Using predocumented data to telescope time into manageable units, college case-taking records of 50,000 former students of the University of Pennsylvania and Harvard University were studied for factors predisposing to fatal stroke later in life. A total of 171 men known to have died from cerebrovascular hemorrhage or occlusion were compared with 684 surviving classmates. The comparison identified and quantified seven precursive characteristics of stroke in terms of mortality ratios. Implicit in the findings is the need to alter these characteristics and measure the effect through subsequent observation.

CHRONIC DISEASE IN FORMER COLLEGE STUDENTS

V. EARLY PRECURSORS OF FATAL STROKE

Ralph S. Paffenbarger, Jr., M.D., Dr.P.H., F.A.P.H.A., and James L. Williams, M.D.

STROKE, long a prominent cause of death at older ages, is increasing in importance as man's life span lengthens. Even in middle life, this composite of diseases, which represents a complication of hypertensive and atherosclerotic processes, makes an appreciable contribution to the mortality record. Among white males in the United States, for example, stroke is the sixth leading cause of death at ages 40-49 years, and it ranks fourth at 50-59, and third, behind heart disease and cancer, at 60-69. Thus the need to avoid stroke, or at least delay it, becomes increasingly evident. Identification of predisposing traits early in life may provide some means toward this goal.

The present study examines host and environmental data recorded during college years for former students from the University of Pennsylvania and from Harvard University who subsequently died from stroke. These data are compared with corresponding information for their surviving college classmates, in search of characteristics that distinguish those students destined to die from this cause. The study is one of a series examining case-taking and other college records for precursors of various diseases that develop in subsequent years.[1-3]

Methods

The population under study consists of over 50,000 male students, representing 15,000 who submitted to case-taking procedures at the University of Pennsylvania from 1931-1940 and 35,000 similarly examined at Harvard University from 1916-1950. Over 4,000 members of these classes have died, while survivors now range in age from 30 to 70 years.

Decedents among the study population

are identified through college alumni offices, and causes of death are based on official death certificates. A total of 171 men are known to have died from stroke, excluding those whose certificates mentioned tumor, blood dyscrasia, trauma, infection, or evidence of rheumatic heart disease. Lack of precision in diagnosis and varying specificity in classification are evident but do not preclude grouping into clinical types of stroke for study purposes.

In terms of clinical type as ascribed on death certificates, the 171 strokes were distributed as follows: 27 (16 per cent) subarachnoid hemorrhage, 78 (46 per cent) intracerebral hemorrhage, 30 (18 per cent) cerebral thrombosis, 8 (5 per cent) cerebral embolus, and 28 (16 per cent) nonspecific types (i.e., apoplexy, cerebrovascular accident, encephalomalacia, and others). The first two types were combined for presentation as "hemorrhagic" stroke and the remainder as "occlusive" stroke. This much pooling was elected because within these two categories the subgroups were similar in mean age at death and in interval between onset and death. The proportions that died in hospital (67 per cent) and that were autopsied (44 per cent) also were similar within these two categories. Agreement of findings for the two schools contributing subjects to the study offered evidence that the clinical types reported on official certificates had meaning and could represent an operational basis for grouping all decedents by type of stroke, i.e., hemorrhagic or occlusive. Except where otherwise indicated, these two groups are presented separately because of differences in certain predisposing characteristics identified.

With reference to factors associated with increased risk of fatal stroke, findings for the 76 autopsied decedents paralleled those for the 95 nonautopsied decedents. This afforded further confidence in the value of the data.

For each of the 171 stroke decedents, four surviving classmates within one year of the same age were randomly chosen as control subjects. Decedents and controls were compared as to the frequency with which each group had certain specific characteristics recorded in college.

Characteristics for study as potential precursors of stroke were chosen from conditions variously associated with other hypertensive and atherosclerotic diseases. Selection of these characteristics was facilitated by prior experience in companion studies of coronary heart disease in the same population.[1,2]

Temporal trends in certain characteristics, e.g., patterns of cigarette smoking and parental death, were noted over the 35 years from 1916 through 1950 when students entered the study. This required comparison of decedents with their *matched* controls as to frequencies and distributions of such characteristics. Significant differences were measured by χ^2 or t-tests, and a probability level of 0.05 was considered meaningful.

Estimated mortality ratios were computed, after the method of Cornfield,[4] for factors associated with increased risk of death from stroke. These ratios express the degree of risk involved with and without the factor.

