REFERENCES

- Adams, R. D. (1958). *Cerebral Vascular Diseases*, p. 23. Transactions of the 2nd Conference of the American Heart Association, Princeton, New Jersey, 1957.
- Carter, A. B. (1960). *Lancet*, **1**, 345.
- Fisher, C. M. (1958). *Neurology (Minneapolis)*, **8**, 311.
- Glynn, A. A. (1956). *Brit. med. J.*, **1**, 1216.
- de Morsier, G., and Tissot, R. (1957). *Thérapeutique des Thromboses Artérielles Cérébrales. Rapp. congrès. franç. Med.*, **1**, 130. Masson, Paris.
- Murphy, J. P. (1954). *Cerebrovascular Disease*. Year Book Publishers, Chicago.
- Sevitt, S., and Gallagher, N. G. (1959). *Lancet*, **2**, 981.
- Vastola, E. F., and Frugh, A. (1959). *Neurology (Minneapolis)*, **9**, 143.
- Wells, C. E. (1959). *Arch. Neurol. Psychiat.*, **81**, 667.
- Wright, I. S., and McDevitt, E. (1954). *Ann. intern. Med.*, **41**, 682.

SURVIVAL AFTER NON-HAEMORRHAGIC CEREBROVASCULAR ACCIDENTS

A PROSPECTIVE STUDY

BY

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The continued search for methods of preventing and treating cerebrovascular disease increasingly emphasizes the need for fuller knowledge of the natural history of this condition. The natural history of a chronic disease can be ascertained in two ways. A retrospective study may be carried out in which an attempt is made to ascertain the fate of a group of patients for whom previous records are available. This method has several disadvantages. Firstly, the initial records, no matter how thorough, rarely give sufficient information about the particular features it is desired to study. Secondly, difficulty may be experienced in tracing the patients. Thirdly, even when patients are traced, detailed information about events occurring between the initial illness and the time of follow-up may not be available. On the other hand, a retrospective study has the not inconsiderable advantage that it can be done quickly, time to study the original records and trace the patients being all that is required. Moreover, the deficiencies revealed may be of value when a prospective study is being designed.

The alternative method is to make a prospective study. This has the advantages that it can be specifically designed to meet the particular problems under investigation, and that steps can be taken to minimize the loss of patients from the follow-up. The main disadvantage is that the course of a chronic disease may need to be followed for months, or more commonly years, and as the patients come under observation serially the study may be very protracted.

A further problem associated with the study of the natural history of a chronic disease is the mode of presentation of the data. The method of presenting survivorship as the percentage of the total number of

patients diagnosed who are known to be alive at the end of, say, five years involves certain fallacies. It takes no account of patients lost to follow-up, who are in effect treated as having died; nor does it take account of the fact that many patients will not have been under observation for the full five years. Another method of presenting the average duration of life from the time of diagnosis to the time of death is likewise fallacious, for it takes no account of the patients who are still alive and who clearly have a better prognosis. The fallacies inherent in these methods of presentation have been well described by Merrell and Shulman (1955), who have shown that "life-tables" give the most accurate picture.

In a previous communication Marshall and Shaw (1959) presented the results of a retrospective study made on a group of patients who had recovered from a cerebrovascular accident. The results were in some respects contrary to expectation. The opportunity presented by the presence of a "control" group in a long-term clinical trial of anticoagulant therapy in patients who had recovered from a cerebrovascular accident believed to be due to non-embolic cerebral infarction has therefore been utilized to make a prospective study of this condition. The results of the first three years of this study are presented here. A special feature has been that the patients have been seen by us at intervals of not longer than a month throughout the period and asked about the occurrence of minor incidents. This was of importance in view of the significance which is attached to transient ischaemic episodes in patients with cerebrovascular disease.

Method and Material

177 patients (122 males and 55 females) have been included in the study to date, their age and sex distribution being given in Table I. These were patients who had recovered from a cerebrovascular accident which had been judged by the clinician caring for the patient at the time of its occurrence, and by ourselves subsequently, as having been due to a non-embolic cerebral infarction. As the patients were to be included in a long-term trial of anticoagulant therapy, they were selected according to strict criteria which have been outlined elsewhere (Hill, Marshall, and Shaw, 1960). The age, blood-pressure, serum cholesterol, electrocardiographic examination, site of lesion, duration of illness prior to admission to the study, and number of prior attacks were determined at the time of admission to the study. The blood-pressure recorded was the mean of six readings taken at hourly intervals, with the patient lying supine. The patients were subsequently seen at intervals of not longer than four weeks, and at each visit were questioned about the occurrence of further episodes. In the case of the nine patients who for one reason or another did not continue to attend regularly, contact was kept by means of visits from the

TABLE I.—Age-and-Sex Distribution

Age in Years	Males	Females	Total
35-39	—	1	1
40-44	4	2	6
45-49	11	5	16
50-54	19	9	28
55-59	38	12	50
60-64	29	15	44
65-69	21	11	32
Total	122	55	177

almoner or through the general practitioner. Thus reliable information was available about all the patients.

