Current Status of the Epidemiology of Brain Infarction Associated with Occlusive Arterial Disease

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Abstract:
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Although large gaps in our knowledge concerning the epidemiology of cerebrovascular disease are apparent, careful inspection of all existing data now makes it possible to see certain patterns emerging which suggest certain risk factors for stroke.

While the problem of differential diagnosis of the various categories of cerebrovascular disease presents a major obstacle to obtaining an undistorted picture of the epidemiological features of stroke from death certificate mortality data, the addition of evidence from prospective studies, including those in Framingham, Massachusetts, reveals that various types of arterial occlusion with cerebral infarction are by far the most prevalent type of stroke. Any specific origin of atherosclerosis remains obscure, as possible etiological candidates including dietary alterations in salt, fat and refined carbohydrate, sedentary living, excessive calories promoting obesity, the cigarette habit and even the mineral content of water in addition to marital status have all been incriminated. However uncertain the final answer is, certain precursors for atherosclerosis, such as hypertension, diabetes, and hyperlipidemia, are important. Of these, hypertension is clearly the most important contributor to stroke incidence. Certain combinations of items carry more risk than do the same items singly. For example, the risk of a brain infarction in diabetics with hypertension is probably about six times that of normal subjects. In persons under 50 at the time of measurement risk of cerebral infarction is possibly ten times higher in those with hypertension and elevated lipids than in those without either elevated. This compounding of risk has pathogenetic, preventive and public health implications.

For purposes of stroke screening alone the most efficient and practical method would be to determine casual blood pressure, although it must be stated that as yet there is uncertainty concerning the change in the risk if such blood pressure is treated.

ADDITIONAL KEY WORDS atherosclerosis risk factors cerebral hemorrhage hypertension diabetes hyperlipidemia cardiac pathology

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A review of the epidemiology of cerebrovascular disease reveals the extent to which we can now identify the stroke-prone person and the factors which place him at increased risk. Large gaps in our knowledge are apparent. Major emphasis will be placed on prospective epidemiological information in general and that from the Framingham Study in particular.

Until 1965 knowledge of the epidemiology of cerebrovascular disease was based mostly on retrospective studies, mortality data, clinical impressions and hospital, autopsy or other often inadequate or nonrepresentative statistics. While confusion and apparently contradictory reports flourished as a result, a more consistent picture is now emerging from prospective population studies.

The Epidemiological Approach

The epidemiological approach to a disease is the study of the circumstances under which it arises and evolves in a population rather than an individual. This has relevance to its origin and evolution in the individual. Epidemiology is concerned with the distribution and rate of occurrence of disease in time and place in relation to both acquired and innate characteristics of groups of people. It aims to delineate the differences between those who go on to incur disease and those who remain resistant to it.

Epidemiological studies usually evaluate spontaneously occurring and interacting factors in a population, rather than those which emerge under precisely defined and controlled conditions. Only the epidemiological field trial approaches the conditions of a controlled experiment. Experimental studies ordinarily tend to deal with individuals or small groups, while epidemiological ones are concerned with large population subgroups.

An epidemiological study may be retrospective or prospective. The former is more economical, quicker, furnishes a larger number of cases and is less tedious to carry out. However, it suffers from the bias of preselection of cases, problems in the choice of proper controls, a lack of uniformly applied criteria and an excess of incomplete, unplanned and unstandardized observations.

A prospective study is more cumbersome, costly and slow to yield results, but can be designed to avoid many of these pitfalls. Prospective studies allow planned observation and relate antecedent population characteristics to the development of disease many years later. Prolonged follow-up may be difficult and losses prohibitive; the basic protocol must be rigidly observed and the population may change while under surveillance. These problems at times make statistical inferences difficult, but prospective studies nevertheless provide the soundest epidemiological information available. Prospective studies provide:

1. Information on the importance of the disease as a force of morbidity and mortality in a defined population.
2. Information on the probability of an attack over the span of many years.
3. A clearer picture of the nature of the problem and the total spectrum of the disease in all who have it.
4. Data concerning the chain of events leading to the disease, including the precursors contributing to its occurrence.
5. Identification of those who are especially vulnerable.
6. A profile of the potential stroke candidate.
7. Clues to pathogenesis so that hypotheses can be constructed and tested.

The Stroke Entity

From the standpoint of investigation as well as management and prophylaxis it is important to distinguish at least four major stroke entities—"thrombosis," embolism, intracerebral hemorrhage, and subarachnoid hemorrhage—which together account for the bulk of cerebrovascular events, referred to collectively as strokes. There is little reason to believe that the epidemiological features of each variety are identical. Hence, studies which deal with undifferentiated "strokes" or "CVA" may well be inadequate and yield misleading information.

THE NATURE OF BRAIN INFARCTION ASSOCIATED WITH OCCLUSIVE ARTERIAL DISEASE

A detailed discussion of the criteria and techniques employed for the diagnosis of the various clinical varieties of stroke is beyond the scope of this report. A considerable expansion of knowledge of the pathophysiology of strokes and of diagnostic techniques over the past two decades has allowed more detailed diagnosis and has broadened the clinical spectrum of the stroke entity, in particular differentiating the temporal profile (transient ischemic attacks, progressing stroke, completed stroke) from the...
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arterial lesion (thrombosis, embolus, hemorrhage) from the brain lesion (transient ischemia, infarction, hemorrhage).

Much remains to be learned about the pathogenesis of strokes. The term “cerebral thrombosis” for the most common type of stroke suggests that an arterial thrombus underlies them all. This is analogous to the situation in coronary disease where the condition now termed “myocardial infarction” was also formerly called “coronary thrombosis.” In both cerebral and myocardial infarction it is often impossible to demonstrate a recent thrombus in the suspected vascular territory by angiography or commonly employed autopsy methods. Angiography may not differentiate a thrombus from an embolus when there is occlusion of a cerebral vessel. Thus, the vascular lesion producing cerebral infarction is often unknown. Histological examination frequently fails to differentiate thrombosis and embolus.

