Familial Incidence of Cerebrovascular Disease

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The value of a study of the familial incidence of a disease does not lie only in providing a risk factor for members of affected families; when the status of a condition is uncertain, the demonstration of different patterns of inheritance among affected persons may establish that distinct disease entities are contained within a common clinical group. Cerebrovascular disease provides a case in point.

Cerebrovascular disease is a generic term embracing clinical syndromes due to lesions in a variety of anatomical sites with different pathology arising from a number of aetiological factors. This in itself would provide no problem if accurate recognition of these various categories during life were possible; in fact, though the clinical syndromes have been defined with increasing precision, diagnosis of the anatomy, pathology, and aetiology of cerebrovascular lesions is still subject to considerable error.

In a previous study, Prineas and Marshall (1966) were able to distinguish two groups within the category diagnosed clinically as non-embolic cerebral infarction. The first group comprised patients who had a diastolic blood pressure below 110 mm. Hg, showed clinical evidence of a large lesion of the cerebral hemisphere which was reflected in a focal disturbance in the electroencephalogram, and who frequently had angiographic evidence of occlusive or stenotic disease of the extra- and intracranial arteries. The second group consisted of patients who had a diastolic blood pressure of 110 mm.Hg or above, showed clinical evidence of a small, deeply situated lesion of the cerebral hemisphere with a normal or bilaterally disturbed electroencephalogram, and who rarely had angiographic evidence of occlusive or stenotic disease of the arteries. The former group was considered to be the result of atherosclerosis and the latter the consequence of hypertensive vascular disease. Indirect evidence as to the validity of this conclusion might be obtained by studying the familial patterns of cerebrovascular disease in these groups.

Studies of the familial incidence of cerebrovascular disease are fraught with difficulty. Though the index patients may be chosen because they have been the subject of unusually close scrutiny, thereby enhancing the accuracy of diagnosis, the same will not obtain for their relatives who may be reported on tenuous grounds to have suffered from 'a stroke'. Confining the study to relatives who have died offers some advantage in that the reported cause of death can be checked by reference to the death certificate. However, the certified cause of death does not always indicate the true cause as Dalsgaard-Nielsen (1956) and Heasman and Lipworth (1966) have shown.

This type of difficulty is usually met by the use of a control group against which the results in the group under study can be compared. But matching index patients and controls for age and sex does not suffice in this case because it is the frequency of disease among their relatives that is being studied. A patient aged 50 years may be the eldest of a sibship extending over some 15 years, whereas the control, also aged 50, may be the youngest of an equally extended sibship. The relatives being compared could well be distributed over three decades. This time span is unacceptable for two reasons.

Firstly, there is evidence that the proportion of cerebrovascular disease attributable to the various pathological and aetiological categories may have changed over recent years. Yates (1964) has provided evidence of a reversal in the proportion of strokes due to haemorrhage and infarction over the years 1932 to 1960. Secondly, in situations in which it is difficult to be certain of the exact cause of death, fashions in death certification undoubtedly change with time. There could well be both a real and a spurious change in the proportion of deaths certified as being due to the various types of cerebrovascular disease during the period under study.

Fortunately these difficulties can be overcome by using the national mortality statistics as the control. These can be employed so as to provide controls who were of the same age and sex at the same time of

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the century as the relatives of the index patients, thus eliminating errors due to changes in the incidence of cerebrovascular disease and its various sub-categories over the decades and to errors in the certification of the cause of death. This method, developed and applied with singular success to the study of coronary heart disease by Slack and Evans (1966), has been used here.

Material and Methods

The index patients consisted of 201 patients (146 men and 55 women) who, after careful clinical assessment, examination of the cerebrospinal fluid, echoencephalography, and angiography were diagnosed as having experienced a completed stroke due to a non-embolic cerebral infarction. The term 'non-embolic' was used to indicate the absence of evidence of emboli from the classical sites in the heart. The possibility of emboli arising from a stenosis of the carotid artery in the neck was not excluded by this use of the term in this study.