The data have been examined from two angles. Firstly, the life expectancy of the patients, and the factors influencing this, have been studied by calculating survival curves according to the method of Merrell and Shulman (1955). Secondly, the incidence of further cerebrovascular episodes, and the influence of various factors on this, have also been examined by means of the χ^2 test with Yates's modification.

Because the study was to be prospective, and based upon personal and frequent observation of the patients, all calculations have been made from the time the patient came under our observation, and not from the time of the first manifestation of the disease. Events prior to the patients' coming under our observation have been studied, but only in relation to the effect they may have had on the prospective data.

As some of the patients were treated with anticoagulant therapy, the calculations have been made on 88 patients who did not receive anticoagulants plus 18 patients who were initially treated, but were withdrawn from treatment when it was decided to exclude those with high blood-pressure, giving a group of 106 patients in all. The conclusions based on this group are confirmed in the analysis of the whole group of 177 patients.

Results

The survival curve for the untreated patients is given in Fig. 1. This shows that at one year 94% of the 72 males and 34 females were alive, and at two years 85% of the males and 89% of the females. The number of events occurring in patients observed for more than 117 weeks was not sufficient to make it worth while prolonging the curve beyond this point.

Influence of Age

The influence of age on survival is shown in Fig. 2, which, as might be expected, reveals that patients of 60 years and over fared slightly worse, though the difference is not significant. Thus at one year the percentage of patients under 60 years (59 patients) who had survived was 96, as against 91 for the patients of 60 years and over (47 patients), and at two years the figures were 88 and 83% respectively.

Fig. 2 also provides some quantitative evidence in support of the view expressed by Carter (1959) that anticoagulant therapy may be more hazardous in older patients. If the patients of 60 years and over who received anticoagulants are included, the percentage survival at two years (76 patients) falls to 75, as against 83 for the untreated group (47 patients), whereas in the

FIG. 1.—Survival curves of untreated male and female patients. In all charts the figures in brackets indicate the number of patients.

under 60 age-group percentage survival in the whole series (101 patients) is 86 as against 88 for the untreated group (59 patients).

Influence of Hypertension

The effect of high blood-pressure was most striking (Fig. 3). At one year, 64 patients whose diastolic blood-pressure as recorded by the method defined was under 110 mm. Hg at the time they came under observation showed 96% survival, whereas 42 patients with a diastolic blood-pressure of 110 mm. Hg or over showed a 90% survival. By two years, however, this gap had widened, figures of 96 and 75% being obtained, with a further drop to 66% by 117 weeks. The curves at 117 weeks differ by more than twice their standard error and are clearly significant.

Influence of Site of Lesion

The influence of the site of lesion upon survival rate is shown in Fig. 4. As there were only six patients with stenosis of the internal carotid artery in the neck, and all survived, these have not been included. At two years 92% of the 66 patients with a focal lesion of the cerebral hemisphere had survived, as compared with 88% of the 10 patients with diffuse hemisphere lesions and 79% of the 25 patients with brain-stem lesions. Though patients with lesions of the brain stem fared worse, the numbers involved are too small to justify any firm conclusions.

Influence of E.C.G. Findings

At the time of their entry to the study 163 patients had an electrocardiographic examination, standard leads I, II, III, aVR, aVL, and aVF, and chest unipolar leads

FIG. 2.—Survival curves separated by age. Broken line includes patients treated with anticoagulant therapy.

FIG. 3.—Survival curves separated by blood-pressure.

V1 to V6 being used. The records were assessed for evidence of left ventricular hypertrophy and ischaemic changes by one of us (A.C.K.). Left ventricular hypertrophy was regarded as present when there was ST depression and progressive T-wave inversion in left ventricular leads, or when the combined S wave V1 (or V2) plus the R wave V5 totalled more than 35 mm., together with normal T waves.

