The Natural History of Carotid Arterial Disease in Asymptomatic Patients With Cervical Bruits

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SUMMARY A prospective study was initiated in January 1980 to follow with Duplex scanning a consecutive series of 167 asymptomatic patients with cervical bruits. Patients were seen at six month intervals for the first year and yearly thereafter. Based on previously validated criteria, disease at the carotid bifurcation was classified into 6 categories: (1) Normal, (2) 1–15% diameter reduction, (3) 16–49%, (4) 50–79%, (5) 80–99%, and (6) occlusion. Patients were evaluated to assess: (1) the occurrence of new neurological symptoms, (2) the stability of the lesions at the carotid bifurcation, and (3) the possible role of risk indicators on disease changes.

During follow-up, ten patients became symptomatic (6 with TIA’s and 4 with stroke). The development of symptoms was accompanied by disease progression in 8 patients. By life table analysis, the annual rate occurrence of symptoms was 4%. The mean annual rate of disease progression to a greater than 50% stenosis was 8%. When progression in all categories was considered, 60% of the sides showed some disease aggravation. The presence of or progression to a greater than 80% stenosis was highly correlated (p = 0.00001) with either the development of a total occlusion of the internal carotid artery or new symptoms.

The major risk factors associated with disease progression were cigarette smoking, diabetes mellitus, and age. Those patients under 65 years of age were most likely to show progression.

Despite high rates of disease progression, this study further supports the contention that it is prudent to follow a conservative course in the management of asymptomatic patients presenting with a cervical bruit. Surgical treatment can be delayed until the appearance of TIA’s or progression of disease to a greater than 80% stenosis.

IN THE PREVENTION OF STROKE, few issues have lead to more controversy than the management of asymptomatic patients with a cervical bruit or a carotid artery lesion. Also, with wider application of noninvasive testing, more carotid lesions are fortuitously discovered, creating a difficult dilemma for physicians forced to deal with this problem. Those who advocate a prophylactic endarterectomy claim a decline in the long-term morbidity and mortality as a result of this procedure. Of major concern, however, is that even in experienced hands, the risk of stroke and death associated with angiography and surgery is not negligible. These considerations have led others to withhold this prophylactic type of surgery until the appearance of the first TIA.

In January 1980, a prospective study was initiated to follow with ultrasonic duplex scanning the course of carotid occlusive disease in a consecutive series of asymptomatic patients presenting with a mid cervical bruit. The aim of the study was to determine (1) the stability of arterial lesions at the carotid bifurcation, (2) the occurrence and type of neurological symptoms during follow-up, and (3) the possible role of risk indicators on disease changes. This report addresses the outcome of these patients over a period extending to three years of follow-up.

Materials and Methods

From January 1980 through June 1982, 1450 patients were referred to the vascular laboratory for evaluation of carotid arterial occlusive disease. From this population, 203 patients (14%), asymptomatic at the time of referral and with a mid cervical bruit at auscultation, were recruited for the study. All patients with a previous history of transient ischemic attack (TIA) or stroke and those who had undergone previous carotid endarterectomy were excluded. Auscultation was performed over the upper chest, the supraclavicular areas and along the anterior border of the sternoclavicular muscles up to the angle of the jaw; the location of the bruits was recorded. All murmurs transmitted from the base of the heart were eliminated and care was taken to exclude venous hums and other nonarterial cervical noises. Each patient was included in the study at the time of the first visit and discovery of the cervical bruit. They were seen at 6 month intervals for the first year and yearly thereafter.

Of the 203 asymptomatic candidates identified, 36
failed to come back for followup. Of these, two died of a myocardial infarction less than 1 year after their initial visit. Of the 34 remaining patients, 24 were contacted and a questionnaire conducted by telephone revealed that all 24 were asymptomatic neurologically. Followup information was not available on 10 patients and attempts to contact them remained unsuccessful. In addition, five other patients were not included in the analysis since one of them underwent bilateral prophylactic endarterectomy shortly after his entry in the study and four underwent an endarterectomy on the side contralateral to an occluded internal carotid artery. Thus, serial studies on the remaining 162 patients were available and constitute the data for this analysis. One patient with diabetes mellitus died of peritonitis at one year.

