PATIENTS WITH SIGNIFICANT but asymptomatic atheromatous plaques at the origin of the internal carotid artery are commonly identified in the investigation of symptomatic cerebrovascular disease by arterial angiography. Such patients are likely to be identified with increasing frequency as the non-invasive Doppler techniques become more reliable and as digital-subtraction angiography becomes more widely available. The proper management of such patients is uncertain as little is known of the natural history of asymptomatic carotid plaques. Some authors advocate an aggressive approach, recommending prophylactic carotid endarterectomy in the belief that such lesions carry a greater risk of subsequent stroke without surgery. Others have found little evidence that these lesions are particularly ominous and recommend a conservative approach, reserving the option of surgical treatment until such time as appropriate symptoms arise. We have carried out a retrospective survey of our patients with such lesions for the purpose of providing additional information regarding their natural history.

Clinical Material

Seventy-three patients with an asymptomatic atheromatous plaque at the common carotid bifurcation producing a significant lesion were available for study. For the purposes of this study, a significant lesion is defined as either a stenosis of the origin of the internal carotid artery of greater than 50%, an obvious ulceration, or both as determined angiographically. The 73 asymptomatic lesions were identified among a group of 324 patients who were investigated and treated by carotid endarterectomy for a symptomatic plaque of the opposite carotid artery. The angiographic nature of the 73 lesions was as follows: stenosis greater than 50% — 50 cases; ulceration only — 6 cases; both — 17 cases. The mean age of the 74 patients was 62 years at the time of the original investigations. Fifty patients (69%) were males and 34 patients (47%) were hypertensive. The patients have been observed for 6 months to 10 years (average 4 years). The only indication for surgical intervention for the asymptomatic lesion has been the development of an appropriate TIA or minor stroke. The use of antiplatelet and anticoagulant drugs in these patients was not standardized and their effects could not be evaluated. Many of the patients were treated before the benefit of aspirin in men was known.

Results

During the period of follow-up, 22 of the patients developed ischemic symptoms in the cerebral or retinal circulations (table 1). In 11 patients (15%) the new ischemic events were either in the territory of the previously symptomatic carotid artery that had undergone endarterectomy or in the vertebro-basilar territory. In 12 patients (16%) the events were in the territory of the initially asymptomatic carotid artery. One patient developed symptoms in both the asymptomatic carotid and vertebro-basilar territories.

The initial manifestation of new cerebral or retinal ischemia was transient in 18 cases and was a stroke in 5 cases. Two of the 5 strokes were in the territory of the previously asymptomatic carotid artery, one was in the territory of the carotid artery that had had endarterectomy, and 2 were in the vertebro-basilar territory. In addition to the 5 strokes occurring as an initial manifestation of ischemia, 3 of the 5 patients who developed TIA’s in the territory of the previously symptomatic carotid artery did not seek medical attention until a stroke had occurred. One of the 3 patients who first developed vertebro-basilar TIA’s later suffered a brain stem stroke.
TABLE 1  Nature and Distribution of the Initial Manifestation of New Ischemic Events in 22 Patients with Significant Asymptomatic Carotid Plaques

<table>
<thead>
<tr>
<th>Vessel territory</th>
<th>Number of events*</th>
<th>TIA</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carotid</td>
<td>12 (16%)</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Previously symptomatic carotid (post-endarterectomy)</td>
<td>6 (8%)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Vertebro-basilar</td>
<td>5 (7%)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>18</td>
<td>5</td>
</tr>
</tbody>
</table>

*One patient had new ischemic symptoms in both the asymptomatic carotid and vertebro-basilar territories.

Thus, in total, 9 of the 73 patients (12%) developed a stroke during the period of follow-up (table 2). Eight of the strokes were cerebral and one was retinal. In only 2 cases (3%) was the stroke in the territory of the initially asymptomatic carotid artery, while in 7 cases (9%) the strokes were in the other two vessel territories.

Three of the 22 patients developed ischemia in the territory of the asymptomatic carotid artery within 7 days of the endarterectomy of the opposite carotid artery. The other 19 patients developed their new symptoms an average of 2.4 years following the endarterectomy. New events in the territory of the asymptomatic carotid artery tended to occur earlier than the ischemic events in the other two vessel territories.

Post-operative angiography (performed 1 to 3 months following operation) was available in 39 of the 73 patients who underwent endarterectomy of a previously symptomatic carotid artery. In every case the endarterectomy site was widely patent. However, in one patient with a 90% stenosis of the asymptomatic carotid the post-operative angiogram revealed that that artery had occluded silently.

Of the 15 patients who developed new ischemic symptoms in either carotid territory more than one week following endarterectomy, ten were re-investigated with angiography (6 cases with an initially asymptomatic carotid artery and 4 cases with a previously symptomatic carotid artery).

