MAJOR MEDICAL TREATMENTS generally advance through various stages of treatment and prevention depending on an understanding of the etiology and natural history of the disease.

In the initial phase, in which usually neither the etiology or natural history are understood, non-specific pharmacological therapy and procedures related to prevention of disability have highest priority. Stroke therapy through the early 1960's probably was in this category. Next, surgical therapy often becomes pre-eminent, especially when well-defined and surgically treatable pathology can be identified. For some diseases, such as certain orthopedic abnormalities and static deformities, further therapeutic advances do not occur. In the case of stroke, the preeminent role of surgery for the treatment of carotid artery disease, developed in the 1960's, led to the Joint Study of Extracranial Arterial Occlusion with the major results reported in the late 1960's and early 1970's. Surprisingly, in spite of the fact that the randomized clinical trial showed no significant differences in surgical versus non-surgical therapy, the evolution of surgical therapy has continued. As noted by Dyken,1 the number of carotid endarterectomies has increased from 15,000 in 1971 to 85,000 in 1982, a 467% increase. This procedure is done far more often in the United States than in England, with Canada apparently in an intermediate position.2 Furthermore, the frequency with which the procedure is done apparently varies substantially within the United States, at least in relationship to transient ischemic attacks. The cost of the procedure, both in terms of dollars and the potential life lost, may be substantial. There have been no further randomized clinical trials of surgical therapy for carotid artery disease. The benefits of the procedure are based on the numerous case reports of its efficacy, as compared to non-surgical, but not randomized patients.3 The commonly accepted belief seems to be that since the mortality and morbidity after endarterectomy has been reduced substantially, the cost benefit must now be in favor of surgical therapy.

The third step in therapeutic advance is the development of specific pharmacological therapy. This step usually depends on the better understanding of etiology and natural history of disease. For some diseases, like peptic ulcer, the specific medical therapy has already most completely supplemented surgical treatment. In the case of stroke disease, the era of specific pharmacological therapy began with the introduction and widespread use of drugs to treat hypertension,4 the major risk factor for stroke, and was followed subsequently by the use of aspirin and other antiplatelet aggregating agents to prevent the common thromboembolic disease especially artery-to-artery embolization.

Clinical trials have clearly demonstrated the benefit of both hypertensive treatment5 and aspirin in preventing stroke. The stroke death rates have been declining for many years,6 but the decline has been accelerated in recent years to about five percent per year, almost certainly due in part to the identification and treatment of diastolic hypertension. A major unanswered question now currently being investigated in a new clinical trial, is the efficacy of the treatment of pure systolic hypertension, a major risk factor for stroke especially in the older age groups.

Interestingly, specific medical therapy does not appear to be replacing surgical therapy, at least not for carotid artery disease. This apparently is due to the multiple etiologies of stroke and the continued belief in the superiority of surgical therapy as compared to antiplatelet agents in patients with surgically accessible carotid artery disease.7

The fourth step in the evolution of treatment is the development of specific preventive methods. Thus, the institution of penicillin and improved living conditions played a preeminent role in the prevention of rheumatic fever and subsequent rheumatic heart disease, practically eliminating both specific medical therapy for the complications of rheumatic heart disease and surgical treatment of valvular rheumatic heart disease.

Prevention of stroke is clearly possible by effective identification, treatment and control of hypertension. The stroke incidence, as well as mortality, is declining. However, stroke is still the third leading cause of death in the United States, and a major cause of both morbidity and mortality especially among the elderly. In 1980 there were about 170,000 stroke deaths,7 and at least 240,000 new strokes among those over the age of 65. Control of other risk factors especially hyperlipoproteinemia and diabetes may further prevent some of the strokes. A recent report of increasing fibrinogen levels suggests that abnormalities of clotting factors and thrombogenesis may also be playing an important role and has preventive implications.8
It is clear, however, that a substantial number of individuals in the community remain at high risk for stroke. The identification of such individuals, so called secondary prevention, and subsequent treatment may further reduce the incidence and mortality due to stroke and be an effective preventive approach. The most amenable technique has been the identification of extracranial vascular disease, specifically carotid artery disease.

