Vascular Disease of the Central Nervous System

Edited by

R. W. Ross Russell

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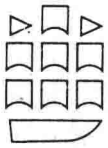
SECOND EDITION



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Preface

Since the first edition of this book was published in 1976 under the title of *Cerebral Arterial Disease* there have been a number of developments both of a practical and theoretical kind. At that time computerised scanning was just coming into general use and it has fully justified its initial promise to the extent that it is now essential in making the early critical decisions in the management of stroke — has the patient with an acute focal deficit had an infarct, a haemorrhage or some other non-vascular event? Not only does this enable therapy to be started earlier but the tightening of diagnostic criteria has enabled treatment and trials of new treatments to be put on a firmer basis.

The other major change in practical management is in the field of vascular surgery and here the position is still far from clear. The new technique of extracranial/intracranial anastomosis has developed rapidly and it is now apparent that an anastomosis can be established with safety and can effectively conduct blood from the scalp to the brain. Does the operation do any good? Probably it does if the patient has a region of brain with a precariously balanced blood supply which from time to time becomes insufficient; probably it does not in the patient with an established infarct; possibly it may in the patient who has made a good recovery following an internal carotid occlusion. The operation is in danger of being applied uncritically to patients in all these categories with no pause for proper assessment, and even the present controlled trial may be unable to answer some of the questions in the foreseeable future.

Medical therapy in acute stroke remains disappointing and the initial hopes which were entertained for the treatment of oedema with osmotic agents or corticosteroids have not been realised. Oedema can be a life threatening complication in massive hemisphere infarction but the effect of energetic treatment has too often been the survival of some severely disabled patients who would otherwise have died. In the posterior fossa however the situation is different; here the recognition and energetic treatment of oedema by both medical and surgical means continues to be well worthwhile.

Thanks largely to increasing awareness of the importance of hypertension and to more effective methods of antihypertensive treatment there are good reasons to expect a decline in stroke in middle-aged patients as well as a continuing reduction in cerebral haemorrhage. Faced with a slowly increasing proportion of elderly patients in the population there seems little likelihood that the overall incidence of stroke will decrease. The rehabilitation of established stroke patients is now claiming some overdue attention. Increasingly sophisticated aids and techniques are becoming available and there is literally no limit to the amount that can be spent on attempting to rehabilitate patients with cerebrovascular disease. In this situation it is essential to deploy limited resources to the best effect. This means looking critically at the results of different physical methods of rehabilitation in the various categories of stroke and comparing the cost-effectiveness in the light of the natural history. Expensive and complicated methods of rehabilitation may prove to be no more effective than simpler and cheaper ones.

In the theoretical field the most notable advance has been our increased understanding of the mechanisms of ischaemia and its effect on oxidative metabolism and regional blood flow made possible by positron emission tomography. This technique

has revealed the complex disturbances which may be found around an ischaemic area and even in the opposite hemisphere — regions of depressed flow and metabolism, regions of absolute or relative hyperaemia, regions of relative vascular insufficiency with maintained metabolism, and even regions of hypermetabolism. The technology is so sophisticated and expensive as to be unsuitable for general use but it will provide an opportunity for assessment of claims made for vasoactive agents and metabolic stimulants to improve brain function at various stages after vascular occlusion. The development of similar isotopic techniques to label glucose, aminoacids, and drugs acting on the brain promises to open a new chapter in neuro-chemistry and neuro-pharmacology.

I am grateful to the team of distinguished contributors to this volume, both to those who have revised their chapters sometimes extensively and to those who have written new chapters. Their responses to my requests and amendments have been prompt, efficient and good-natured and have made editing a pleasure rather than a labour.

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R.W.R.R.

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1

Epidemiology of cerebrovascular disease

William B. Kannel and Philip A. Wolf

INTRODUCTION

Reduction of stroke incidence requires the identification and treatment of candidates for cerebrovascular disease. To await signs of a compromised cerebral circulation is to take an unacceptable risk since only ten percent of strokes are preceded by TIAs (Whisnant, 1974). There is little to suggest that the devastating consequences of stroke will be ameliorated by more expert medical or surgical management of the completed episode. A more fruitful approach is to deal with its precursors rather than to delay treatment until the stroke is imminent or has already occurred. Stroke is a consequence of a long-term process and not a chance or random event as the term 'cerebral vascular accident' implies. The association between brain infarction and atherosclerosis elsewhere indicates that it is part of a generalized vascular disease.

Epidemiologic investigation of the way cerebrovascular disease evolves in the general population has identified a number of host and environmental contributors. Major reductions in death and disability from stroke will come from prevention; such a program depends upon identification and treatment of the stroke-prone person.

