An Evaluation of the Epidemiology of Atherothrombotic Brain Infarction

WILLIAM B. KANNEL
PHILIP A. WOLF
THOMAS R. DAWBER

Review of the epidemiology of atherothrombotic brain infarction (ABI) based largely on 18 years of prospective data from the Framingham cohort reveals that stroke is a potent force in morbidity and mortality, that hypertension is its dominant precursor, that it can be predicted and suggests that only a preventive approach can substantially reduce stroke morbidity.

Data from Framingham on the relative frequency of the major types of stroke found in the community reveal that 57 percent are due to ABI and only 17 percent to intracranial hemorrhage—two-thirds of which is subarachnoid. Lacunar infarcts are common accounting for 13 percent of ABI's in men and 23 percent in women.

Despite the sizeable geographic, seasonal and secular trends in stroke mortality, few environmental determinants of stroke have been uncovered. However, established hallmarks of the candidate for an atherothrombotic stroke include: hypertension (systolic or diastolic), glucose intolerance, high normal hemoglobin, the cigarette habit (men only), abnormal lipids (under age 60) and cardiac impairments. Many unresolved issues remain. Nevertheless, it is possible to identify a tenth of the general population from which half the strokes will emerge. This provides a rational basis for establishing a program of prevention.

Over the past decade, prospective epidemiologic investigations at Framingham have begun to enrich our understanding of the way strokes arise, evolve and terminate fatally (Kannel, 1971). The characteristics of the potential stroke candidate, his fate once the disease appears, and the factors which affect this are becoming increasingly clear. The purpose of this report is to review the current status of the epidemiology of cerebrovascular disease relying heavily on Framingham data and focusing on atherothrombotic brain infarction (ABI), the most frequent type of stroke.

Current assessment of the epidemiology of atherothrombotic brain infarction reveals that it is a potent force in morbidity, that it can be predicted, that it is more disabling than lethal, and that its control requires a preventive approach. A number of major contributors to ABI incidence have been identified, providing a basis for an effective prophylactic program.

The Epidemiologic Approach

This report will use the Framingham data extensively to examine many pertinent issues. The Framingham cohort of 5,184 men and women, free of stroke and aged 30-62 at onset of the study, were examined and classified at entry and biennially thereafter. Their records included a variety of personal attributes and living habits suspected of contributing to the major clinical manifestations of atherosclerosis. Over the ensuing 20 years they have been followed for the development of clinical evidence of cardiovascular disease, including strokes. Criteria, methods of examination and sampling procedure and response rates have been described in detail elsewhere (Gordon et al., 1971). Follow-up of this representative population sample has been reasonably complete, with about 80 percent receiving every possible biennial examination and the remainder seen at less frequent intervals. Only about two percent have been completely lost.

The Framingham Study was begun in 1949 to study the epidemiology of coronary heart disease and hypertension. The study was undertaken in Framingham, Massachusetts, under the director of the National Heart and Lung Institute. Two-thirds of the town residents aged 30-59 were selected by random sampling and invited to participate in the study. Two-thirds of this group participated. Knowledge of the characteristics or disease outcomes of the non-participant is limited. For several years after the onset of the study, the incidence and causes of death were determined and, as might be expected, were somewhat higher than in the examined population. We may therefore conclude that the failure to obtain full participation of the study population may have led to some underestimates of the incidence of the disease under investigation. However, with no knowledge of their characteristics (i.e., risk factors) even this conclusion is speculative.

From Framingham and other prospective studies, information has been provided on the probability of an attack over many years, a clearer picture of the total spectrum of the disease in all who have it, the chain of events leading to the disease, its precursors, hallmarks of vulnerability, clues to pathogenesis and a profile of the potential stroke candidate. Each of these features of the epidemiology of cerebrovascular disease will be explored in this report.

While the epidemiologic approach explores the origins and evolution of stroke in a population sample, it also has relevance to its occurrence in the individual. A prospective study although costly, slow to yield results, and more cumbersome, can be designed to avoid many of the pitfalls of the retrospective study and provides the soundest epidemiologic information available.

The Stroke Entity

Epidemiologic studies have been hampered by ill-defined, non-uniform criteria for a stroke and either failure or inability to distinguish among the major stroke entities. Since the underlying pathology differs, there is little reason to believe that the epidemiologic features of each variety are identical. For this reason, studies which deal with undifferentiated strokes could be misleading. At least four major stroke entities should be distinguished: atherothrombotic brain infarction, cerebral embolus, intracerebral hemorrhage, and subarachnoid hemorrhage. Furthermore, to gain a better understanding of the precursors of strokes and their natural history, it would appear desirable to distinguish those ABIs due to extracranial vascular disease and those due to lesions in the small penetrating branches deep within the brain substance. It is difficult to distinguish these various subdivisions of stroke by clinical evaluation or even postmortem studies.

A considerable expansion of knowledge of the pathophysiology of stroke has taken place over the past two decades, differentiating the temporal profile (transient ischemic attacks, progressing stroke, completed stroke), the arterial lesion (thrombosis, embolus, hemorrhage, arteriolar disorganization), and the brain lesion (transient ischemia, infarction, lacunes and hemorrhage). New diagnostic procedures, such as computerized axial tomography, have great potential for differentiating among strokes and distinguishing strokes from other conditions (Baker, 1975).

Much remains to be learned about the pathogenesis of cerebral vascular disease. The term ''cerebral thrombosis'' would seem obsolete since ischemic cerebral attacks can, and often do, occur in the absence of a demonstrable occlusion; they may be caused by an embolus from more proximal atherothrombotic lesions or may de-

rive from a less well-defined process in the smaller penetrating branches, producing lacunar infarcts. When there is occlusion of a cerebral vessel, angiography and even histological examination frequently do not allow differentiation of an embolus from a thrombus.

Transient Ischemic Attacks

The exact nature of the transient, ischemic, cerebral attack which fails to produce a permanent neurologic deficit is unclear. Somewhat akin to angina in the heart or intermittent claudication in the limbs, these reversible attacks have more ominous import in the head because of the greater vulnerability of the brain to hypoxia. Current assessment suggests that most of these attacks arise from proximal atherosclerotic disease in the extracranial vessels supplying the brain from which microemboli composed of either thrombotic or atheromatous material break off. The attacks usually last only minutes to an hour but may persist for as long as 24 hours. The longer they last, the more likely it becomes that a brain infarction has occurred.

There is now evidence to suggest that a greater percentage of strokes than was formerly believed arises from disease in the brachiocephalic vessels. Because of the accessibility of these arteries to surgery, interest has focused sharply on their role in the pathogenesis of stroke. Estimates of the percentage of brain infarctions which are due to such arterial lesions vary widely (Fisher, 1951; Fisher, 1965). Accurate appraisal of the importance of extracranial vascular disease in the occurrence of strokes is difficult to obtain because this often co-exists with intracranial disease, and cannot be accurately detected without invasive procedures. It is not uncommonly present in asymptomatic persons. If all components of the intracranial circulation are normal, even complete occlusion of a single extracranial artery does not necessarily produce a cerebral infarction. On the other hand, an extracranial arterial lesion may generate emboli which may occlude an intracerebral vessel leading to a brain infarction, even if the pattern of intracranial flow is normal. Because of the complexity of these interrelationships, it often is difficult on clinical grounds alone to determine if a cerebral infarction is due to extracranial, intracranial, or combined disease. It is unlikely, because of the foregoing, that prospective epidemiologic studies will in the forseeable future pro-

vide valid information on the natural history of extracranial vascular disease. Such disease, rather than a unique entity, is only one facet of the atherosclerotic process affecting the brain.

The risk of brain infarction in persons with asymptomatic blocked extracranial vessels is unknown. In persons with transient cerebral ischemic symptoms, the risk of developing a completed stroke, recurrent symptoms, and remissions are variously estimated from clinic studies (Kuller, 1974; Toole et al., 1975). Risk of a stroke would appear to range from four to 16 percent per year (Report Joint Committee for Stroke, 1974). The danger of a stroke would appear to be greatest in the weeks or months follow-ing its onset and in those having more frequent attacks (Report Joint Committee for Stroke, 1974). It is alleged that transient ischemic attacks precede 30-50 percent of completed cerebral in-farcts (Report Joint Committee for Stroke, 1974). These selected data very likely overestimate the transient ischemic attacks as a hallmark of impending ABI. But this represents only the subgroups of transient ischemic attacks referred to neurologic services. More representative data from prospective population studies is urgently needed.

Lacunar Strokes

A subgroup of atherothrombotic brain infarction which should be distinguished from the general category usually subtended under the rubric of "cerebral thrombosis" is the lacunar infarction (Fis-her, 1969). This is to be distinguished from the "lacunar state" often erroneously used to describe a smooth progressive loss of in-tellect in the elderly without the episodic events which are the hallmark of occlusive vascular disease. Fisher (1965) has dist-inguished focal neurologic deficits which he has correlated with lacunes deep within the brain substance which present clinically as a pure motor hemiparesis (Fisher, 1965); pure sensory stroke (Fis-her and Cole, 1965); crural paresis with homolateral ataxia (Fisher and Curry, 1965); or dysarthria with clumsiness of one hand (Fis-her, 1967). In Framingham, based on careful clinical evaluation at the time of the ictus, they were found to be relatively common, ac-counting for 13 percent of ABIs in men and 23 percent in women. Whether these lacunar infarcts can be reliably distinguished clinically from occlusive cerebral vascular disease involving the larger intracranial and extracranial vessels remains to be de-

monstrated. However, more information is needed on their precursors and natural history.

Cerebral Embolus

Cerebral embolus is most accurately diagnosed when it occurs in young persons with a source for embolus in the heart and cardiac dysrhythmia, and is accompanied by emboli to other organs. When it occurs in older persons, even in the presence of atrial fibrillation or a recent myocardial infarction, it may be difficult to distinguish from an ABI with thrombotic occlusion. Based on careful postmortem dissections, it has been alleged that as many as half of ischemic strokes may in fact be embolic in origin (Jorgensen and Torvick, 1966). Thus, the distinction between these two entities is problematic.

Intracranial Hemorrhage

Intracerebral hemorrhage is usually distinguishable from a subarachnoid hemorrhage on clinical grounds, and each is distinguishable from an ABI or an embolic occlusion if the spinal fluid is also examined.

The problem of diagnosis of stroke, or differential diagnosis of the type of stroke constitutes an obstacle to obtaining an undistorted picture of the epidemiological features of stroke, particularly from mortality data. Review of death certificate statistics gives undue prominence to intracerebral hemorrhage and appears grossly to underestimate the occurrence of subarachnoid hemorrhage and cerebral infarction resulting from thrombosis or embolism (Table 1).