The angiographic findings in the 6 patients who developed ischemia in the previously asymptomatic carotid territory revealed a significant progression of the lesion in every case (fig. 1a and 1b). None of the arteries had completely occluded, however, These 6 patients, as well as the 3 patients who developed ischemia in the asymptomatic carotid within 7 days of surgery on the opposite side, underwent uneventful endarterectomy on the newly symptomatic vessel.

Four of the 6 patients who developed recurrent ischemic symptoms in the territory of the artery that had previously been operated on had repeat angiography. In 3 patients the endarterectomy site was widely patent and smooth (fig. 2a and 2b). No other lesions were identified in these cases to account for the new ischemic episodes but it is possible that 2 of the 3 patients suffered a hypertensive lacunar stroke, as they were hypertensive. One patient had a small, but definite, area of ulceration at the prior endarterectomy site that was presumably the source of his recurrent ischemia.

The angiographic nature of the lesions originally noted in the asymptomatic carotid artery were analyzed in relation to the thirteen ischemic events that occurred in that vessel territory to see if there was any difference in the frequency of the ischemic events (table 3). All three types of asymptomatic lesions had a similar rate of ischemia, but it is of interest that the only instances of infarction occurred in the group with stenosis of greater than 50%. An ulcerated plaque was

![Figure 1a](http://stroke.ahajournals.org/)

**Figure 1a.** Right carotid angiogram (lateral view). This 57 year old woman underwent left carotid endarterectomy for a left hemisphere TIA. The right carotid angiogram revealed an asymptomatic common carotid bifurcation plaque with a 50% stenosis of the internal carotid artery origin with mild ulceration.
not associated with infarction in our patients. There
was a higher incidence of ischemic events, and in
particular infarction, the greater the stenosis (table 4).
Although this is an interesting trend, the number of
cases is insufficient to draw any firm conclusions re-
garding the relationship.

During follow-up, 13 patients (18%) died (table 5).
This was most frequently the result of cardiovascular
disease. However, 3 of the patients died as a result of
stroke (1 involving the asymptomatic carotid artery
and 2 involving the vertebro-basilar system). The aver-
age time to death from discovery of the asymptomatic
lesion was 3 years.

Discussion

Patients with significant, angiographically proven,
but asymptomatic carotid bifurcation plaques are com-
monly identified among those undergoing carotid end-
arterectomy for a symptomatic lesion. Levin and
Sondheimer found 60 such patients with greater than
50% stenosis among 230 patients undergoing carotid
surgery (26%). Podore et al. noted 95 patients with
some degree of asymptomatic stenosis among 202 sur-
gical cases (47%); 51 of whom had a stenosis greater
than 50% (25% of total). We found 73 patients with a
50% or greater stenosis, ulceration, or both among a
group of 324 similar patients (23%). Patients with sig-
nificant asymptomatic lesions are also discovered, al-
though less frequently, in the course of cerebral
angiography for other intracranial pathology, and dur-
ing investigation of disease in other vascular systems.

Unfortunately, there is little information available
regarding the natural history of the proven, but asymptom-
atic carotid lesion that will serve as a guide to the
intelligent care of such patients. The relevant literature
is summarized in table 6. Three reports are of
limited usefulness as the authors have failed to provide
information regarding ischemic events in cerebrovas-
cular territories other than the initially asymptomatic
carotid artery. Although none of the reports except that
of Moore et al. indicate any great risk of stroke, the
reports may be grouped according to two radically
different proposals for the management of these
patients.

Three papers advise a conservative approach. Levin
and Sondheimer followed 60 patients with at least a
50% stenosis for a minimum of 2 years. None devel-
oped a stroke. Two developed appropriate TIA's at
which time they underwent carotid endarterectomy. Their recommendation was to observe such patients until their lesions became asymptomatic. Humphries et al.\textsuperscript{4} followed a similar group of patients. Although 15\% developed ischemic events in the territory of the asymptomatic lesion, all but one patient had TIA's. Their recommendation was similar to that of Levin and Sondheimer. Johnson et al.\textsuperscript{5} found a very low incidence of ischemia in the asymptomatic carotid artery which may reflect the fact that he was following many minor lesions. All strokes occurred in other vessel territories. They were unable to recommend prophylactic surgery.

Two papers advise prophylactic surgery. Moore et al.,\textsuperscript{1} in the only study devoted exclusively to consideration of ulcerated plaques, reported a remarkable incidence of stroke (10/29 or 34\%) in patients with major ulcers, and recommended surgery in that group. The curious feature of the report is the total absence of premonitory TIA's in any of the patients. Podore et al.\textsuperscript{2} observed a low incidence of stroke in the asymptomatic artery (3\% over 5 years) but inexplicably advised in favour of prophylactic surgery.

