This study reports a number of findings from an epidemiologic study of patients with cerebrovascular disease and of controls. The findings are not definitive, but they suggest more precise hypotheses for further study.

AN EPIDEMIOLOGICAL STUDY OF CEREBROVASCULAR DISEASE

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A REVIEW of the literature reveals a surprising lack of epidemiological interest in cerebrovascular disease which is presently the third leading cause of death and which, in addition, accounts for a large segment of the problem of chronic illness and disability in the United States.

This paper reports the findings of a study designed to compare the selected personal, clinical, and family characteristics of a group of persons who had experienced a stroke with those of a suitable group of controls. The study population was drawn from the group of white Baltimore residents aged 45-69 who were hospitalized at the Montebello State Hospital during the period from December 1, 1961, to December 31, 1962. Approximately 80 per cent of the patients who met the age and residence criteria for the study were interviewed and subsequently classified as *cases* or *controls*.

Before obtaining personal and family information from the patients, a screening interview was administered to detect defects in orientation, memory, and communication. When such defects were found, the necessary information was obtained from a close relative. Family information was obtained through official death records of deceased family members.

Those patients who had ever had a documented stroke were the cases; all other patients were allocated to one of two control groups according to the presence or absence of clinically diagnosed cardiovascular disease as determined by diagnostic studies on admission to the hospital. A total of 255 patients were interviewed, of whom 126 were cases and 129 were controls. The controls included 43 persons with a diagnosis of cardiovascular disease (control I) and 86 persons who had no cardiovascular disease diagnosis (control II). Table 1 shows the age and sex distribution of cases and controls.

A number of variables related to the collection and processing of data were examined in order to detect the presence of any biases which might interfere with case-control comparisons. Two of these factors—the time period of hospital admission and the type of interview informant—were taken into account in the analysis of data. Age-adjusted methods of data analysis were used in comparing the cases and controls.

Table 1—Age and sex distribution of study groups

Age	Cases		Control I		Control II	
	No.	%	No.	%	No.	%
			Male			
45-49	3	4.5	3	15.8	11	26.8
50-54	9	13.6	3	15.8	8	19.5
55-59	14	21.2	0	0.0	12	29.3
60-64	23	34.9	5	26.3	6	14.6
65 and over	17	25.8	8	42.1	4	9.8
All ages	66	100.0	19	100.0	41	100.0
			Female			
45-49	4	6.7	1	4.2	4	8.9
50-54	2	3.3	2	8.3	8	17.8
55-59	10	16.7	1	4.2	7	15.5
60-64	11	18.3	7	29.2	8	17.8
65 and over	33	55.0	13	54.1	18	40.0
All ages	60	100.0	24	100.0	45	100.0

The differences found when cases and controls were compared with respect to their personal, clinical, and family characteristics, together with certain descriptive data, constitute the results of this study. The findings will be described and then discussed in terms of their consistency with etiologic hypotheses found in the clinical literature.

Clinical Characteristics

In order to provide a reference point for interpretation of results and for comparison with other studies, it is essential that the clinical characteristics of the case and control groups be described. All patients in the case group had a diagnosis of cerebral thrombosis, embolism, or hemorrhage (ISC 330-334) and this was the first stroke episode for three-fourths of the group. Cerebral thrombosis was the most frequent diagnosis among the cases, accounting for 86 per cent of the entire group. Second in frequency was the diagnosis of cerebral embolism for 4 per cent of the males and 10 per cent of the females.

Table 2—Age-adjusted frequencies of heart disease and diabetes diagnoses among study groups by sex

Diagnosis	Case		Control I		Control II		Combined Controls	
	Male	Female	Male	Female	Male	Female	Male	Female
Type of heart disease diagnosis								
No heart disease	27.4	31.1	18.4	10.2	100.0	100.0	70.6	69.1
Arteriosclerotic	59.3	48.4	51.6	78.0	0.0	0.0	23.4	25.8
Hypertensive	28.5	43.7	18.1	43.7	0.0	0.0	8.4	12.0
Rheumatic	2.1	8.2	3.4	0.0	0.0	0.0	0.7	0.0
Diabetes	14.1	32.9	26.1	35.3	9.1	18.0	—	—

Table 3—Comparisons of proportions of study groups reporting residence in the upper socioeconomic half

Comparison Groups	Weighted Mean Difference %*	Standard Error†	Probability‡
Males			
Case vs. control I	+21.3	14.8	>0.05
Case vs. control II	+26.6	10.5	<0.05
Case vs. combined control	+21.1	6.8	<0.01
Females			
Case vs. control II	+15.1	11.5	>0.05
Case vs. combined control	+17.4	10.3	>0.05
Both Sexes			
Case vs. control I	+14.6	10.0	>0.05
Case vs. control II	+16.9	8.1	<0.05
Case vs. combined control	+16.5	7.1	<0.05

* + indicates an excess of cases.
† Standard Error of Weighted Mean Difference.
‡ Probability that a difference as large as this is due to chance.