At the time of each visit, the following protocol was followed:

**Standard Questionnaire**

A standard questionnaire was used at each visit to detect any new symptoms that might have developed.6 Medical records and hospital discharge summaries were requested for all persons found to have had a stroke. The stroke events were all documented clinically by a neurologist and computerized tomography of the brain was available in each case. For all deceased patients, medical records were also requested and death certification determined. Additional data gathered on each subject included medical history of cardiac and vascular disease, the presence or absence of known risk factors, and the form of treatment.

**Duplex Scanning**

At each visit, an ultrasonic duplex scanner was used to evaluate the extracranial portion of the carotid arteries. This method combines a B-mode imager* and a pulsed Doppler unit with real-time spectral analysis.† (Figure 1)

The assessment of carotid artery disease by this method depends upon the interpretation of spectral changes in the centerstream velocity patterns recorded from specific sites along the carotid arteries. The parameters used for classification of the spectra include peak systolic frequency, diastolic frequency, the amount of spectral broadening during systole, and the overall shape of the waveforms. Using these features, disease at the carotid bifurcation is classified into 6 categories: normal, 1–15% diameter reduction, 16–49% diameter reduction, 50–79% diameter reduction, 80–99% stenosis, and occlusion. Validation of the methods has shown an overall agreement of 82% with contrast angiography.7,8 The ability to recognize normal arteries (specificity) is 84% and the sensitivity of the method of ability to identify disease is 99%. In each category of disease, the accuracy is about 80% when compared to angiography. (Table 1)

†FFT Spectrum Analyser, Honeywell Medical Systems, Denver, Colorado.

Statistical Analysis

Serial duplex studies were tabulated to determine the transition between disease states over measured time periods. Rates of events (progression or appearance of symptoms) for successive intervals of follow-up were combined in an actuarial or life-table analysis.9 From the life table, mean annual rates of events were calculated after accounting for the number of patients seen at each time interval. Twelve potential risk indicators and second-order combinations were examined to evaluate their relationship with the occurrence of disease progression. These factors were: (1) age, (2) sex, (3) history of high blood pressure, (4) treatment for high blood pressure, (5) measured systolic blood pressure, (6) measured diastolic blood pressure, (7) history of ischemic heart disease, (8) history of peripheral arterial occlusive disease, (9) history of diabetes mellitus, (10) smoking habits, (11) treatment with aspirin, and (12) treatment with dipyridamole. The statistical procedures used include the Fisher's exact test, the Student t-test, the odds ratio, Kolmogorov-Smirnov test for ordinal scaled data, and stepwise discriminant analysis from the Statistical Package for the Social Sciences.10

**Results**

1) **Population Characteristics**

The age ranged from 27 to 86 in the study population, with a mean of 63.6 ± (S.D.) 9.6. The male to female ratio is 2:1 (110/52).

2) **Distribution of Disease and Bruits**

Bruits were bilateral in 73 patients and unilateral in 89 patients. Thus, of the 324 sides available for followup, 73% or 235 were associated with a bruit. The noninvasive study performed at the time of recruitment showed that 8 of the 324 internal carotid arteries were normal (2%), 96 arteries (29%) were in the 1–15% category, 106 (33%) were 16–49% lesions, 93 (29%) were 50–79% stenoses, 9 (3%) were 80–99% lesions and 12 (4%) were occluded. The disease distribution at the zero point in the study population and the proportion of sides with bruits in each category of disease are shown in figure 2. For each category of disease, the proportion of sides with a bruit varies from 67 to 89%. Three of the 12 occluded sides (25%) were associated with a bruit, however. For the purpose of this study, all the sides, whether associated with a bruit or not, were included in the analysis.

