The Carotid Bifurcation Plaque: Pathologic Findings Associated with Cerebral Ischemia

ANTHONY M. IMPARATO, M.D., THOMAS S. RILES, M.D., AND FREDERICK GORSTEIN, M.D.

SUMMARY Embolization from or decreased flow through cervical carotid and vertebral arteries causes ischemic stroke syndromes. Specific pathologic findings were studied in 50 symptomatic patients who underwent 69 carotid endarterectomies. Detailed analyses of their carotid plaques included correlations between photographs of gross specimens, microscopic findings, angiograms, preoperative symptoms and long-term postoperative follow up. Carotid plaques were primarily fibrous with significant (> 70%) stenoses encountered in 70% of the arteries. Stenoses were due to simple fibrous thickening in only 20%; the remainder due to intraplaque hemorrhage, atheromatous debris and, least often, luminal thrombus with or without ulceration. Intramural hemorrhage was frequent in plaques associated with focal neurologic symptoms and may have preceded localized collections of atheromatous debris. Ulceration occurred in 1/3 of all plaques, symptomatic or not. It is concluded that the carotid plaques start as fibrointimal thickening evolving to symptomatic stages by the occurrence of one or more of a number of pathologic changes, intraplaque hemorrhage being prominent. A single rational therapeutic regimen seems impossible until patients can be classified according to their pathologic changes diagnosed non-invasively.

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ALTHOUGH THERE has been a marked increase in the number of papers referring to ischemic stroke syndromes during the past 20 years, culminating in the publication of a periodical devoted exclusively to the subject,1 some basic concepts now recognized2 were first described over 100 years ago. The role of the cervical carotid arteries in the pathogenesis of the syndrome was described as early as 1856 by Savory.3 Carotid-cerebral embolization was appreciated by Chiari4 in 1904. Nevertheless, precise knowledge of the pathogenesis of cerebral ischemia, essential for rational therapeutic programs, is still lacking.5–10

The introduction of cerebral angiographic techniques by Moniz21 and the clinical pathologic correlations established by Fisher, in monographs published in 1951 and 1954, serve as the basis for the modern management of patients suffering from or threatened with ischemic strokes.4–11 Fisher described a variety of pathologic changes in carotid arteries in patients dying of stroke. He recognized the 2 basic mechanisms by which carotid arterial lesions produce cerebral ischemia. Embolization from or decreased flow through the carotids were implicated. The protective role of collateral circulation through the circle of Willis was also appreciated as was the importance of hemorrhage occurring within atherosclerotic carotid plaques as a cause of cerebral ischemia.

Since Eastcott, Pickering and Rob's first published report of the successful operative intervention on a carotid artery in 1954,14 there has been sufficient surgical experience to emphasize the importance of the cervical carotid and, probably, the vertebral arteries in the pathogenesis of ischemic stroke syndromes.2 There is not available, however, sufficient information which helps in the understanding of the development of the carotid plaque and its evolution to a stage at which cerebral ischemia occurs. This report of the gross and microscopic findings in carotid bifurcation plaques, correlated with clinical syndromes in patients undergoing carotid bifurcation operative procedures, is intended to stimulate investigation of the reasons for the differential evolution of these plaques.

Methods

Fifty patients who underwent 69 carotid endarterectomies at New York University Hospital between 1969 and 1976 were selected for study. Selection was from a total group of 850 who had such procedures and was determined primarily by the availability of a photograph of the gross appearance of the carotid plaque either in situ or immediately upon its removal. This was matched with its microscopic features and correlated with preoperative symptoms, angiographic findings, and postoperative course. Symptoms were classified as focal or non-focal, transient or permanent. They were considered to be transient if completely resolved in less than 24 hours.

Indications for surgery in this group (table 1) were transient attacks in 30 patients, sustained focal neurologic deficits in 14 and non-focal cerebral symptoms in 6. This distribution of indications for operation is slightly skewed in favor of transient ischemic attacks when compared to the entire carotid surgical group in which the distribution was more nearly 50% TIA and 50% sustained neurologic deficit. In addition, 15 patients with focal neurologic deficits underwent prophylactic reconstruction of the asymptomatic contralateral carotid for specific indications. These included stenosis of 70% or greater in the asymptomatic artery, marked irregularity of the contour of the asymptomatic plaque on the angiogram or the findings of a friable plaque on the symptomatic side with either ulceration, atheromatous debris or intraplaque hemorrhage. In several instances when there was marked predominance of the symptomatic artery over the asymptomatic vessel as determined by the filling pattern of the intracerebral vessels by angiogram, the...
asymptomatic non-predominant vessel was repaired first, in an attempt to improve collateral circulation during the period of clamping of the symptomatic artery. Four of the 6 patients with non-focal neurologic symptoms had bilateral carotid endarterectomies for flow-obstructing lesions.