A detailed family history extending to the parents and to the brothers and sisters of each patient—comprising 1106 persons in all—was obtained. For the 628 who were known to have died, the age of the person and the year and place of death were recorded. The 71 relatives who had either died abroad, or before the age of 20 years, or who had suffered an accidental death in war or peace were discarded. The death certificates of the remaining 557 were sought from the Registrars General for England and Wales, Scotland, Northern Ireland, and Eire, respectively; 410 were found, leaving 147 in whom the search was unsuccessful. These various figures are tabulated in Table I.

TABLE I
DETAILS OF INDEX PATIENTS AND RELATIVES
IN THE STUDY

	Males	Females	Total
Index patients	146	55	201
Relatives total	764	342	1106
Relatives dead	465	163	628
Relatives fate unknown	9	1	10
Death certificates not sought:			
Died abroad	9	2	11
Accidental death (war and peace)	22	2	24
Died before age 20 years	28	8	36
Death certificates sought but not found	98	49	147
Death certificates traced	308	102	410

Tables were then constructed to show the risk of being certified as having died from cerebral haemorrhage, thrombosis, or embolism in each decennial age-group at each quinquennium of the century. The following rubrics of the International Statistical Classification of Diseases, Injuries and Causes of Death are applicable according to the decade: 1921–30 (3rd revision) 74a, b; 1931–39 (4th revision) 82a, b; 1940–49 (5th revision) 83a, b, c; 1950–57 (6th revision) 331, 332; and 1958+ (7th revision) 331, 332. The risk factor was obtained by dividing the number of death certificates in the ap-

propriate rubric in the Registrar-General's classification of causes of death for each decennial age-group in each quinquennium of the century by the total population in the corresponding group as obtained from the national census figures.

The relatives of the index patients were then allotted to life-tables in which each decennial age-group and each quinquennium of the century were separated. As the parents of the index patients could not be considered to be at risk for the purposes of this study before the index patient was born they entered the table according to their age-group in the middle of the quinquennium in which the index patient was born. The parents left the table in the middle of the quinquennium in which they themselves died or, if they had survived, in 1967 when the study closed.

The sibs of the index patients presented more difficulty as the younger sibs were not alive in the year the index patient was born. Moreover, the risk of being certified as having died from cerebral haemorrhage, thrombosis, or embolism in the first two decades of life is negligible. Accordingly, the sibs entered the table in their appropriate age-group in the middle of the quinquennium in which the index patient attained the age of 20 years. They left the table in the same manner as did the parents.

From these tables the number of years in which the relatives were at risk was calculated. Surviving relatives under the age of 75 years were allotted a full life-expectancy for the quinquennium in which they left the table. Relatives of 75 years and over were allowed the life expectancy given in the National Life Tables as reproduced in Table II.

TABLE II
LIFE EXPECTANCY IN YEARS OF
PERSONS AGED 75 YEARS AND OVER

Year	Males		Females	
	75–84	85–94	75–84	85–94
1930–45	6.4	6.4	7.4	7.4
1946–50	5.8	3.5	6.9	4.2
1951–60	6.4	4.3	7.7	4.7
1961–65	6.4	4.1	8.0	5.0
1966–67	6.2	3.8	7.9	4.9

The number of 'relative-years at risk' among those aged 35 years and over is given in Table III.

The number of deaths certified as being due to the cerebral haemorrhage, thrombosis, or embolism to be expected among the relatives was then calculated for each decennial age-group at each quinquennium of the century by multiplying the number of 'relative-years at risk' in each group by the appropriate risk factor for the entire population in that group. The number of deaths actually observed in each group was then ascertained by allotting the death certificates obtained to their appropriate group. The observed and expected number of certificates were then compared according to a Poisson distribution. As the incidence of both observed and expected deaths from cerebral haemorrhage, thrombosis,

TABLE III
YEARS AT RISK OF RELATIVES OF INDEX PATIENTS

Age of Relatives (yr.)	Fathers	Mothers	Brothers	Sisters
<i>Male Patients</i>				
55-64	978.4	1011.0	809.9	1027.3
65-74	696.3	832.2	219.7	290.2
75-84	179.5	352.2	10.8	32.1
85-94	14.8	41.2	—	—
Total	1869.0	2236.6	1040.4	1349.6
<i>Female Patients</i>				
55-64	375.9	397.9	282.0	365.9
65-74	283.8	287.8	101.5	152.0
75-84	81.3	103.4	6.2	16.2
85-94	8.2	14.5	—	—
Total	749.2	803.6	389.7	534.1

or embolism was so small among relatives below the age of 55 years, these were discarded, the remainder of the study being confined to relatives aged 55 years and over.