3) **Progression of Internal Carotid Arterial Disease**

Disease progression was defined as a change of disease classification by at least one category, from a less severe to a more severe one, from the first visit to the last visit. During the course of the study, 26 patients underwent a prophylactic endarterectomy on one side shortly after their initial visit. Ten additional endarterectomies were performed at various times during the study: four followed the appearance of symptoms on the appropriate side and six were performed on the side contralateral to an occlusion. Operated patients were
all kept in the study for surveillance of the contralateral side. When an endarterectomy was performed on one side, the last visit tabulated for that side was the visit just prior to the endarterectomy. Review of serial studies for the 162 patients revealed that 101 patients (62%) remained unchanged on both sides, 50 (31%) showed disease progression on one side only, and 11 (7%) showed disease progression in both internal carotid arteries.

At 6 months, 103 patients with 197 initially patent internal carotid arteries returned for study. At that time, endarterectomy had been performed on 23. Excluding initially occluded and all operated vessels, progression had occurred in 30 (30/174 = 17%), and 5 (5/180 = 3%) classified less severely (table 2). Two of the patients experienced a TIA, one with an initial 80–99% stenosis and the other who progressed from 50–79% to 80–99%. Both subsequently had a successful endarterectomy. One vessel with an 80–99% stenosis became occluded without causing symptoms.

At 12 months, 95 patients with 171 initially patent arteries were studied. Endarterectomy had been performed on 16. Progression had occurred in 30 (30/107 = 28%) since the first visit and was less severe in four (table 4). One patient developed a TIA associated with a stable 1–15% lesion. Another patient, who reported a TIA associated with progression from 50–79% to 80–99% stenosis during the first 12 month period, suffered a stroke during the second 12 month period associated with progression on to a total occlusion.

At 36 months, 17 patients with 33 initially patent internal carotid arteries were studied. Endarterectomy had been performed on seven. Progression had occurred in 10 sides (10/26 = 38%) (table 5). One patient developed a TIA associated with progression from a 16–49% lesion to an 80–99% stenosis. Another patient suffered a stroke associated with progression from a 16–49% to 80–99% lesion. A third patient who went from a 50–79% to total occlusion (fig. 3) stenosis in three years suffered a stroke at 38 months.

Since the discovery of the bruits and recruitment did not occur simultaneously in all cases, lengths of follow-up are not equal at any given date and a single-

### Table 1: Concordance Duplex Scanning vs. Angiography

<table>
<thead>
<tr>
<th>Duplex results (% diameter reduction)</th>
<th>Angiography</th>
<th>Normal</th>
<th>1–15%</th>
<th>16–49%</th>
<th>50–79%</th>
<th>80–99%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>47</td>
<td>9</td>
<td></td>
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<td>56</td>
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<td>1–15%</td>
<td>4</td>
<td>49</td>
<td>8</td>
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<td>61</td>
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<tr>
<td>16–49%</td>
<td>14</td>
<td>62</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>80</td>
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<td>1</td>
<td>7</td>
<td>56</td>
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<td>72</td>
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<td>22</td>
<td>1</td>
<td>28</td>
<td></td>
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<td>38</td>
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<td></td>
<td></td>
<td>336</td>
</tr>
</tbody>
</table>

### Figure 1. Real time B-mode image with pulsed Doppler cursor. Flow is routinely sampled from the low common carotid artery (L-CCA), the high common (h-CCA), the proximal (p-ICA) and distal (d-ICA) internal and from the external carotid artery (ECA). The Doppler angle is set to 60° with the vessel axis on the image.