Findings

Death certificates indicated that 19 (11 per cent) of the 171 strokes, 17 of occlusive type and two of hemorrhagic type, had associated coronary heart disease. Seven certificates, two for hemorrhagic and five for occlusive stroke, mentioned diabetes. Forty-three (41 per cent) of the hemorrhagic strokes and 14 (21 per cent) of occlusive strokes were reported with associated hypertension or hypertensive heart disease. Ten (10 per cent) hemorrhagic and 19 (29 per cent) occlusive strokes were reported with associated arteriosclerosis.

Table 1—Age distribution at death from stroke

Age at death (years)	Hemorrhagic stroke		Occlusive stroke		Total stroke	
	No.	%	No.	%	No.	%
20–29	5	4.8	3	4.5	8	4.7
30–39	21	20.0	7	10.6	28	16.4
40–49	28	26.7	10	15.2	38	22.2
50–59	39	37.1	27	40.9	66	38.6
60–69	12	11.4	19	28.8	31	18.1
Total	105	100.0	66	100.0	171	100.0
Mean	47* ± 10		52* ± 10		49 ± 10	

* Significantly different at <0.01.

The interval between onset of symptoms and resulting death was recorded on three-quarters of the death certificates for each type of stroke. Decedents from cerebrovascular hemorrhage were more apt to die within one day (63 per cent) than decedents from cerebrovascular occlusion (29 per cent).

The total of 171 deaths from stroke accounts for 4 per cent of all deaths (4,200) and 7 per cent of deaths from natural causes (2,600) recognized to date in the study population.

Mortality rates for total stroke computed for successive quinary groups were similar when compared over 25-, 30-, and 35-year intervals. However, over the years 1930-1960 a shift in clinical type was noted, namely an increasing mortality from occlusive stroke and a decreasing mortality from hemorrhagic stroke.

The 171 students who later died of stroke had a mean age of 19±3 years at time of college case-taking. Their mean age at death from stroke (Table 1), an "interim mean" to January 1966, was 49±10 years, and was significantly lower for hemorrhagic stroke (47±10 years) than for occlusive stroke (52± 10 years). This difference may represent, in part, a shift in diagnostic custom rather than a biologic influence.

Cigarette Smoking

Stroke decedents had reported a higher frequency of cigarette smoking at time of college case-taking (45 per cent) than the control subjects (31 per cent) as shown in Table 2. Also, among smokers a larger proportion of stroke decedents (21 per cent) had smoked ten or more cigarettes per day than had their controls (11 per cent), and decedent smokers had tended to average a greater number of cigarettes per day (11 vs. 10). This proclivity to smoke cigarettes in college was evident for decedents of all clinical subgroups and at each age of death from stroke.

A further finding on cigarette smoking was the tendency for decedents from occlusive stroke to have smoked more by each index of measurement than did decedents from hemorrhagic stroke. Pipe and cigar smoking did not provide sufficient data to measure any effects.

Blood Pressure

Stroke decedents, as compared with controls, had registered higher mean levels of both systolic (126 vs. 122

Table 2—Cigarette smoking at time of college case-taking

Use of cigarettes	Hemorrhagic stroke		Occlusive stroke		Total stroke	
	Decedents N=95	Controls N=369	Decedents N=63	Controls N=246	Decedents N=158	Controls N=615
Per cent smokers	41.7	31.5	50.0*	31.1	45.0*	31.3
Per cent smokers 10+/day	17.9	11.1	25.4*	11.4	20.9*	11.2
Mean number per day	10±6	9±6	12±6	10±6	11±6	10±6

* Significantly different from controls at <0.01.

mmHg) and diastolic (77 vs. 76) blood pressure at time of college case-taking (Table 3). For both measurements it was found that the higher the blood pressure level, the greater the risk of death from stroke.

Table 3 also shows that significantly more stroke decedents (45 per cent) than controls (31 per cent) had had systolic blood pressure levels of 130+ mmHg. Six per cent of the stroke decedents had registered systolic blood pressure levels of 150+ mmHg as contrasted with 3 per cent of controls. Corresponding frequencies for diastolic levels of 90+ mmHg were 18 and 12 per cent, and 100+ mmHg frequencies were 5 and 4 per cent.

Differences in blood pressure levels between decedents and controls were stronger for students who later died from hemorrhagic stroke than for those who succumbed to occlusive stroke.

Height and Weight

Stroke decedents tended to be somewhat shorter than controls at time of college case-taking. The difference was more marked for cerebrovascular occlusion than for hemorrhage. Table 4 shows the decedents from occlusive stroke to have averaged nearly an inch shorter (68) than controls (69). Shorter body stature tended to correlate with death from occlusive stroke at all ages.