Apart from changes of infarction, non-specific ischaemic changes were regarded as present only when there were changes in at least two leads. Among the abnormalities were Q waves, ST depression greater than 0.5 mm., and low-voltage and abnormally shaped T waves. In three records demonstrating left bundle-branch block this was thought to be of ischaemic origin. In the two cases of atrial fibrillation there was also evidence of ischaemic changes.

FIG. 4.—Survival curves separated by site of lesion.

FIG. 5.—Survival curves separated according to electrocardiographic findings.

The influence of an abnormal E.C.G. upon survival in the untreated group is shown in Fig. 5, which indicates that those patients with evidence either of left ventricular hypertrophy or of ischaemic changes fared worse than those whose E.C.G. was normal. The difference between these two curves is greater than twice their standard error and is significant. This applies whether untreated patients alone are considered or those receiving anticoagulants are included.

Of the 11 patients who died from a cardiac cause, seven had an abnormal E.C.G. at the time of their admission to the study, three had a normal record, and in one the record was not done. Among the 13 patients who died from a cerebrovascular cause, 12 had an abnormal E.C.G. and one had a normal record. Five of the cardiac deaths were due to a cardiac infarction, two of the patients being among those treated with anticoagulants.

Influence of Other Factors

Among other factors studied was serum cholesterol: the patients whose serum cholesterol level at the time they came under observation was 250 mg. or over (23 patients) were compared with those with a reading of under 250 mg. (81 patients). There was no significant difference between these two groups. The effect of the length of time which had elapsed between the first evidence of cerebrovascular disease and the time of coming under our observation was also studied. The 75 patients in whom the disease had been clinically manifest for two years or less were compared with the 31 in whom there had been symptoms for more than two years. There was no significant difference between these two. Likewise, the 84 patients who had experienced only one cerebrovascular incident before coming under observation were compared with the 22 who had experienced two or more incidents. Again there was no significant difference in their survival rate.

Incidence of Further Non-fatal Cerebrovascular Accidents

The incidence of further non-fatal cerebrovascular accidents for the untreated patients is shown in Table II, which indicates that 11 of the 72 men and 4 of the 34 women experienced further episodes. The influence of age, blood-pressure, site of lesion, an abnormal E.C.G., and serum cholesterol on the incidence of further non-fatal cerebrovascular accidents has been calculated for both the untreated patients and the whole series, but in no instance was anything significant found. The data are given in Table II.

TABLE II.—Incidence of Further Cerebrovascular Accidents in Untreated Cases and in Whole Series

	Sex		Age		B.P.		E.C.G.		Cholesterol		Prior Attacks		Duration of Disease Prior to Study		Hemi-sphere Dif-fuse	Hemi-sphere Focal	Brain Stem	Internal Carotid
	M	F	< 60	60 +	< 110	110 +	Normal	Ab-normal	< 250	250 +	1	2 +	< 2 Yrs.	2 Yrs. +				
Untreated Cases																		
Further attacks	11	4	10	5	9	6	5	14	13	2	8*	7*	9	6	3	8	3	1
No further attacks	61	30	49	42	55	36	39	39	68	21	76	15	66	25	7	58	22	4
Total	72	34	59	47	64	42	44	53	81	23	84	22	75	31	10	66	25	5
Whole Series																		
Further attacks	17	6	16	7	14	9	7	14	19	4	11†	12†	12‡	11‡	3	14	5	1
No further attacks	105	49	85	69	114	40	71	71	112	49	127	27	115	39	11	105	33	5
Total	122	55	101	76	128	49	78	85	131	44	138	39	127	50	14	119	38	6

* Significant at 1% level. † Significant at 0.1% level. ‡ Significant at 5% level.

Influence of Number of Attacks Prior to Admission.—The effect of this factor in the untreated group is shown in Table II, which reveals that 8 of the 84 patients who had experienced only one episode before coming under observation had a further episode during the time of observation. Of the 22 patients who had two or more attacks before coming under observation, seven had further episodes. This difference is significant ($P<0.01$). When the number of patients for analysis is increased by including those who received anticoagulant therapy (whole series) the difference becomes more significant ($P<0.001$).

Influence of Time Prior to Admission.—The influence of the length of time which had elapsed between the first manifestation of the disease and the time of admission to the study is given in Table II. The higher incidence of further episodes in patients whose symptoms had been present for more than two years before coming under observation was not significant in the smaller untreated group, but reached the 5% level in the larger sample provided by the whole series.