Frequency of Types of Stroke

Estimates of the relative frequency of the major clinical manifestations of cerebral vascular disease vary widely, depending on whether the general population samples, hospitalized cases or autopsy material is used (Kannel, 1971). Because it contains all the cases, hospitalized or not, and the living as well as the dead, prospective data based on a general population sample, such as that from Framingham, probably provides the least distorted informa-

tion on the relative frequency of each variety of stroke. These data, based on 196 confirmed strokes evolving in the population sample over 18 years of follow-up reveal that 57 percent were ABIs; intracranial hemorrhage occurred in only 17 percent and in two-thirds of these, the bleeding was subarachnoid not intracerebral (Table 2). About 15 percent appeared to be due to emboli originating in the heart. Other prospective studies concur in the finding of a much lower proportion of strokes attributable to intracerebral hemorrhage than reported in mortality statistics. Since the case fatality rate is so much higher for intracerebral hemorrhage than ABI, this is understandable.

Size of the Problem

Strokes in general and ABI in particular represent a formidable and possibly a growing threat in the world. The chance of an ABI before age seventy is approximately one in 20. Stroke is the third ranking cause of death in the U.S.A., following coronary heart disease and cancer. Although strokes primarily afflict the elderly, one fifth occur in persons under age 65, often during their most productive years. There are approximately 500,000 new strokes and 200,000 deaths from this cause annually in the U.S.A., or about 11 percent of the total mortality (NIH, 1971). The estimated prevalence at any one time is 20/1000 in the 45-54 age group, 60/1000 at 65-74 and 95/1000 at ages 75-84 (NIH, 1971). Of all decedents in the Framingham cohort, stroke had occurred in 15 percent but was certified the underlying cause in five percent of men and eight percent of women. Thus, based on Framingham data, it would appear that death certificate data classified by underlying cause underestimates strokes in the background of decedents by more than half. It is estimated that 1.6 million persons in the U.S.A. are afflicted by stroke. It is a severely disabling malady leaving 40 percent requiring special services and 10 percent total care.

The nature of the lesion in the brain, the inability of the brain to tolerate more than very brief periods of ischemia, and the lack of regenerative capacity, preclude any substantial improvement in the neurologic deficit incurred, once a completed stroke has occurred. Further innovations in the management of already established disease, no matter how ingenious, cannot effect a substantial improvement in stroke morbidity and mortality. Prevention requires early identification of highly vulnerable persons prior to

symptoms and vigorous and sustained prophylactic management of the factors which predispose. Considerable progress has been made in this regard, making it possible to interrupt the chain of events in the evolution of this devastating illness which robs persons of their dignity, self-esteem, physical prowess, and self-sufficiency. ABI is the only major atherosclerotic event that fails to show a clear male predominance except for premature ABIs (Table 3). The reason for the greater immunity of women to coronary than to cerebral atherosclerosis is unclear. It may derive from the fact that atherosclerosis proceeds more slowly in the cerebral vessels so that it does not reach major proportions until women have already lost the relative immunity of their premenopausal, reproductive years.

Geographic Variation

While the incidence of ABI is distressingly high, it is not uniformly so. The incidence of hemorrhagic and ischemic strokes appears to be distinctly higher in some populations than others (Kurtze, 1969; Gifford, 1966; Baker et al., 1967; Williams et al., 1969, WHO, 1969). The reason for this is obscure. Differences in death certification practices, diagnostic sophistication, hospital admission practices, variations in the prevalence of hypertension, as well as genetic differences all seem to be involved.

Native Japanese are alleged to have a high incidence of intracerebral hemorrhage, but a low incidence of cerebral infarction (Stallones, 1965; Baker, 1969; Katsukis, 1969). The reverse is the case for American born Japanese, while for Hawaiian Japanese the proportion of each variety of stroke is equal. Taken at face value, mortality statistics from Japan suggest that the incidence of intracerebral hemorrhage has been declining, while that of cerebral infarction has been rising (WHO, 1969).

Within the U.S.A., there appear to be large differences in incidence and prevalence of stroke (President's Commission on Heart Disease, 1964; Borhani and Mayer, 1968). All varieties of stroke appear to be more common in the East South Central region than elsewhere, and least common in the Rocky Mountain States. In any region, there are reported differences in the average age of strokes in blacks vs. whites and, less consistently, between the two sexes. These differences are to a great extent, but not entirely, due to regional differences in fashions in certifying causes of death.

Although the observation of geographic variation in stroke mortality is not particularly helpful in understanding the causes of strokes, it does justify a search for genetic, ethnic and environmental predisposing factors. It also helps to identify vulnerable persons and places where stroke candidates can be found for investigation or intervention. It is of particular interest in this regard that the geographic variation in prevalence of hypertension and the percentage of the population which is black correspond reasonably well with that of the stroke mortality.

Hallmarks of Vulnerability

In any geographic area, in any race, in either sex and at any age, the incidence of ABI is far from uniform, and those who are highly vulnerable can be identified. ABI is primarily an atherosclerotic disease, and on this account ought to share the same precursors as coronary heart disease (CHD). Because of an alleged disparity in the prevalence of CHD and ABI in different geographic areas and races, it has been suggested that etiologic factors may differ. ABI is in fact more related to aging and hypertension and less to obesity, blood lipids, cigarettes and physical activity than CHD (Kannel, 1971). However, the differences appear to be more a matter of degree than kind, since persons who develop CHD are decidedly at increased risk of ABI and vice versa (Table 4).

Obesity is weakly related to the occurrence of ABI, very likely because it promotes atherogenic traits—particularly hypertension (Fig. 1). The effect of overweight is only significant and sizeable for women in Framingham. Other studies have found that the obese are more prone to strokes (NIH, 1971).

The relation of *cigarettes* to stroke is less well established than to the development of occlusive peripheral arterial disease or coronary heart disease (Paffenbarger and Wing, 1967; Kahn, 1966; Hammond and Garfinkle 1969). In the Framingham cohort among men, heavy cigarette smokers (> 20 cigarettes per day) had almost three times as many premature, atherothrombotic brain infarctions as non-smokers. The impact of cigarettes was dose-related but diminished with advancing age. The effect was independent of all the major identified contributors to stroke incidence and was especially deleterious in those otherwise at high risk, particularly hypertensives and diabetics (Fig. 2).

In women, only a suggestive relationship not reaching

statistical significance was found. However, there were few heavy cigarette smokers among them, many did not inhale, and there were too few strokes under age 55 to permit assessment of the impact of cigarettes.

Despite less conclusive evidence for stroke, persons prone to stroke are also at high risk of occlusive peripheral arterial disease and coronary disease. Avoidance of cigarettes would seem prudent.

The association of *blood lipids* with ABI is considerably weaker than for CHD (Williams et al. 1969; WHO, 1969; Stallones, 1965; Baker and Katsukis, 1969; Katsukis and Hirota, 1966), and appears to apply only to distinctly premature strokes in persons whose lipids were characterized in early adult life (Kannel, 1971, Gordon et al., 1971). Both triglyceride-rich pre-beta and cholesterol-rich beta lipoprotein were related to the development of precocious ABIs in the Framingham cohort, statistically significant only for men (Fig. 3). Also, regardless of lipoprotein pattern, risk was proportional to serum cholesterol value under age 60. There is only weak evidence associating cerebral infarction with abnormalities in blood lipids when measured over age 55 (Table 5) (Kannel et al; 1965; Cumings et al., 1967). In the absence of other contributors to risk of ABI, the influence of lipid is feeble—at any lipid value, risk of brain infarction varies over more than a 10-fold range, depending on the number and intensity of other contributors to stroke (Fig. 4). Even in CHD, however, where a strong relationship is evident in both sexes, the effect of lipids wanes with advancing age, and little effect would be expected beyond age 65 (Kannel, 1971; Gordon et al., 1971) when most strokes occur.

Hypertension both systolic and diastolic (Kannel, 1971; Gordon et al., 1971), is strikingly related to stroke incidence. This is true at all ages in both sexes, even in otherwise low risk persons. The effect is independent of other associated factors (Kannel et al., 1970). In contrast to the modest effect of lipids, the blood pressure has a marked influence on the risk of ABI whatever the level of lipid (Fig. 7). Contrary to expectation, not only is risk of ABI more reliably and efficiently estimated from systolic than diastolic pressure, but from casual as well as basal pressures. Because there is no evidence of a decrease in the impact of systolic pressure with advancing age (Fig. 5), it is probable that even the isolated systolic hypertension characteristic of the aged, inelastic artery is an important contributor to stroke incidence (Colandrea et

al., 1970). Also, comparison of the risk gradients in the two sexes reveals nothing to suggest that, as far as strokes are concerned, women tolerate hypertension better than men (Fig. 5).

Aside from age, blood pressure is the most common and most potent independent contributor to ABI incidence thus far identified. This is true to the extent that it can be ascertained from a comparison of standardized multivariate regression coefficients for a set of the major identified contributors to ABI incidence (Table 5). Epidemiological, animal, experimental, and spontaneous observations in humans suggest that blood pressure must play a critical role in atherogenesis (Fisher, 1954). The low pressure components of the circulation (e.g., veins, pulmonary arteries) are characteristically immune to the atherosclerosis despite the fact that they are bathed by the same lipid-laden blood. When the pressure is raised by pathology, atheromata appear even in these segments of the circulation. There are evidently pressures below which atheromata will not form.

There is evidence that, no matter how assessed, persons with impaired glucose tolerance develop a distinct excess of ABIs (Kannel, 1971; Grunnet, 1963). They also appear less likely to survive the attack. The associated lipid abnormalities, hypertension, and obesity characteristic of diabetics accounts for much, but not all, of the excess risk of the diabetic. In high or low risk subjects, and at any level of blood pressure, risk of ABI is increased in those with impaired glucose tolerance (Fig. 6). Either because of the greater severity of the diabetes or a different metabolic defect, the insulin-treated diabetics also have a greater risk than those not requiring insulin (Garcia et al. 1973).

The more atherogenic traits present, the greater the susceptibility to ABI. Risk rises impressively the greater the strength of the combined factors, particularly in those who smoke cigarettes and have ECG-LVH (Fig. 7).

It thus appears that at the advanced age at which most strokes occur, hypertension becomes the over-riding factor. While the same risk factors appear to operate in ABI as in other atherosclerotic diseases they seem to do so with less effect, requiring a longer exposure.

Cardiac Impairments

Any evidence of target organ involvement in the hypertensive is associated with an enhanced risk of ABI. This is either a reflection

of the severity and duration of the associated hypertension or an additional effect of impaired cardiac or renal function (Wolf et al., 1973). Thus, risk of ABI becomes ominous when CHD (Table 4), ECG-LVH, or cardiac enlargement on X-ray appear (Fig. 8). Aside from being a hallmark of sustained hypertension and evidence of vulnerability of the cardiovascular apparatus to it, poor cardiac function evidently directly precipitates some strokes, since at any level of blood pressure, risk of ABI is enhanced when evidence of cardiac impairments such as ECG-LVH appears (Fig. 9). Risk of cerebral infarction is increased almost five-fold in persons with CHD, and this excess persists at three-fold after adjustment for blood pressure (Kannel, 1971). The converse is also true; whether cardiac impairments are present or not, the gradients of risk rise similarly in proportion to the blood pressure (Kannel, 1971). The appearance of congestive failure is ominous indeed.