In terms of a ponderal index (height

Table 3—Blood pressure at time of college case-taking

Blood pressure (mmHg)	Hemorrhagic stroke		Occlusive stroke		Total stroke	
	Decedents N=105	Controls N=416	Decedents N=64	Controls N=258	Decedents N=169	Controls N=674
Systolic						
Per cent 130+	45.7*	29.1	43.8	34.9	45.0*	31.3
Per cent 150+	7.6*	3.1	3.1	3.9	5.9	3.4
Mean	127*±16	121±14	124±12	122±13	126*±15	122±14
Diastolic						
Per cent 90+	18.1	12.0	17.2	13.2	17.8	12.5
Per cent 100+	6.7	4.3	3.1	3.5	5.3	4.0
Mean	77*±12	75±11	78±10	77±12	77±12	76±12

* Significantly different from controls at <0.05.

Table 4—Height and weight at time of college case-taking

Factor	Hemorrhagic stroke		Occlusive stroke		Total stroke	
	Decedents N=104	Controls N=417	Decedents N=66	Controls N=262	Decedents N=170	Controls N=679
Height						
Per cent <68 in.	30.8	25.9	36.4	30.2	32.9	27.5
Mean	68.8±2.6	69.1±2.7	68.0*±2.6	68.9±2.8	68.5*±2.6	69.0±2.7
Weight						
Height-adjusted mean	145.1±22.0	145.2±18.8	147.7±21.3	144.0±19.9	146.0±21.7	144.8±19.2
Ponderal index						
Per cent <12.9	29.8	23.6	36.4	25.2	32.4*	24.2
Mean	13.2±0.4	13.2±0.5	13.0*±0.7	13.2±0.5	13.1±0.5	13.2±0.5

* Significantly different from controls at <0.05.

divided by cube root of weight), the stroke decedents tended to be heavier than controls at time of college case-taking, the difference again being more marked for occlusion than for hemorrhage. Average ponderal index for decedents was 13.1 and for controls 13.2 (Table 4). One-third of the decedents had had a ponderal index of less than 12.9, while only one-quarter of their controls showed this degree of body fatness. Figures for height-specific and height-adjusted body weight paralleled these findings. However, measures of chest expansion, vital capacity, posture, musculature, and nutritional status did not correlate with death from hemorrhagic or occlusive stroke.

Parental Mortality

A history of parental mortality was recorded at the time of college case-taking. As seen in Table 5, higher percentages of stroke decedents than control subjects (26 vs. 17 per cent) had lost a father or mother from any cause. Also, more stroke decedents than controls (12 vs. 4 per cent) had lost one or both parents from some form of cardiovascular-renal disease. The trend of these differences in total and cardiovascular-renal deaths among parents held for each type of stroke and at each age of death from stroke. Associations were stronger for students who later died of occlusive stroke than for those who died of hemorrhagic stroke.

Table 5—History of parental mortality at time of college case-taking

Per cent with a parent dead	Hemorrhagic stroke		Occlusive stroke		Total stroke	
	Decedents N=104	Controls N=416	Decedents N=66	Controls N=258	Decedents N=170	Controls N=674
Any cause	25.0	17.8	27.3*	15.9	25.9*	17.1
Cardiovascular-renal cause	9.0	4.7	16.1*	2.4	11.7*	3.8

* Significantly different from controls at <0.05.

The deceased parents of stroke subjects and those of controls had died at about the same age (46±8 years), and the living parents of each group were alike in average age (50±7 years), when their sons entered college.

Other Factors

Some factors were recorded on case-taking forms only during certain years at one or the other school, and their frequencies are available for only some of the study subjects. One such factor is a "sensation of heart beating" which was reported (Table 6) for a significantly higher percentage of stroke decedents (42 per cent) than controls (22 per cent). Whether this symptom represented a physical or psychological trait, it differentiated at each age of death the stroke subjects from their respective controls, and the direction of difference was sustained for both hemorrhagic and occlusive groups.

In contrast to this finding on heart consciousness or sensation, stroke and control subjects were found not to be differentiated by such characteristics as pulse rate or rhythm, presence of heart murmurs, dyspnea on exertion, sugar or protein in the urine, or hemoglobin level at time of college case-taking.