Estimates of the relative frequency of the major varieties of cerebrovascular disease vary depending upon the sample on which they are based. Autopsy studies generally overestimate the frequency of intracerebral hemorrhage owing to its lethality. Cerebral atherosclerosis is almost ubiquitous in the elderly. Some 5% of such autopsies show recent encephalomalacia and 5% show intracranial occlusions. Among those with thromboembolic occlusions at postmortem half are in the carotid—in its intracranial and extracranial segments. One-fourth are found in the middle cerebral and posterior circuits respectively. Occlusions of major cerebral vessels are not always accompanied by focal infarctions; about half are not. Also, encephalomalacia is not invariably accompanied by intracranial occlusion.1

The problem of differential diagnosis presents a major obstacle to obtaining an undistorted picture of the epidemiological features of stroke from death certificate mortality data. The relative frequency of the different types of strokes as reported in mortality statistics has varied widely in different geographical areas and over time. Based on average annual mortality reported from some 18 countries, Kurtzke estimated that some 3% of cerebrovascular deaths are attributable to subarachnoid hemorrhage, 29% to thromboembolic, 54% to intracerebral hemorrhage and 14% to “other cerebrovascular disease.”1 Hospital series, depending as they do on the populations they serve and the type of illness they attract, are much too variable to provide useful estimates of the relative proportions of the different varieties of stroke.

Population surveys provide the best available information on the relative frequency of the major types of cerebrovascular disease. These suggest that subarachnoid hemorrhage comprises about 12%, intracerebral hemorrhage 16%, thromboembolism 62% and “other cerebrovascular disease” 10% of strokes.1 The distribution of the different varieties of stroke probably varies with age and sex; but most prospective studies of stroke have not been in progress long enough to provide this detailed information, and population studies which include women are not common.

Framingham data are quite consistent with these estimates based on population surveys. An occlusive event with cerebral infarction was by far the most prevalent type of stroke, accounting for some 60%. Intracranial hemorrhage accounted for only 20% with subarachnoid hemorrhage, not intracerebral hemorrhage, predominating and comprising two-thirds of them. About 14% were embolic from the heart (fig. 1). Other prospective studies concur in the finding of a much lower proportion of strokes attributable to intracerebral hemorrhage than reported in mortality statistics.2-5

A recent study of the frequency of each major variety of cerebrovascular disease in the Rochester population from 1945 through 1954 by Whisnant and colleagues using Mayo Clinic records also reveals a gross overstatement in the literature concerning the incidence of intracerebral hemorrhage. Their data indicate that cerebral infarction may be as much as four to six times more common than intracerebral hemorrhage in the age range 45 to 64 and even more common at older ages. With a 50% autopsy confirmation they found that intracerebral hemorrhage accounted for only 10% of the strokes and subarachnoid hemorrhage for 5%.3

The prevalence of the clinical stages of cerebral events due to arterial occlusive disease can only be estimated from a clinical series. Variations are so great that little significance is
attached to a cooperative study cited by Kurtzke where 8% of thromboembolic strokes were transient ischemic attacks and half of the cerebral infarcts due to thrombosis were classified as “evolving.” Carotid system thromboses were twice as common as vertebral. From a number of sources embolism from a cardiac source appears to comprise about 10% of “thromboembolic” disease. However, based on careful postmortem dissections it appears that a larger proportion (about half) of ostensibly thrombotic strokes are in fact embolic in origin.

**TRANSIENT ISCHEMIC ATTACKS**

Whether transient ischemic attacks as a clinical stage should be regarded by the epidemiologist as a separate category of occlusive cerebrovascular disease is uncertain. The vagaries of definition, diagnosis, and patient selection make it difficult to precisely identify patients and define the natural history of the disease. The single isolated episode is the most difficult to interpret. The critical hemodynamic factor precipitating each attack is still uncertain, and vasospasm, transient systemic hypotension and small emboli in persons with atherosclerotic stenosis have all been evoked. The latter is currently the most popular. Transient ischemic attacks do seem to be associated with severe atherothrombotic involvement of the cerebral circulation, and it is not unreasonable to expect that the precursors of TIA will be similar to those that predispose to completed stroke (cerebral infarction). Evidence relating transient ischemic attacks to extracranial cervical arterial disease is substantial. There is an important gap in our knowledge, which concerns how often transient ischemic attacks precede completed strokes and the risks entailed. Population studies will assist in providing these data.

**LACUNES**

Whether “lacunar disease” should be included within the general category of brain infarction associated with occlusive arterial disease is uncertain. Heretofore, as with Alvarez’s “little strokes,” the term “lacunar disease” has been used to refer to a brain which contains multiple areas of cystic infarction—a situation not uncommonly encountered in postmortem studies of the brain, particularly in the elderly. It is believed to be associated with dementia in

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**FIGURE 1**

Relative frequency of various types of cerebrovascular disease (16 years). Men and women 30-62 at entry: Framingham study.
the aged. If a patient has a smooth gradual progressive loss of intellect without episodic events which are the hallmark of significant occlusive cerebrovascular disease, there is no justification for making a diagnosis of “lacunar disease” or of atherosclerotic dementia as is often done. In this context the categorical term “lacunar disease” has little meaning to the epidemiologist concerned with occlusive arterial brain infarction.

Fisher, however, has recently described episodic neurological deficits which he has correlated pathologically with lacunes deep within the brain substance. He has identified four pathologically verified syndromes: pure motor hemiplegia, pure sensory stroke, crural paresis with homolateral ataxia, and dysarthria with clumsiness of one hand. The circumscribed nature of the focal neurological deficit, a stuttering onset and clearing in days to weeks are alleged to be diagnostic hallmarks. Lacunes found in the brain are usually multiple, suggesting a tendency to recur. Fisher has concluded that these lesions are due to disease of small penetrating branches of intracranial arteries and result from hypertension. There is some evidence that these lesions may not be occlusive in nature. Some careful studies of brain sections have tended to incriminate microaneurysms with small resorbed hemorrhages as a possible basis for these lesions. Whether these can be clinically distinguished from occlusive cerebral vascular disease involving the larger intracranial and extracranial vessels remains to be demonstrated. In any event, we need more information on their precursors and natural history whether they be identified clinically or at postmortem examination.