Carotid angiograms were interpreted as showing lesions which interfered with flow if the lumen of either the common or the internal carotid artery was narrowed by 70% or more in any view of a series of biplane films. This was observed in 61 of the 100 vessels studied. The presence or absence of atherosclerosis in the intracranial vessels was noted. Distinction was made between irregular and smooth contours of carotid vessels and, within the context of this paper, the term "ulceration" refers only to the pathological finding of a disrupted intima. Irregular contours, although frequently associated with ulceration of the intima or mural thrombus, in many instances, represented smooth cul de sacs within fibrotic plaques.

Pathological morphology of the carotid plaques was determined after a review of photographs taken of each fresh endarterectomy specimen, in situ or immediately upon removal, as well as operative descriptions provided by the surgeon.

Series of cross sections and, where appropriate, longitudinal sections of each specimen were studied by light microscopy. Decalcification was usually necessary. A graded scale for the principal pathological changes was developed and included: degree of luminal compromise, presence of and degree of ulceration, presence of mural thrombus and its degree of organization, intramural hemorrhage. Each specimen was independently studied and graded by at least 2 observers.

Finally, a follow up of each patient was obtained. In patients with transient episodic hemispheric neurological deficits, the conclusion was that the carotid artery lesions were responsible for the symptoms if the patient was free of symptoms in the follow up period which ranged from 6 months to 9 years. If symptoms persisted, an effort was made to determine other causes. In sustained neurological deficits, the correlation between the carotid disease and the symptoms could only be presumptive.

### Results

In general, the plaques removed from the carotid bifurcations differed considerably from patient to patient. However, they shared 2 characteristics. The typical extent of involvement of the distal common and proximal internal and external carotid arteries was shared by most plaques (fig. 1). The single component found in all plaques was fibrous tissue (figs. 2, 3). Otherwise, the gross and microscopic appearances differed and ranged from simple fibrous plaques which resembled those experimentally produced by hyperdynamic alteration to complex, compound, "typical" atherosclerotic plaques containing intramural hemorrhage, atheromatous debris, surface ulcerations and luminal thrombus (fig. 4). Not all plaques contained all these elements. Although stenosis greater than 70% of transverse diameter occurred in 70% of all plaques removed, in only 20% was this due to simple fibrous proliferation (fig. 5). In the remainder, stenosis was associated with and apparently due to intraplaque hemorrhage, (fig. 6) intraplaque atheromatous debris with or without hemorrhage (fig. 7) or luminal thrombus deposition with or without ulceration (fig. 8).

Thrombus occurred under varied conditions and was either gray, pink or red. Gray or pink thrombus was found sometimes at sites of marked stenosis from smooth fibrous plaques, at other times with ulceration, on occasion in association with intramural hemorrhage and at other times not associated with either stenosis, ulceration or mural hemorrhage. This type of thrombus was interpreted as having been formed while blood flow was still rapid and was initiated by the adherence of platelets to the arterial wall. Microscopically, lines of Zahn are found, representing alternating bands of platelets and fibrin with relatively few trapped red blood cells. Red clot was encountered distal and proximal to areas of marked stenosis or in association with totally occluded arteries and was interpreted as having occurred where blood flow had either ceased or become extremely sluggish. Microscopically, lines of Zahn were absent and all blood elements were fairly evenly dispersed.

Intramural hemorrhage was recognized as recent (fig. 9) or remote (fig. 10) and was listed as "significant" only if it made up at least 50% of the thickness of a plaque. Frequently, it was associated with atheromatous debris in the plaque, especially if there was evidence of repeated hemorrhages (fig. 11). Hemorrhage could be incriminated in the production of stenosis when, as shown in figure 6, it was found completely encompassed by an unbroken cap of plaque which bulged into the lumen. Before this fact was fully appreciated, fragmentation of the plaque during removal resulted in the mistaken conclusion that intramural hemorrhages were intraluminal clots. As shown in figure 12, on occasion intramural hemorrhage was found associated with an ulcerated or broken intima, heretofore interpreted as a primary intimal tear with secondary intramural dissection of blood. The more frequent finding of contained intra-
mural hemorrhage suggests the more likely interpretation that the ulceration is secondary to intramural hemorrhage from ruptured vasa vasorum. Both laminated gray thrombus and stasis red clot have been found in association with intramural hemorrhages.