The sibling status of their original families differentiated students who later died from occlusive stroke and their classmates. Only-child status was reported at college case-taking for 24 per cent of occlusive strokes but for only 12 per cent of their controls (Table 6). No such differentiating characteristic was found for hemorrhagic strokes. The association between absence of siblings and increased risk of fatal occlusive stroke must be regarded as tentative, however, since an independent effect of early parental mortality was not shown in the small sample available for study.

Nine personality traits concerned with mood, thought, and behavior were self-assessed on questionnaires by students from the University of Pennsylvania. Although the number of subjects is too small to be conclusive, each of these traits failed to differentiate stroke decedents from controls.

During college years, a significantly smaller percentage of varsity athletes was found among students who became stroke decedents (7 per cent) than among controls (15 per cent). The find-

Table 6—Other factors assessed during college years

Factor	Hemorrhagic stroke		Occlusive stroke		Total stroke	
	Decedents	Controls	Decedents	Controls	Decedents	Controls
Heart consciousness						
Ratio*	10/25	18/94	3/6	8/26	13/31	26/120
Per cent	40.0	19.1	50.0	30.8	41.9†	21.7
Only-child status						
Ratio	17/101	68/412	15/63	30/255	32/164	98/667
Per cent	16.8	16.5	23.8†	11.8	19.5	14.7
Varsity athlete						
Ratio	8/105	66/420	4/66	40/264	12/171	106/684
Per cent	7.6†	15.7	6.1	15.2	7.0†	15.5

* Numerator equals number with factor; denominator, number at risk.
† Significantly different from controls at <0.05.

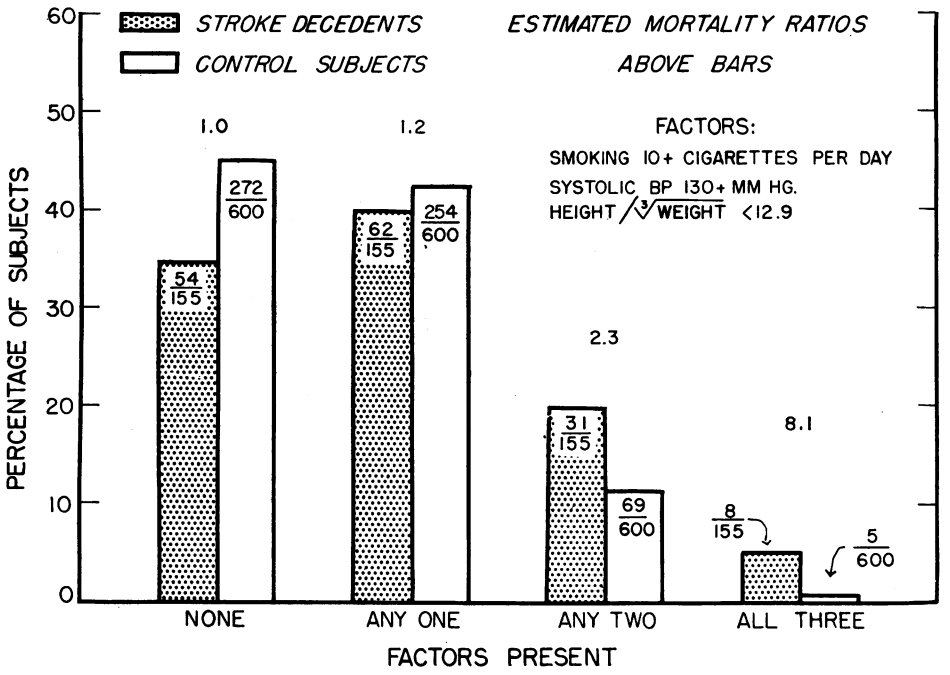

Figure 1—Percentage of stroke decedents and control subjects with combinations of specified factors at time of college case-taking

ings persisted for both hemorrhagic and occlusive groups. Other parameters indicating interest and ability in college sports, such as participation in multiple sports and years of play, suggested that physical activity had an effect of sparing from early stroke death.

College records permitted appraisal of a variety of other sociocultural characteristics sometimes associated with hypertensive or atherosclerotic diseases. For example, items related to history of childhood infections or to religious affiliation did not differ between decedents and controls. Neither did geographical area of origin, size of original community, or marital status as student correlate with subsequent death from hemorrhagic or occlusive stroke.