Stroke does not as readily lend itself to epidemiologic study as does coronary heart disease because it generally occurs later in life and its incidence and mortality rates are substantially lower (Shurtleff, 1974) than those for coronary heart disease (CHD). In order to achieve equivalent results the cohorts studied must be larger and followed for longer periods. Alternatively, entry into the study at a later age may be considered, but this carries the liability of lower response rates and loss of impact of risk factors presumably due to the overwhelming associative strength of age itself. Although neither as common nor as lethal as coronary heart disease, cerebrovascular disease is nevertheless the most devastating clinical manifestation of hypertension and atherosclerosis. The victim is often deprived of his dignity, ability to communicate, independence and physical capacity.

Diagnosis of an event, particularly as to specific type, is more difficult than for CHD because of less pathognomonic laboratory tests such as the ECG or enzyme abnormalities available for myocardial infarction. There are still no uniformly applied indications for the timing or performing of specific tests such as lumbar puncture, cerebral arteriography, CT-scan, brain scan, or noninvasive studies of carotid patency. Even at autopsy of fatal cases it may be difficult to differentiate accurately between intracerebral hemorrhage, hemorrhagic infarct and subarachnoid hemorrhage when there has been extensive destruction of brain and vascular structures. Ischemic brain infarction may be due to thrombosis or embolism and it is often difficult to distinguish between the two alternatives.

Despite these problems epidemiology studies have been carried out yielding useful information about the way strokes evolve, their precursors and prognosis.

Information has been obtained from prospective epidemiologic studies such as that at Framingham on the incidence of strokes in the general population, the way they evolve, hallmarks of vulnerability, a profile of potential candidates, clues to its pathogenesis and the disability and mortality which ensues. The importance of stroke as a cause of morbidity and mortality in the increasingly elderly population warrants an exploration of each of these

features of the epidermiology of stroke, using data from the Framingham Study and elsewhere.

EPIDEMIOLOGIC ASSESSMENT OF THE STROKE ENTITY

Prevalence

Estimates of the prevalence from general population samples are sparse and the figures obtained are rather diverse (Table 1.1). There were some 1.8 million strokes estimated by the American Heart Association in 1977; a prevalence roughly equal to that of rheumatic heart disease and almost half that of coronary heart disease (Fig. 1.1). The prevalence increases with age and is substantially higher for blacks, particularly at younger ages (Kurtzke, 1976a).

Cerebrovascular disease is also a major contributor to disability accounting for half the patients hospitalized for neurologic disease. In the Framingham Study, 31 percent of stroke survivors needed assistance in self-care, 20 percent required assistance in ambulation and 71 percent had an impaired vocational capacity when examined an average of 7 years after stroke (Gresham et al, 1975; Gresham et al, 1979). Some 16 percent remain institutionalized.

A preventive approach to cerebrovascular disease is necessary because there is little hope of reversing established brain damage. The potential for salvage is particularly important in the case of stroke, which has a high incidence of permanent disability among survivors. The fatality rate in the acute stage is only 15 percent, but of the survivors, 50 percent suffer permanent disability. Of the estimated two million cases of post-stroke disability in the United States, one-third are age 35–65 wage earners who have become unemployable because of their stroke disability. The estimated annual cost

Table 1.1 Cerebrovascular disease: age-specific prevalence rates both sexes

*Rochester, Minnesota 1970 (a)**		*English General Practices 1955–6 (b)†*		*U.S. Health interviews 1978‡*	
Age	*Prevalence/ 100 000 populations*	*Age*	*Prevalence/ 100 000 population*	*Age*	*Prevalence/ 1000 population*
<35	10	15–44	30	<45	1.1
35–44	200				
45–54	440	45–64	400	45–64	12.3
55–64	810				
65–74	3560	65+	2930		
75+	5970			65+	44.9
Total	612	Total	486	All ages	8.0
Age-adjusted (to U.S. 1960)	556	Age-adjusted (to U.S. 1960)	363		
(Cases)	(303)	(Cases)	(1862)	(Interviews)	(134 000)

(a) Matsumoto et al 1973.
(b) Logan and Cushion 1958.
* Modified from Kurtzke 1976a.
† Modified from National Center for Health Statistics 1978.

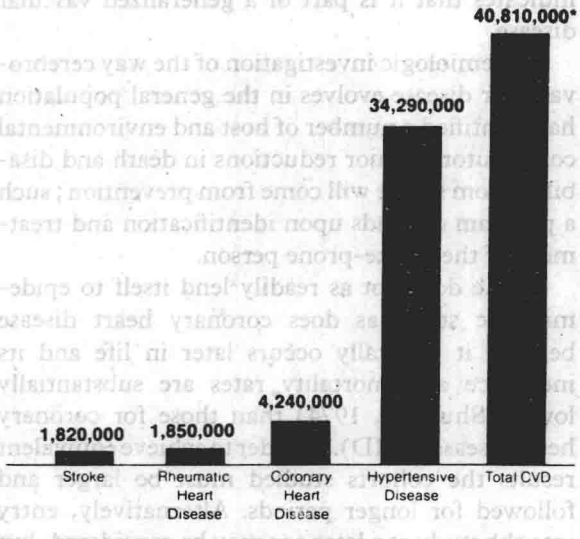


Fig. 1.1 Estimated prevalence of the major cardiovascular diseases (United States, 1977).

of care for stroke disability is three billion dollars. There are further costs of care during the acute stage of hospitalization. Thus, the potential rewards, in both health care and resources, of detection of stroke candidates and preventive treatment are obvious.