EXTRACRANIAL VASCULAR DISEASE

The clinical and pathological features and significance of occlusive disease of the extracranial portions of the carotid arteries in strokes were emphasized by Fisher a number of years ago. Because of the surgical accessibility of these arteries, interest has focused on the role of these arterial lesions in the pathogenesis of stroke. However, if all components of the intracranial circulation are normal the occlusion of a single extracranial artery does not ordinarily cause cerebral infarction. Sudden occlusion of an extracranial artery associated with an abnormal pattern of intracranial flow may cause cerebral infarction, or an extracranial arterial lesion may generate emboli which cause cerebral infarction by occluding the distal portion of an intracranial artery. Because of the complexity of these interrelationships it is not feasible, on clinical grounds alone, to demonstrate that a specific cerebral infarction is due to extracranial, intracranial or combined arterial disease. Similarly, prospective studies have not provided valid information on the natural history of significant extracranial vascular disease. It is likely that extracranial vascular disease is only one more facet of the general atherosclerotic process rather than a unique entity.

NATURAL HISTORY OF ATHEROSCLEROSIS

It has been established by McGill and others that atherosclerotic lesions appear first in the aorta, later in the coronary arteries and lastly (as late as the third and fourth decade) in the cerebral arteries. As a consequence the clinical manifestations of this progressive disorder tend to appear first in the coronary and later in the cerebral vessels. The aorta, owing to its large caliber, appears to be able to tolerate a large amount of atherosclerotic deposit before giving rise to clinical consequences. The reason for this difference in the onset of atherosclerosis in different parts of the circulation is not clear. Local anatomical factors certainly must be considered. Also, a given amount of involvement in a particular vessel may be disastrous in one person while innocuous in another, depending upon the balance of the cerebral circulation. The configuration of the circle of Willis with regard to communicating arteries may at times be critical. Extracranial vascular disease may be critical if the intracerebral circulation is compromised and well tolerated if not.

Environmental Factors

It is not unreasonable to consider whether man, by altering his environment in the interest of “progress,” has at the same time exacted a toll in incidence of cerebrovascular disease. Possible etiological candidates include dietary alterations in salt, fat and refined carbohydrate, sedentary living, excessive calories promoting obesity, and the cigarette habit. Alterations in the mineral content of the water, and even marital status, have been incriminated.
Evidence implicating drinking water has emerged, beginning with reports in Britain in 1957 that hard waters with a high calcium content were associated with lower rates of cardiovascular disease, including cerebrovascular accidents. A Swedish study confirmed this, but only for women. It is difficult to accept this as a confirmed contributor to cerebrovascular mortality in view of other negative reports, lack of an adequate explanation for the findings and failure to exclude other confounding variables.

It is alleged, based largely on insurance statistics, that the unmarried have an extra burden of cardiovascular disease. Because disease status can also determine marital status and unmarried persons who take out insurance may suspect ill health, these data are difficult to accept unless obtained prospectively from a random sample.

Differences in cerebrovascular mortality among countries and time trends in mortality can be used to support or formulate etiological hypothesis. However, this has been an uncertain, speculative enterprise at best. The presence of such differences may suggest the existence of powerful environmental influences, but it does not identify them, and the difficulty of interpreting such data, which are generally inaccurate, has led to differences in opinion as to whether sizable variations do exist.

Some evidence does suggest wide geographic variations in the incidence and mortality from cerebrovascular disease. If the reports are taken at face value, there have been unusually high mortality rates in Japan, Finland, West Germany, Scotland and Uruguay. The range from the highest (Japan) to the lowest (Israel and Mexico) encompasses a sevenfold difference. High-incidence areas generally have an excess of intracerebral hemorrhage. The range for "thrombotic strokes" is much less striking.

The basis of these differences (if they are indeed real) is environmental rather than genetic is suggested by the studies of Gordon. Comparing the stroke death rates of Japanese in Japan, Hawaii and the U. S. mainland, he found a progressive decrease from Japan to Hawaii to the U. S. mainland. It is interesting, however, that coronary death rates increased in the same progression, suggesting either that intracerebral hemorrhage is due to different causes than coronary heart disease or that a diagnostic substitution has taken place in ascribing a cause to sudden death.

More recent studies of cerebrovascular disease, with autopsy control, suggest that cerebrovascular disease in Japan is less divergent from Western rates both as a cause of death and in the ratio of intracerebral hemorrhage to thrombotic strokes. Kurtzke reviewed the evidence for a geographic distribution of cerebrovascular disease and decided that reporting differences could easily account for most of the apparent variation. He concluded that the geographic distribution of cerebrovascular death is essentially uniform, and that clustering of high-rate areas is not a feature of cerebrovascular mortality. Regions of high reported cerebrovascular mortality are, he notes, generally areas of less adequate medical facilities. However, while the existence of geographic and racial patterns of cerebrovascular mortality within the U. S. may be attributed to variation in diagnostic habits of death certification, it is interesting that these correspond quite well with the reported prevalence of hypertension, a remarkable coincidence. Reported cerebrovascular mortality within the U. S. reveals the highest rates in the southeast—two and one-half times that of the lowest, the southwest. This is only partially attributable to the difference in population composition.

A decrease in overall cerebrovascular mortality has been noted in the U. S., Canada, and Japan. An increase has been reported in the republic of Ireland, with little or no change in England and Wales. Such decrease as may have occurred has been greatest among the younger age groups of stroke victims. Kuller et al., in a study of time trends in the U.S.A., in Baltimore and Memphis between 1930 and 1960, concluded that there was a substantial decline in cerebrovascular disease rates among all race and sex groups, greatest in the age groups 45 to 54. The decline was, however, in intracerebral hemorrhage, with cerebral infarction and "thrombosis" in both cities showing an increase. While there appeared to be an acceleration in the rate of decline since the
introduction of effective antihypertensive therapy, the decline in intracerebral hemorrhage mortality preceded it. Also, it is inexplicable for cerebral infarction, also a complication of hypertension, to simultaneously rise with the introduction of effective antihypertensive therapy.