Combinations of High-Risk Factors

Figure 1 shows the percentage distributions of stroke decedents and controls in relation to combinations of higher levels of cigarette smoking, blood pressure, and body weight at time of college case-taking. Hemorrhagic and occlusive stroke are considered together to increase the stability of the small numbers concerned. Mortality ratios also are given in the figure, and express proportionally the risk of fatal stroke associated with a factor, or combination of factors, as opposed to the risk in the absence of all three factors. Thus a mortality ratio of two means that individuals with a factor have twice the risk of stroke mortality found among those without any factor. Mortality ratios for one, any combination of two, and all three of these "factors of excess" are 1.2, 2.3, and 8.1, respectively. The findings imply that combinations of these factors have an additive effect.

Figure 2 gives corresponding comparisons for combinations of three "factors

of deficit," namely shortness of stature, early parental death, and nonparticipation in varsity sports as assessed during college. Mortality ratios for one, two, and all three of the specified factors are 2.3, 3.6, and 3.9. This pattern implies that combinations of these deficit factors have less than an additive effect.

Figure 3 gives mortality ratios for six of the factors associated with increased risk of death from stroke. Ratios are given for each factor and all paired combinations. The latter expresses proportionally the risk of fatal stroke associated with both factors as opposed to risk from only one or neither factor. Estimated prevalence ratios are given in the figure as percentages of single or paired factors in control subjects.

Taken alone, a high mortality ratio has diagnostic or predictive value, and when accompanied by a high prevalence ratio it acquires preventive importance. Of special note, any combination of "heavy cigarette smoking" with another factor presents a high mortality ratio signifying high risk of death from stroke. Also, "higher levels of blood pressure" linked with any other factor identifies a need for control procedures because of combined high mortality and prevalence ratios.

Discussion

Students who later died from stroke contrasted noticeably with their classmates in several physical and social

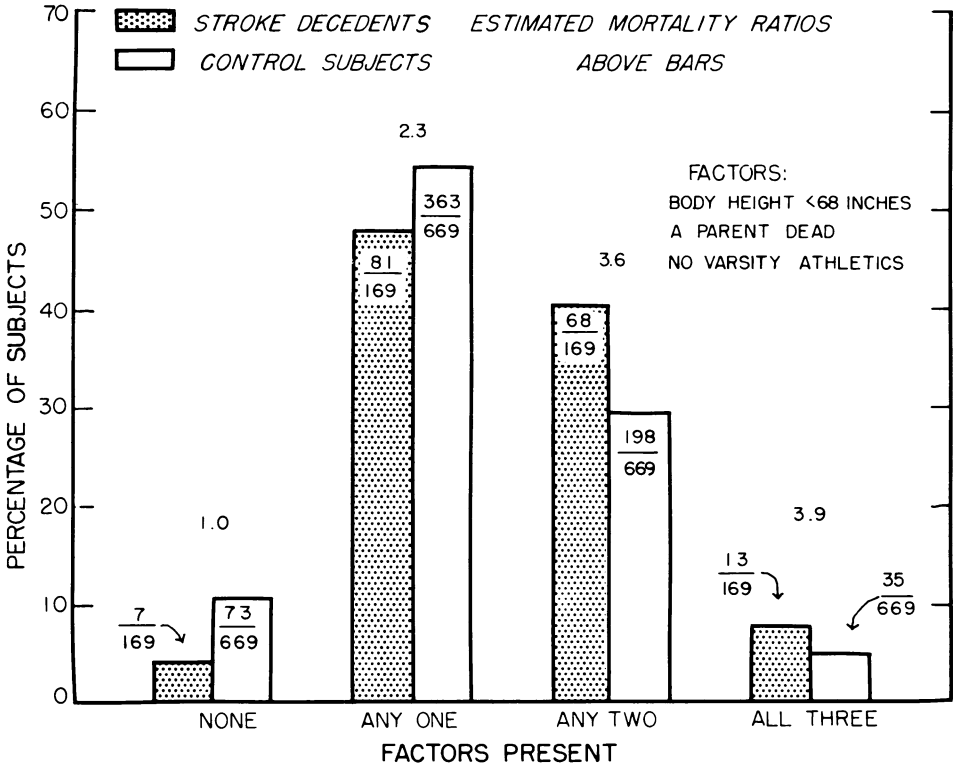

Figure 2—Percentage of stroke decedents and control subjects with combinations of specified factors assessed during college