Incidence

About 500 000 new strokes occur annually within the United States. The incidence reaches major proportions only after age 55, but no age group is completely spared. The reported incidence rates vary depending on whether the sample was derived from the general population or hospitalization, its age composition and whether recurrent strokes were included.

The incidence of strokes generally, and atherothrombotic brain infarctions (ABI) specifically, in the Framingham Study increased with age in both sexes but more precipitously in women than in men (Table 1.2). Only under age 55 is the male

Table 1.2 Incidence of stroke and myocardial infarction by age and sex, 20 year follow-up. Framingham study. Men and women, age 45–74

	Average annual incidence per 10 000					
Age	*Strokes — all types*		*Atherothrombotic brain infarctions*		*Myocardial infarctions*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
45–54	20	9	10	6	48	9
55–64	32	29	20	18	91	19
65–74	84	86	52	55	111	51
45–74	34	29	20	18	72	19

preponderance characteristic of atherosclerotic disease apparent. Comparing brain and myocardial infarction, there is a marked male predominance at all ages for myocardial infarction and almost four myocardial infarctions occur in men for each brain infarction. For women, the incidence of each is virtually identical. For reasons which are not clear, ABI is the only major clinical atherosclerotic manifestation which fails to exhibit a preference for males. This may stem from the fact that cerebral atherosclerosis, which begins later in life than in other vascular territories, does not reach major proportions until women have already lost their premenopausal immunity to atherosclerotic vascular disease.

Kurtzke estimated an incidence rate of 2 per 1000 per year for all ages combined (Kurtzke, 1976b). The Joint Committee for Stroke Facilities estimated that stroke death rates in 1972 increased from 1 per 1000 at ages 45–54, to 3.5 per 1000 at 55–64 and to 9 per 1000 at ages 65–74 (Table 1.3).

Table 1.3 Estimated annual incidence rates for stroke per 1000 population (both sexes, all races)*

Age group	*Probable minimum*	*Midpoint*	*Probable maximum*
35–44	—	0.25	—
45–54	0.6	1.00	1.8
55–64	2.5	3.50	5.0
65–74	6.0	9.00	12.0
75–84	15.0	20.00	25.0
85 and older	—	40.00	—

Notes on use of estimated incidence rates:
1. Rates for males tend to approach the maximum and those for females the minimum estimates.
2. Rates for blacks are probably generally higher than for whites.
3. These rates for the most part are based on studies of first events only, so that to derive a figure for total case load, an adjustment should be made for recurrent strokes. Our best estimate is that the rates would be 25 percent higher if recurrent cases are included.

* (Report of the Joint Committee for Stroke Facilities, 1972).

These estimates are similar to those prospectively obtained in the Framingham Study (Table 1.2). Framingham data suggest that the chances of suffering a stroke before age 70 are one in twenty. Although strokes occur most often late in life, 20 percent occur in persons under age 65.

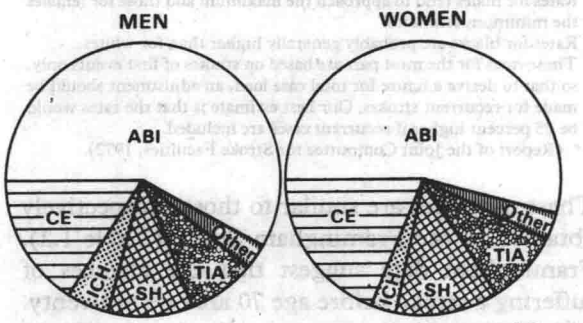
Frequency of strokes by type

The prevalence of the major varieties of cerebral vascular disease is uncertain and varies depending on the source of the data. Because of its lethal nature, parenchymal brain hemorrhage is overrepresented in autopsy data. Data from hospitals and neurology clinics are subject to selective bias and are likely to over-emphasize strokes that are severe and require hospitalization. General population survey data are more representative but often suffer from small numbers of the less common types of stroke, making precise estimates of frequency difficult (Kurtzke, 1976a).

The Harvard Cooperative Stroke Registry suggests that about half of strokes (53 percent) are 'thrombotic'; and of these about two-thirds involve large arteries producing infarctions while the remaining third affects small penetrating arteries

causing the small deep brain infarcts known as lacunes (Mohr et al, 1978). Of the thrombotic strokes, 18 percent of all events are a result of atherothrombotic disease of the carotid artery, 16 percent from disease of vertebral and basilar arteries and 19 percent lacunar infarcts. Embolism appears to account for 31 percent of all strokes and intracranial hemorrhage from hypertension or ruptured aneurysm accounts for 10 percent and 6 percent respectively.