Localized collections of intramural atheromatous debris (fig. 13) frequently resembled intramural hemorrhages both in location and configuration inviting the conclusion that they were the residual of such hemorrhages, especially since they were frequently associated with evidence of old hemorrhage both grossly and microscopically. Such collections as debris were also found to be ulcerated, acting as potential sources of atheroemboli.

“Significant” intramural hemorrhage was the single finding which occurred at a much higher incidence in plaques taken from carotid arteries thought to be responsible for focal neurologic deficits compared to those removed from either asymptomatic carotid arteries or those thought to be responsible for non-focal symptoms (table 2).

Ulceration was generally superficial, exposing either atheromatous material of the plaque for several millimeters (fig. 14), the cavity of an intramural hemorrhage (fig. 12) or simply a fibrous plaque (fig. 15). Ulceration was observed in about 1/3 of all patients whether taken from the symptomatic or asymptomatic artery (tables 3, 4, 5). In only one instance the ulceration appeared to be resurfaced with flat cells, suggestive of a reparative process. In only 5
FIGURE 1. Characteristic extent of involvement of the carotid bifurcation by atherosclerosis which involves the distal common and proximal 1 to 3 cm of the internal and external carotid arteries. Plaque removed from the origin of the superior thyroid artery is marked by an arrow.

FIGURE 2. The common component of carotid bifurcation plaques is fibrous tissue shown in transverse section under low power magnification (X 30).

FIGURE 3. Fibrous carotid bifurcation plaque at high magnification illustrating the transition from media to thickened intima marked by arrow.

FIGURE 4. Complex "compound" carotid plaque containing atheromatous debris, intramural hemorrhage and surface thrombus.

FIGURE 5. Marked stenosis of internal carotid artery resulting from extensive fibrous intimal thickening producing transient hemispheric symptoms.

FIGURE 6. Marked stenosis of the internal carotid artery produced by an intraplaque hemorrhage. An asymptomatic plaque opposite a symptomatic compound plaque (fig. 3). Note that the hemorrhage is completely contained by non fissured fibrous plaque.

FIGURE 7. Marked stenosis of an internal carotid artery due to intraplaque atheromatous debris which was frequently associated with signs of remote intraplaque hemorrhage. The light arrow marks the intramural debris. Note the similarity in configurations of fresh hemorrhage and circumscribed collections of atheromatous debris.

FIGURE 8. Marked stenosis of an internal carotid artery resulting from luminal thrombus, marked by arrow.

FIGURE 9. Microscopic appearance of recent intraplaque hemorrhage.

FIGURE 10. Microscopic appearance of remote intraplaque hemorrhage recognizable from hemosiderin found within the plaque.

FIGURE 11. Photograph of a symptomatic internal carotid plaque showing association of intramural atheromatous debris with evidence of repeated intramural hemorrhage.

FIGURE 12. Recent intramural hemorrhage in the symptomatic carotid artery with evidence of ulceration marked by arrow. The frequent finding of intraplaque hemorrhage unassociated with intimal tears justifies the conclusion that hemorrhage is usually a precursor of ulceration and not the result of intimal tears and subsequent dissection.

FIGURE 13. Atheromatous debris (light arrow) within the wall of a fibrous plaque often bore a marked resemblance in shape to intramural hemorrhages (compare figs. 6 and 12) suggesting that such amorphous debris is the residue of earlier intramural hemorrhage. Lumen marked by dark arrow.

FIGURE 14. Ulcerations of plaque were usually superficial as shown in the gross photograph.

FIGURE 15. Photograph of microscopic section of an ulcer in a symptomatic internal carotid fibrous plaque covered by layers of fibrin producing a smooth surface.

FIGURE 16. Symptomatic carotid plaque containing laminated thrombus in a non-ulcerated cul-de-sac.

Discussion

The striking role that the extracranial cerebral circulation plays in the development of ischemic stroke has been repeatedly stressed since 1856. Precise details, however, have been slow to accumulate and,

TABLE 2 Distribution of Ulceration, Mural Thrombus, Stenosis and Hemorrhage in 69 Plaques as Related to Clinical Symptoms

<table>
<thead>
<tr>
<th>Focal symptoms</th>
<th>Symptomatic side</th>
<th>Asymptomatic side</th>
<th>Non focal symptoms</th>
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<tbody>
<tr>
<td>Number of plaques</td>
<td>44</td>
<td>15</td>
<td>10</td>
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<tr>
<td>Ulceration</td>
<td>15 (30%)</td>
<td>5 (33%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Mural Thrombus</td>
<td>9 (20%)</td>
<td>0 (0)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Stenosis (&gt;70%)</td>
<td>36 (62%)</td>
<td>8 (53%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>32 (73%)</td>
<td>9 (60%)</td>
<td>4 (40%)</td>
</tr>
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</table>

of the 21 ulcerated plaques studied was mural thrombus also present (fig. 16), and these 5 plaques were all removed from the symptomatic vessels.