Results

The number of deaths certified as due to cerebral haemorrhage, thrombosis, or embolism observed and expected among the relatives aged 55 years and over of all the male and female index patients is given in Table IV. The overall picture did not

TABLE IV

OBSERVED (O) AND EXPECTED (E) DEATHS CERTIFIED AS DUE TO CEREBRAL HAEMORRHAGE, THROMBOSIS, OR EMBOLISM IN RELATIVES OF INDEX PATIENTS

Age of Relative (yr.)	Fathers		Mothers		Brothers		Sisters	
	O	E	O	E	O	E	O	E
<i>Male Patients</i>								
55-64	1	1.51	1	1.51	0	1.29	0	1.34
65-74	2	3.97	7	4.44	1	1.25	0	1.37
75-84	4	2.88	8	5.40	1	0.27	0	0.46
85-94	1	0.46	0	1.32	0	0.00	0	0.00
Total	8	8.82	16	12.67	2	2.81	0	3.17
<i>Female Patients</i>								
55-64	0	0.57	1	0.59	1	0.53	1	0.52
65-74	1	1.66	1	1.57	1	0.59	0	0.73
75-84	0	1.32	1	1.67	0	0.09	0	0.23
85-94	0	0.25	0	0.53	0	0.00	0	0.00
Total	1	3.80	3	4.36	2	1.21	1	1.48

suggest that the relatives of patients with non-embolic cerebral infarction were unduly liable to be certified as dying from cerebral haemorrhage, thrombosis, or embolism. But among the mothers of the male patients a slight, but statistically insignificant, excess of observed over expected deaths was found (observed 16, expected 12.67).

In the previous study of Prineas and Marshall

(1966) in which there had appeared to be two groups within the category of non-embolic infarction, the patients had been separated according to the level of their diastolic blood pressure into those below 110 mm.Hg and those of 110 mm.Hg and above. Accordingly the index patients in the present series were similarly separated into two groups according to the level of their diastolic pressure and the prevalence of deaths certified as due to cerebral haemorrhage, thrombosis, or embolism among their relatives compared (Tables V and VI). The excess of observed deaths among the mothers of the male index patients was again apparent but only among the mothers of the index patients whose diastolic pressure was under 110 mm.Hg (13 observed, 10

TABLE V

OBSERVED (O) AND EXPECTED (E) DEATHS CERTIFIED AS DUE TO CEREBRAL HAEMORRHAGE, THROMBOSIS, OR EMBOLISM IN RELATIVES OF MALE INDEX PATIENTS SEPARATED BY BLOOD PRESSURE

Age of Relative (yr.)	Fathers		Mothers		Brothers		Sisters	
	O	E	O	E	O	E	O	E
<i>Diastolic BP under 110 mm.Hg</i>								
55-64	0	1.18	1	1.19	0	0.96	0	1.11
65-74	1	3.21	4	3.45	1	0.93	0	1.20
75-84	4	2.47	8	4.23	1	0.22	0	0.39
85-94	1	0.39	0	1.15	0	0.00	0	0.00
Total	6	7.25	13	10.02	2	2.11	0	2.70
<i>Diastolic BP 110 mm. Hg. or over</i>								
55-64	1	0.33	0	0.32	0	0.33	0	0.23
65-74	1	0.76	3	0.99	0	0.32	0	0.17
75-84	0	0.41	0	1.17	0	0.05	0	0.07
85-94	0	0.07	0	0.17	0	0.00	0	0.00
Total	2	1.57	3	2.65	0	0.70	0	0.47