Cerebral infarction is the major cause of stroke, approximately 75% of these strokes occur in the carotid circulation and 50% of the individuals will have major abnormalities of the carotid artery on angiographic examination. However, only 15% probably have surgically accessible and treatable lesions.

Three approaches are considered: A first approach might be the identification of patients with transient ischemic attacks, and subsequent surgical or medical therapy. Only about 10% of all strokes are preceded by transient ischemic attacks. There is also a relatively short time period between the initial transient ischemic attacks and subsequent stroke: that is, the risk of a stroke is greatest in the time period immediately after the initial transient ischemic attack. Patients with carotid artery disease, who subsequently have a stroke, may have a much higher prevalence of prior transient ischemic attack, estimated as high as 46% in the Joint Study of Extracranial Arterial Disease. Thus, the identification of patients with transient ischemic attacks and their subsequent treatment may be of specific benefit at least in terms of stroke related to carotid artery disease.

Probably 5–6% of TIA patients have a stroke per year. The increasing frequency of reported endarterectomy may be due to the improved identification and treatment of TIA in the community. It is unlikely that a system of self-referral of patients with TIA symptoms for further evaluation by their physician, and subsequent referral for surgical therapy is going to have a major effect on the incidence and mortality due to stroke. The morbidity and mortality following carotid endarterectomy, as noted in many studies, remains high. Many patients may not seek help prior to their stroke, and physicians may not recognize the TIA symptomatology. Furthermore, only about half of the TIA’s have ipsilateral carotid artery disease. Attempts to develop questionnaires to identify TIA patients in the community have not been very successful. Treatment of all identified TIA patients with aspirin might reduce the subsequent stroke risk by 50% at least among men. Wider use of aspirin or other antiplatelet aggregating agents among patients with suspected TIA might be of some benefit.

A second approach might be to identify individuals who have carotid artery disease. A variety of non-invasive procedures are available. Such techniques make it possible to identify the degree of carotid artery stenosis, the location of the lesion, and some aspects of the functional defects in terms of decline in both carotid artery blood pressure distal to the stenosis and relative blood flow.

The most common initial screening technique is auscultation of the neck in order to identify carotid bruits that may be associated with underlying carotid artery stenosis. There are many possible reasons for “noises in the neck.” Careful evaluation is required to separate the appropriate bruits related to the carotid artery from other pathophysiological sounds. The quality of the examination of the neck and the proper classification of such bruits is probably quite variable.

The epidemiology, natural history, and treatment of carotid bruits is confusing because of the paucity of well-defined studies. The prevalence and incidence of bruits is higher in older individuals, as is the risk of stroke. Further analysis will be limited therefore to the 65 + age group excluding individuals over the age of 80.

There are approximately 20,000,000 people between the ages of 65–80. The prevalence of carotid artery bruits is estimated at about 5% in this age group. Thus, 1,000,000 people probably have carotid artery bruits. The incidence, the number of new bruits per year, is about one percent a year or about 190,000 new bruits among the remaining 19 million people. A recent study suggested that 77% of individuals with bruits have a greater than 50% narrowing of the diameter of the carotid artery when evaluated by a continuous wave doppler technique.

Thus 770,000 of the individuals with prevalent carotid bruits and 146,300 of the incident cases have significant carotid artery disease. If every one of the 1,000,000 individuals identified as having bruits had a non-invasive evaluation at a cost of about $200/study the total cost would be about 200 million dollars just for testing alone. Such screening would well be worth the cost if it could be shown to lead to the prevention of a substantial number of strokes without further risk to the patient. The cost of stroke care in the United States in 1980 was 5.1 billion dollars.