A major omission from this group of study cases is the data referable to total carotid occlusion which, at present, generally is considered a contraindication to carotid surgery.

In the follow up study all patients with only transient ischemic attacks were free of symptoms for periods of 6 months to 9 years except for HK who had 2 episodes of left hemispheric TIAs in the immediate postoperative period. Another patient, GG, had a stroke after discharge which involved the left cerebral hemisphere. This resolved but was followed by a stroke referable to the right cerebral hemisphere leaving the patient with a profound left hemiparesis. Repeat angiograms showed patent reconstructions but severe intracranial disease. For each patient, the pathological and clinical data were carefully correlated in an effort to understand the relationship between the plaque morphology and the symptoms.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
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<th>Pathology</th>
<th>Operative side</th>
<th>Contrastral side</th>
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<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>JB</td>
<td>TIA</td>
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<td>R</td>
<td>++++</td>
<td>+</td>
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<tr>
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<td>L</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>TIA</td>
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<td>-</td>
<td>+</td>
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<td>TIA</td>
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<td>+</td>
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<td>L</td>
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<tr>
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periodically, questions have been raised regarding their true importance. In the Joint Study of Extracranial Arterial Occlusions the presumptive evidence of their importance was emphasized by the fact that approximately 75% of all patients in the study had significant extracranial arterial lesions producing 30% or more stenosis as diagnosed from angiograms. Stenosis occurred much more frequently than occlusion, and the carotid artery bifurcation was the most frequently involved artery with the vertebral arterial origins second in frequency.22 This, together with the recognition of the significance of Hollenhorst plaques20 illustrated that cerebral ischemia could occur either from interference with blood flow through the cerebral vessels in the neck because of high grade stenoses or obstructions, or because of embolization to cerebral arteries. The mechanisms by which stenoses and embolic episodes occur, however, have not been accurately studied. The importance of thrombus formation at the carotid bifurcation as a major factor responsible for cerebral ischemia has been largely accepted without documentation21, 22 and has led to extensive studies of anticoagulant and antiplatelet aggregating substances with controversial results on effectiveness in preventing strokes.

The degree of stenosis required to bring about reduction of blood flow in carotid arteries was shown by Crawford,23 during intraoperative measurements, to be 70% or more narrowing of the cross-sectional diameter. Our studies show that a variety of seemingly unrelated pathologic events may contribute to the occurrence of stenosis of the carotid system with the area of the carotid bulb and bifurcation being most commonly involved. The common denominator is the fibrotic plaque at the carotid bifurcation, which may develop in response to hemodynamic factors.24-26

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
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<th>Intramural hemorrhage</th>
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<td>+ + +</td>
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*Subclavian steal.
smooth muscle cells which morphologically may resemble endothelial cells but may not share all their non-thrombogenic properties. Thus relatively minor alterations in flow, platelet “stickiness” or blood coagulability might result in thrombus formation.

The most surprising finding in this study was the frequency of intraplaque hemorrhage and the varied mechanisms by which hemorrhages could result in cerebral ischemia.

The severity of symptoms need not correlate with the extent of the pathologic process in the carotid arteries (tables 3, 4, 5). For any given patient it is impossible to predict how much stenosis will be tolerated before cerebral ischemia is encountered because of the extreme variability in collateral flow. Once regional blood flow has been reduced to a critical level fluctuations of cardiac output and blood pressure may cause intermittent episodes of cerebral ischemia. During carotid endarterectomy patients have lost consciousness on clamping the internal carotid artery, but after raising blood pressure with vasopressors, clamping has been tolerated.

The evidence for cerebral embolization, first described by Chiari, has not been documented directly in all patients. Hollenhorst described atheroemboli and calcific particles in the retinal vessels of patients with carotid bifurcation disease. The frequent reports of surface changes found in removed carotid bifurcation plaques and the reported surgical relief from repeated cerebral ischemic episodes support the concept of the origin of emboli from the carotid bifurcations. In 26% of 69 vessels observed, either intraluminal thrombus, friable atheromatous material or intramural hemorrhage were found, each a possible source of emboli. The incidence of at least one of these findings was 75% on the carotid plaques of those patients with focal episodic attacks. A variety of changes have been incriminated in the development of nidi for emboli. These included intraplaque hemorrhage with and without ulceration or thrombosis, ulceration of a collection of atheromatous intraplaque debris with or without thrombosis, possible ulceration of intraplaque collections of lipid containing macrophages and, finally, the formation of smooth cul-de-sacs within fibrous plaques allowing deposition of thrombosis.