Table 4—Comparison of female study groups with respect to proportion who reported foreign birth

Comparison Groups	Weighted Mean Difference %*	SE†	P‡
Case vs. control I	+25.8	9.3	<0.01
Case vs. control II	+11.8	7.9	>0.05
Case vs. combined controls	+15.8	6.4	<0.05

See footnotes in Table 3.

Table 5—Weighted mean differences and their probabilities in case-control comparisons of proportion employed in "heavy industry" and "transportation" in job of longest duration

Comparison Groups	Weighted Mean Difference %*	SE†	P‡
Case vs. control I	+22.8	10.3	<0.01
Case vs. combined control	+18.8	8.3	<0.01

See footnotes in Table 3.

The arterial sites most commonly associated with the stroke were the middle cerebral and internal carotid arteries. Internal carotid artery involvement was six times more common among males than among females. This sex ratio is consistent with, though of greater degree than, that noted in other reported case series.[1] Almost all of the patients had hemiparesis of some degree with right-sided impairment predominating.

By definition, all the control I subjects had a cardiovascular disease diagnosis. Most of the males had been admitted to the hospital because of peripheral vascular disease; most of the females because of fractures sustained in accidental falls. Cancer, diabetes, arthritis, and neurological diagnoses were also present as primary or secondary diagnoses.

About one-third of the control II subjects had been admitted to the hospital because of accidental injuries requiring rehabilitative treatment. Neoplasms, arthritis, neurological disease, and various other disorders accounted for most of the remaining admissions.

None of the control II subjects had a cardiovascular disease diagnosis.

Because of the association of arteriosclerosis, hypertension, and diabetes, with strokes, the distribution of these conditions was examined in the case and control groups. However, selection problems influencing disease associations among hospitalized populations limit the inferences which can be made from these data.[2] Table 2 shows the age-adjusted frequencies of heart disease and diabetes among the study groups.

1. It was observed among the cases that:

a. about one-third had no clinically diagnosed heart disease,
b. the frequency of rheumatic heart disease, hypertensive heart disease, and diabetes was higher among females than among males,
c. males had a higher frequency of arteriosclerotic heart disease than did females.

2. In the control I group, it was found that:

a. females had a higher frequency of both arteriosclerotic and hypertensive heart disease than males,
b. males had a higher frequency of rheumatic heart disease than did females and slightly more diabetes.

3. Comparison of case and control I groups shows:

a. similar frequencies of diabetes and hypertensive heart disease among the females, but a higher frequency of arteriosclerotic heart disease among control I females,
b. a lower frequency of diabetes and a higher frequency of hypertensive heart disease among case males.

Mean systolic blood pressures, based on one determination made on each subject at the time of hospital admission, were compared by age and sex groups. The female cases had higher mean pressures than case males in all but one age group, while the cases of both sexes had mean pressures which tended to be consistently higher than those of controls.

All patients whose primary admitting diagnosis had been arthritis, neoplasm, or accidental injury were selected as controls for further comparisons with the case group. The cases had a higher

Table 6—Number and per cent of male study group whose work histories included employment in the operation or servicing of motor vehicles

Reported Motor Vehicle Employment	Case		Combined Controls	
	No.	%	No.	%
Yes	14	21.2	4	6.7
No	52	78.8	56	93.3
Total	66	100.0	60	100.0

Chi-square (1df) = 5.44 ($p = <0.05$).

Table 7—Comparison of proportion of study groups reporting only one type of occupation in work history

Comparison Groups	Weighted Mean Difference %*	SE†	P‡
Case vs. control I	+21.0	13.6	>0.05
Case vs. control II	+27.6	10.8	<0.05
Case vs. combined controls	+25.5	9.3	<0.05

See footnotes in Table 3.

Table 8—Comparison of study groups with respect to the proportion whose life-time work histories suggest no occupational mobility

Comparison Groups	Weighted Mean Difference %*	SE†	P‡
Case vs. control I	+16.5	13.5	>0.10
Case vs. control II	+25.2	10.7	<0.01
Case vs. combined controls	+21.6	9.3	<0.01

See footnotes in Table 3.