Heart disease such as valvular deformity, congenital defects, SBE, myocardial infarction, dysrhythmias, conduction defects, and congestive failure are associated with a marked excess risk of strokes, including ABI (Friedman et al., 1968). Stroke is an important complication of the insertion of prosthetic valves. Less well appreciated than the foregoing is that there is a high prevalence of cardiac impairments in stroke-prone or stroke patients. About 75 percent have one or more of the following: coronary disease, ECG abnormalities, an enlarged heart, or congestive failure. These undoubtedly directly contribute to the occurrence of strokes in susceptible persons, but also are an important source of co-morbidity. They are chiefly responsible for the truncated survival in the stroke patient (Schiffman, 1970).

Systemic Disease

Strokes rarely occur under age 45. When they do, it is likely that some systemic disorder such as a collagen disease, diabetes, polycythemia, sicklemia, or other blood dyscrasia, SBE, macroglobulinemia, or severe hypoglycemia is responsible. Above age 44, such causes are seldom found, and the major "risk factors" are usually the only stigmata found.

Studies at Framingham have demonstrated an association of *blood hemoglobin* values within the normal range and incidence of ABI (Kannel et al., 1972). This excess risk in those at the upper limits of the normal range is largely, but not entirely explained by

an association of hemoglobin values with blood pressure and the cigarette habit (Kannel et al., 1972). This finding has been confirmed elsewhere, but requires further evaluation.

The Stroke Profile

In general, the more contributors to stroke incidence present, the greater the risk an ABI will occur (Figs. 7,9). Arbitrary categorical assessments have pragmatic utility and will definitely detect high risk persons. Unfortunately, they will also miss a substantial proportion of persons with a comparable degree of risk who are excluded because of marginal values of multiple risk factors.

There is no question that blood pressure is the major contributor to ABI incidence. Judging by the size of multivariate regression coefficients, suitably standardized for the different units of measurements, it is clear that blood pressure is the dominant contributor to stroke incidence, exerting the largest independent effect. Hypertension, besides accelerating cerebral atherogenesis is the basis of other serious conditions affecting the cerebral circulation: impaired cardiac function which may precipitate strokes in persons with critically narrowed vessels, lacunar strokes from multiple, tiny infarcts deep in the brain substance, and intracerebral hemorrhage or rupture of saccular aneurysm weakened by atherosclerosis.

As strong a factor as hypertension is, the risk of ABI varies profoundly at any blood pressure level depending on the associated risk factors (Figs. 2,6,9). Thus, blood pressure, or any other factor, is best viewed as an ingredient of a stroke profile. Using a multiple logistic formulation which describes the conditional probability of an ABI, and in which the constants of the intercept are known (Fig. 2), a handbook can be computed using an efficient set of variables. This allows the estimation of risk of an ABI for any combination of values in each sex and age group (Table 6).

ABI is part of a larger problem of cardiovascular disease. The set of variables employed for its prediction must reflect this. Also, the variables used must each make some independent contribution to risk; they should be safe and practicable, using ordinary office procedures and simple laboratory tests. Ideally, they should be obtained by an office nurse or technician. An efficient set is: a casual

blood test for cholesterol and sugar, a blood pressure, an ECG, and a cigarette history. This combination will estimate risk of ABI over more than a 30-fold range (Table 7). It can detect a tenth of the general population from which not only about half the ABIs will emerge (Table 7), but also 40 percent of the occlusive peripheral arterial disease, as well as 25 percent of the coronary disease. It is to be hoped that measures which are used successfully to prevent ABI will carry the considerable bonus of protecting against the more common and more lethal coronary disease and disabling intermittent claudication.

Preclinical Cerebral Atherosclerosis

As in other parts of the circulation, severe advanced atherosclerosis may exist for long periods prior to the appearance of either transient ischemic cerebral symptoms or a brain infarction. The earliest evidence that this may be present is provided by the biologic hallmarks of accelerated atherogenesis—elevated blood pressure, lipid abnormalities, and impaired glucose tolerance. In persons with one or more of these atherogenic traits, evidence of an impaired cerebral circulation can sometimes be obtained by auscultation for cervico-cranial vascular bruits over the neck, head or eye, palpation of superficial temporal, facial, occipital, subclavian and carotid pulses, variation of pressures and pulses in the upper extremities, opthalmodynamometry and X-ray examination for calcification of vessels in the neck, and blood pressure lower in the arms than in the opthalmic arteries. There are no dynamic tests considered safe which bring out latent ischemia. Rarely, vetebrobasilar artery insufficiency may be precipitated by exercising one or the other arm (subclavian steal syndrome).

Invoking guilt by association, persons with any of the aforementioned atherogenic traits who exhibit any of the foregoing physical findings may be presumed to have preclinical ischemic cerebral vascular disease, even though, taken alone, none are pathognomonic.

Despite a large number of clinical follow-up studies, it is still not possible to determine whether cranio-cervical bruits have predictive value in the *asymptomatic* population.

Death and Disability

ABI is more disabling than lethal. The case-fatality rate in ABI is about 20 percent. Even if the victim of the transient ischemic at-

tack or ABI survives the attack, his future is not bright. Disability is considerable and 40 percent will have some residua. Only 10 percent have virtually no residual impairment. About 25 percent will no longer be independent in self care, while 10 percent will end up confined to chronic care facilities. Mortality within two years will be about 20 percent for women and 33 percent for men. Coronary disease and congestive failure are the major causes of death in stroke patients, and their survival is much more drastically curtailed when this co-morbidity appears. Following recovery, it is this co-morbidity from cardiovascular disease which determines survival.

Environmental Factors

Despite the reported sizeable geographic differences in stroke mortality and the seasonal and secular trends in stroke incidence, few environmental determinants of stroke incidence have been established. Although the cigarette habit and living practices leading to obesity appear to have some influence, diet, salt, drinking water, coffee, alcohol, physical activity, and psychosocial factors have yet to be firmly linked to stroke incidence.

It is a common lament that almost everything one enjoys in life is apt to be either illegal, immoral, or fattening. Lately it seems necessary to add—and hazardous to the heart and blood vessels. The list of indicted factors has grown to include the quality of the community water supply, alcohol, sedentary living, a rich gourmet diet, cigarettes, salt, and lately coffee.

Alcohol and Coffee It is not unreasonable to consider whether "stimulating beverages" used daily may over the years damage the cardiovascular apparatus directly or by the effects on the blood pressure, lipids, clotting, or myocardial irritability. Alcohol has been incriminated by some in intracerebral hemorrhage. Evidence for an effect in ABI is lacking. In the Framingham cohort, no sizeable significant association of alcohol intake with the incidence of cerebral infarction could be demonstrated in either sex (Fig. 10). Evidently the transient lipid derangements and cardiomyopathy which occur with excessive use of alcohol do not occur enough in the general population or are not associated with an increased incidence of strokes.

Lately coffee has been indicted in coronary disease (Jick and Slone, 1972). However, prospective data reveal no statistically significant association of coffee intake with either CHD or ABI

(Fig. 11). No consistent effect is noted by age in the two sexes with a trend confined to older women which is not statistically significant. It is encouraging to find, that as regards the ABI, the dinner cocktail and the coffee break are not hazardous.

Psychosocial Factors   Paffenbarger and co-workers have suggested a role of personality pattern, life style and work in the occurrence of stroke (Paffenbarger and Williams, 1967; Paffenbarger and Wing, 1967; Paffenbarger et al., 1970).

The Pill   There is some information to suggest that strokes may be more common than expected in young women taking oral contraceptives (Bauer et al., 1973). Evidently cigarette smoking may enhance stroke risk in women taking oral contraceptives since the combined effect exceeds that of either alone (Collaborators Group, 1975). Since in some women the pill may provoke hypertension, lipid abnormalities, and impaired glucose tolerance (either de novo or by unmasking prior tendencies), an excess of atherothrombotic disease is not unexpected. However, while the relative risk may be high, the absolute risk of CVA is apparently minuscule. Nevertheless, since alternative methods of contraception are available, it would seem reasonable to monitor atherogenic traits in women on the pill and prescribe other contraceptives in those exhibiting progressive atherogenic features. No firm conclusions can be drawn from the current evidence available on the occurrence of stroke in young women on hormonal agents, owing to the paucity of cardiovascular disease in this age group.

Seasonal Variation   The incidence of cerebral infarction is lower in summer than winter months (McDowell et al., 1970). The reason for this is unclear. It does provide a pathogenetic clue to factors precipitating strokes which may be controllable.

Water Quality   An uneven distribution of C-V mortality has been noted with a belt of high mortality along the east coast from Georgia northward to Maine. Since the east coast of the U.S. is characterized by soft drinking waters, Schroeder's (1960) suggestion that the quality of drinking water may be important in C-V mortality seems worthy of consideration. Areas with exceptionally soft water supplies do have quite high reported C-V mortality (Shroeder, 1960; Dudley et al., 1969; Saner and Broud, 1970; Biorck et al., 1965; Crawford et al., 1968; Foder et al., 1971). The

relation to stroke in particular is more speculative. More rigorously designed studies are required before conclusions can be reached concerning the relation of water hardness to sudden death or stroke.

Unresolved Issues

A review of what is known about the epidemiology of stroke reveals that while we know a good deal and possibly enough to recommend prophylactic measures, there are still large gaps in our knowledge. The human and economic costs are enormous, suggesting that we must press on and find the means for assuring that this devastating illness does not continue to be the reward for reaching a venerable stage in life.

The search for additional stroke precursors must continue because the differences in vulnerability between or within populations are not entirely explained by the identified factors. Also, many controversial, contradictory and inconclusive findings of potential importance remain to be clarified. Among these are: is there a male predominance in ABI? Why does atherosclerosis proceed more slowly in the cerebral circulation? How important is the cranial arterial anatomy in the occurrence of stroke? What are the epidemiological features of lacunar strokes?

The role of cigarettes requires further clarification. Why does it not affect women? What is the mechanism? A number of retrospective studies have shown some association between cigarettes and stroke. However, the relationship remains inconclusive. The prospective epidemiologic data have been difficult to interpret because of one or more defects, including: small numbers, failure to distinguish intracerebral hemorrhage from brain infarction, inclusion of women with the men, and inattention to the age at stroke.