Changes in death certification practices make reported secular trends in cerebrovascular mortality extremely difficult to interpret. Kurtzke, after a careful analysis, concluded that no substantial change in mortality from stroke has occurred over this century. The rise in "cerebral thrombosis" mortality may be largely a result of coding and diagnostic fashion, since "other cerebrovascular disease" and intracerebral hemorrhage vary inversely with thrombosis. The reported decline in intracerebral hemorrhage mortality and concomitant increase in cerebral infarction, while provocative, is difficult to interpret and accept at face value. In any event, to speculate on the reasons for these secular trends seems unpromising. Information on host and environmental contributions to stroke incidence and mortality will arise more surely from prospective epidemiological studies. The efficacy of the control of hypertension in preventing strokes will be assessed with confidence only from controlled clinical trials of antihypertensive agents in hypertensive stroke-prone persons. Encouraging results along this line are beginning to appear. Even among persons surviving completed strokes, mortality was almost halved by effective antihypertensive therapy in victims under age 65.

SEASONAL VARIATION
The presence of seasonal variation in stroke incidence would suggest possibly controllable environmental precipitating factors in those predisposed. There does appear to be a sizable seasonal variation in incidence and death rates, with the peak in January and February and the lowest mortality in July and August. Wylie found a definite seasonal variation from a summer low to a winter high in 1958 in both the U. S. and England. Whether these swings are due to some other factor such as secondary infection is uncertain.

LIVING HABITS
Much of the foregoing epidemiological evidence for variations in cerebrovascular mortality with race, migration, time and season would suggest a potent environmental influence at work in stroke mortality, if it could be taken at face value. But so many physical, cultural and other features of the environment could be involved that this line of investigation hardly clarifies the situation. It does, however, justify

![Figure 2](http://stroke.ahajournals.org/DownloadedFromStroke-AHAJournals.org)
a further search for specific environmental contributors to stroke incidence and mortality in prospective studies relating antecedent personal characteristics of individuals to subsequent stroke incidence.

Virtually everyone appears susceptible to atherosclerosis and, ultimately, to its most devastating manifestation—stroke. However, in predisposed persons certain living habits seem to delay or hasten strokes. While genetic endowment certainly helps determine susceptibility, families share more than genes. Spouses as well as sibs tend to share hypertension, lipid abnormalities, obesity and the cigarette habit.

**Cigarette Habit**
The cigarette habit evidently predisposes to cerebral infarction, as well as lethal coronary attacks. In Framingham male cigarette smokers had more than three times the nonsmokers’ risk of having a cerebral infarction (fig. 2). It may increase the risk in women as well, but there were too few women smokers who inhaled and too few strokes among them to permit a valid assessment at this time. It is not clear that smoking actually affects the rate of cerebral atherogenesis, and some other mechanism may be involved. Cigarettes have not been uniformly demonstrated to be associated with cerebral infarction in prospective studies, and more confirmation of this association is required.

**Physical Activity**
Men who are physically more active within occupational groups such as transportation workers, longshoremen, and postal workers, as well as the general population, have been found to sustain fewer lethal coronary attacks. Prospective epidemiological studies of the relation of habitual level of physical activity to risk of developing a stroke are scarce. In a recent study of coronary and stroke mortality in longshoremen, Paffenbarger and co-workers found no relation of physical activity at work to stroke while demonstrating the expected lower coronary mortality in the more physically active.82

![Graph](image_url)

**FIGURE 3**
Risk of Atherothrombotic brain infarction (14 years) according to obesity and blood pressure status. Men and women 30-62 at entry: Framingham study.
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Physical activity appears to protect against coronary mortality largely by promoting collateral circulation rather than by retarding atherogenesis. Collateralization is probably provoked by the increased pressure gradient between adjacent obstructed and patent vessels or by the biochemical changes in the intervening ischemic parenchymal tissue. Moderate exercise more directly affects the oxygen and blood flow requirements of the myocardium than it does the brain. This may explain the lack of protection of physical activity against the brain infarction despite its having the same underlying atherosclerotic process as coronary disease.

OVERWEIGHT
Adiposity is generally a product of faulty living habits such as sedentary living and overeating. It is associated with hypertension, high lipid values, impaired carbohydrate tolerance and cardiac malfunction. On this account an excess of strokes would be expected among the obese. But this does not occur: the obese fare no worse than their leaner cohorts, whether hypertensive or not (fig. 3). Even hypertensives added little further to their risk by being obese. Also, the impact of hypertension was substantial whether or not the subject was obese. Obesity does not appear to contribute much to cerebral infarction mortality, despite its atherogenic accompaniments.

ALCOHOL
Alcohol habits did not appear to be related to the incidence of cerebral infarction in either men or women (fig. 4). Thus, there was no evidence that the transient lipid derangements produced by alcohol result in an excess of cerebral infarction. There was also no evidence for the familiar belief that an improvement in circulation alleged to occur with moderate alcohol consumption protects against strokes. There is some recent evidence to suggest that alcohol may predispose to intracerebral hemorrhage, but this requires confirmation.

Genetic Factors
It has long been believed that strokes are a consequence of getting old and a function of the type of vasculature inherited. There is evidence to support this pessimistic view. It has
been observed that atherosclerosis tends to run in families so that, in a sense, one's fate is preordained at the moment of conception. A number of epidemiological observations bear on the possibility of genetic influences in stroke including racial variation, sex ratio, familial aggregation, age trends and variable resistance to stroke precursors among others.

**RACE**

Mortality statistics point to a marked excess of cerebrovascular mortality among nonwhites, particularly Negroes and Japanese. Thus, it has been repeatedly inferred that strokes, especially intracerebral hemorrhage, are much commoner in Negroes than in whites in the U.S.A., and that strokes are phenomenally common in Japan. But this excess may be exaggerated as a consequence of variations in death certification practices, sophistication of medical facilities, diagnostic fads, or even problems with selective population undercounts. Also, it is the more poorly defined rubrics of "cerebral hemorrhage" and "other cerebrovascular disease" which provide this excess.

The high cerebrovascular mortality reported from Japan could easily be inflated by diagnostic fashion, for only 10% of the deaths thus certified were confirmed as such by autopsy in a recent study. On the other hand, from studies of cerebrovascular disease in Wales and England, Ashby concluded that genetic factors predominate, relating higher cerebrovascular mortality in Wales to "Welshness." Some prospective epidemiological studies which have applied criteria more uniformly have found no real differences in white and Negro cerebrovascular disease rates. Racial differences in cerebrovascular mortality evidently cannot be cited as proof of genetic factors. Even if the racial differences are real, they may also reflect environmental differences.