Some authors have attempted to draw conclusions regarding the natural history of carotid bifurcation plaques using data from patients with asymptomatic carotid bruits.\textsuperscript{8,9} Such attempts are unconvincing and arguments based on the study of patients with bruits are hardly relevant to the very specific question of the natural history of the definite carotid plaque, as the over-all correlation between carotid bruit and demonstrable carotid disease is only about 60\% according to Fields' estimate.\textsuperscript{7} Moreover, the large population studies of asymptomatic cervical bruits such as the Evans County study\textsuperscript{10} and Framingham study\textsuperscript{11} clearly indicate that such bruits are associated with a low incidence of infarction in the territory of the bruit.

Our study indicates that patients with significant asymptomatic carotid plaques who have had contralateral carotid surgery for a symptomatic lesion are at high risk for future ischemia in all vessel territories (30\% during a follow-up averaging 4 years). Johnson et al.\textsuperscript{5} found a 23\% incidence of ischemia with an average follow-up of 32 months, while Levin and Sondheimer\textsuperscript{3} reported only a 7\% incidence. In our patients new events occurred on the average 2 years following endarterectomy, with the highest incidence in the territory of the previously asymptomatic vessel (16\%). However, the majority (83\%) of the initial episodes in the asymptomatic carotid artery were TIA's rather than stroke, offering an opportunity to deal with such lesions as they became symptomatic. With the exception of the report of Moore et al.\textsuperscript{1} all the other reports on this subject (table 6) have also found that the initial ischemic event related to a previously asymptomatic carotid plaque is most likely to be a TIA. This is a somewhat unexpected finding as it is generally thought that at least 50\% of stroke victims present without premonitory TIA's.\textsuperscript{12} Although the highest overall rate of ischemia was in the asymptomatic carotid territory, we found significant rates in the opposite carotid (8\%) and vertebro-basilar (7\%) territories. The incidence of stroke in our patients was similar in all three vessel territories.

Re-investigation with angiography of those patients who developed ischemia in the previously asymptomatic carotid artery revealed progression of the plaque in all cases. In contrast, 3 of the 4 patients with recurrent symptoms in the territory of the previously operated carotid artery failed to show recurrent

<table>
<thead>
<tr>
<th>Asymptomatic lesion</th>
<th>Number of patients</th>
<th>TIA</th>
<th>Amaurosis fugax</th>
<th>Stroke</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis &gt; 50%</td>
<td>50</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Stenosis with ulceration</td>
<td>17</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (18%)</td>
</tr>
</tbody>
</table>
disease at the endarterectomy site. Such a finding is a reminder that not all cerebral ischemia arises from lesions at the carotid bifurcation, and endarterectomy is thus no absolute guarantee of protection against the future. The fact that there is a definite incidence of recurrent ischemia following endarterectomy has been the subject of a recent report by Owens et al., and may even occur following prophylactic surgery on an asymptomatic vessel. Whether or not the degree of stenosis and extent of ulceration relates to the future risk of an asymptomatic carotid plaque is not known. The report of Moore et al. suggests that plaques with "major" ulceration carry an extraordinary risk of stroke. We had too few such patients to confirm or deny their finding. Some authors regard the highly stenotic asymptomatic lesion as carrying a greater risk of stroke, although Podore et al. and Johnson et al. were unable to confirm this relationship. We saw a trend to a greater incidence of ischemia with increasing stenosis in our patients (table 4), but the number of instances is too small to draw any firm conclusions.

Our patients experienced a high rate of death during follow-up (17%), most often the result of coronary vascular disease. This is in keeping with other reports that indicate that the risk of death within 5 years of carotid endarterectomy is approximately 25%. In summary, we found that patients with a significant angiographically identified, but asymptomatic common carotid bifurcation plaque have a high rate of subsequent cerebral ischemia. However, the majority of the initial ischemic events are transient. The risk of stroke in our cases was equal in all vessel territories. There is little evidence from this report, representing patients already symptomatic from cerebrovascular disease, or from the literature, that the risk of stroke in the absence of premonitory TIA's in an asymptomatic plaque is such that there is an obvious advantage to prophylactic surgery. This is even more the case when consideration is given to the inherent risk of surgery, the evidence of late stroke in the operated vessel and in other cerebral vascular territories, and the high rate of death from other vascular causes in the group of patients. The exception may be the patient with a high degree (>90%) of stenosis of the asymptomatic vessel. In the absence of a randomized prospective trial comparing the management of such lesions either by prophylactic surgery or by surgery delayed until the lesion becomes symptomatic, we recommend that a conservative approach be taken, and that such patients be educated as to the symptoms of cerebral ischemia, kept under regular review and considered for surgery only if appropriate symptoms arise. The use of aspirin in our centre is now standard for all patients for 6 weeks following endarterectomy and is recommended for long-term use in all men.