### Figure 2. Disease distribution in the study population. The number of sides in each category is shown. The dotted areas represent the sides with bruits.
period type of analysis can distort the rates of events studied. A patient may have progressed at 6 months and not been seen yet for subsequent visits, while another one may have been seen at every visit period without evidence of progression. Similarly, a patient may have progressed early and appear as a progression on every subsequent visit. To obviate the problems inherent to the structure of the study, the actuarial or life table analysis was chosen to provide a more accurate means of estimating true rates of events. The major advantage of this approach is that it utilizes all the available data, each subject being counted for whatever time he has been followed, no matter how brief. Furthermore, the rates of events for successive intervals are combined in a way that eliminates distortion, and makes the estimated rates more reliable. The absolute endpoints for the life-table analysis shown in figure 4 were: (1) symptoms (TIA or stroke), (2) disease progression in the ICA from a less than 50% to a more than 50% diameter reducing lesion, and (3) evidence of progression in all categories of disease. The analysis showed an annual rate of occurrence of symptoms of 4%. At 3 years, 36% of the sides initially classified in a less than 50% category progressed to a more than 50% lesion. The averaged annual rate of progression to this category of disease was 8%. When progression in all categories are considered, 60% of the sides will have progressed after three years.

4) Symptoms, Occlusions and Disease Progression

Spontaneous appearance of symptoms occurred in 10 patients. Three patients suffered unheralded thrombolic strokes, one had a TIA followed by a stroke and six had TIA's only (table 6). In addition, one patient suffered a stroke during a contrast angiography on the side of a stable 16–49% lesion. That patient was asymptomatic prior to the angiography. Symptoms in all 10 patients occurred on the side of a bruit. No stroke was lacunar and none was due to intracranial hemorrhage. Progression of disease in the ipsilateral ICA preceded the occurrence of spontaneous stroke in three of four cases (fig. 5). Only one of these patients had warning TIA's prior to the stroke. In one patient, an occlusion of the internal carotid artery was documented at the time of entry in the study and a brain infarction occurred on the ipsilateral side one year later. The TIA's also followed a progression to a more than 80% stenosis in all but one case. In this case, the ICA on the appropriate side had a stenosis of less than 15% diameter reduction which did not progress during followup.

A total of 10 sides occluded during followup. Two-thirds (6/10) occurred during the first year of followup, 2 during the second year, and 2 during the third year. The occlusive event was associated with a stroke affecting the ipsilateral hemisphere in 3 cases and with a TIA in one. Although 40% of the occlusions occurred on sides with minimal extent of disease initially, marked disease progression to a greater than 80% lesion was always observed before occlusion when serial studies were available (fig. 6). This relationship was not observed in 3 cases. In these 3 cases, the follow-up periods prior to the discovery of the occlusion were 12, 12 and 24 months. It is possible that an

<table>
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<th>Table 2</th>
<th>Follow-up Visit at 6 Months</th>
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<tr>
<td>Initial Classification</td>
<td>1–15%</td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
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<tr>
<td>1–15%</td>
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<tr>
<td>16–49%</td>
<td>5</td>
</tr>
<tr>
<td>50–79%</td>
<td>7</td>
</tr>
<tr>
<td>80–99%</td>
<td>4</td>
</tr>
<tr>
<td>100%</td>
<td>4</td>
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</tbody>
</table>

* TIA (2).
†Stroke (2) — one during angiography (the 16–49% lesion).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Follow-up Visit at 12 Months</th>
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<td>Initial Classification</td>
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</tr>
<tr>
<td>Normal</td>
<td>3</td>
</tr>
<tr>
<td>1–15%</td>
<td>31</td>
</tr>
<tr>
<td>16–49%</td>
<td>4</td>
</tr>
<tr>
<td>50–79%</td>
<td>36</td>
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<tr>
<td>80–99%</td>
<td>1</td>
</tr>
<tr>
<td>100%</td>
<td>9†</td>
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</tbody>
</table>

* TIA (2).
†Stroke (2) — one during angiography (the 16–49% lesion).