**AGE AND SEX**

The sex ratio of cerebrovascular deaths appears from mortality statistics to have

![Figure 5](image-url)

**FIGURE 5**

Risk of A.B.I. (16 years) according to age at entry. Men versus women 30-62 at entry: Framingham study.
gradually changed, with increasing male predominance. The male predominance has been reported less pronounced for nonwhites. But again, prospective epidemiological studies within a defined population sample generally fail to show this, even for cerebral infarction. In Framingham, the male predominance so characteristic of the other major manifestations of atherosclerosis was not found in cerebral infarction incidence. Only in persons sustaining early strokes (under age 50 at entry to the study) was there a distinct male predominance (fig. 5). In women, cerebral infarction and myocardial infarction incidence rates were similar at all ages. In men coronary rates were four to ten times higher than cerebral infarction. Beyond age 50 at entry the difference is no longer evident. Even in coronary heart disease, the relative immunity of females wanes with advancing age; and, since most cerebral infarctions occur late in life, this may account for the lack of a male predominance. The lack of a striking male predominance in cerebral infarction rates is a rather consistent finding in prospective studies in the U.S.A. and Australia.

Human aging is characterized by a logarithmic increase in death rate. Atherosclerosis and hypertension similarly increase with age. Stroke may be looked upon as a concomitant of aging, and as preventable only to the extent that we can reverse the “aging process.” As in virtually every other “chronic and degenerative” disease the most powerful variable associated with stroke incidence is age; and strokes in young persons can be looked upon as the extreme, or tail, of the distribution. All of the known “risk factors” taken together cannot entirely account for the striking age trend in stroke incidence. Whether this is simply a reflection of the biological consequences of aging or a time-dose product of acquired risk factors is unknown.

At any age, however, some persons in either sex are clearly more vulnerable than the rest, depending on the stroke precursors in their makeup. Young adults sustaining cerebral infarctions almost invariably have had one or more predisposing traits such as hypertension, diabetes or cardiac impairment. Some persons reach advanced age with little cerebral atherosclerosis, suggesting that atherosclerotic aging phenomena are not inevitable. We must learn what is responsible for this immunity and what, as regards risk of a stroke, makes the potential stroke victim old beyond his years.

**Ingredients of the Stroke Profile**

Prospective epidemiological studies reported since 1965 provide the least distorted, most credible information on the natural history of cerebrovascular disease—information which brings consistency to mortality statistics and accuracy to estimates of the relative frequency of each variety of stroke, its precursors and its impact as a force of mortality and morbidity.

These prospective studies indicate that cerebrovascular diseases are indeed a major cause of morbidity and mortality, in the U.S.A. and elsewhere. The prevalence in the U.S.A. is somewhere between 1.5 and 2.5 million in persons under 60 years of age. Based on data from Framingham, Massachusetts, Rochester, Minnesota, and Hisayama, Japan, it would appear that brain infarctions occur in a ratio of four to one over intracerebral hemorrhages.

**Atherogenic Precursors**

Aside from age and sex there are a number of personal attributes which identify the highly vulnerable candidate for a stroke. The lack of a distinct male predominance, the high cerebrovascular incidence in low coronary incidence areas, and the racial differences in cerebrovascular and coronary mortality suggest that occlusive cerebrovascular disease and coronary heart disease differ in their pathogenesis. But this is not borne out in prospective epidemiological studies, which suggest a common underlying cause. A much higher concurrence of cerebral infarctions and other major atherosclerotic diseases has been demonstrated than can be accounted for by chance.

Risk of cerebral infarction is almost five times as great in persons with coronary heart disease, and this excess persists at threefold after adjustment for concomitant hypertension (fig. 6). Strokes occurring within six months of a myocardial infarction have been excluded from consideration, so cerebral embolus from a mural thrombus cannot account for this. Intermittent claudication is also associated with an increased incidence of strokes. Friedman also demonstrated that, conversely, coronary attacks were more frequent in stroke cases than controls.

Taking age into account, the serum lipids, blood pressure and carbohydrate tolerance.
appear to be the principal determinants of the rate of atherogenesis. However, the evidence that accelerated atherogenesis predisposes to cerebral infarction is not nearly as strong as the evidence for its role in coronary heart disease.

SERUM LIPIDS
There is a good deal of evidence from animal and autopsy studies to link certain serum lipid patterns to atherogenesis. If there is some common pathway through which diverse factors promote atherogenesis, it seems likely to be a derangement of lipid metabolism. Yet case-comparison studies of serum lipids in persons with cerebrovascular disease have not always shown higher serum cholesterol values in stroke cases. Where differences were found, they have not been as striking as in coronary disease. Whether this implies a lesser role of lipids in cerebral atherogenesis or the influence of selective mortality in those with high serum cholesterol values is not clear. It has been suggested that serum triglycerides may be more closely related to risk of cerebral vascular disease than is serum cholesterol.

Prospective epidemiological studies of the role of lipids in cerebral infarction also indicate that atherothrombotic risk is not as strongly related to serum lipid characteristics as is coronary risk. Except for cerebral infarction in the young, evidence that lipids accelerate cerebral atherosclerosis is disappointingly weak. This is not surprising since the impact of lipids on incidence wanes considerably with advancing age, even in the case of coronary disease where the relationship is strong, and most cerebral infarctions occur in advanced age. The association of lipids with cerebral infarction incidence can be demonstrated only in those who are under 50 when the lipid was measured. In this age group risk appears related to lipid values—triglyceride rich prebeta lipoprotein as well as cholesterol. Also, at any level of lipid risk varied over a wide range, depending on the associated blood pressure (fig. 7). This suggests that if cerebral infarct occurs in the absence of hypertension at a young age lipid abnormalities may be at fault. In general, however, with atherothrombotic strokes occurring late in life, after exposure for several decades to the generally high lipid values encountered in the U.S.A., hypertensives appeared to have enough lipids to produce cerebral atheromata.

![Risk of atherothrombotic brain infarction (16-year follow-up) according to prior CHD status. Men and women 30-62 at entry: Framingham study.](http://stroke.ahajournals.org/)

**Figure 6**
DIABETES

While the acute metabolic consequences of diabetes leading to acidosis, coma and death have been dramatically affected by modern methods of diabetes control, there is little evidence that the long-term cardiovascular sequelae have been similarly ameliorated by tight control of carbohydrate intolerance with insulin or oral hypoglycemic agents.