TABLE VI

OBSERVED (O) AND EXPECTED (E) DEATHS CERTIFIED AS DUE TO CEREBRAL HAEMORRHAGE, THROMBOSIS, OR EMBOLISM IN RELATIVES OF FEMALE INDEX PATIENTS SEPARATED BY BLOOD PRESSURE

Age of Relative (yr.)	Fathers		Mothers		Brothers		Sisters	
	O	E	O	E	O	E	O	E
<i>Diastolic BP under 110 mm.Hg</i>								
55-64	0	0.44	0	0.49	1	0.46	0	0.47
65-74	0	1.27	1	1.23	1	0.58	0	0.71
75-84	0	1.07	1	1.14	0	0.09	0	0.23
85-94	0	0.19	0	0.19	0	0.00	0	0.00
Total	0	2.97	2	3.05	2	1.13	0	1.41
<i>Diastolic BP 110 mm.Hg and over</i>								
55-64	0	0.13	1	0.10	0	0.07	1	0.05
65-74	1	0.39	0	0.34	0	0.01	0	0.02
75-84	0	0.25	0	0.53	0	0.00	0	0.00
85-94	0	0.06	0	0.34	0	0.00	0	0.00
Total	1	0.83	1	1.31	0	0.08	1	0.07

TABLE VII

OBSERVED (O) AND EXPECTED (E) DEATHS CERTIFIED AS DUE TO CEREBRAL HAEMORRHAGE, THROMBOSIS, OR EMBOLISM IN RELATIVES OF MALE INDEX PATIENTS SEPARATED BY RESULTS OF ANGIOGRAPHY

Age of Relative (yr.)	Fathers		Mothers		Brothers		Sisters	
	O	E	O	E	O	E	O	E
<i>Angiogram Normal</i>								
55-64	1	0.89	0	0.81	0	0.64	0	0.74
65-74	2	2.42	2	2.78	0	0.71	0	0.48
75-84	3	1.79	4	2.93	1	0.17	0	0.24
85-94	1	0.28	0	0.67	0	0.00	0	0.00
Total	7	5.38	6	7.19	1	1.52	0	1.46
<i>Angiogram Abnormal</i>								
55-64	0	0.62	1	0.70	0	0.65	0	0.60
65-74	0	1.55	5	1.66	1	0.54	0	0.89
75-84	1	1.09	4	2.47	0	0.10	0	0.22
85-94	0	0.18	0	0.65	0	0.00	0	0.00
Total	1	3.44	10	5.48*	1	1.29	0	1.71

* $p < 0.03$.

TABLE VIII

OBSERVED (O) AND EXPECTED (E) DEATHS CERTIFIED AS DUE TO CEREBRAL HAEMORRHAGE, THROMBOSIS, OR EMBOLISM IN RELATIVES OF FEMALE INDEX PATIENTS SEPARATED BY RESULTS OF ANGIOGRAPHY

Age of Relative (yr.)	Fathers		Mothers		Brothers		Sisters	
	O	E	O	E	O	E	O	E
<i>Angiogram Normal</i>								
55-64	0	0.31	1	0.32	1	0.27	1	0.31
65-74	1	0.94	1	0.90	1	0.25	0	0.51
75-84	0	0.64	1	0.99	0	0.06	0	0.22
85-94	0	0.02	0	0.37	0	0.00	0	0.00
Total	1	1.91	3	2.58	2	0.58	1	1.04
<i>Angiogram Abnormal</i>								
55-64	0	0.26	0	0.27	0	0.26	0	0.21
65-74	0	0.72	0	0.67	0	0.34	0	0.22
75-84	0	0.68	0	0.68	0	0.03	0	0.01
85-94	0	0.23	0	0.16	0	0.00	0	0.00
Total	0	1.89	0	1.78	0	0.63	0	0.44

expected). The excess did not reach a level of statistical significance.

The diastolic blood pressure had been used in the previous study as a means of distinguishing between patients who were thought to be suffering primarily from atherosclerotic occlusive disease of the arteries and those with mainly hypertensive vascular disease. It was thought that the angiographic findings which were available in the present study might provide a more precise means of differentiating between these two groups.