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Follow-up Visit at 24 Months</th>
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<tbody>
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<td>Initial Classification</td>
<td>1–15%</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
</tr>
<tr>
<td>1–15%</td>
<td>22*</td>
</tr>
<tr>
<td>16–49%</td>
<td>4</td>
</tr>
<tr>
<td>50–79%</td>
<td>29</td>
</tr>
<tr>
<td>80–99%</td>
<td>0</td>
</tr>
<tr>
<td>100%</td>
<td>2</td>
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</table>

* TIA (1).
†Stroke (1).
TABLE 6 Relationship Between Disease Progression Beyond 80% Diameter Reduction and Symptoms/Occlusion

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Disease status on follow-up</th>
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<tbody>
<tr>
<td>No complication</td>
<td>&lt;80%</td>
</tr>
<tr>
<td>TIA only</td>
<td>1</td>
</tr>
<tr>
<td>TIA with occlusion</td>
<td>0</td>
</tr>
<tr>
<td>TIA followed by stroke and occlusion</td>
<td>0</td>
</tr>
<tr>
<td>Stroke with occlusion</td>
<td>0</td>
</tr>
<tr>
<td>Asymptomatic occlusion</td>
<td>3</td>
</tr>
<tr>
<td>Total complications</td>
<td>4</td>
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</tbody>
</table>

with internal carotid artery stenoses in excess of 80% (11/24 = 46%) than in those with lesions between 0 and 79% stenoses (4/262 = 1.5%, p < 0.00001). The incidence of ipsilateral symptoms (stroke or TIA) in the high risk group is 33% (8/24), significantly higher than in the 0.4% (1/262) incidence in low risk patients (p < 0.00001). While no spontaneous strokes occurred in the low risk group, the incidence was 12.5% in patients with an 80-99% stenosis (p = 0.0005). The odds for all complications in the high risk group (80-99% ICA stenosis) compared to the lower risk group (0-79% ICA stenosis) are 54:1 and the odds for symptoms are 130:1. The majority of the events occur within 6 months of the finding of an 80-99% stenosis, the mean interval to the event is 4.9 months.

5) Disease Progression and Blood Pressure

Of the 162 patients considered at risk of disease progression, 89 reported a positive history of high blood pressure (HBP) and 40% of these (36/89) showed progression during follow-up, similar to the 34% (25/73) progression in patients without hypertension history. In patients with hypertension (SBP > 160 mm Hg or DBP > 95 mm Hg) detected at study entry the progression rate (31/77 = 40%) was similar to progression in normotensive subjects (30/85 = 35%). Comparing the patients with progression to those with

intermediate severe stenosis stage would have been observed if follow-up had been more frequent between the original visit and the discovery of the occlusion.

The relationship between the state of the initial disease progression and the occurrence of either an occlusion or symptoms is shown in figure 5 and figure 6 and summarized in table 6. The risk of complication (TIA, stroke and occlusion) is much higher in the patients

FIGURE 3. Real time spectral waveforms, time vs. frequency. Spectral changes observed on a 59 year old asymptomatic patient. A 50–79% lesion was observed on the left side and remained stable throughout the follow-up period. On the right side, the lesion progressed from a 16–49% lesion in May 1980 to a 80–99% stenosis in October 1982. Two months later, the patient suffered a right hemispheric stroke and the ipsilateral internal carotid artery was found occluded.

FIGURE 4. Life table analysis. The annual rate of symptoms was 4%. The mean annual rate of progression from a less than 50% to a greater than 50% lesion was 8%. When disease progression in all categories is considered, about 60% of the sides will have progressed after 3 years of follow-up.

FIGURE 5. Disease progression in symptomatic patients. Ten patients developed spontaneous symptoms (6 TIA's and 4 strokes). This diagram shows the disease changes that preceded the occurrence of TIA’s (T) and stroke (S).
Disease progression preceding occlusion. Of 10 patients progressing to occlusion, one reported a TIA associated with occlusion (T) and two suffered stroke (S).

no progression, no difference was found in the cumulative distribution or systolic blood pressure (Kolmogorov-Smirnov 2-tailed test: \( p = 0.55 \)) or diastolic blood pressure (K-S test: \( p = 0.55 \)).