Table 9—Comparison of proportions of male study groups who reported duration of last job as ten years or more

Comparison Groups	Weighted Mean Difference %*	SE†	P‡
Case vs. control I	+32.4	13.6	<0.05
Case vs. combined controls	+11.7	9.2	>0.05

See footnotes in Table 3.

frequency of both diagnosed arteriosclerotic and hypertensive heart disease than these selected controls with an excess which was comparatively larger for males. There was also an excess of diabetes among cases which was larger for females.

Personal Characteristics

Cases and controls were compared with respect to education, socioeconomic status, nativity, occupational history, marital history, and menstrual and childbearing patterns. In this analysis, expected numbers for case and control groups were calculated on the basis of the age- and sex-specific proportions in the total study population. Cochran's weighted mean difference method[3] was then used to determine whether large differences in the age-specific frequencies of a given characteristic were significant. Each of the study groups was compared also with the Baltimore Standard Metropolitan Statistical Area population in terms of those demographic characteristics which were available in published reports of the 1960 census.[4]

These comparisons indicated that case and control groups were similar with respect to:

1. years of school completed,
2. occupational classification of the last job,
3. religious preference of native born subjects,
4. recency of employment (males).

Statistically significant differences were found with respect to the following attributes of cases:

1. an excess of males and of both sexes combined residing in the upper socioeconomic half as indicated by census tract of the last residence (Table 3),
2. an excess of foreign born women (Table 4),
3. an excess of males whose reported work histories indicated:
   a. a long period of employment in the industrial categories of "transportation" and "heavy industry" (Table 5),
   b. employment in at least one job which involved the operation and servicing of motor vehicles (Table 6),
   c. employment patterns characterized by fewer changes of occupation, less social mobility from first to last job, and longer duration of the last job, as compared with control I males (Tables 7, 8, 9),
4. an excess of ever-married males and females who were married rather than

Table 10—Comparison of study groups with respect to the proportion of ever-married reporting their present marital status as married, separated, or divorced, by time of hospital admission

Time of Hospital Admission and Comparison Groups (Both Sexes)	Weighted Mean Difference %*	SE†	P‡
	Separated or Divorced		
Total admissions case vs. control I and II combined	−14.4	5.0	<0.01
Case vs. control II	−15.7	5.7	<0.01
New admissions only case vs. control I and II combined	−12.1	5.0	<0.05
	Presently Married		
Total admissions cases vs. controls I and II combined	+16.0	6.5	<0.05
Case vs. control II	+20.4	7.4	<0.01

* (−) indicates a deficiency of cases, (+) an excess.
† Standard Error of Weighted Mean Difference.
‡ Probability that a difference as large as this could be due to chance.

Table 11—Mean ages (years) of female study group at menarche and menopause

Study Group	Menarche		All Menopause		Natural Menopause	
	Mean Age (Years)	S.D.	Mean Age (Years)	S.D.	Mean Age (Years)	S.D.
Present Study						
Case	13.5	1.5	49.3*	3.8	50.6	2.74
Control I	13.5	1.9	43.8	7.5	46.7	5.44
Control II	13.8	1.4	45.4†	7.2	47.4	4.87

* Four cases had not passed menopause.
† Two controls had not passed menopause.

separated or divorced at the time of hospital admission (Table 10),

5. an older mean age for females at menopause when either natural menopause alone or the combined experience, including artificial menopause, is considered (Tables 11, 12),
6. fewer abortions in terms of the proportion of total pregnancies or the proportion of women experiencing one or more of these events (Table 13),
7. an excess of reported complications of pregnancy, particularly those described in association with high blood pressure (Table 14).

Family Characteristics

All subjects were asked to provide information about their parents, siblings, spouses, and offspring. The 233 probands in the family study reported a total of 2,265 relatives of whom 1,200 were living and 1,005 were dead at the time of interview. Deaths were verified by certificates obtained from official sources in the United States and other countries. Death certificates were found for more than 90 per cent of the case and control relatives who died in 1920 or later. Only the parents and siblings were included in this analysis because of the small number of deaths among spouses and offspring.