### Table 4: Incidence and Type of Initial Ischemic Events in the Territory of 50 Stenotic but Asymptomatic Carotid Arteries Related to the Degree of Stenosis

<table>
<thead>
<tr>
<th>Degree of stenosis</th>
<th>Number of patients</th>
<th>TIA</th>
<th>Stroke</th>
<th>Total events</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–69%</td>
<td>31</td>
<td>4</td>
<td>0</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>70–89%</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>90% +</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>3 (33%)</td>
</tr>
</tbody>
</table>

### Table 5: Cause of Death in 13 Patients

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>3</td>
</tr>
<tr>
<td>Asymptomatic carotid</td>
<td>1</td>
</tr>
<tr>
<td>Vertebro-basilar</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
</tr>
</tbody>
</table>

### Table 6: Summary of Reports Regarding the Incidence of Cerebral Ischemia in Patients with an Angiographically Proven but Asymptomatic Carotid Plaque

<table>
<thead>
<tr>
<th>Authors</th>
<th>Asymptomatic lesion</th>
<th>Number of patients</th>
<th>Length of follow-up</th>
<th>Asymptomatic carotid</th>
<th>Opposite carotid</th>
<th>Vertebro-basilar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TIA</td>
<td>Stroke</td>
<td>TIA Stroke</td>
</tr>
<tr>
<td>Levin and Sondheimer, 1973</td>
<td>stenosis &gt; 50%</td>
<td>60</td>
<td>2–12 years</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Humphries et al, 1976</td>
<td>stenosis &gt; 50%</td>
<td>182</td>
<td>2–12 years (mean 32 mos)</td>
<td>26</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Johnson et al, 1978</td>
<td>stenosis &gt; 10%</td>
<td>77</td>
<td>mean 2 yrs</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Moore et al, 1978</td>
<td>major ulcer</td>
<td>29</td>
<td>5 years</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>minor ulcer</td>
<td>38</td>
<td>5 years</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Podore et al, 1980</td>
<td>stenosis (any degree)</td>
<td>67</td>
<td>5 years</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Present report, 1981</td>
<td>stenosis &gt; 50% and/or ulcer</td>
<td>73</td>
<td>1–10 years (mean 4 yrs)</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Effects of Promethazine on the Energy Metabolism of Normoxic and Hypoxic Rat Brain

V. MacMillan, M.D.

SUMMARY The metabolic effects of intraperitoneal administration of promethazine on normoxic, hypoxicemic and hypoxemic-oligemic rat brain were assessed by measurement of the cerebral contents of energy phosphates, and selected glycolytic-citric acid cycle intermediates. In normoxic brain promethazine (25-100 mg/kg⁻¹) was associated with unaltered adenylates, increased glucose and aspartate and decreased pyruvate, lactate and malate; a pattern which was compatible with cerebral metabolic depression. Hypoxemic animals receiving either saline or promethazine (25 mg/kg⁻¹) showed equivalent decreases in ATP and increases in lactate which indicated that promethazine had no significant effect on the metabolism of the acutely hypoxic brain. In animals exposed to hypoxemia plus right carotid artery occlusion (oligemia) the promethazine treated group (25 mg/kg⁻¹) showed significantly lower ATP and higher AMP contents which suggested an adverse effect on the metabolism of the acutely hypoxic-oligemic brain. It is concluded that promethazine does not beneficially alter the energy metabolism of the acutely hypoxic or hypoxic-oligemic brain.

A RECENT REPORT has indicated that the phenothiazine chlorpromazine has a major protective effect on ischemic liver.¹ In this study although treated and untreated animals showed equivalent metabolic changes during a 3 hour ischemic exposure, animals pretreated with chlorpromazine (20 mg/kg) showed little or no evidence of liver cell necrosis during a 24 hour restitution from the ischemic exposure. In addition chlorpromazine treated animals showed improved post-ischemic regeneration of hepatic ATP stores and a reduced accumulation of tissue and mitochondrial calcium which markedly increased in the untreated post-ischemic liver. The results of these experiments suggested that the action of chlorpromazine was not related to a modifying effect on the intensity of the ischemia, but rather to a prevention of some critical cellular reaction to ischemia. Due to the prominent membrane effects of the phenothiazines,² it was suggested that this protective action could be related to a primary prevention of ischemic membrane damage or to a blockage of calcium flux across damaged membranes. A second possibility considered was that the chlorpromazine action was related to an inhibition of phospholipase activation during or following ischemia.

The sensitivity of mammalian brain to hypoxia-

References


From the Department of Medicine, University of Toronto, Toronto, Ontario, Canada, MSS 1A8.

Address for correspondence: Dr. V. MacMillan, Room 7214, Medical Sciences Bldg., University of Toronto, Toronto, Ontario, Canada, MSS 1A8.

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Q J Durward, G G Ferguson and H W Barr

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