Using the Fisher Exact Test, no relationship was found between carotid artery disease progression and sex \( (p = 0.35) \), history of ischemic heart disease \( (p = 0.52) \), or history of peripheral vascular disease \( (p = 0.54) \).

6) Disease Progression and Treatment

The decision to treat and the form of treatment were left entirely to the discretion of the referring physician. Of the 162 patients considered at risk for progression, 23% (38/162) were taking aspirin alone on a regular basis, 6% (9/162) were taking dipyridamole alone, and 23% (37/162) were taking aspirin and dipyridamole on a regular basis. Dosages were not recorded. The proportion of patients who showed progression during followup, was the same whether the subject was taking aspirin and dipyridamole in combination (37%; 14/37), aspirin or dipyridamole alone (34%; 16/47) or was taking neither of these drugs (40%; 31/78). No patients were taking anticoagulants.

7) Disease Progression and Age

In the group of subjects older than 65 years at the time of entry into the study, the proportion of those who progressed was found to be lower (29%; 22/76) than in the younger group (45%; 39/86). The difference was statistically significant \( (p = 0.02 \) Fisher Exact). This difference could not be explained by length of followup. The mean followup was 16 ± 9.6 months for the younger group and 14.5 ± 9.5 months for the older group. There is a gradual increase in the prevalence of severe lesions with age (fig. 7). Observation of higher progression in the younger group may thus only reflect a difference in the initial disease distribution. The relationship between age and progression seems to disappear after accounting for the original state of disease (fig. 8).

8) Disease Progression and Cigarette Smoking

Of the 162 patients at risk for progression, 121 (75%) had a positive history of smoking. Of these, 42% (51/121) showed disease progression during followup compared to 24% (10/41) of the non-smokers \( (p = 0.03) \).

In order to evaluate possible benefit of stopping smoking, the subjects with a positive history of ciga-
cervical bruit. While the presence of bruit signaled an increased risk of ischemic heart disease and death, this rate is more than twice the expected incidence, up to eight years in the Framingham study. Although asymptomatic patients with a cervical bruit followed persons. Wolf et al reported a stroke rate of 12% in 171 smoking (47%, 36/77). The trend is statistically significant (P = 0.04, table 7).

9) Disease Progression and Diabetes
A positive history of diabetes was reported by 19 (12%) of the 162 patients followed. Because of the small number of diabetic patients, no attempt was made to distinguish the type of diabetes and form of treatment. Occurrence of disease progression was found to be higher (58%; 11/19, 95% CI = 36% to 80%) in the diabetic group than in the non-diabetic group (35%; 50/143; p = 0.04).

Discussion
Over the past several years, a great deal of attention has been paid to the finding of a bruit over the midportion of the neck as a possible indicator of carotid artery stenosis. This interest was particularly heralded by the report of Thompson et al. who noted a significant incidence of TIA's (27%) and stroke (17%) in 138 patients followed for an average of 46 months. Supported by others, Thompson et al. recommended prophylactic endarterectomy in selected symptomatic patients, claiming a decline in the incidence of TIA's (4.5%) and stroke (4.6%) due to the procedure. However, the nonoperated control population used in their study was not randomly chosen, and the report included all types and location of stroke without regard to the site of the bruit. While this approach is appealing with regard to stroke prevention, other reports have presented differing views. Two important population-based, epidemiological studies have documented the clinical implications of cervical bruits found in asymptomatic persons. Wolf et al reported a stroke rate of 12% in 171 asymptomatic patients with a cervical bruit followed up to eight years in the Framingham study. Although this rate is more than twice the expected incidence, about half of the strokes were nonischemic in nature, due to emboli originating from the heart or were not appropriate to the side of the bruit. From the rural Evans county, Georgia study, Heyman et al reported a stroke rate of 14% in asymptomatic patients with a cervical bruit. While the presence of bruit signaled an increased risk of ischemic heart disease and death, there was a poor correlation between the location of the bruit and the side of the stroke.