Accordingly, the index patients were next separated into two groups, depending on whether or not the angiogram showed evidence of stenotic or occlusive disease. The observed and expected deaths certified as due to cerebral haemorrhage, thrombosis, or embolism among the relatives of all the male index patients were compared in Table VII and among the relatives of all the female index patients in Table VIII. The excess of deaths certified as due to cerebral haemorrhage, thrombosis, and embolism among the mothers of the male index patients was shown to be due entirely to an excess in the group in which the index patients had angiographic evidence of occlusive disease (observed 10, expected 5.48, $p < 0.03$). No significant difference emerged among the other relatives of the male index patients or among the relatives of the female index patients.

In order to validate further this observation, a control group of persons who had not suffered a stroke was obtained. These were to be compared, for the reasons already mentioned, not with the index patients directly but with the national mortality

statistics, to see if any significant difference emerged. 800 marriage counsellors working in a voluntary organization were circulated and asked for details of their own past medical history and of the cause of death among their parents and sibs who had died. 201 controls who themselves had no history of cerebrovascular disease were selected to give a group of the same sex and age (within the same quinquennial age group) as the index patients. Life-tables were then prepared for the relatives of this control group in the same way as had been done for the relatives of the index patients, the observed deaths from cerebral haemorrhage, thrombosis, and embolism being compared with the number expected from the national mortality statistics. The results among the relatives of the controls who had been matched with index patients with abnormal angiograms are given in Table IX. This shows no excess of deaths certified as due to cerebral haemorrhage, thrombosis, or embolism among the mothers of the control male subjects, thus strengthening the probability that the excess among the mothers of the male index patients was more than a chance finding.

Because of the relation which exists between atherosclerosis in the carotid and coronary arteries (Mitchell and Schwartz, 1965), it was thought profitable to ascertain the prevalence and pattern of deaths certified as due to disease of the coronary arteries among the relatives of the index patients. The following rubrics of the International Statistical Classification of Diseases, Injuries and Causes of Death apply: 1931-39 (4th revision) 94; 1940-49 (5th revision) 94a; 1950-57 (6th revision) 420.1;

TABLE IX

OBSERVED (O) AND EXPECTED (E) DEATHS
CERTIFIED AS DUE TO CEREBRAL HAEMORRHAGE,
THROMBOSIS, OR EMBOLISM IN RELATIVES OF
CONTROL SUBJECTS FOR INDEX PATIENTS WITH
ABNORMAL ANGIOGRAMS

Age of Relative (yr.)	Fathers		Mothers		Brothers		Sisters	
	O	E	O	E	O	E	O	E
<i>Male Controls</i>								
55-64	0	0.13	0	0.13	0	0.14	0	0.11
65-74	1	0.57	1	0.62	0	0.14	0	0.15
75-84	0	0.68	1	1.10	0	0.01	0	0.00
85-94	1	0.28	1	0.31	0	0.00	0	0.00
Total	2	1.66	3	2.16	0	0.29	0	0.26
<i>Female Controls</i>								
55-64	0	0.06	0	0.10	0	0.08	0	0.08
65-74	1	0.24	0	0.37	1	0.11	0	0.12
75-84	0	0.25	0	0.58	0	0.00	0	0.01
85-94	0	0.09	0	0.31	0	0.00	0	0.00
Total	1	0.64	0	1.36	1	0.19	0	0.21

TABLE X

OBSERVED (O) AND EXPECTED (E) DEATHS
CERTIFIED AS DUE TO DISEASE OF CORONARY
ARTERIES IN RELATIVES AGED 55 YEARS AND
OVER OF INDEX PATIENTS SEPARATED BY RESULTS
OF ANGIOGRAPHY

	Fathers		Mothers		Brothers		Sisters	
	O	E	O	E	O	E	O	E
<i>Male Patients</i>								
Normal angiograms	3	4.6	5	4.1	3	1.9	2	4.1
Abnormal angiograms	4	3.2	4	3.1	1	1.8	0	3.8
Total	7	7.8	9	7.2	4	3.7	2	7.9
<i>Female Patients</i>								
Normal angiograms	0	2.2	3	1.3	0	1.1	1	1.5
Abnormal angiograms	0	2.0	2	0.9	0	0.6	3	1.6
Total	0	4.2	5	2.2	0	1.7	4	3.1

and 1958+ (7th revision) 420.1. Cases certified before 1931 were not included, as disease of the coronary arteries was not distinguished as a separate category before that year.