In a prospective study of longshoremen followed for 18 years, Paffenbarger et al. (1971) and Wing (1972) found no relation between *fatal* stroke incidence and cigarette use. In former college students an excess of *non-fatal* stroke in alumni was found (Paffenbarger and Williams, 1967; Paffenbarger and Wing, 1971).

The Dorn study of United States government life insurance policy holders found a smokers' stroke *death* rate of only 1.5 times that of non-smokers (Kahn, 1966). Doll and Hill (1964) investigating British physicians showed an even lower relative risk of 1.2 for

stroke *mortality* in smokers without a dose relationship and no lower rate in ex-smokers. Nomura et al. (1974) also found no relation of the cigarette habit to *fatal* stroke but did find a possible association with morbidity in younger age groups. This was consistent with Paffenbarger's experience (and Wing, 1967; and Wing; 1971).

Data on women are especially scarce. A retrospective collaborative study in young women 15 — 44 with a stroke showed that 73 percent were smokers, opposed to a 43.4 percent nonhospitalized control group (Bauer et al., 1973). Evidently, cigarette smoking may enhance stroke risk in women taking oral contraceptives, since the combined effect exceeded that of either alone. The independent effect of obesity in each sex needs further investigation. The role of lipids in premature strokes requires confirmation, particularly for women. The role and mechanism of isolated systolic hypertension in ABI should be investigated. The way in which congestive failure and chronic atrial fibrillation predisposes to strokes needs better documentation.

The natural history of stroke is still poorly understood, including the role of extracranial vascular disease in transient ischemic attacks and the hazard of brain infarction in both. The actual fact and reason for geographic variation in stroke incidence and type of stroke needs further elucidation. The rate of recurrences in ABI victims and factors related to this have yet to be clearly worked out. The factors other than the neurologic deficit which influence disability in the stroke victim need to be better defined.

The differences in the epidemiologic features of ABI and intracerebral hemorrhage need to be more clearly defined as do the relative frequency of different types of strokes in different population subgroups. Precursors of intracranial hemorrhage aside from hypertension need to be sought. The role of hypertension and atherogenic precursors in subarachnoid and intracerebral hemorrhage need to be investigated further. These and many other questions need to be answered. However, we have much useful information in hand and what we do not know should not deter us from efforts to combat the stroke menace.

Preventive and Clinical Implications

Unless effective intervention can be implemented, there is little point in seeking out presymptomatic stroke candidates either from the general population or physicians' practices. The delivery of ef-

fective stroke prophylaxis is no simple enterprise. It entails a sustained, intensive, sophisticated effort. We know well how to identify highly vulnerable persons and to estimate their risk of a stroke with reasonable precision, employing nothing more than ordinary office procedures and readily available laboratory tests. Coping with the risk factors once identified is another matter.

Most medical practitioners are primarily concerned with the medical management of persons already ill. They derive a sense of accomplishment chiefly from dealing with medical crises requiring astute, definitive diagnosis and therapy to relieve symptoms and to ameliorate a life-threatening situation here and now. The skills and interests necessary to produce modification in living habits or to alter risk attributes in apparently well persons are of a different sort than those required to relieve suffering. The therapeutically oriented physician, overburdened in caring for those already ill and by the medical care delivery system in which he operates, is unlikely to devote much time to the apparent ''medical trivia'' which are the concerns of a stroke prevention program. This physician has exhibited little enthusiasm for doing so.

Unless some means for correcting the factors responsible for the stroke candidate's high risk can be mobilized in his behalf, identifying presymptomatic, stroke-prone persons may be counterproductive. There is an assault on his sense of security; his job, insurance eligibility, and recreational preferences may be affected, and a long-term dependence on physicians and medicines promoted. Alternatively, he may be falsely reassured of perpetual immunity.

Existing medical practice is not particularly oriented to effective preventive programs. This makes it necessary to find those features of the present medical care delivery system which can be converted to such uses without competing for those scarce medical resources essential to caring for the ill. More than a casual effort is required. It may be necessary for a new breed of medical personnel to evolve, primarily concerned with adult preventive medicine and oriented in the fashion of pediatrics or obstetrics, rather than in internal medicine or surgery. Such practitioners will regard the occurrence of strokes in well persons under surveillance as failures rather than the first indication for medical management.

The single most important feature of stroke prophylaxis is early, vigorous, and sustained control of hypertension. Control of moderate to severe hypertension has been convincingly de-

monstrated to prolong lives and delay the occurrence of strokes (Kannel, 1971; Freis, 1970; Toguchi and Freis, 1967). Fear that reducing pressure in persons with cerebral atherosclerosis will produce strokes thus seems unfounded since, in the balance, fewer strokes occur. If anything, reducing blood pressure seems to improve cerebral blood flow and cardiac performance (Kannel et al., 1970). For those fearful of lowering pressures to normal in the stroke candidate, there is the alternative of producing a partial control which has also been shown to prevent hypertensive complications (Toguchi and Freis, 1967). The benefits of reducing mild degrees of hypertension and isolated systolic hypertension remain to be demonstrated. If instituted early enough in life, control of hypertension can rationally be expected to slow the accelerated pace of atherogenesis in the cerebral circulation. Despite massive evidence that hypertension promotes cardiovascular disease in general, and strokes in particular, there is evidence that we are doing a poor job in controlling hypertension in the general population. Most of it goes undetected and even the recognized hypertensives do not often receive adequate treatment or any treatment at all. It is no simple matter to convince either asymptomatic hypertensives to take costly, symptom-provoking medicines for an indefinite period, or their physicians to prescribe them. We must find ways to motivate them to do so.

Since many factors contribute to stroke, a multifactorial intervention should prove more efficacious than attention to hypertension alone. Failure to take into account other relevant factors may result either in over-reacting or under-reacting to the blood pressure. However, while the efficacy of controlling hypertension is clear, few other prophylactic measures are of proven efficacy in the presymptomatic stroke candidate. Neither hygienic, nor medical, nor surgical measures have been shown conclusively to delay stroke.

In asymptomatic persons, hygienic measures such as a less rich, less salty diet, more exercise, maintenance of a lean body, and avoidance of cigarettes is recommended as a useful supplement to treatment of elevated blood pressure.

Weight reduction would appear to be a key hygienic measure since weight loss has been shown to be accompanied by a reduction of serum lipids and blood pressure, and an improvement in carbohydrate tolerance. Direct evidence that this will reduce the

risk of a stroke is lacking, but it is clear that overweight stroke-prone persons can improve their stroke risk profile by losing weight.

Neither is there evidence that avoidance of cigarettes, lowering lipids or improving carbohydrate tolerance will in fact prevent strokes. The skeptic may prefer to use the lipid and blood sugar values primarily to determine the need for antihypertensive therapy. A broader concept of diabetes control which includes normalization of lipids, blood pressure, and overweight as well as carbohydrate tolerance may finally achieve a postponement of the atherosclerotic cerebral sequelae of diabetes.

While exercise may be an important feature of a comprehensive program to reduce stroke mortality, it is not likely to have as great an impact as avoidance of cigarettes, weight control, dietary regulation, and, above all, control of hypertension. Emotional and psychological factors may or may not play a role in the development of strokes, but they must influence the prevalence of risk factors and persons' reactions to them. These factors also affect adherence to corrective measures and adjustment to the altered life style after a stroke.

Although the evidence does not justify a return to the ancient practice of leeching, the finding that high-normal hemoglobin values are associated with an increased incidence of stroke does have possible, pathogenetic, preventive, and therapeutic implications.

ABI is one feature of atherosclerotic disease. The underlying pathological features of the process in the cerebral, cardiac and peripheral circulation are very similar; so it is not surprising that they share precursors although they may do so with different intensity (Gordon et al., 1971). Not only do persons with atherosclerotic disease share precursors, but those at high risk of one are also at increased risk of the others (Gordon et al., 1971). Manifestations of atherosclerosis concur with a greater frequency than can be accounted for by chance. That the major atherosclerotic diseases share some precursors (with some notable exceptions) and that those with one clinical manifestation are at increased risk of another strongly suggests, in addition to a common pathogenesis, that prophylactic measures designed to prevent one may prevent the others as well.

In those predisposed by atherogenic traits, strokes may be pre-

cipitated by exacerbations of hypertension, hypoglycemia, microemboli, hypotension, and impaired cardiac function. Evidence of impending strokes such as vascular bruits, pulse differences, abnormal dynamometry, thermographic differences, and transient ischemic attacks provide a therapeutic challenge. We need to know the effects of antihypertensive therapy, vascular surgery, anticoagulents, antiplatelet agents, and cardiac drugs in such persons in delaying ABIs. There is increasing evidence that strokes are preventable. However, we must continue to evaluate alternative methods of prevention in well-designed trials. There is little to indicate that stroke will be conquered by more expert management of the completed brain infarction. The best answer to this devastating illness is prevention. Prophylaxis in the presymptomatic stage is more likely to be efficacious than prophylaxis in the stage of transient, ischemic, cerebral attacks.

TABLE 1

Distribution of Cerebrovascular Deaths

	Proportion of all Cerebrovascular Diseases %
Subarachnoid hemorrhage	4.5
Cerebral hemorrhage	22.2
Cerebral thrombosis	28.5
Cerebral embolism	0.5
Other specified acute	1.5
Acute but ill-defined cerebrovascular disease	26.9
Other cerebrovascular disease	15.8

Source: National Center for Health Statistics—1968.

TABLE 2

Frequency of Strokes by Type
Framingham Study: 18-Year Follow-Up
Men and Women 30-62 at Entry

	Men		Women		Total	
	No.	*%*	*No.*	*%*	*No.*	*%*
Atherothrombotic brain infarction	52	54	59	61	111	57
Transient ischemic attacks[a]	8	8	3	3	11	6
Cerebral embolus	13	13	17	17	30	15
Subarachnoid hemorrhage	12	12	12	12	24	12
Intracerebral hemorrhage	6	6	4	4	10	5
Other	7	7	3	3	10	5
Total	98	100	98	100	196	100

[a]TIA only.