Diabetes is clearly associated with both large and small vessel disease, with multiple lipid abnormalities, and with obesity and hypertension. Thus, it is not surprising that impaired glucose tolerance has often been observed in stroke candidates. Some post-mortem studies disclosed that diabetes is associated with an increase in the frequency of cerebrovascular atherosclerosis. On the other hand, some authorities suggest that the incidence of cerebrovascular disease is not higher in diabetics. Prospective data at Framingham also indicated increased risk of cerebral infarction in persons with even modest evidence of impaired glucose tolerance (fig. 8). The associated atherogenic variables, however, do not appear to explain all of the excess risk of diabetes. Evidently there is some unique effect of diabetes in vascular disease.

Perhaps early attention to lipid and lipoprotein patterns and hypertension in the control of "diabetes" would be more successful than preoccupation solely with the carbohydrate intolerance. There is some disquieting evidence to suggest that hypoglycemic agents may actually promote atherogenesis. Insulin stimulates lipogenesis in adipose tissue and may do likewise in vascular tissue. Animal experiments have revealed that intravenous insulin plus C-14-labeled substrate containing either glucose or acetate leads to much greater incorporation of substances into aortic lipids than when substrate alone is injected. Since maturity-onset diabetics have high serum insulin levels, fat deposition in the arterial walls may be actually stimulated by this insulin which also inhibits tissue lipase in arterial tissue and allows lipid accumulation. This is still quite speculative but must be considered as one possible reason for the refractoriness of the vascular sequelae of diabetes to treatment.
Risk of cerebrovascular accident in diabetes (16 years) according to diabetic status: Framingham study.

Since high blood pressure is so clearly the most important precursor of stroke, a detailed examination of its relationship to cerebral infarction is indicated. Based on prospective data from Framingham, a reasonably undistorted picture of the evolution of essential hypertension into stroke can be obtained.

Hypertension was the principal factor among the various hallmarks of increased vulnerability to cerebral infarction as revealed by discriminant analysis. It made a substantial independent contribution, even allowing for the influence of other related factors. Age and sex trends in blood pressure and stroke were similar, with a male predominance at younger ages and a higher incidence in women at older ages (fig. 9). The probability of developing cerebral infarction was strikingly related to the antecedent casual blood pressure level, systolic no less than diastolic (fig. 10), with no evidence that the impact of systolic pressure over diastolic lessens with advancing age.51

**CARDIAC IMPAIRMENTS**

Trends in the incidence of cerebral infarction in relation to blood pressure were similar whether or not cardiac impairments were present. However, within any blood pressure category those with cardiac impairments were at greater risk (fig. 11).
Risk of cerebrovascular accident (16 years) according to blood pressure status and evidence of cardiac impairment. Men and women 30-62 at entry: Framingham study.

Risk of atherothrombotic brain infarction (16-year follow-up) according to prior ECG-LVH status. Men and women 30-62 at entry: Framingham study.
EPIDEMIOLOGY OF BRAIN INFARCTION

Persons with electrocardiographical left ventricular hypertrophy had a ninefold increase in risk of cerebral infarction which persisted at threefold after adjustment for co-existing hypertension (fig. 12). Cardiac enlargement on x-ray was associated with a threefold greater risk of cerebral infarction, but there was no increase in risk when the cardiac enlargement was not accompanied by ECG-LVH (fig. 13). As indicated previously, persons with prior coronary heart disease had a threefold increase in risk after adjustment for associated hypertension (fig. 6). All of the foregoing suggests that impaired cardiac function may provoke strokes in predisposed persons. Atrial fibrillation is associated with a substantial increase in occlusive strokes, even when associated cardiac impairments and hypertension are taken into account. While the presumption that these strokes are embolic cannot be refuted with certainty, there is every likelihood that some are "thrombotic."

The data presented imply that hypertension, besides accelerating atherogenesis, may precipitate strokes by impairing cardiac function as well as by mechanically damaging diseased vessels or reflexly reducing cerebral blood flow. Hypertension assumes a grave significance for risk of stroke when ECG-LVH or coronary heart disease appears. The data suggest that more attention should be paid to casual systolic and diastolic blood pressure elevations, even prior to evidence of target involvement and fixed diastolic elevation. A controlled clinical trial to test this hypothesis would seem overdue.

HEMOGLOBIN

“Elevated” blood hemoglobin may also be cited as a possible stroke precursor. Within the normal range of hemoglobin values risk has been found to be proportional to the blood hemoglobin concentration. Hemoglobin values at the upper end of the “normal” distribution (i.e., greater than 15 gm in men and 14 gm in women) carried about twice the risk of lower values (fig. 14). However, a relationship of hemoglobin level to hypertension was also
stated, suggesting a possible mechanism. When allowance is made for this associated hypertension only a small residual effect of hemoglobin concentration is discernible. Pathogenetic mechanisms to be considered include chronic dehydration, altered blood viscosity, oxygen transport, dynamics of flow, an influence on clotting characteristics and elaboration of erythropoietin by the ischemic hypertensive kidney.

**Stroke Profiles**

The portrait of the prime candidate for a stroke is still a bit hazy. Information on the strength of the contribution of the ingredients, singly and in combination, is still imprecise owing to limited numbers generated from prospective studies. There is evidence to suggest, however, that combinations of risk attributes (figs. 7, 11, 12, 15) carry more risk than do the same attributes singly. For example, the risk of a brain infarction in diabetics with hypertension is probably about six times that of normal subjects. In persons under 50 at the time of measurement, risk of cerebral infarction is possibly ten times higher in those with hypertension and elevated lipids than in those without either elevated (fig. 7). About 40% of cerebral infarctions occurred in the 10% of the population with four or more of the identified precursors (fig. 15). This compounding of risk has pathogenetic, preventive, and public health implications. For purposes of stroke screening alone the most efficient and practicable method would be to determine casual blood pressure. Adding more costly and cumbersome lipid and glucose determinations and an ECG would detect only a moderate number of stroke susceptibles who escape the blood pressure dragnet. For pathogenetic purposes and office screening, where these other determinations will be made for other purposes as well, a more intensive screening would be useful. For pathogenetic purposes, an assessment of the net contribution of these multiple interrelated risk factors would be quite important, but such an assessment must await the accumulation of more data from prospective epidemiological studies.