Patients with Transient Ischaemic Episodes.—Only 2 of the 177 patients experienced transient ischaemic episodes. Both had multiple episodes of neurological deficit, each of only brief duration. Both patients were receiving anticoagulant therapy, but neither appeared to benefit; the frequency of the attacks waxed and waned from several attacks a day to one a week or so without relation to the intensity of the therapy. The attacks continued throughout the period of observation but in neither patient led to a major episode.

Causes of Death

Of the 177 patients 28 died. The causes of death are given in Table III, 15 being confirmed by necropsy. The table shows that vascular disease in some system was by far the commonest cause of death.

TABLE III.—*Causes of Death*

Cerebrovascular	13
Coronary thrombosis	5
Other cardiac causes	6
Pulmonary embolism	1
Ruptured dissecting aortic aneurysm	1
Other causes	2
	<hr/> 28

Prognostic Factors

An attempt was made to see if a combination of allegedly adverse prognostic factors was present in the patients who died. A positive score was given for an abnormal electrocardiogram, serum cholesterol of 250 mg. or over, diastolic blood-pressure of 110 mm. Hg or over, more than one attack before coming under observation, and a non-fatal recurrence during the time of observation. The number of positive scores in the patients who died was not significantly higher than it was in those who had survived.

Discussion

The life expectancy of these patients who had recovered from a cerebral infarction declined during the period of observation at a rate of about 6% a year. Comparison with other series is not very satisfactory, because of the factor of selection which inevitably arises and influences considerably the type of case included even under so specific a term as a non-embolic cerebral infarction. For example, Pincock (1957) followed 101 patients for six to eight years, but all of his patients were males. He found that 55 had died, which is a

mortality rate not appreciably different from that of the present series. Similarly, Lindgren (1958) followed 65 patients with occlusion of the internal carotid for periods varying from 2 to 18 years, and found 29 deaths in all. Robinson and his colleagues (1959) prepared life-tables for 1,018 patients with a cerebral thrombosis and found a five-year mortality of 59%. All of these studies were retrospective, however.

A comparable prospective study was that of David and Heyman (1960), who followed 100 patients for two years, half of them being re-examined and half contacted by questionnaire. They found a 33% mortality over two years, which is much higher than that in the present study. Adams and Merrett (1961) followed 736 "hard-hit survivors" of strokes of varying causes and found that 50% of those under 65 years could be expected to survive six years and 50% of those over 65 three and a half to four years.

The value of a study of the natural history of a disease does not lie solely in the measure of overall mortality that it provides. Of more importance is information about the factors which influence prognosis, and the guidance which may be given regarding future lines of therapeutic endeavour. The most striking feature in the present study was the adverse effect of hypertension upon survival, the two-year life expectancy decreasing from 96 to 75%. This finding confirmed that of Lindgren (1958) in his series. The observation is of considerable importance, for it has been suggested (McMichael, 1952) that the occurrence of a cerebrovascular accident in a patient with hypertension contraindicates hypotensive therapy, or at least demands great caution in its use. Smirk (1957), on the other hand, did not think that "an old hemiplegia of mild degree" contraindicated the use of hypotensive agents, though he mentioned that lowering the blood-pressure in acute cases was sometimes followed by a temporary increase in the neurological deficit. This fear of reducing the cerebral blood-flow below the critical level has tended to dominate the approach to therapy in hypertensive patients who have evidence of cerebrovascular disease. That hypotensive episodes may induce further cerebrovascular symptoms is not to be denied, but the crux of the problem is the frequency with which this occurs when modern hypotensive agents are used by people with experience. The risk would need to be high to outweigh the severe mortality associated with untreated hypertension found in this study. The present figures justify a more enterprising approach to hypotensive treatment to see if this will reduce mortality.

The second striking feature was the marked tendency for patients who had experienced several cerebrovascular accidents before coming under observation to have further accidents. This is in keeping with the findings of Pincock (1957) and of David and Heyman (1960). Indeed, so pronounced is this difference that it suggests that patients with cerebral infarction might be divided into two groups. The first comprises those patients who experience one cerebral infarction and have had no recurrence for many years. These may be termed the inactive group. The second comprises those patients who continue to have cerebrovascular episodes. These may be termed the active group.