TABLE 3

Average Annual Incidence of Atherothrombotic Brain Infarction
According to Age and Sex
18-Year Follow-Up

Age	Men			Women		
	Person-Yrs. at Risk	*No. of Events*	*Rate Per 10,000*	*Person-Yrs. at Risk*	*No. of Events*	*Rate Per 10,000*
45-54	14068	12	9	17612	9	5
55-64	10354	23	22	13672	23	17
65-74	3706	14	38	5176	24	46
All Ages (45-74)			17			15

Average Annual Incidence of Myocardial Infarction by Age and Sex
18-Year Follow-Up

45-54	13514	56	41	17456	12	7
55-64	9416	84	89	13106	23	18
65-74	3100	31	100	4728	22	47
All Ages (45-74)			66			16

TABLE 4

Annual Incidence of Brain Infarction According to
Prior Coronary Heart Disease Status:
Framingham Study 16-Year Follow-Up:
Men and Women 30-62

	AVERAGE ANNUAL INCIDENCE OF ABI PER 10,000					
	Men Prior CHD		Women Prior CHD		Both Sexes Prior CHD	
Age at Entry	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*
< 45	0.5	4.6	0.2	0.0	0.3	3.7
45-54	1.2	5.6	0.9	9.3	1.0	7.2
55-62	1.5	4.5	2.5	5.8	2.1	5.1

TABLE 5

Standardized Multivariate Regression Coefficients of Six Specified Contributors
to Incidence of Atherothrombotic Brain Infarction: Framingham Study,
18-Year Follow-Up

	Coefficient		T-value	
	Men	*Women*	*Men*	*Women*
Systolic blood pressure	.619	.501	5.57	4.62
Age	.545	.537	3.65	3.67
Serum cholesterol	.210	.109	1.62	0.85
Cigarettes	.441	−.011	3.01	−0.07
LVH by ECG	.108	.221	1.30	3.63
Glucose intolerance	.052	.150	0.45	1.81

Note: Persons at risk of developing atherothrombotic brain infarction are those
persons aged 45 to 74 years and free of cerebrovascular accident at exam.

TABLE 6

Probability (per 1,000) of Developing Atherothrombotic Brain Infarction in Eight Years According to Specified Characteristics: The Framingham Study, 18-Year Follow-Up. 55-Year-Old Man

LVH-ECG Negative

Does Not Smoke Cigarettes

	SBP	105	120	135	150	165	180	195
	Chol							
Glucose Intolerance Absent	185	2	4	5	8	13	19	29
	210	3	4	6	9	14	21	32
	235	3	4	7	10	16	24	36
	260	3	5	8	12	18	27	40
	285	4	6	9	13	20	30	45
	310	4	6	10	15	22	33	50
	335	5	7	11	16	25	37	56
	SBP	105	120	135	150	165	180	195
	Chol							
Glucose Intolerance Present	185	5	7	11	17	25	38	57
	210	5	8	12	19	28	43	64
	235	6	9	14	21	32	47	71
	260	7	10	15	23	35	53	79
	285	7	11	17	26	39	59	87
	310	8	13	19	29	44	66	97
	335	9	14	22	33	49	73	107

Smokes Cigarettes

	SBP	105	120	135	150	165	180	195
	Chol							
Glucose Intolerance Absent	185	5	7	11	16	24	37	55
	210	5	8	12	18	27	41	61
	235	6	9	13	20	30	46	68
	260	6	10	15	22	34	51	76
	285	7	11	17	25	38	57	84
	310	8	12	18	28	42	63	93
	335	9	14	21	31	47	70	103
	SBP	105	120	135	150	165	180	195
	Chol							
Glucose Intolerance Present	185	9	14	21	32	48	72	106
	210	10	16	24	36	54	80	117
	235	12	18	27	40	60	89	130
	260	13	20	30	45	67	98	143
	285	14	22	33	50	74	109	158
	310	16	25	37	55	82	121	173
	335	18	27	41	62	91	133	190

LVH-ECG Positive

Glucose Intolerance Absent

Chol	SBP 105	120	135	150	165	180	195	SBP 105	120	135	150	165	180	195
185	3	4	6	10	15	23	34	5	8	12	19	29	43	64
210	3	5	7	11	17	25	38	6	9	14	21	32	48	72
235	3	5	8	12	19	28	42	7	10	16	24	36	54	80
260	4	6	9	14	21	31	47	8	11	17	26	40	60	88
285	4	7	10	15	23	35	53	8	13	20	30	44	66	98
310	5	7	11	17	26	39	59	9	14	22	33	50	74	109
335	5	8	13	19	29	44	65	11	16	24	37	55	82	120

Glucose Intolerance Present

Chol	SBP 105	120	135	150	165	180	195	SBP 105	120	135	150	165	180	195
185	6	9	13	20	30	45	67	11	17	25	38	57	84	123
210	6	10	15	22	33	50	75	12	19	28	42	63	93	136
235	7	11	16	25	37	56	83	14	21	31	47	70	104	150
260	8	12	18	28	42	62	92	15	23	35	53	78	115	165
285	9	13	20	31	46	69	102	17	26	39	59	87	127	182
310	10	15	23	34	52	77	113	19	29	44	65	96	140	199
335	11	17	25	38	58	85	125	21	32	49	72	107	154	218

Framingham men aged 55 years have an average SBP of 137 mm HG and an average serum cholesterol of 234 MG%. Sixty percent smoke cigarettes, 1.3 percent have definite LVH by ECG and 6.2 percent have glucose intolerance. At these average values the probability of developing atherothrombotic brain infarction in eight years is 11/1000.

TABLE 7

Risk of ABI in 8 Years According to Stroke Profile[a]

Decile of Risk	% of ABI Cases in Decile		Probability of ABIs	
	M	*F*	*M*	*F*
1	0.0	0.0	.0004	.0003
2	0.0	0.0	.0009	.0008
3	0.0	0.0	.0017	.0014
4	2.7	2.3	.0029	.0025
5	2.7	4.5	.0044	.0043
6	8.1	9.1	.0066	.0065
7	0.0	6.8	.0093	.0096
8	5.4	4.5	.0136	.0137
9	35.1	25.0	.0220	.0208
10	45.9	47.7	.3623	.3520

Excludes persons with RHD, CHD, CHF, CVA, or IC from population at risk.

[a]Ingredients of profile: systolic blood pressure, cholesterol, glucose tolerance, cigarettes, ECG-LVH, age.

RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION
ACCORDING TO RELATIVE WEIGHT
MEN AND WOMEN 45-74, FRAMINGHAM STUDY
18 YEAR FOLLOW-UP
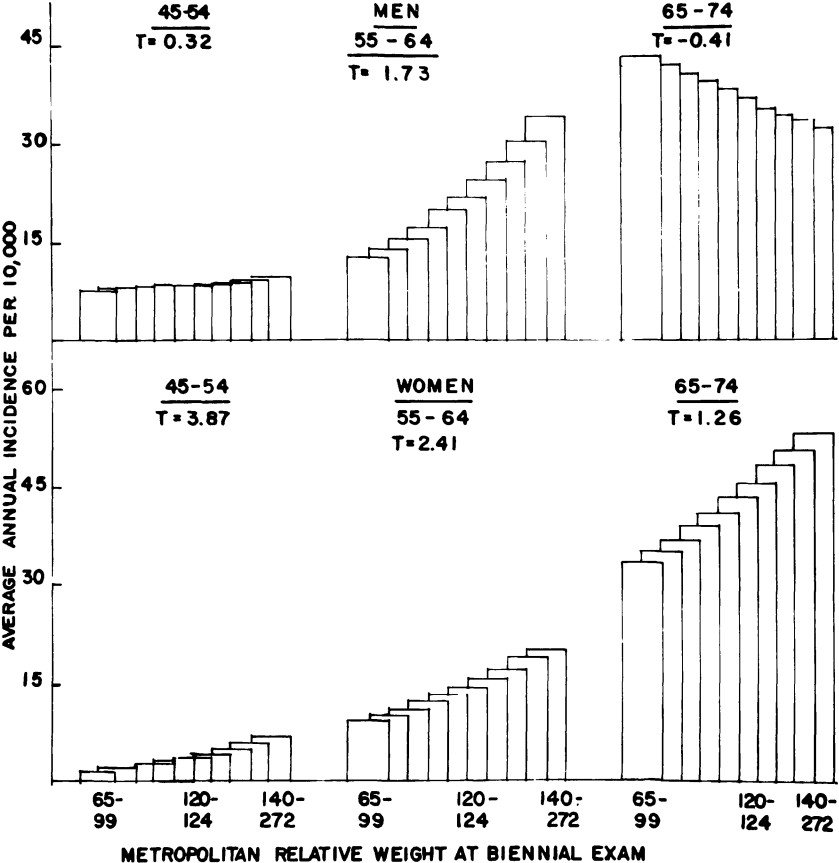
SOURCE: FRAMINGHAM MONOGRAPH NO. 30

FIG. 1.

PROBABILITY OF ATHEROTHROMBOTIC BRAIN INFARCTION IN 8 YEARS
ACCORDING TO CIGARETTE HABIT HIGH vs LOW RISK MEN AGE 55
FRAMINGHAM STUDY · 18 YEAR FOLLOW-UP
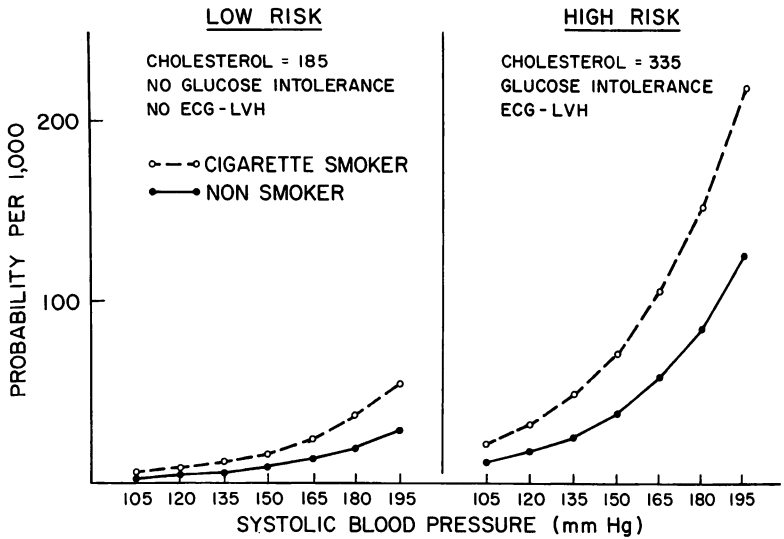
SOURCE · FRAMINGHAM MONOGRAPH NO. 28

FIG. 2.

RELATIVE RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION
ACCORDING TO LIPOPROTEIN CONCENTRATION
MEN AND WOMEN 30-62 AT ENTRY · FRAMINGHAM STUDY
18 YEAR FOLLOW-UP
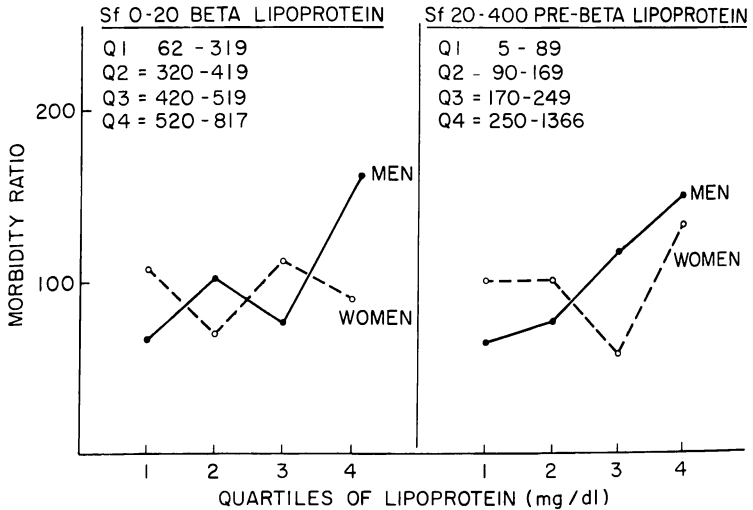
FIG. 3.