Case and control relatives were compared with respect to their mortality experience from (1) cerebrovascular disease, (2) cardiovascular disease, and (3) all causes of death. Deaths were assigned to the stroke and heart disease categories if one of the designated conditions was mentioned on the death certificate. Thus, persons who died *with* cerebrovascular disease or *with* cardio-

Table 12—Results of t test comparisons of mean ages at menopause of female study groups, by type of menopause

Comparison Groups	Natural Menopause		All Menopause	
	t	P	t	P
Case vs. control I	2.2	<0.05	2.8	<0.05
Case vs. control II	2.9	<0.05	2.9	<0.05
Control I vs. control II	0.4	>0.05	0.7	>0.05

Table 13—Comparison of abortion experience* reported by study group females who were their own interview informants

Comparison Groups	Weighted Mean Difference %†	SE‡	P§
Case vs. control I	−3.6	1.09	<0.05
Case vs. control I and II	−2.2	0.78	<0.05

* Based on person years exposed to pregnancy.
† (−) indicates a deficiency of abortions among cases.
‡ Standard Error of Weighted Mean Difference.
§ Probability that a difference as large as this could be due to chance.

Table 14—Number and per cent of study group pregnancies associated with reported complications during pregnancy and/or delivery, by age of pregnancy

Age at Pregnancy	Case Pregnancies			Control I Pregnancies			Control II Pregnancies		
	Total No.	With Complications		Total No.	With Complications		Total No.	With Complications	
		No.	%		No.	%		No.	%
15-19	7	0	0.0	6	0	0.0	11	1	9.1
20-24	22	1	4.5	16	0	0.0	30	1	3.3
25-29	23	7	30.4	15	0	0.0	25	0	0.0
30-34	18	3	16.7	8	1	12.5	17	0	0.0
35-39	9	3	33.3	5	0	0.0	12	0	0.0
40-44	4	0	0.0	0	0	0.0	7	0	0.0
All ages	83	14	16.8	50	1	2.0	102	2	2.0

vascular disease are included in these comparisons. Observed numbers of deaths among case and control I relatives were compared with the expected numbers obtained by applying the appropriate control II death rate to the average population at risk in either the case or control I group. Comparisons were made for each individual class of relative and for female relatives (mothers and sisters) and male relatives (fathers and brothers).

These comparisons resulted in the following statistically significant findings (Table 15):

1. an excess of deaths from cerebrovascular disease (ISC 330-334) among parents and among male and female relatives of cases,
2. an excess of deaths from cardiovascular disease (ISC 400-468) among brothers and among male and female relatives of cases,
3. an excess of deaths from all causes beginning about age 40 among male relatives of cases and among female relatives of control I subjects.

The large excess of deaths from cerebrovascular disease among parents of cases, as shown by observed-to-expected ratios of 4.7 for mothers and 3.0 for fathers, cannot be accounted for by any of the usual sources of bias. A consistent excess of stroke deaths found also among the siblings of cases lends added support to the familial aggregation finding. Although there was an excess of stroke deaths among some categories of control I relatives, the differences were generally small, except for brothers.

The excess of cardiovascular disease deaths among some case relatives appeared to stem from two different situations. Among brothers only, there appeared to be a true increased frequency of hypertensive disease. Among female relatives, however, the excess seems to be accounted for by an increased frequency of cerebrovascular disease among hypertensive females. In other words, the statistically significant excess of heart disease among female relatives of cases disappears if the death certificates of those females having both stroke and heart disease are omitted.

Discussion

The findings of this study are consistent with a number of etiological hypotheses found in the literature. The existence of a familial aggregation of strokes has long been inferred from clinical observations and life insurance risk studies.[5-7] The finding of a marked excess of stroke deaths among parents and male and female relatives of cases in this study is consistent with, though not conclusive of a genetic hypothesis. Because of the small numbers of deaths, the findings on siblings as a group are

inconclusive. One question of interest is whether this familial aggregation of strokes is secondary to the presence of hypertension and diabetes—diseases known to have a family component. This seems to be an unlikely explanation in view of the very similar frequencies of these two diseases among case and control I subjects (Table 2). A number of observations here suggest sex differences in the mortality patterns of both stroke and control I relatives which should be investigated further.

A number of findings here would lend support to an "emotional stress" hypothesis.[8] Social status inconsistency is suggested by differences in residence, occupational class, and nativity among cases. The excess of foreign-born females may have some meaning in terms of separation from close relatives and adaptation to a new culture. One study reported higher stroke mortality among new emigrants.[9] However, the female cases in the present study were not recent emigrants but were more likely than controls to have come to this country alone. Other findings which suggest a life situation different from that of controls are the marital stability of cases and the job stability of case males.