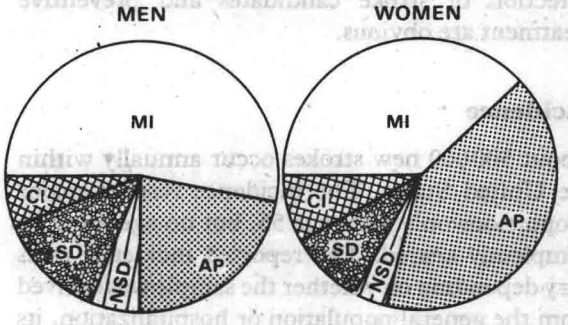
Data from the Framingham Study, based on a general population survey routinely assessed for strokes at biennial intervals, are in close agreement with the Stroke Registry as to the frequency of atherothrombotic brain infarcts and intracranial hemorrhages (Wolf et al, 1978a). See Fig. 1.2.



		Percent of Cases	
		Men	Women
ABI	Atherothrombotic Brain Infarction	58%	54%
CE	Cerebral Embolus	16%	19%
ICH	Intracerebral Hemorrhage	5%	3%
SH	Subarachnoid Hemorrhage	10%	12%
TIA	Transient Ischemic Attacks Only	8%	9%
Other		3%	3%

Fig. 1.2 Frequency of stroke by type. Men and women age 65–74: the Framingham study, 26 year follow-up.

Because uncomplicated TIAs are also included, the percentages may be somewhat understated. It is interesting that the frequency of the various types is quite similar in the two sexes. It is also noteworthy that, even in the same advanced age group (65–74), there is a predominance of myocardial infarction in males over females (Fig. 1.3) while in the same cohort brain infarction frequencies are quite similar. It is difficult to determine the precise proportion of strokes that are due to extracranial vascular disease. Carotid artery disease appears to account for some 18 percent of strokes. It is likely that the frequency of small intracerebral hemorrhages is greater than indicated in these data and will be found to be larger when CT scan data become more readily available.



		Percent of Cases	
		Men	Women
MI	Myocardial Infarction	53%	38%
CI	Coronary Insufficiency	8%	8%
SD	Sudden Death	13%	9%
NSD	Non-Sudden death	6%	4%
AP	Angina Pectoria	22%	41%

Fig. 1.3 Frequency of coronary heart disease by type. Men and women age 65–74, the Framingham study, 26 year follow-up.

Autopsy studies of the relative frequencies of stroke types give very different results but they may be unreliable (Kuller, 1978). It is likely that hospital-based data are also fallible. The best data must be presumed to be the community-based incidence studies. From these Kurtzke has estimated that 8 percent of stroke incidence is due to subarachnoid hemorrhage, 12 percent intracerebral hemorrhage and 69 percent thromboembolism of which 3–8 percent are due to embolism. The remaining 11 percent are ill-defined strokes (Kurtzke, 1976a).

Mortality

In 1977, cerebrovascular disease accounted for nearly 182000 deaths in the USA comprising nearly a tenth of the total mortality (Vital Statistics of the United States, 1977) See Fig 1.4. This may be an underestimate because death certificates by underlying cause often fails to note the contribution of a past stroke. Stroke fatalities rank third among all causes of death in most affluent countries, exceeded only by heart disease and cancer.

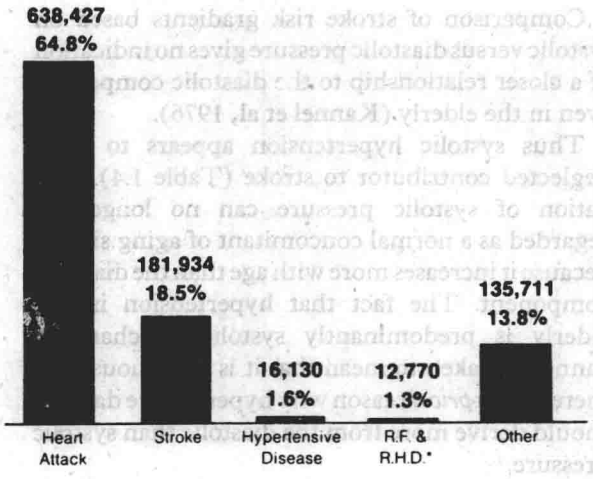


Fig. 1.4 Deaths due to cardiovascular diseases by major type of disorder (United States, 1977).

RISK FACTORS

Major reductions in disability and death from stroke will come from prevention rather than from more effective medical or surgical treatment. It is a universal finding among all epidemiologic studies that the most important risk factor for stroke, whether infarction or hemorrhage, is hypertension.

There is also general agreement that both elevated pressure and cardiac abnormalities are powerful contributors to stroke incidence. Factors which have been inconsistently incriminated are glucose intolerance, blood lipids, elevated hematocrit and cigarette smoking. Further confirmation is needed concerning the suggestion that *lower* serum cholesterol and LDL-cholesterol may be associated with increased risk of brain infarction in women and intracerebral hemorrhage in men. The association of alcohol with an increased risk of stroke is highly suggestive. Few environmental factors have been conclusively linked to stroke incidence.