The natural history of a carotid artery bruit and the implications of treatment, therefore, become of critical importance. It is obviously not the bruit that results in the stroke but the underlying pathology, resulting either in decrease of the effective blood flow to the brain or more likely artery to artery embolization. Thus, any evaluation of carotid artery bruit and subsequent therapy should include an evaluation of the underlying carotid artery disease. None of the two population-based followup studies include this information. In the Framingham Study, the two year incidence of stroke was 3% in men and 4% in women among individuals who had carotid artery bruits, a 2–3-fold increased risk. However, only 6 of 21 strokes and 4 TIA’s were ipsilateral to the carotid bruit. Of a total of 21 strokes, 6 had TIA’s prior to stroke. The risk of coronary artery disease was also increased among those with carotid bruits.

The Evans County study was a six year followup of 1620 individuals over the age of 40, 70 of whom had a carotid artery bruit. Over a six year period, 10 (13.9%) of them had a stroke, a risk of about 2% per year, similar to that in the Framingham Study. The risk of a
bruit and subsequent stroke increased with age and level of systolic blood pressure greater than 160. The risk of stroke compared to the general population when adjusted for age was 7.5 fold higher in men compared to the 1.6 fold increase in women. In the Framingham Study, the risks were higher in women than in men. Like the Framingham Study, however, only 3 of the 10 strokes had an ipsilateral carotid artery lesion. The risk of coronary artery disease again was substantially increased.

The conclusion from these two studies suggested that carotid artery bruits were a measure of systemic vascular disease and not specifically a risk factor for ipsilateral carotid artery stroke. Neither study, however, provided any information about the underlying carotid artery pathology nor about subsequent treatment.

The most recent studies have included some measure of carotid artery disease but are not population-based. The Toronto Asymptomatic Bruit Study included 500 individuals with carotid artery bruits. During a 30 month followup there were 28 neurological ischemic events among 25 patients, 22 were ipsilateral to the bruit. There were however only 5 strokes, 2 denovo and 3 among 26 TIA patients. The risk of an ischemic event was about 15%/year among those that had 75% stenosis or greater as compared to 3% for those with less than 75% stenosis. The rate of stroke of about 1% over 30 months was low and primarily limited to those with greater than 75% stenosis.

The Seattle group used a duplex scanning technique, the combination of B mode echo and pulsed doppler. The technique was reported to have a 99% sensitivity and an 84% specificity. They evaluated 1450 patients referred to the vascular laboratory. Approximately 14% (203) were found to have an asymptomatic mid-cervical bruit. Of the 203, 162 were available for further evaluation. Seventy-three of the patients had bilateral and 89 unilateral bruits. Significant vascular disease defined as greater than 50% narrowing of the diameter was noted in 40% of the carotid arteries in the 162 patients.

The frequency of bruits increased slightly with the extent of carotid artery narrowing up to total occlusion. Progression of carotid artery disease was evaluated at six months and then at yearly intervals and progression was judged to have occurred if there was an increase in the degree of stenosis from one category to the next, that is from 20 to 40% to greater than 50%, etc. Sixty-two percent of the patients remained unchanged, 50 (31%) had progression on one side, and 11 (7%) progression on both sides.

During a three year followup the rate of TIA, stroke, or completed occlusion was about 4% per year. There were 6 TIA (2.4/year), 3 strokes (1.2/year), and 1 TIA and stroke (0.4/year). The annual rate of progression of lesions from less than 50% diameter narrowing to greater than 50% was about 8% per year. All strokes occurred among the 24 individuals who had progressed to greater than 80% diameter narrowing, as did all but 1 of the 6 TIA's. Among those with an 80% or greater diameter narrowing, there was a 35% risk of occlusion, or stroke, or TIA at six months and 46% at 12 months; while for those with less than 80% diameter carotid narrowing, the risk was only 1.5% at six months. However, less than 10% of arteries progressed to greater than 80% narrowing over this three year period.

Thus overall, the risk of stroke among patients who have carotid bruits is only 1–2% per year. However when combined with extensive carotid artery stenosis, the risk rises substantially. Most treatment decisions should therefore be based on either prevention of the progression of the carotid artery disease related in this study and others to age, cigarette smoking, diabetes; or to the treatment of those who have the bruit and extensive carotid artery stenosis to the less than 10% of the patients with greater than 80% carotid artery narrowing. In order to identify these patients, however, it would require serial reevaluations probably at yearly intervals using high quality non-invasive methods in which the sensitivity and specificity of the procedures are carefully documented when compared to carotid angiography. Furthermore, no data are available on the efficacy of treatment of such patients in terms of the prevention of stroke or cardiovascular death.