**COURSE OF CLINICALLY MANIFEST DISEASE**

Once the signs of focal neurological deficit begin to make their appearance, either transiently or progressively, the fear of a lethal or
disabling stroke is justified. We lack precise information on the magnitude of the risk without medical or surgical intervention. Such information is needed for proper evaluation of prophylactic management.

So few physicians now feel justified in denying either anticoagulants or surgery to patients with transient ischemic cerebral attacks that it is probably no longer possible to examine the natural history of such attacks. Persons in whom reversible focal neurological deficits endure less than 24 hours appear to be at high risk of completed strokes, and as many as 20% to 40% can be expected to have a lethal or incapacitating stroke within five years. The spontaneous remission rate is uncertain, and reports vary between 25% and 75%. There is some evidence that transient ischemic attacks in the vertebrobasilar territory carry a better prognosis than do those in the carotid territory.\textsuperscript{58}

Some encouraging results on the surgical management of accessible carotid lesions in patients with transient ischemic attacks are beginning to appear which suggest that surgical correction may reduce the rate of occurrence of new strokes by one-third.\textsuperscript{64} The concept that surgery will abolish intermittent ischemic cerebral symptoms, reduce the risk of a completed stroke, and prolong survival in persons so afflicted should be tested.

**SURVIVAL**

Prospective studies of relatively young representative samples of the general population suggest that 15% to 20% of victims sustaining their first stroke die early. Only about 40% to 50% survive five years or longer.\textsuperscript{2} However, representative survival statistics are still in a primitive state. Population studies which include milder cases provide a less-distorted assessment of stroke prognosis, usually more encouraging than those from a hospital series. Nevertheless, the picture that is emerging does not engender optimism. Recurrences appear to be the rule; about one-quarter will eventually die of another stroke, and most of the rest from cardiovascular disease. Persons with strokes have a death rate about seven times higher than expected from the age-matched general population.\textsuperscript{56} In those surviving the acute phase, subsequent mortality is three to five times greater than the general population.\textsuperscript{56} There is little reason to expect that the higher
early mortality and the long-term excess mortality will be greatly affected by more diligent therapy in those with the completed catastrophe. However, there is some encouragement in reports of improved mortality and recurrence experience after strokes in those whose hypertension has been controlled.\textsuperscript{27, 29} Even if the stroke victim survives the catastrophe his troubles are not over. A sizable proportion will have disabling neurological residuals, and if another stroke does not add to their plight, associated cardiovascular disease will.

Among 71 subjects with brain infarctions in Framingham, 21\% of the men and 13\% of the women died in the same biennial examination interval. With the numbers available, there is no statistical significance to the sex differences noted. These findings are similar to those of others. If the one-third who had co-existing coronary heart disease or congestive failure are eliminated, survival is much better with only about 5\% succumbing in the same examination interval. Also, while only 58\% of men with cerebral infarction were alive at four years, 75\% of those without co-existing coronary disease or congestive failure survived (table 1). It appears that especially in men the co-existing cardiac disease is the major source of poststroke mortality.

Whisnant et al. at the Mayo Clinic found that 40\% of stroke victims who died did so of related causes and 10\% died of another stroke. Cardiac disease accounted for almost twice as many deaths as did a subsequent stroke.\textsuperscript{3}

**Discussion**

Vascular disease of the brain is part of a larger problem of cardiovascular diseases which together are responsible for half the annual toll of death in the U.S.A. The problem of the etiology of stroke and each of the several cerebrovascular diseases is largely one of atherosclerotic disease and hypertension. With the population living to a more advanced age and nutritional and infectious disease largely under control, cerebrovascular disease is now the third leading cause of death. There is little to suggest that stroke, the second ranking vascular killer, will be conquered by more expert management of the completed episode. Basically, the extent and gravity of the neurological deficit incurred are determined by the kind and location of the vascular lesion or lesions; and, once the brain in the territory of the vessel undergoes infarction, it can neither be resurrected nor compensated for to any large extent. The best answer to this devastating illness is a preventive approach.

**PREVENTIVE IMPLICATIONS**

Cerebrovascular "accidents" may not be simply accidents of nature, to be accepted as an inevitable hazard of advanced age. The vulnerable can be identified long in advance, and the probability of their coming to grief with a stroke estimated. A profile of the potential stroke candidate is slowly emerging from prospective epidemiological studies.

The precursors of cerebral infarction can be divided into three general categories: factors which accelerate atherogenesis, those which precipitate strokes in the predisposed, and those which signify impending attacks. Chief among the atherogenic factors are serum lipids, hypertension and impaired carbohydrate tolerance—precursors common to each of the major clinical manifestations of atherosclerosis. Possible precipitating factors include: hypertension, hypotension, hypoglycemia, impaired cardiac function and microemboli from proximal atherosclerotic disease and other sources of emboli. Evidence of impending

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**Table 1**

Survival After Initial ABI. Men and Women 30 to 62 on Entry

<table>
<thead>
<tr>
<th>Years after diagnosis</th>
<th>All ABI</th>
<th>Men Excluding CHD &amp; CHF</th>
<th>All ABI</th>
<th>Women Excluding CHD &amp; CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>78.8</td>
<td>95.2</td>
<td>86.8</td>
<td>95.8</td>
</tr>
<tr>
<td>2</td>
<td>66.7</td>
<td>83.3</td>
<td>81.2</td>
<td>91.0</td>
</tr>
<tr>
<td>4</td>
<td>58.3</td>
<td>74.1</td>
<td>75.5</td>
<td>78.9</td>
</tr>
</tbody>
</table>

*Stroke, Vol. 2, July-August 1971*
strokes include such signs of extracranial vascular disease as vascular bruits, pulse differences, abnormal ophthalmodynamometry, thermographic differences and transient ischemic attacks.