Because ABI, the most common variety of stroke shares a common pathology with CHD, it might be expected that they would also share common risk factors. However, there are a number of differences which are both noteworthy and unexplained. Although subjects with CHD are at a five-fold increased risk of stroke and CHD risk profiles will identify stroke candidates with equal or greater efficiency (Kannel, 1978), the impact of some CHD risk factors are surprisingly weak. Thus, hypertension predisposes to both. Serum total cholesterol, obesity and cigarettes are rather weak stroke risk factors. This may derive from the advanced age at which strokes occur, when even for CHD these risk factors lose their impact (McGee, 1973).

At the present time the main risk factors for ABI are: hypertension, CHD, CHF, ECG abnormalities, diabetes, certain systemic diseases affecting cerebral blood flow, blood viscosity and coagulation, complications of operations on the heart and great vessels and certain medications such as oral contraceptives.

Cerebral embolism is chiefly a consequence of valvular disease, myocardial infarction and irregularities in cardiac rhythm (chiefly atrial fibrillation) or complications of cardiac operations.

Intracranial hemorrhage is a consequence of congenital anomalies, AV malformations, hypertension and interference with blood clotting.

Atherogenic personal attributes

Hypertension

Of the various risk attributes known to contribute to the occurrence of strokes, hypertension has been shown to play a dominant role (Whisnant, 1974; Kannel, 1971; Kannel, 1976; Kannel and Wolf, 1975; Kannel et al, 1978; Kannel et al, 1971). The relationship seems to be just as strong for non-embolic cerebral infarction as it is for intracranial hemorrhage. Not only is hypertension the most powerful contributor to stroke incidence, but it is also a highly prevalent one so that the attributable risk is greatest for hypertension as well. The risk of stroke is related to the height of the blood pressure, not only among hypertensives but throughout the range of blood pressure, with no discernible critical value of systolic or diastolic pressure which delineates the stroke candidate from the general population (Whisnant, 1974; Kannel, 1971; Kannel, 1976; Kannel & Wolf, 1975; Kannel et al,

1978). There is no evidence that the influence of blood pressure diminishes with advancing age.

Systolic hypertension

Both stroke and hypertension reach major proportions in the elderly. Since there is a disproportionate rise in systolic pressure with advancing age, systolic hypertension is common in the elderly. For some time this was regarded as a harmless consequence of progressive rigidity of the arteries in advanced age. It has now been shown that this isolated systolic hypertension is far from innocuous and it is accompanied by a 2–4 fold increased risk of stroke (Colandrea et al, 1970). Some remain sceptical, however, suggesting that the systolic hypertension is only a sign of a rigid diseased vessel which is the true culprit. This distinction is important if we are to make proper decisions about prophylactic treatment of isolated systolic hypertension (O'Malley & O'Brien, 1980).

This issue has been examined in the Framingham Study. It was found that the prevalence of isolated systolic hypertension (>160/<95 mmHg) increased from 2 percent in those 60–69 to 11 percent among those 70–79. An excess occurrence of strokes was noted among those with isolated systolic hypertension in all age-sex subgroups which was generally of the same order of magnitude as observed in those with elevations of both systolic and diastolic pressure. The data indicated that not only is the use of diastolic pressure in the elderly stroke candidate less efficient but may actually be misleading in persons with elevated systolic pressure. This may be because diastolic pressure is less accurately determined by the indirect method in the elderly than is the systolic pressure (Master & Lasser, 1971).

Analysis, using the depth of the dicrotic notch as an indication of elastic recoil of the arterial circulation, carried out in the Framingham cohort, strongly suggests that the elevated systolic pressure is more than an innocent sign of rigid arteries and makes an independent contribution to risk (Kannel et al, in press JAMA). Multivariate analysis including the systolic pressure, age and arterial rigidity judged from the pulse wave configuration shows a strong effect of pressure taking rigidity and age into account.

Comparison of stroke risk gradients based on systolic versus diastolic pressure gives no indication of a closer relationship to the diastolic component even in the elderly (Kannel et al, 1976).

Thus systolic hypertension appears to be a neglected contributor to stroke (Table 1.4). Elevation of systolic pressure can no longer be regarded as a normal concomitant of aging simply because it increases more with age than the diastolic component. The fact that hypertension in the elderly is predominantly systolic in character cannot be taken to mean that it is innocuous, and there is no *a priori* reason why hypertensive damage should derive more from the diastolic than systolic pressure.