A third approach would be to use non-invasive methods to identify individuals in the population with “significant carotid artery stenosis.” Only one study has carefully documented the prevalence of carotid artery stenosis in selected but defined populations. Hennerici et al., used direct continuous wave doppler examinations to study 375 patients with severe peripheral vascular disease, 264 with coronary artery disease and 1370 from a normal but “high risk population.” The frequency of carotid artery disease, defined as more than 50% narrowing of the lumen, was much higher in those with peripheral vascular disease, 32.8% than with coronary artery disease, 6.8%, or “high risk,” only 5.9%. A recently completed study in Pittsburgh also noted a 20% frequency of carotid artery bruits among individuals over the age of 60, with a mean age of 71, participating in a clinical trial of systolic hypertension in the elderly. The carotid bruits were correlated with the ankle/arm blood pressures, a measure of peripheral vascular disease and with a history of intermittent claudication. Those with bruits were about four times as likely to have an abnormal ankle/arm blood pressure index. Cigarette smoking was further related to both carotid artery bruits and to ankle/arm blood pressure abnormalities. These results plus the previous findings from both the Framingham and Evans County Studies substantiate the relationship between carotid artery disease and generalized vascular abnormalities. The carotid bruit and subsequent carotid artery stenosis should therefore not be treated as an isolated pathological process, but as part of a generalized systemic vascular disease.

Using this database from Hennerici further, the prevalence of carotid artery stenosis defined as greater than 50% narrowing of the diameter was 5% among those patients 65 years of age. This would yield about one million people of these 20 million over the age of ...
65 with extracranial arterial stenosis. The number of new strokes as noted in this age group is about 240,000/year. About one-third of the strokes are related to large artery disease, primarily carotid. Thus, of the one million individuals with carotid stenosis, one might expect about 80,000 strokes, or a rate of about 7 strokes/100 individuals/year.

In the Hennerici study, carotid artery bruits were found in only 27.6%, 34 of 123 individuals, who had significant carotid artery disease as defined by the Doppler technique. Furthermore, in 23% of the cases in which a bruit was identified, the Doppler examination was normal. Thus, examination and referral of patients with bruit alone would substantially underestimate the number of patients at risk based on their extensive carotid artery disease.

A report by Busuttili has further demonstrated the importance of hemodynamically significant stenosis and risk of stroke in patients with carotid artery disease. Using the oculopneumoplethysmography (OPPG), they found that the risk of stroke was exceedingly low in the "non-hemodynamically significant" carotid stenosis, but occurred in 12 of 125 with "significant stenosis" within 2.5 years.

The need for studies that include both the careful measurement of bruits and the extent of carotid artery disease and further evaluation of the lesions over time is obvious. The current database is probably poor, inaccurate and may be leading to costly clinical decisions both in terms of money and lost lives. The average length of stay of patients with extracranial vascular disease surgery is 9 days. At about $300/day the hospital cost alone is probably at least $3,000 and $255 million for the 85,000 procedures in 1982.

Carotid artery disease, whether identified by bruit and subsequent non-invasive evaluations or directly by non-invasive technique, is part of a generalized systemic atherosclerotic disease and must be approached as such. Thus, techniques to prevent the complications of atherosclerotic disease including treatment of hypertension, hyperlipidemia, prevention of cigarette smoking, reduction of the tendencies towards thrombosis, etc., must have high priority. Furthermore certain high risk populations, such as those with peripheral vascular disease, diabetes, and systolic hypertension should be ideal candidates for careful evaluation.

The quality of these evaluations both in terms of the evaluation of the bruits, the non-invasive laboratory documented low mortality and morbidity. 22 Thus, of the one million individuals with carotid stenosis, one might expect about 80,000 strokes, or a rate of about 7 strokes/100 individuals/year.

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