When attempts are made to evaluate the natural history of carotid bifurcation lesions by the presence of bruits alone, there are serious problems since not all cervical bruits are associated with significant internal carotid artery disease. The results reported in this study are consistent with previous findings in our laboratory in that more than half of the internal carotid artery lesions on the side of a cervical bruit were reduced by less than 50% diameter reduction. In fact, very severe lesions and occlusions are often not associated with an audible bruit. In order to study the natural history of patients with bruits, it is therefore essential to assess the extent of the lesions that are associated with the bruit.

All the natural history studies previously reported monitored the clinical outcome as the primary endpoint. While clinical endpoints are the most important concerns, they are rarely specific enough to document the basis for the event. Despite all the interest expressed in detecting carotid arterial disease, it is surprising that so little information exists on the natural history of such lesions. This is due to the fact that, up until recently, only contrast angiography could be used to estimate the extent of atherosclerotic disease. The only arteriographic data on the fate of carotid artery lesions was reported by Javid et al. Repeat angiograms were performed in 93 patients at intervals of 1 to 9 years (mean of 3 years). Only patients with lesions that reduced the arterial diameter by less than 60% were included in the study. When changes in the disease state were expressed in annual percent changes from the initial findings, disease progression of less than 25% per year was noted in at least one side in 22% of the non-operated patients. Although age, sex and diabetes did not appear to influence the rate of progression in their series, hypertension, the presence of a bruit and the initial extent of the disease all appeared to be directly related to the likelihood of rapid changes in the carotid plaques. Since duplex scanning has been shown to have excellent sensitivity and specificity in evaluating carotid artery disease, it is ideal for longitudinal studies.

Using the duplex scanner, serial studies in our population showed frequent changes in the disease classification over fixed time periods. Overall, 31% of the subjects showed some disease progression on one side only during the followup period and 7% on both sides. While disease changes were often important between the time of entry in the study and the last visit, disease progression by more than one category was not observed between two successive studies, except in 3 cases. This pattern suggests that, when disease worsening occurs, it is possible to monitor the successive changes over time. In all three cases where disease progressed by more than one category on successive visits, the original lesion was a less than 50% stenosis originally, and these arteries were found occluded at the following visit. The time intervals between the original visit and the finding of the occlusion were 12,

<table>
<thead>
<tr>
<th>TABLE 7 Influence of Cigarette Smoking on Disease Progression</th>
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</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Progressed</td>
</tr>
<tr>
<td>Total</td>
</tr>
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<td>Incidence</td>
</tr>
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Test for trend
\[ X^2 = 6.026; \text{d.f.} = 1; p = 0.014. \]
The rates of progression found in this population are surprisingly high. Our findings suggest that when a lesion is classified as a less than 50% stenosis, one out of three (33%, 95% confidence limits; 9.5%, 57%) will have progressed to a more than 50% stenosis after 3 years. It is possible to be confident about this estimate since distinction between a less than 50% and a more than 50% stenosis by duplex scanning bears a positive predictive value of 97% and a negative predictive value of 96% when compared to contrast angiography.7 When all types of progression are considered, 3 out of 5 patent arteries will have progressed to a more severe category of disease after 3 years.

Age at the time of entry into the study, diabetes and smoking habit were found to be independent contributing factors to the risk of progression. It is generally known that, of all risk factors, age has the strongest and most consistent association with atherosclerotic lesions.21 When our population was stratified by decade, the proportions of moderate and severe plaques increased with age (fig. 7). After accounting for the initial state of disease, the relationship between age and progression decreased in our population (fig. 8).

A positive history of cigarette smoking emerged as an important risk factor for carotid artery disease progression. Discontinuing smoking appeared to decrease the risk of progression. The risk of progression was 47% (36/77; 95% CI = 36% to 58%) for those who continued smoking during the study, 34% (15/44; 95% CI = 20% to 48%) for those who quit smoking before entering the study, and 24% (10/41; 95% CI = 11% to 38%) in those who had never smoked.