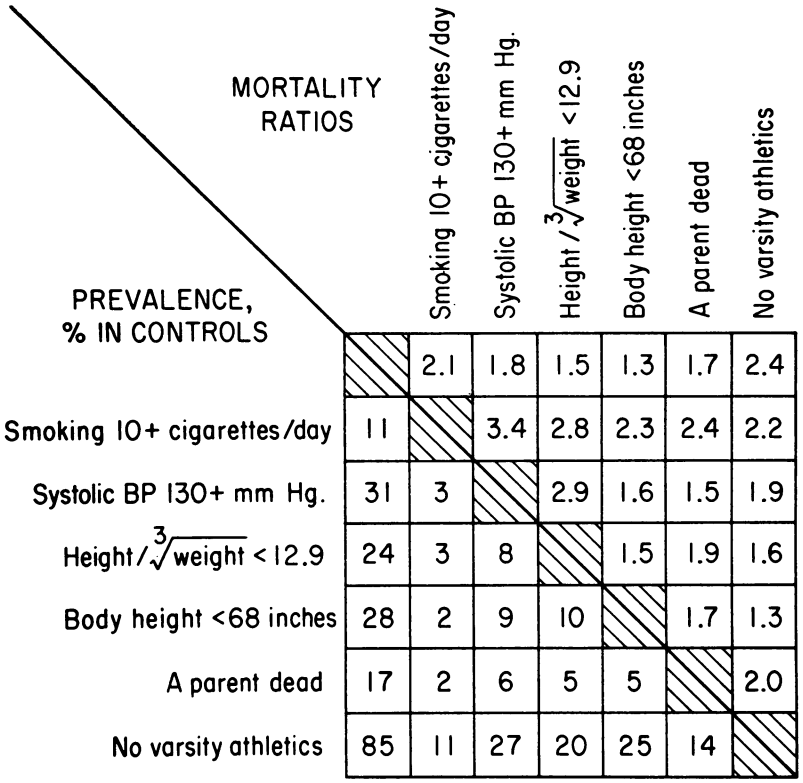

Figure 3—Estimated mortality ratios (stroke) and prevalence ratios for specified factors assessed during college years

traits assessed during college years. To a limited degree, some traits tended to differentiate future hemorrhagic and occlusive stroke decedents. Additional data are needed to establish firm relationships between these traits and the basic pathologies of stroke.

Several characteristics predisposing to fatal stroke paralleled those for fatal coronary heart disease.[1] Heavier smoking of cigarettes, higher levels of blood pressure, increased body weight, earlier parental death, and less indulgence in varsity sports appear with their expected importance. Combinations of these characteristics again increased the risk of death from hypertensive and atherosclerotic processes.

Increased heart consciousness is a perhaps less anticipated correlate of both stroke and coronary death. This gives reason to speculate on possible interrelationships with cardiovascular inadequacy or inefficiency. Cardiac malfunction, perhaps signalled as heart awareness, may limit physical development and independently lead to stroke or coronary heart disease. Conversely, other physiologic or psychologic tendencies of the short-statured may result in lack of support of an originally healthy cardiovascular system.

When more detailed distinctions are sought between the closely related entities of hemorrhagic and occlusive stroke, attention must return to the roles

of diagnostic convention and death certification. It is likely, in the present study, that some stroke decedents entered in one category belong in the other. The search for specifics is blurred by such difficulties.

Summary

Of 50,000 male former students who had entered the University of Pennsylvania or Harvard University between 1916 and 1950 and submitted to case-taking procedures, 171 are known to have died from stroke. Two-thirds of these deaths were ascribed to subarachnoid or intracerebral hemorrhage, and the remainder were considered occlusive in origin. To the extent that these classifications are meaningful, fatal hemorrhagic stroke occurred at an earlier age and with a shorter interval between onset and death than did fatal occlusive stroke.

Four control subjects for each stroke decedent were chosen at random from his surviving classmates of equivalent age. Comparison of case-taking and other college records of decedent and control groups identified seven characteristics predisposing to fatal stroke: cigarette smoking, higher blood pressure, increased body weight, shorter body stature, early parental death, heart consciousness, and nonparticipation in varsity sports.

In general, these precursors were indicative of both hemorrhagic and occlusive stroke. Cigarette smoking, obesity, short stature, and early parental death were more strongly correlated with occlusive than with hemorrhagic stroke, whereas the reverse was true for higher levels of blood pressure.

Combinations of precursive factors further increased the risk of fatal stroke, particularly heavy cigarette smoking and higher levels of blood pressure occurring together or with other elements.

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Dr. Paffenbarger is chief, Field Epidemiological Research Section, National Heart Institute, US Public Health Service (25 Evergreen St.), Framingham, Mass. 01701, and lecturer on epidemiology, Harvard University School of Public Health, Boston, Mass. Dr. Wolf is affiliated with the Field Epidemiological Research Section, National Heart Institute.

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