Table 1.4 Two-year incidence of stroke according to level of systolic and diastolic blood pressure men and women, age 50 to 79: the Framingham study, 24-year follow-up

	Systolic blood pressure					
	<140		*140–159*		*160+*	
Diastolic blood pressure	*At risk*	*Rate/1000 age adj.*	*At risk*	*Rate/1000 age adj.*	*At risk*	*Rate/1000 age adj.*
Men						
<90	6735	5.3	1816	7.4	544	21.0
90–94	478	6.5	911	12.1	499	10.8
95+	137	13.1	761	12.3	1372	24.8
Women						
<90	7827	3.8	2894	6.6	1295	9.6
90–94	344	0.0	1195	8.3	1009	11.9
95+	91	0.0	684	18.6	2192	16.8

While it is clear that isolated systolic hypertension constitutes a substantial risk factor for stroke, it is still uncertain whether this situation can be corrected by antihypertensive treatment and at what cost in side effects. Treatment is less often successful for systolic than diastolic hypertension in the elderly and it is sometimes necessary to reduce diastolic pressures to very low values in order to achieve the desired lowering of systolic pressure (Koch-Weser, 1976; Seligman et al, 1977).

Since the evidence available now indicates that the increased risk of strokes associated with systolic hypertension is probably a direct result of the pressure, it seems likely that lowering the systolic pressure would be efficacious. However, only a controlled trial can determine the indications, best drugs, dosage, side effects, benefits and hazards of

such an endeavor. Because of the high risk of stroke in persons with isolated systolic hypertension such a trial seems long overdue.

Lipids

The relationship of serum lipids to development of coronary disease is well established; the association for stroke has been inconsistent. This has been attributed to the advanced age at which strokes generally occur since even in coronary disease the relationship of serum total cholesterol to risk becomes markedly attenuated beyond age 55. For coronary disease the relationship re-emerges when the cholesterol is fractionated into lipoprotein components.

At the time of the eleventh biennial examination of the Framingham cohort, a complete lipid profile was obtained on all subjects, still free of cerebrovascular disease. In the course of the subsequent six years of follow-up 55 strokes occurred among the men and 44 among the women, with 30 of these being brain infarctions in the men and 21 in the women. In this 49–82 year old age group there was a striking *positive* relationship of the LDL-cholesterol to risk of coronary disease even when other risk factors are taken into account, and in both sexes. For stroke (Table 1.5), there was a *negative* relationship to LDL-cholesterol which was substantial and highly significant in women (Kannel et al, in press, Stroke). This strong negative relationship was demonstrable both for brain infarction and for all other types of stroke combined. For HDL-cholesterol, as in coronary disease, there was a modest *negative* relationship for both sexes; the coefficients, however, were not statistically significant. For VLDL-cholesterol, no substantial or significant relationship to stroke incidence was noted in either sex.

Clearly more data are needed on cholesterol lipoprotein fractions in stroke, both from Framingham and elsewhere. However, thus far it must be concluded that the relation of lipoprotein cholesterol fractions to stroke may well differ from that for CHD. There is evidently a strong *negative* relationship for the atherogenic LDL-cholesterol component to both strokes in general and brain infarctions in particular, which requires explanation. This is curious in view of the *positive* correlation for CHD demonstrable as expected in the same cohort within the same advanced age range. For stroke as for CHD, HDL-cholesterol appears to exert a modest protective effect as anticipated.

The inverse relationship of LDL-cholesterol and stroke incidence in these data on older subjects is consistent with findings reported from a study of Japanese in Hawaii, where an inverse relation between total cholesterol and stroke incidence was found (Kagan et al, 1980). In these studies, however, the inverse relationship applied only to hemorrhagic strokes.

Table 1.5 Incidence of stroke and ABI by serum total cholesterol level 20 year follow-up. Framingham study. Men and Women 65–74

Serum total cholesterol level (mg/dl)	*Person-years at risk*	*Stroke incidence*			
		No. of cases		*Rate/1000 year*	
		Stroke	*ABI*	*Stroke*	*ABI*
Men					
<190	690	12	8	174	116
190–234	1920	12	7	62	36
235–294	1700	7	5	41	29
295+	304	5	4	164	132
Women					
<190	254	9	6	354	236
190–234	1122	12	5	107	45
235–294	3490	22	14	63	40
295+	1410	12	10	85	71

ABI = Atherothrombotic Brain Infarction.
Stroke = Stroke (all types).

Diabetes

The discovery of insulin in 1921 provided the means of preventing the ketoacidosis and coma of diabetes, but has not greatly influenced the atherosclerotic sequelae of diabetes. The cardiovascular hazards of diabetes are widely acknowledged but there has been some uncertainty as to whether it is truly an independent risk factor. Only recently have prospective epidemiologic data begun to clarify the role of diabetes in cardiovascular morbidity (Blacket et al, 1973; Tibblin et al, 1975; Garcia et al, 1973).

