal thrombotic carotid sinus occlusion. Future studies should focus on the relevance of nonocclusive plaque instability at the carotid sinus and its relation to stenosis and cerebral emboli, as well as to atherosclerosis elsewhere in the body, both stable and unstable. Detection of unstable carotid plaque by noninvasive radiographic means remains a research priority. We also suggest that fatal intracranial carotid artery occlusion rarely follows this coronary paradigm and that further pathology study is required to determine the nature and consequences of intracranial atheroma.

Acknowledgments

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