EIGHT YEAR PROBABILITY OF ATHEROTHROMBOTIC BRAIN INFARCTION
ACCORDING TO SERUM CHOLESTEROL AND OTHER RISK FACTORS:
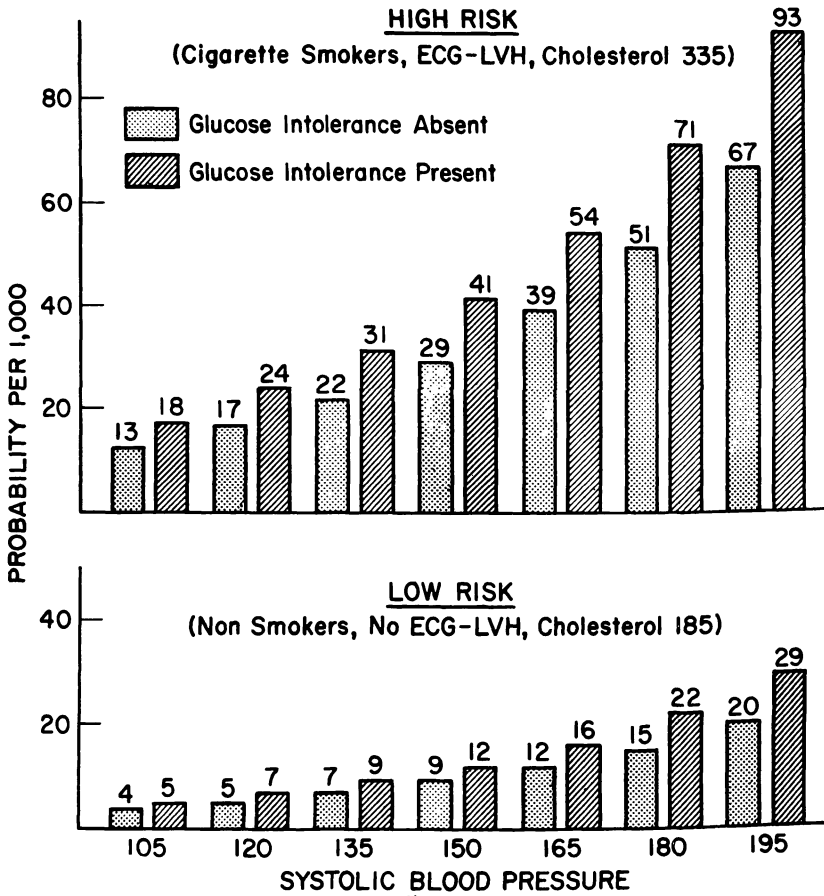MEN AGE 50: FRAMINGHAM STUDY: 18 YEAR FOLLOW-UP

LOW RISK — No ECG-LVH, SBP=105, Non Smoker, No Glucose Intolerance

HIGH RISK — ECG-LVH Present, SBP=195, Smoker, Glucose Intolerance Present

SERUM CHOLESTEROL (mg/dl)

PROBABILITY PER 1,000
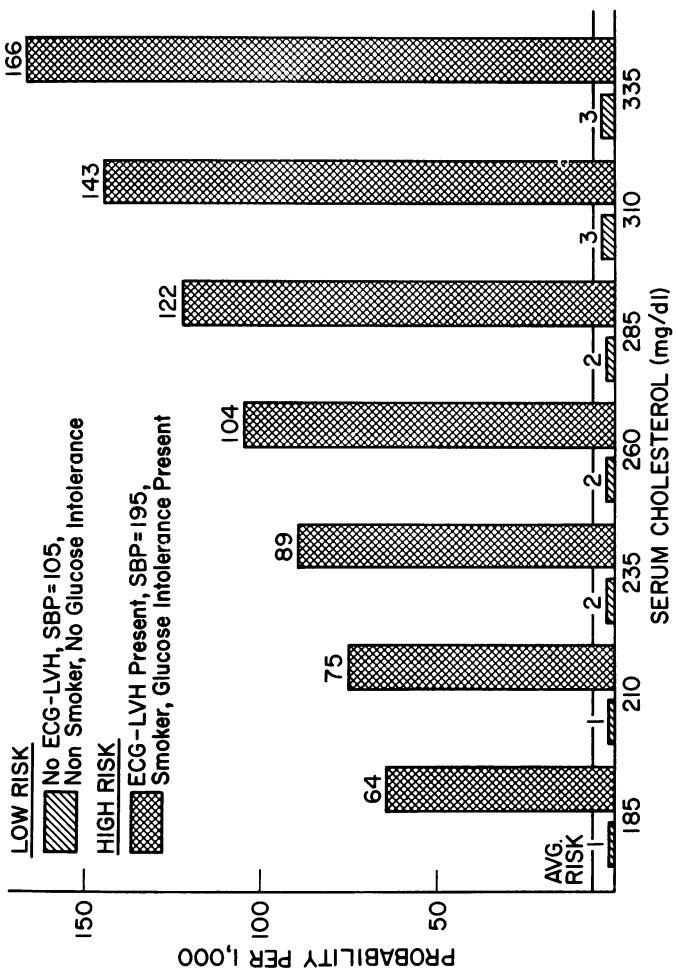
SOURCE: Framingham Monograph #28

Fig. 4.

PROBABILITY OF DEVELOPING ATHEROTHROMBOTIC BRAIN INFARCTION
IN 8 YEARS ACCORDING TO SYSTOLIC BLOOD PRESSURE
LOW RISK PERSONS 40-70; FRAMINGHAM STUDY
18 YEAR FOLLOW-UP
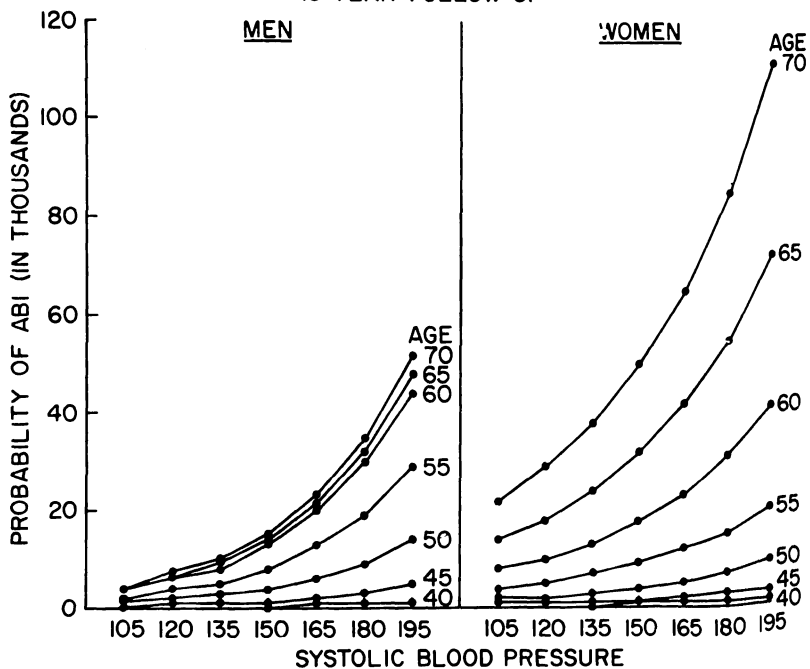
Persons with Cholesterol 185, Normal Glucose Tolerance,
No ECG-LVH, Non Smoker. SOURCE: Framingham Monograph No. 28.

Fig. 5.

RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION IN 8 YEARS
ACCORDING TO DIABETIC STATUS AND LEVEL OF
OTHER RISK FACTORS 55 YEAR OLD WOMEN
FRAMINGHAM STUDY: 18 YEAR FOLLOW-UP

FIG. 6.

RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION IN 8 YEARS
ACCORDING TO INTENSITY OF ATHEROGENIC TRAITS
(CHOLESTEROL; BLOOD PRESSURE, GLUCOSE INTOLERANCE)
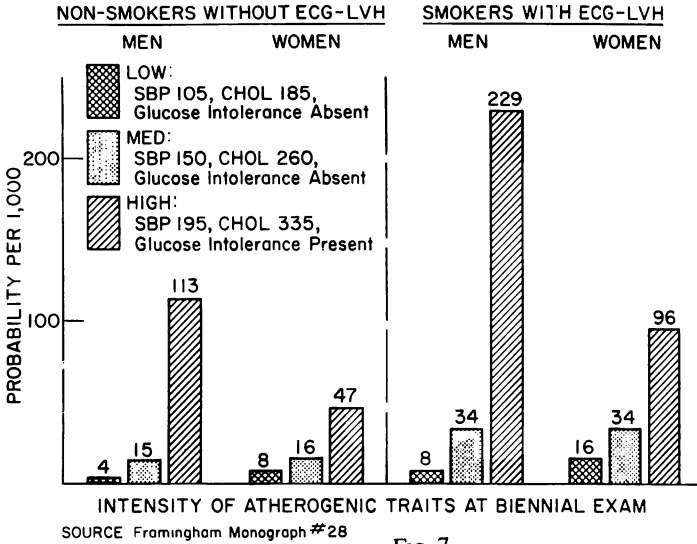MEN AND WOMEN AGE 60, FRAMINGHAM STUDY: 18 YEAR FOLLOW-UP

FIG. 7.

RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION
ACCORDING TO CARDIAC IMPAIRMENTS
MEN AND WOMEN 45-74 AT EXAM
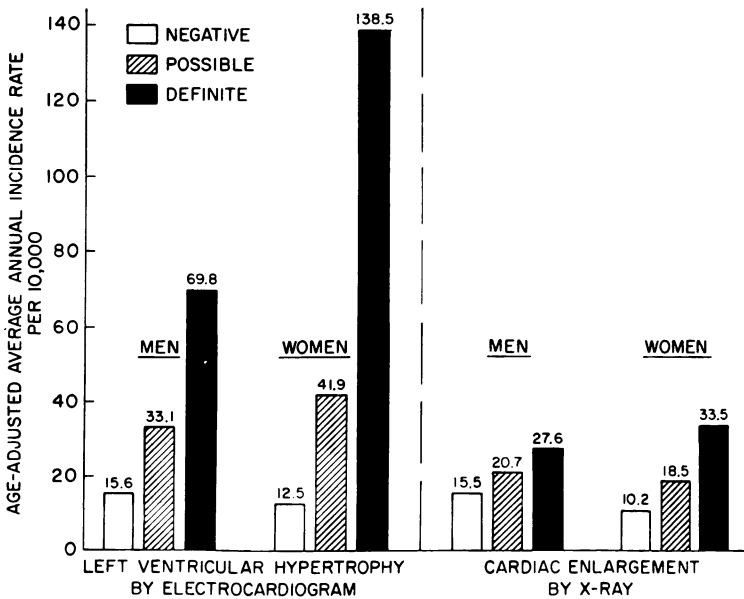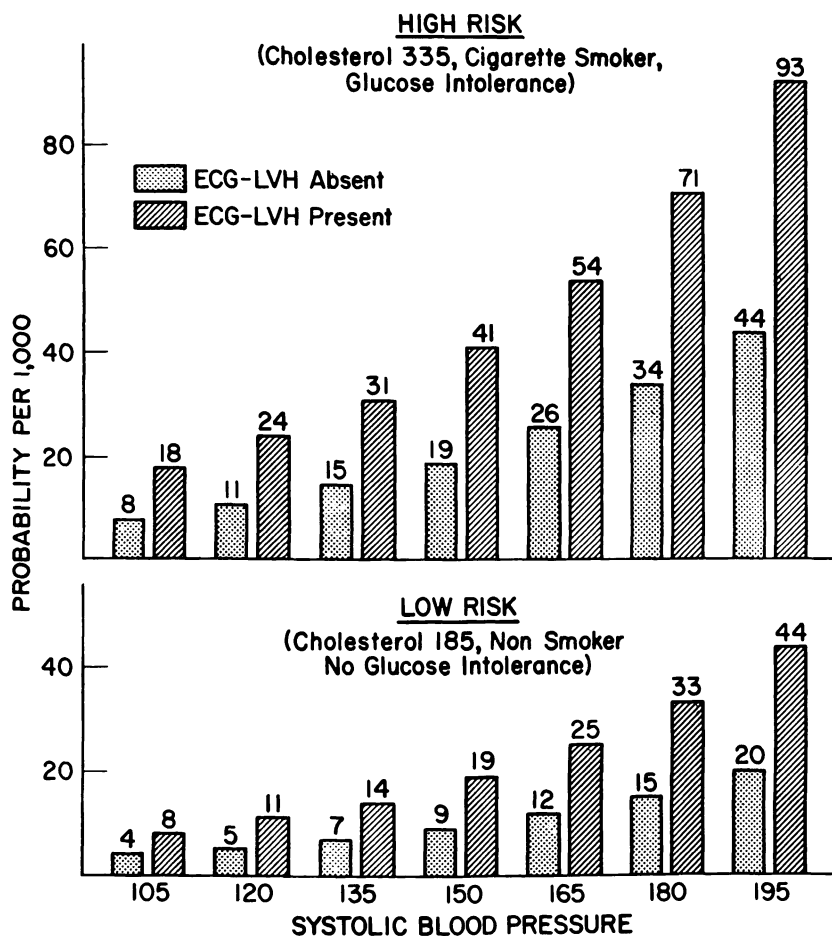FRAMINGHAM STUDY: 18-YEAR FOLLOW-UP

SOURCE: MONOGRAPH NO 29 TABLES 9-11, 9-12

FIG. 8.

RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION IN 8 YEARS
ACCORDING TO ECG-LVH AT SPECIFIED LEVEL OF
SYSTOLIC BLOOD PRESSURE AND OTHER RISK FACTORS
55 YEAR OLD WOMEN, FRAMINGHAM STUDY: 18 YEAR FOLLOW-UP

HIGH RISK
(Cholesterol 335, Cigarette Smoker,
Glucose Intolerance)

☐ ECG-LVH Absent
▨ ECG-LVH Present

LOW RISK
(Cholesterol 185, Non Smoker
No Glucose Intolerance)

PROBABILITY PER 1,000

SYSTOLIC BLOOD PRESSURE

SOURCE: Framingham Monograph #28

FIG. 9.

RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION
ACCORDING TO ALCOHOL INTAKE
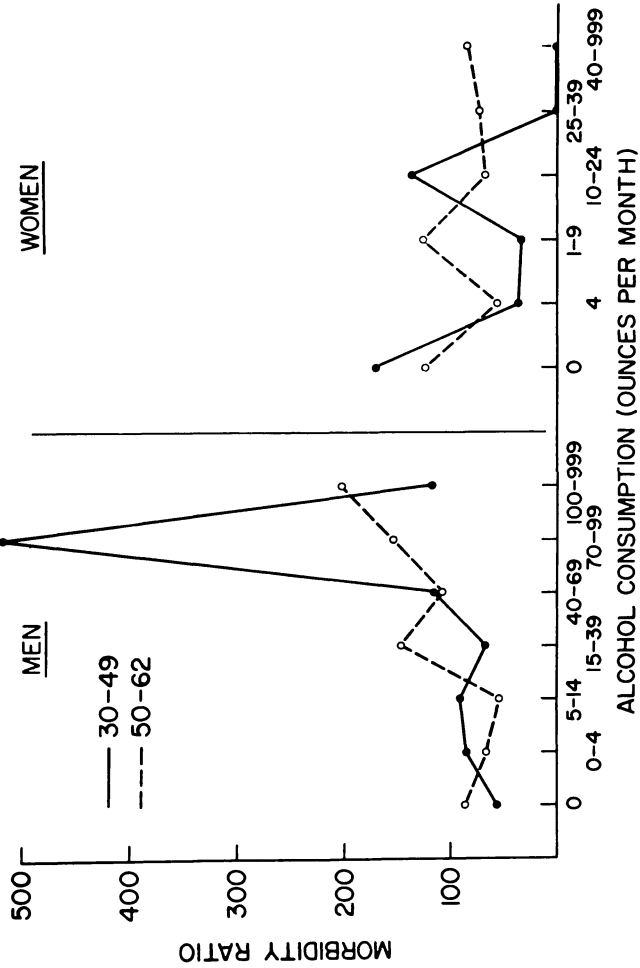MEN AND WOMEN 30–62 AT ENTRY: FRAMINGHAN STUDY
18–YEAR FOLLOW–UP

Fig. 10.

RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION
ACCORDING TO COFFEE INTAKE AT EXAM 4
MEN AND WOMEN 35-69 AT EXAM 4
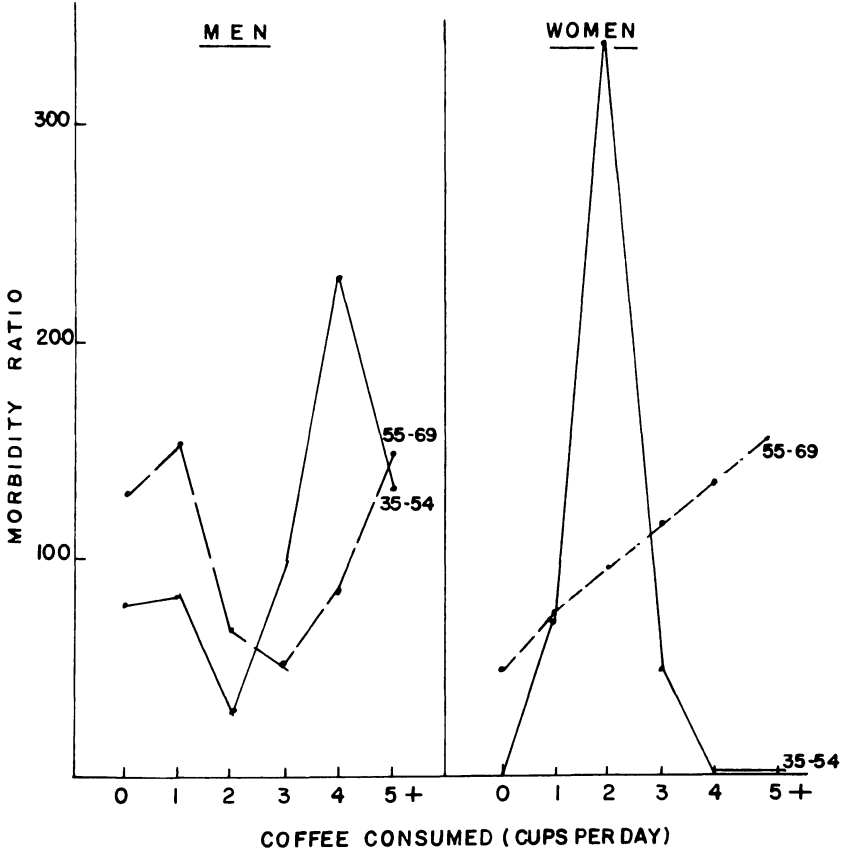FRAMINGHAM STUDY: 18 YEAR FOLLOW-UP

FIG. 11.

William B. Kannel, M.D.
National Heart Institute
Heart Disease Epidemiology Study
123 Lincoln Street
Framingham, Massachusetts 01701

Philip A. Wolf, M.D.
Boston University School of Medicine
80 East Concord Street
Boston, Massachusetts 02118

Thomas R. Dawber, M.D.
Boston University School of Medicine
80 East Concord Street
Boston, Massachusetts 02118

References

Baker, A.B., G.C. Flora, J.A. Resch, et al.
    1967   ''The geographic pathology of atherosclerosis: a review of the literature with some personal observations on cerebral atherosclerosis.'' Journal of Chronic Diseases 20:685 – 706.

Baker, A.B., and E.D. Katsukis
    1969   ''Stroke: U.S. and Japan. A study of caucasian and oriental population.'' Geriatrics 24:83 – 84.

Baker, H.L. Jr.
    1975   ''Computerized transaxial tomography (EMI scan) in the diagnosis of cerebral vascular disease experience at the Mayo Clinic.'' Pp. 195 – 201 in Wisnant, J.P., Sandoh, B.A. (eds.), Cerebral vascular diseases 9th Conference. New York: Grune & Stratton.

Bauer, R., W. Bauer, J. Coatsworth, et al.
    1973   ''The collaborative group for the study of stroke in young women. Oral contraception and increased risk of cerebral ischemia or thrombosis.'' New England Journal of Medicine 288:871.

Biorck, G., H. Bostrom, and A. Widstrom
    1965   ''On the relationship between water hardness and death rate in cardiovascular disease.'' Acta Medica Scandinavia 178:239.

Borhani, N.O., and J.S. Mayer (eds.)
　1968　Medical Basis for Comprehensive Community Stroke Programs. Washington, D.C.: National Institutes of Health.

Colandrea, M.A., G.D. Friedman, M.Z. Nichaman, and C.N. Lynd
　1970　"Systolic hypertension in the elderly. An epidemiologic assessment." Circulation 41:239–245.