Prospective population studies such as the Framingham Study indicate that the greatest impact of diabetes is on occlusive peripheral arterial disease (Table 1.6). The reason for this is obscure considering that the arterial lesions produced in

Table 1.6 Incidence of cardiovascular events according to diabetic status, men and women, age 45–74: the Framingham study

	Age-adjusted average annual incidence per 1000					
	Men			*Women*		
	Diabetic	*Non-diabetic*	*Risk ratio*	*Diabetic*	*Non-diabetic*	*Risk ratio*
Cardiac failure	7.6	3.5	2.2	11.4	2.2	5.2
Intermittent claudication	12.6	3.3	3.8	8.4	1.3	6.3
Brain infarction	4.7	1.9	2.5	6.2	1.7	3.7
Coronary disease	24.8	14.9	1.7	17.8	6.9	2.6

the head, heart and limbs are similar. The relative impact of diabetes for atherothrombotic brain infarction is, however, substantial, greater in women than in men, and exceeds that of coronary heart disease, the most common sequel of diabetes on an absolute scale. In terms of attributable risk, which takes into account the prevalence of diabetes as well as its potency as a risk factor, diabetes also accounts for a greater proportion of brain infarctions than myocardial infarctions (Table 1.7).

Table 1.7 Population attributable risk of diabetes for cardiovascular events, men and women, age 45–74: the Framingham study

	Attributable fraction	
	Men	*Women*
Brain infarction	10.1	14.3
Coronary disease	3.8	7.7
Intermittent claudication	13.6	2.7
Cardiac failure	7.7	18.6

Attributable fraction = $(R_2-R_1) \times P/R$
R_2 = Age-adjusted cardiovascular disease rate in those with diabetes
R_1 = Rate in those without diabetes
R = Rate in total population
P = Prevalence of diabetes

Table 1.8 Probability (per 1000) of brain infarction in 8 years among diabetics according to level of other risk factors, men and women, 55 years of age the Framingham study, 18-year follow-up

	Men								
Chol	*Systolic blood pressure*				*Chol*	*Systolic blood pressure*			
	105	*135*	*165*	*195*		*105*	*135*	*165*	*195*
185	5	11	25	57	185	6	13	30	67
235	6	14	32	71	235	7	16	37	83
285	7	17	39	87	285	9	20	46	102
335	9	22	49	107	335	11	25	58	125
	ECG-LVH negative					ECG-LVH positive			
	Women								
Chol	*Systolic blood pressure*				*Chol*	*Systolic blood pressure*			
	105	*135*	*165*	*195*		*105*	*135*	*165*	*195*
185	2	4	7	13	185	5	9	16	27
235	3	6	11	19	235	7	13	23	40
285	5	9	15	27	285	11	19	33	57
335	7	13	22	39	335	15	27	47	81
	ECG-LVH negative					ECG-LVH positive			

Average risk of brain infarction for 55 year old men, 11/1000; women 10/1000.

Diabetes exerts an impact on the incidence of brain infarction, which is independent of other risk factors. After adjustment for differences in other associated cardiovascular risk factors (systolic blood pressure, serum total cholesterol, cigarette smoking and LVH by ECG) the relative impact of diabetes on brain infarction incidence is the same 2.2-fold increase in each sex.

There is considerable variability in the incidence of brain infarction among diabetics depending on the level of other risk factors (Table 1.8). Although the higher level of cardiovascular risk factors in diabetics could conceivably account for the increased risk of brain infarction, the increased propensity to stroke is not entirely a function of the associated risk factors. Multivariate analysis indicates a significant two-fold net effect of diabetes taking correlated risk factors into account.

Environmental factors

Despite reported sizeable geographic variation and secular trends in stroke mortality, only a few environmental contributors to the occurrence of stroke have been identified.

Personality, type of work and lifestyle have all been suggested as possible factors. Diets too rich in calories, saturated fat and cholesterol and deficient in fiber and complex carbohydrates have been incriminated in hyperlipidemia. High salt intake

in susceptible persons may promote hypertension. Cigarette smoking, while not a strong stroke risk factor, nonetheless contributes to the problem by promoting coronary heart disease which in turn predisposes to stroke. Alcohol appears to contribute by raising blood pressure.

Cigarette smoking

Cigarette smoking, which so clearly is related to the rate of development of CHD and occlusive peripheral arterial disease, is unaccountably only weakly associated with stroke. The correlation is confined to men under age 65, with maximum impact below age 55 (Table 1.9). This is reminiscent of CHD where the risk also decreases with advancing age and cannot be demonstrated beyond age 65. Since most strokes occur beyond age 65, cigarette smoking does not rank high among the risk factors for stroke. It is curious that this does not apply for atherosclerotic disease involving the legs where even women beyond age 65 who smoke are at substantially increased risk.

Table 1.9 Risk of occlusive arterial disease and atherothrombotic brain infarction according to cigarette habit. The Framingham study. 20 year follow-up, men, age 45–74

	Average annual incidence per 10 000					
	Intermittent claudication			*Atherothrombotic brain infarction*		
Cigarettes smoked/day	*Age* 45–54	55–64	65–74	*Age* 45–54	55–64	65–74
None	10	30	58	5	17	52
Under 20	15	45	65	8	20	52
20	21	67	74	12	24	52
Over 20	30	100	83	18	28	53

Although the impact is modest, marginally significant, and confined to men below age 65, the effect where it exists is an independent one, not accounted for by the associated risk factors.