Although the observations made in this selected group of plaques cannot be subjected to statistical analysis because of the manner of selection, they are representative of the findings in approximately 850 carotid bifurcation operations performed at New York University Medical Center. They emphasized the unexpected frequency of intraplaque hemorrhage, the relative infrequency of thrombus formation and the universality of the fibrous plaque as the probable initiating event which then became altered in a number of ways. This study emphasizes the importance of ulcerations which may occur in a variety of ways, and of stenoses whose mode of development may be equally varied. It is fallacious to attempt to treat all patients as though thrombus formation were the prime factor in the development of ischemia. Nine of 50 patients had ischemic symptoms while on aspirin therapy and a tenth was receiving coumadin. Two of these 10 had thrombus on the plaque surfaces.

In attempting to determine the causes for the variety of pathologic findings beyond the initial fibrous plaque we could find no single factor operative in all patients. Comparisons of bilateral plaques in the same individuals seemed to indicate similarities between paired plaques suggesting that the conversion of the simple non-stenosing fibrous plaque to a symptomatic stenotic fibrotic plaque or a compound plaque by one of a number of pathways is neither capricious nor accidental nor truly an inherent feature of the atherosclerotic process. Rather, one or more mechanisms operating in different patients determine the pathways for the conversion and final appearance of the plaques.

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endothelial cells of the cerebral arteries in SHR.

To obtain further information concerning changes in edema,2-3 Cellular hyperplasia and hyaline degenera-
tion of parenchyma.4" The present study was attempted to study the development of lesions in both vessels and brain organic arterial endothelial changes, inducing in-
trusion of pial arteries and intracerebral arterioles, as
these vascular changes imply that functional and
ment of hypertensive cerebrovascular lesions is discussed.

SUMMARY Endothelial cells of the cerebral arterial system in spontaneously hypertensive rats were in-
vestigated by scanning electronmicroscopy and found to show progressive changes such as increased micro-
villi, numerous plasmalemmal pits, enlargement of the cells and well-developed marginal folds. Regressive
changes, such as balloon-like protrusions and crater-like cave-ins, were also observed. Platelet adhesion to the
injured endothelial surface of cerebral arteries was frequent. The significance of these changes in the develop-
ment of hypertensive cerebrovascular lesions is discussed.

SPONTANEOUSLY HYPERTENSIVE RATS (SHR), as developed by Okamoto and Aoki,1 show various vascular lesions, which can involve cerebral vessels and cause cerebral bleeding, necrosis and edema.4-8 Cellular hyperplasia and hyaline degenera-
tion of pial arteries and intracerebral arterioles, as well as fibrinoid necrosis, microaneurysm and throm-
The excised basal arteries of the brain were further im-
mersed in the same fixative for one hr, washed in 0.1%
three times and post-fixed in 1% OsO4 in the same buffer solution for one hr. After dehydration in a graded concentration of ethanol, the specimens were passed through isomyl acetate, dried by the critical point method, coated with gold and ex-
ammed under a Hitachi scanning electron microscope

Materials and Methods

Nine male SHR of the A8 substrain (stroke-prone)
(SHRSP) and 8 control male rats of Wistar Kyoto
strain (WK) ranging in age from 8 to 52 weeks were
used. Systolic blood pressure was measured by the tail
pulse pick-up method. Under sodium pentobarbital
anesthesia animals were perfused through the left vent-
tricle with saline at 37°C, followed by 2.5%
glutaraldehyde in 0.1 M phosphate buffer (pH 7.4).

Results

Blood pressures of SHR and control animals are
shown in the table. Scanning electronmicroscopy in the
control animals showed a large number of micro-
villi on the luminal surface of the endothelial cells of
the cerebral arteries at branching sites. In areas other
than branching sites only a small number of micro-
villi on the endothelial cells were seen. In SHR, the
endothelial cells on the cerebral arteries had a large
number of microvilli distributed diffusely not only at
branching sites but elsewhere (fig. 1).

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Scanning Electron Microscopic Study of Endothelial Cells
of Cerebral Arteries from Spontaneously Hypertensive Rats

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AND SHIGERU AMANO, M.D.

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