Until we come to regard the occurrence of a stroke in a patient under periodic medical surveillance as a medical failure, little progress will be made against this devastating malady. Physicians strive to keep people living to advanced age. Stroke must not be the reward for achieving this venerable stage of life. Prevention of strokes will require the cultivation of a healthy respect for what is now regarded as "medical trivia."

There is presently little assurance that strokes are preventable, but the magnitude and the nature of the problem compel us to evaluate the possibility of prevention by means of well-designed clinical trials. While early detection and correction of extracranial vascular disease and transient ischemic attacks may eventually delay some strokes and prolong some lives, this approach is not likely to have a major impact on overall stroke morbidity and mortality. There is no escaping the conclusion that the best solution is the prevention of atherosclerosis, hypertension and cardiac disease. The answer lies in detection and correction of these stroke precursors in youth.

We still lack the data necessary to assess most of the prophylactic measures which appear rational, including correction of hypertension, impaired glucose tolerance and cardiac malfunction; reduction of weight, blood lipids and the hematocrit; increased physical exercise; and giving up cigarettes. Mounting evidence from clinical trials suggests that effective lowering of high blood pressure will prevent many "thrombotic" strokes and intracranial hemorrhages. Untreated or inadequately managed hypertensives have been repeatedly found to sustain more strokes than normotensives or adequately treated hypertensives. Since even "trivial" hypertension appears to be associated with a substantial increase in risk of strokes (fig. 10), awaiting the onset of severe fixed diastolic hypertension or evidence of target organ involvement before intervening would appear imprudent.

Enhanced diagnostic capability allows identification of secondary hypertension. With the proper combination of drugs and weight control, most essential hypertension can now be managed without great hazard or inconvenience, if therapy is initiated before pressures become fixed at a high level and before damage has been done to vital organs. Essential hypertension, however, must be sought out in the apparently well population, since most subjects are unaware of their pressure and, even among known hypertensives, only a minority are consistently receiving long-term therapy. Hope for significant inroads against cerebrovascular disease rests largely upon the detection, evaluation and long-term care of these asymptomatic hypertensives.

**Summary**

This review of the current status of cerebrovascular disease epidemiology has emphasized a number of gaps in our knowledge, as well as our uncertainty about some previously accepted information. These imperfections can be convincingly resolved only by additional prospective epidemiological information.

The impact of cerebrovascular disease as a force of morbidity and mortality is undoubtedly great, but we do not know just how great, because of imprecise clinical impressions with inadequate pathological documentation, and selected hospital or autopsy statistics unrepresentative of the populations from which they arise. Kurland estimates that about 400,000 persons who die each year had a stroke either causing or contributing to the death. In Framingham among persons between 30 and 60 years of age followed over 14 years, there was an average annual incidence of 1.5 per 1,000. More prospective incidence data from different geographic areas are needed, since some suspect that the rates are not uniform.

The relative frequency of the different varieties of cerebrovascular disease is also in doubt. Estimates systematically derived from more representative population samples differ considerably from those derived from clinical, autopsy or mortality reports. The latter appear to grossly overestimate the frequency of intracerebral hemorrhage. Also, subarachnoid hemorrhage may account for more of the intracranial hemorrhages. We are not sure how much of the problem of brain infarction is due to thrombosis, atherosclerotic narrowing or microemboli in large extracranial vessels, in medium intracranial arteries or small penetrating branches. The precursors and natural
history of each variety of brain infarction are not well understood.

When it is suspected that several clinical diseases are different features of a common underlying pathological process, sharing etiological precursors, it is useful to compare their epidemiological features. While there are some differences, the major atherosclerotic diseases have more in common than not, and those with one clinical manifestation are at increased risk of another. At present we cannot accurately distinguish potential cerebral infarction candidates from those destined for coronary attacks or intermittent claudication. The vascular pathology on angiography or postmortem is remarkably similar.

The lack of a clear male predominance suggests a different pathogenetic mechanism for cerebral infarction, but there is a clear male predominance in cerebral infarction occurring early enough in life so that the relative immunity enjoyed by the premenopausal female is expressed. The apparent disparity of time trends, in geographic variation and racial predilection would also suggest a different pathogenesis for cerebral infarction, were it not for the uncertain validity of the mortality statistics on which these findings are based.

Geographic variation in stroke incidence suggests potent environmental influences at work. Reported differences in time trends and geographic and racial incidence are difficult to accept at face value, owing to imprecise diagnosis, variation in medical facilities and fashions in death certification. Contrary to suggestions from mortality data, prospective population studies suggest that age-specific rates are similar for Caucasians, Negroes and Japanese in regard to brain infarction and intracerebral hemorrhage.

Atherogenic precursors such as hypertension, diabetes and hyperlipidemia are common to all the major clinical manifestations of atherosclerosis. However, in the case of strokes, lipids are a prominent feature in the background of only the young stroke victim. Hypertension is clearly the most important contributor to stroke incidence. Epidemiological data suggest that hypertension not only accelerates cerebral atherogenesis but may precipitate strokes as well. By contributing to the development of impaired cardiac function, it further adds to the risk. Hypertensives evidently do not require cardiac impairments to become a stroke victim; but when the latter occurs, the hazard increases about threefold.

Direct assessment of environmental influences has failed to identify many living habits which contribute to stroke incidence. Habits of sloth and gluttony expressed as obesity appear unrelated to the rate of development of cerebral infarction. Physical activity, which appears to protect against coronary mortality, appears unrelated to cerebral infarction. The cigarette habit, however, at least in men, is distinctly associated with all major atherosclerotic diseases, including cerebral infarction.

Strokes are part of a larger problem of cardiovascular disease, especially in persons with hypertension, cardiac impairments, and atherosclerotic vascular disease. These will have to be controlled if a substantial reduction in morbidity and mortality from cerebral infarction is to be achieved. In particular, hypertension with or without symptoms should be detected early in life and effectively controlled. This should also reduce coronary, occlusive peripheral arterial, and congestive failure morbidity and mortality.

Though many persons with multiple stroke risk factors escape the fate implied, it would seem the height of folly to count on this immunity. There is still no guarantee that their conversion to a "low-risk" type is the same as being that way naturally, but conversion does seem worth a try, since the measures required are not very hazardous and are worthwhile for other reasons as well.

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Current Status of the Epidemiology of Brain Infarction Associated with Occlusive Arterial Disease

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