Diet

Comparison of national differences in diet, feeding experiments in animals and human metabolic studies have all suggested that an excess of calories, saturated fat and cholesterol may be responsible for the hypercholesterolemia regularly found in populations where CHD is highly prevalent (National Diet-Heart Study Final Report, 1968). Although dietary factors may influence atherogenesis, perhaps by elevating LDL-cholesterol values, evidence that alterations in diet reduce stroke risk is lacking.

Coffee

An association between coffee drinking and coronary disease has been alleged, based on retrospective studies. This has not stood up to prospective study scrutiny and appears to derive from difficulties with controls and failure adequately to take into account the associated cigarette habit. The relationship to stroke is even more tenuous (Dawber et al, 1974).

Obesity

The Framingham Study findings on the relation of stroke incidence to body weight throws some light on pathogenesis. In general, stroke incidence in Framingham tends to increase with weight, more prominently in women, in whom the relationship is statistically significant. Multivariate analysis suggests that the association derives from higher pressures (and possibly blood sugars) in the obese. Hence, a high stroke incidence in the obese is not unexpected. However, in the elderly (65–74), there is a *negative* trend in stroke incidence in relation to relative weight which may be related to the inverse association of LDL-cholesterol with stroke incidence.

Water

An association between soft water and atherosclerotic cardiovascular mortality including stroke has been noted and a cause and effect relationship suggested (Schroeder, 1960). A recent review has failed to demonstrate an independent effect on vascular disease mortality (Hammer & Heyden, 1980.)

Alcohol

Although a *negative* association between alcohol intake and coronary heart disease incidence has

been found, some have also noted an increased risk of CHD among excessive drinkers. A possible explanation for this beneficial effect is a strong positive association of moderate alcohol intake with HDL-cholesterol and a negative association with atherogenic LDL-cholesterol. Curiously, there are indications that, if anything, alcohol promotes strokes. This observation may be related to the association between alcohol and hypertension.

The Hisayama Study in Japan, studies in Honolulu Japanese and in Caucasians in Alabama have shown an increase risk of hemorrhagic strokes (Marshall, 1971; Peacock et al, 1972; Omae et al, 1976; Kagan et al, 1980). The Framingham Study data also have suggested an association between alcohol intake and stroke, including brain infarction (Table 1.10).

Table 1.10 Risk of stroke according to alcohol intake: the Framingham study men, age 35–64

Oz. alcohol per month	*Age-adjusted incidence per 1000*	
	Strokes (all types)	*Brain infarction*
None	58	22
1–10	61	26
11–30	68	30
31–400	79	51

Physical activity

An association between physical inactivity and the risk of CHD was first demonstrated by Logan (1952) and by Morris and co-workers in 1953. While it can be argued with some conviction that there is a beneficial effect of physical activity to CHD incidence and mortality, the relationship to stroke is tenuous (Paffenbarger et al, 1978). Sedentary work activity has not been associated with an increased incidence of stroke in spite of the associated enhanced risk of MI (Marquardsen, 1969). Framingham data show an inverse relationship but this is neither substantial nor statistically significant.

Climate

Climate appears to influence both stroke and coronary heart disease mortality; death from either is apparently lowest in areas where environmental temperatures range between 60–79°F (Rogot & Padgett, 1976). Death rates from both diseases rise with declining temperature and abundant snow fall. Apparently either extreme of temperature promotes strokes and heart attacks, because the rates also increase when ambient temperatures exceed 79°F. These temperatures correlations are particularly evident for elderly persons.

The reasons for seasonal variation in stroke incidence are unclear. The lower incidence in summer in northern climates may provide a clue to ways of reducing the risk of stroke (Schuman et al, 1964).

Migration

From carefully controlled collaborative studies it seems clear that Japanese immigrants to the USA and their offspring have a substantially lower prevalence and mortality from stroke than do ethnically similar residents in Japan (Worth et al, 1975; Kagan et al, 1976). Since there is little difference in the prevalence of hypertension, but a substantial difference in fat and protein intake between migrant and indigenous Japanese, protein and fat malnutrition has been cited as predisposing to stroke (Kagan et al, 1974; Kimura, 1976). There is some experimental evidence derived from feeding spontaneously hypertensive rats which supports this contention (Yamori et al, 1976).

It is interesting that the lower prevalence of stroke in migrants from Japan is associated with a higher occurrence of CHD, another atherosclerotic vascular disease (Marmot et al, 1975; Robertson et al, 1977).

Other host factors

Impaired cardiac function

Hypertensives are especially prone to develop cardiac impairments such as ECG abnormalities, cardiac enlargement on X-ray and arrhythmias such as atrial fibrillation. They are also more likely to develop coronary heart disease and congestive heart failure (Shurtleff, 1974; Kannel & Sorlie, 1975). On this account alone, cardiac impairments should be associated with an increased risk of stroke, and they are (Fig. 1.5).