Collaborators Group for the Study of Stroke in Young Women
　1975　"Oral contraceptives and stroke in young women, associated risk factors." Journal of the American Medical Association 231:718–722.

Crawford, M.D., M.J. Gardner, and J.N. Morris
　1968　"Mortality and water hardness of local water supplies." Lancet 1:827–831.
　1971　"Cardiovascular disease and the mineral content of drinking water." British Medical Bulletin 27:21–24.

Cumings, J.N., I.K. Grundt, J.T. Holland, et al.
　1967　"Serum lipids and cerebrovascular disease." Lancet 2:194–195.

Doll, R., and A.B. Hill
　1964　"Mortality in relation to smoking: Ten years observations of British doctors." British Medical Journal 1:1399–1410.

Dudley, E.G., R.A., Belden, and B.C. Johnson
　1969　"Climate, water hardness and coronary heart disease." Journal of Chronic Diseases 22:25.

Fields, W.S.
　1966　Surgery for Occlusive Cerebrovascular Disease: Progress Report of the Joint Study of Extracranial Arterial Occlusion. Pp. 245–253 in Millikan, C.H., R.G. Siekert, and J.P. Whisnant (eds.), Cerebrovascular Diseases: Transactions of the Fifth Conference. New York: Grune & Stratton.

Fisher, C.M.
　1951　"Occlusion of the internal carotid artery. American Medical Association." Archives of Neurology and Psychiatry 65:346–377.
　1954　"Occlusion of carotid arteries; further experiences. American Medical Association." Archives of Neurology and Psychiatry 72:187–204.
　1965　"Pure sensory stroke involving face, arm, and leg." Neurology 15:76
　1967　"A lacunar stroke: The dysarthria clumsy hand syndrome." Neurology 17:614.
　1969　"The arterial lesions underlying lacunas." Acta Neuropathology 12:1–15.

Fisher, C.M. and M. Cole
    1965   "Homolateral ataxia and crural paresis: a vascular syndrome."
                Journal of Neurology, Neurosurgery and Psychiatry 28:48.

Fisher, C.M., and H.B. Curry
    1965   "Pure motor hemiplegia of vascular origin." Archives of Neurology
                13:30.

Fisher, C.M., I. Gore, N. Okabe, and P.D. White
    1965   "Atherosclerosis of the carotid and vertebral arteries—extracranial
                and intracranial." Journal of Neuropathology and Experimental
                Neurology 24:455—476.

Foder, J.G. L.J. Pfeiffer, and V.S. Papezik
    1971   "Relationship of drinking water quality to cardiovascular mortality in
                Newfoundland." Canadian Medical Association Journal 108:
                1369—1373.

Freis, E.D.
    1970   "Veterans Administration Cooperative Study Group on Antihyperten-
                sive Agents. Effects of treatment on morbidity in hypertension."
                Journal of the American Medical Association 202:1028—1034.

Friedman, G.D., D.B. Loveland, and S.P. Ehrlich
    1968   "Relationship of stroke to other cardivascular disease." Circulation
                38:533—541.

Garcia, M., P.M. McNamara, T. Gordon, and W.B. Kannel
    1973   "Cardiovascular complications in diabetes." Early Diabetes Ad-
                vances in Metabolic Disorders, Supplement 2:493—499.

Gifford, A.J.
    1966   "An epidemiological study of cerebrovascular disease." American
                Journal of Public Health 56:452—461.

Gordon, T., P. Sorlie, and W.B. Kannel
    1971   An epidemiological investigation of cardiovascular disease. Coronary
                heart disease, atherothrombotic brain infarction, intermittent
                claudication. A multivariate analysis of some factors related to their
                incidence: The Framingham Study 16 year follow-up. Section 27.
                Bethesda, Maryland: U.S. Government Printing Office.

Grunnet, M.L.
    1963   "Cerebrovascular disease: diabetes and cerebral atherosclerosis."
                Neurology 13:486—491.

Hammond, E.C., and L. Garfinkle
1969   "Coronary heart disease, stroke and aortic aneurysm." Archives of Environmental Health 19:167 – 182.

Jick, H., and D. Slone
1972   "Coffee drinking and acute myocardial infarction. Report from the Boston Collaborative Drug Surveillance Program." Lancet 1: 1278 – 1281.

Jorgensen, L., and J. Torvik
1966   "Ischemic cerebrovascular diseases in an autopsy. Series I. Prevalence, location and predisposing factors in verified thrombo-embolic occlusions and their significance in the pathogenesis of cerebral infarction." Journal of Neurological Science 3:490 – 509.

Kahn, H.A.
1966   The Dorn Study of Smoking and Mortality Among U.S. Veterans: Report on 8-½ years of Observation. National Cancer Institute, Monograph number 19, pp. 1 – 25.

Kannel, W.B.
1971   "Current status of the epidemiology of brain infarction associated with occlusive arterial disease." Stroke 2:295 – 318.

Kannel, W.B., T.R. Dawber, and P.M. McNamara
1965   "Vascular disease of the brain—epidemiologic aspects: The Framingham Study." American Journal of Public Health 55:1355 – 1366.

Kannel, W.B., T. Gordon, P.A. Wolf, and P.M. McNamara
1972   "Hemoglobin and the risk of cerebral infarction: The Framingham Study." Stroke 3:409 – 420.

Kannel, W.B., P.A. Wolf, J. Verter, and P.M. McNamara
1970   "Epidemiologic assessment of the role of blood pressure in stroke: The Framingham Study." Journal of the American Medical Association 214:301 – 310.

Katsukis, E.C., and Y. Hirota
1966   Current Concept of the Frequency of Cerebral Hemorrhage and Cerebral Infarction in Japan. Pp. 99 – 111 in Cerebral Vascular Disease, American Heart Association Transactions of the 6th Conference. New York: Grune and Stratton.

Kuller, L.H.
1974   "The transient ischemic attack. A critical review of anticoagulent and surgical therapy. Current concepts of cerebrovascular disease." Stroke 9:23 – 26.

Kurtze, J.F.
1969   Epidemiology of Cerebrovascular Disease, Heidelberg, New York:
        Springer-Verlag.

McDowell, F.W., J. Louis, and K. Manohan
1970   "Seasonal variation of non-embolic cerebral infarction." Journal of
        Chronic Diseases 23:29–37.

Meyer, J.S., A.G. Waltz, J.W. Hess, et al.
1969   "Serum lipid and cholesterol levels in cerebrovascular disease."
        Archives of Neurology 1:303.

National Institutes of Health
1971   Arteriosclerosis. A Report by the National Heart and Lung Institute
        Task Force on Arteriosclerosis. Department of Health, Education and
        Welfare, Publication number 72-219, Volume II.

Nomura, A., G.W. Comstock, L. Kuller, and J.A. Tomascia
1974   "Cigarette smoking and strokes." Stroke 5:483–486.

Paffenbarger, R.S., Jr.
1972   "Factors predisposing to fatal stroke in longshoremen." Preventive
        Medicine 1:522–528.

Paffenbarger, R.S., Jr., A.S. Gima, M.E. Laughlin, et al.
1971   "Characteristics of longshoremen, related to fatal coronary disease
        and stroke." American Journal of Public Health 61:1362–1370.

Paffenbarger, R.S., Jr., M.E. Laughlin, A.S. Gima, et al.,
1970   "Work activity of longshoremen as related to death from coronary
        heart disease and stroke." New England Journal of Medicine
        282:1109–1114.

Paffenbarger, R.S., Jr., and J.L. Williams
1967   "Chronic disease in former college students. Early precursors of fatal
        stroke." American Journal of Public Health 57:1290–1299.

Paffenbarger, R.S., Jr., and A.L. Wing
1967   "Characteristics in youth predisposing to fatal stroke in later years."
        Lancet 1:753–754.

1971   "Chronic disease in former college students XI. Early precursors of
        non-fatal stroke." American Journal of Epidemiology 94:324–430.

Paterson, J.C., L. Dyer, and E.C. Armstrong
1960   "Serum cholesterol level in human atherosclerosis." Canadian
        Medical Association Journal 82:6–11.

President's Commission on Heart Disease, Cancer and Stroke
1964   Volume 1. Washington, D.C.: United States Printing Office.

Report of the Joint Committee for Stroke Facilities
1974   "II: Transient focal cerebral ischemia: epidemiological and clinical aspects." Stroke 5:276–287.

Robinson, R.W., N. Higano, and W.D. Cohen
1963   "Comparison of serum lipid levels in patients with cerebral thrombosis and in normal subjects." Annals of Internal Medicine 39:180–185.

Saner, I.A., and F.R. Broud
1970   "Geographic patterns in the risk of dying." Man Geological Society of America 123:131.

Schiffman, J.
1970   "Survival following certain cardiovascular events. An epidemiological investigation of cardiovascular disease." Kannel, W.B., and T. Gordon (eds.). Section 25, National Heart and Lung Institute.

Schroeder, H.A.
1960   "Relations between mortality from cardiovascular disease and treated water supplies." Journal of the American Medical Association 172:1902.

Shurtleff, D.
1970   "An epidemiological investigation of cardiovascular disease. Some characteristics related to the incidence of cardiovascular disease and death: The Framingham Study 16 year follow-up." Section 26. Bethesda, Maryland: United States Government Printing Office.

Stallones, R.A.
1965   "Epidemiology of cerebrovascular disease: A review." Journal of Chronic Diseases 18:859–872.

Toguchi, J. and E.D. Freis
1967   "Partial versus complete control of blood pressure in the prevention of hypertensive complications." Circulation Research Supplement 1, 36:195–201.

Toole, J.F., and A.N. Patel
1967   Cerebrovascular Disorders. First Edition. New York: McGraw-Hill Book Company.

Toole, J.F., R. Janenky, K. Choi, et al.
    1975   "Transient Ischemic Attacks due to atherosclerosis. A prospective study of 160 patients." Archives of Neurology 32:5 – 12.

Williams, A.O., J.A. Resch, and R.B. Loewenson
    1969   "Cerebral atherosclerosis—a comparative autopsy study between Nigerian and American Negroes and caucasians." Neurology 19:205 – 210.

Wolf, P.A., W.B. Kannel, P.M. McNamara, and T. Gordon
    1973   "The role of impaired cardiac function in atherothrombotic brain infarction: The Framingham Study." American Journal of Public Health 63:52 – 58.

World Health Organization
    1969   World Health Statistics Report. Volume 22, number 9.

Wylie, E.G., and W.K. Ehrenfeld
    1970   Extracranial Occlusive Cerebrovascular Disease: Diagnosis and Management. First Edition. Philadelphia, Pennsylvania: W.B. Saunders Company.

Yates, P.O., and E.C. Hutchinson
    1961   "In cerebral infarction: the role of stenosis of the extracranial cerebral arteries." Medical Research Council (London) Special Report Number 300:1 – 95.