The results separated by the findings on angiography are given in Table X, the decennial age-group 55 years and over being combined. This revealed no significant excess of deaths certified as due to disease of the coronary arteries among the relatives of either male or female index patients, nor did separation of the index patients into those with and those without angiographic evidence of occlusive disease of the cerebral arteries permit any pattern to emerge.

Discussion

The results of this study might at first sight seem to suggest that the genetic factor in cerebrovascular disease is negligible. In this it differs from ischaemic heart disease where the risk of death certified as due to ischaemic heart disease is increased five or sixfold among male relatives of male patients with this condition, twofold for the female relatives of male patients and sevenfold for the female relatives of female patients (Slack and Evans, 1966). Closer inspection of the present data, however, reveals that the mothers of the male index patients with angiographic evidence of occlusive disease of the extra- and intracranial vessels show a just significant excess of deaths certified as due to cerebral haemorrhage, thrombosis, or embolism.

This finding emphasizes first the general point that cerebrovascular disease is a generic term covering a number of different entities. In this it differs considerably from the term 'ischaemic heart disease' which designates a more uniform condition. Unless patients diagnosed as suffering from cerebrovascular disease are separated—as far as is possible in the light of current knowledge and with the aid of available techniques—into subgroups, important observations will be lost. Secondly, the finding indicates that the distinction among cases of non-embolic cerebral infarction into those suffering primarily from atherosclerotic occlusive disease and those with hypertensive vascular disease, previously suggested by Prineas and Marshall (1966), is valid.

The fact that the excess of deaths certified as due to cerebral haemorrhage, thrombosis, or embolism is present in the mothers and not in the sisters of the index patients deserves comment, for these two groups are genetically speaking the same. It will be appreciated that it is not suggested that genetic factors alone are responsible for cerebrovascular disease. Environmental factors, and in particular the ageing process, are important. The discrepancy between mothers and sisters can readily be explained on the grounds that the latter have not yet had time to develop manifestations of cerebrovascular disease. A prolonged follow-up study of the sisters would be of great interest.

More difficult to explain is the absence of any significant excess of coronary artery disease among any of the relatives. This is the more surprising in view of the finding by Slack and Evans (1966) that the relatives of patients with ischaemic heart disease showed a twofold increase of deaths certified as due to cerebrovascular disorders.

There is some evidence that atherosclerosis tends to affect the coronary arteries before the cerebral

vessels with the results that more severe atherosclerosis presents as coronary artery disease rather than as cerebrovascular disease. Whether patients present with the latter rather than with the former may not be a matter of chance. Presentation with cerebrovascular disease may well be the result of atherosclerosis of a milder degree in those families so that coronary artery disease is not found as frequently.

Though the limitations of the clinical situation make it likely that the term cerebrovascular disease will persist for some time to come, it should be recognized that the term has little precise significance. Unless energetic attempts are made to categorize more precisely the patients in this indeterminate group there will be little advance. Without this categorization natural history and prognosis cannot be assessed in a meaningful manner, nor can the interpretation of biochemical observations such as the pattern of blood lipids and physiological data such as the disturbances in regional cerebral blood flow be properly attempted. Moreover, as these categories are the result of different aetiological mechanisms, rational therapy cannot proceed. More extended studies of the familial incidence of cerebrovascular disease by the techniques employed here may well contribute to the establishment of further diagnostic categories on a sound basis.

Summary

The prevalence of deaths certified as due to cerebral haemorrhage, thrombosis, or embolism among the relatives of index patients with non-embolic cerebral infarction has been examined. There was a just significant excess of such deaths among the mothers of male index patients with angiographic evidence of occlusive disease of the extra- and intracranial vessels. The implications are discussed.

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