Work histories of case males suggest also the possibility of physical or emotional stress arising from work operations such as operating moving machinery.[10] A potentially stressful situation in terms of exposure to agents such as carbon monoxide is suggested by the excess of case males whose work was associated with motor vehicle operation. This finding and the relationship between carotico-vertebral stenosis and carbon monoxide overexposure which has been mentioned in the literature[11]

Table 15—Observed and expected numbers of deaths from selected causes and observed-to-expected ratios for case and control I relatives based on mortality experience of control II relatives, by study group and type of relative

Study Group and Type of Relative	Cause of Death: All Causes			Cerebrovascular Strokes (330-334)			Heart Disease (400-468)		
	Observed No.	Expected No.	O/E Ratio	Observed No.	Expected No.	O/E Ratio	Observed No.	Expected No.	O/E Ratio
Case									
Mothers	111	96.0	1.1	28	6.0*	4.7	64	46.1	1.4
Fathers	110	85.9*	1.3	20	6.7*	3.0	51	34.0	1.5
Sisters	92	78.9	1.2	11	9.3	1.2	31	16.9	1.8
Brothers	141	114.5	1.2	6	4.1	1.5	55	33.8*	1.6
Female Relatives†	167	160.2	1.0	39	10.7*	3.6	95	67.0*	1.4
Male Relatives‡	215	165.0*	1.3	26	10.5*	2.5	103	62.7*	1.6
Control I									
Mothers	38	23.8*	1.6	2	0.9	2.2	15	10.8	1.4
Fathers	38	37.6	1.0	2	2.9	0.7	19	15.4	1.2
Sisters	38	24.5*	1.5	3	1.5	2.0	3	5.0	0.6
Brothers	61	53.3	1.1	7	1.9	3.7	19	16.1	1.2
Female Relatives†	59	41.5*	1.4	5	2.4	2.1	18	16.6	1.1
Male Relatives‡	83	75.0	1.1	9	4.9	1.8	38	28.7	1.3

* $P<0.05$.
† Mothers, sisters (age 20 and over).
‡ Fathers, brothers (age 20 and over).

Table 16—Comparison of pregnancy and abortion experience of Catholic and non-Catholic study group females

Study Group	Catholic vs Non-Catholic					
	Total Pregnancies			Abortions		
	WMD (%)*	SE†	P‡	WMD (%)	SE	P
Case	+ 2.4	2.8	>0.05	—	—	—
Control I	+ 1.7	6.8	>0.05	+15.7	4.0	<0.05
Control II	+12.1	3.4	<0.05	+ 2.9	1.4	<0.05

* + indicates an excess among Catholics.
† Standard Error of Weighted Mean Difference.
‡ Probability that a difference as large as this is due to chance.

suggest that a more detailed study of the environmental exposures of stroke patients would of great interest.

Interest in an endocrine hypothesis arises from sex differences observed in the incidence of coronary heart disease and from observations concerning the protective effect of female sex hormones in atherosclerosis. The control I females had an excess of abortions and a low mean age at menopause, findings which are in agreement with other studies[12] and which are consistent with an endocrine hypothesis. In direct contrast to these findings, case females were significantly older at menopause, reported fewer abortions, and an excess of pregnancy complications. These findings for cases suggest the influence of a different endocrine pattern. Comparison of pregnancy rates among Catholic and non-Catholic females in this study suggests also that there may be endocrine influences on fertility among the case and control I females (Table 16).

These differences between case and control I females are supported also by findings on fertility and artificial menopause which, although not significant, are consistent in direction.

The finding of an excess of pregnancy complications among case females provides confirmation by retrospective study of the observations that strokes are a frequent cause of death for eclamptic women.[13] It should be recalled, however, that no effort was made to validate the childbearing histories obtained by interview.

The association of cerebrovascular disease with hypertension, arteriosclerotic heart disease, and diabetes is of great interest. The suggestion advanced in recent papers that hypertension is strongly associated with cerebral thrombosis as well as with cerebral hemorrhage[14,15] is supported by the finding of relatively high systolic pressures and a high frequency of hypertensive heart disease among the cases in this study, 80 per cent of whom had a cerebral thrombosis diagnosis.

Although cerebrovascular disease has often been equated with atherosclerotic heart disease clinically, there are differences in the mortality patterns of the two diseases which do not support such a close association.[9,16,17] The findings of this study, particularly those regarding family mortality patterns and menstrual and childbearing experience, would seem to indicate epidemiologic dissimilarity between the two diseases.

Conclusion

In conclusion, it should be pointed out that the results of this study cannot be considered as definitive for many reasons. The stroke patients were not representative of all such patients in the community. In addition there are un-

known selective factors which may have introduced biases into the case—control comparisons. However, the findings which have been reported should be useful in formulating more precise hypotheses for investigation in a larger study.

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