Our data also show that diabetes mellitus is a very prominent risk factor for carotid artery disease progression. This relationship stands even after correcting for age. Since progression was particularly prone in patients less than 65 years old, the effect of other risk factors in that population was particularly interesting. Diabetes increased by a factor of 2 and smoking by a factor of 1.6 the risk of progression in the young group (table 8). Since there were only 10 young diabetics, it was not possible to study the additional effect of smoking on progression in that population. However, in the young, nondiabetic population, smoking increased the rate of progression from 26% (9/35) for the nonsmoking to 49% (21/43) for the smoking group (p = 0.03).

Hypertension is also recognized as an important risk factor for the development of atherosclerosis.22 As a predictor for stroke, it has been shown that all components of blood pressure, i.e., the systolic and diastolic levels, the mean and pulse pressures are important.23 When correlated to carotid artery disease progression by Javid et al.,9 hypertension appeared to be a significant factor in predicting the likelihood of rapid changes in the carotid sinus atheroma. When different components of blood pressure were examined as potential risk factors for disease progression in our population, neither a positive history of hypertension nor treatment for hypertension, systolic and diastolic pressure levels or the blood pressure ratio, emerged to be significant. Since the findings in this study appear to be contrary to currently held views, the relationship between hypertension and disease progression will require a more vigorous assessment in future studies.

Perhaps the most fascinating observation from this followup study is the fact that a very close relationship was found between disease progression and the appearance of ischemic neurologic deficit or subsequent internal carotid artery occlusion. Based on these facts, the clinical approach to asymptomatic patients presenting with carotid artery lesions may have to be redefined. Of 162 patients serially followed, 5 developed an ischemic stroke. One of these occurred during an unnecessary arteriogram on the side of a less than 50% diameter reducing stenosis while 4 occurred spontaneously. Of these 4 spontaneous strokes, three occurred without warning TIA's for an overall rate of unpredictable stroke of 1.8% (estimated annual stroke rate of 1%). The estimated annual rate of incidence of TIA's is 3%. It is interesting to note that although 90% of the spontaneous symptoms were associated with a more than 80% stenosis at the time of occurrence of the symptoms, 40% occurred on sides that were narrowed by a less than 50% stenosis at the time of recruitment. Not considering the stroke that occurred on the side of an already occluded internal carotid artery, 89% of the symptoms (4 of 5 isolated TIA's and all 3 spontaneous strokes) were preceded by a disease progression to a greater than 80% stenosis. A disease progression beyond 80% also preceded the occurrence of an occlusion in all cases where sequential studies were available. Progression of a lesion to a more than 80% stenosis is an important warning observation since it carries a 35% risk of ischemic symptoms or ipsilateral occlusion within 6 months and a 46% (95% CI = 26% to 66%) risk at 12 months. Conversely, only 1.5% (4/260; 95% CI = 0.53–3.9%) of the lesions that remained in a less than 80% category developed a complication; one TIA occurred on the side of a stable 1–15% stenosis and 3 sides silently occluded.

These findings strongly suggest that it is safe to follow at 6 month intervals asymptomatic patients with a less than 80% diameter reducing lesion of their carotid arteries and to delay angiography and consideration for surgery until the first appearance of TIA or the finding of a marked progression of the disease. In fact, if the principle has been followed that asymptomatic
patients with a more than 50% stenosis should have an angiogram and a prophylactic endarterectomy. 77 patients would have been prophylactically operated on and 68 of these without proven benefit. Complications would still have occurred in 7 patients not selected for operation (2 TIA's, 3 occlusions and 2 strokes). On the other hand, if only those with evidence of progression to a more than 80% has been selected for prophylactic operation, 24 endarterectomies would have been performed during the followup period. The only complications that would have escaped prevention were 1 episode of amaurosis fugax on the side of a stable 1–15% stenosis and one stroke on the side of an internal carotid artery that was originally occluded. In addition, 3 internal carotid occlusions would have occurred without any associated symptoms on the side of a mild original lesion for which progression was not documented due to lack of followup visits.

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