The concept of activity and inactivity, though familiar to cardiologists in their consideration of ischaemic heart disease, has received little attention in cerebrovascular disease. Concepts such as occlusion or stenosis of

vessels, falls in blood-flow below a critical level, and the adequacy of collateral circulation have dominated thinking. Little attention has been paid to the state of the blood passing through the stenosed segments or via collateral vessels. It is worth while investigating the possibility that a disturbance of the dynamic balance which exists between the coagulation and fibrinolytic systems in the blood may provide a more satisfactory explanation for recurrent cerebrovascular episodes than do the mechanistic explanations, such as hypotensive episodes or recurrent emboli, which have been hitherto invoked.

The concept of activity and inactivity has further importance, for, if patients could be assigned to the appropriate group, therapy need only be given to those in an active state of the disease. It has been shown that anticoagulant therapy is not without hazard when given to all types of patient who have recovered from a cerebral infarct (Hill *et al.*, 1960). But there may be special groups who will benefit from anticoagulant therapy. The experience of Fisher (1958) in the treatment of patients who are having numerous minor transient episodes suggests that they constitute one such group. Patients of the type encountered in the present study who experience recurrent major episodes might constitute another group, and are worth studying from this point of view.

The influence of repeated cerebrovascular accidents on survival must also be considered. In their retrospective study, Marshall and Shaw (1959) found only 7 patients with recurrences among 102 survivors. They raised the possibility that the incidence might have been much higher among those who had died but on whom information on this point was lacking. Pincock (1957) found a higher mortality among those who had recurrent episodes, and David and Heyman (1960) observed that a history of a previous infarct increased the mortality from a subsequent infarct from 25 to 61%. In the present study there was no significant difference in the life expectancy between those patients who had experienced only one attack prior to coming under observation and those who had experienced two or more attacks. Nor did the occurrence of attacks subsequent to the patients' coming under observation appear to be closely related to prognosis for life. Though one patient had five episodes in the two years prior to death, this pattern was not found among the other patients who died.

An important prognostic factor which emerged from the study was the presence of changes indicative of left ventricular hypertrophy or of ischaemic heart disease in the electrocardiogram. Patients with these changes fared much worse so far as life expectancy was concerned, though they did not appear to be more liable to non-fatal cerebrovascular accidents. This diminished survival rate was partly due to the occurrence of coronary thrombosis in this group; but that was not the whole explanation, for there was a significantly higher incidence of abnormal E.C.G. records among those who died from a cerebrovascular cause.

The commonest cause of death was a cerebrovascular accident, but this only slightly exceeded cardiovascular causes. The fact that 26 of the 28 patients died from some form of cerebrovascular disease underlines the well-known fact that cerebrovascular disease is but one manifestation of the diffuse disease of atherosclerosis.

The assessment of a patient with cerebrovascular disease cannot therefore be based on the neurological findings alone, but must take into account the presence and degree of activity of vascular disease in other systems.

The minute incidence of transient ischaemic episodes in this series is remarkable, especially in view of the great interest these episodes have aroused. The low incidence was not due to failure to diagnose such cases, for the patients were seen regularly at monthly intervals and questioned about the occurrence of any symptoms since their previous visit. The fact that only two patients experienced this type of episode makes it impossible to say anything about their significance in heralding a major stroke, or of their general prognostic value. Certainly they do not appear to be a common residuum of a cerebral infarction, nor in the present series studied prospectively did they give warning of an impending infarction.

The value of a study of the natural history of a disease is not what it records about the past but the signposts it erects for the future. This study has high-lighted two problems for further study. The first is the correct management of patients who have recovered from a cerebral infarction but who have hypertension. Will carefully controlled hypotensive therapy improve their prospects, and, if so, should it be combined in suitable cases with anticoagulant therapy or not? The second problem is whether patients with cerebrovascular disease can be divided prospectively into two groups—those in whom the disease is active and those in whom it appears to be inactive; and, if so, what is the aetiological basis of this difference, and how should the groups be treated? The continued study of the natural history of the condition over a longer period, and the reappraisal of material from these standpoints, may lead to a closer understanding of this polymorphic disease.

Summary

177 patients who had recovered from a cerebral infarction were admitted serially to a prospective natural history study over a period of three years; the factors influencing their progress have been measured by means of life-tables.

The presence of a diastolic blood-pressure of 110 mm. Hg or over or of an abnormal E.C.G. significantly impaired life expectancy.

Patients who had experienced several cerebrovascular accidents before coming under observation had a significantly higher incidence of subsequent attacks.

The indications provided by the study for further work in cerebrovascular disease are discussed.

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REFERENCES

- Adams, G. F., and Merrett, J. D. (1961). *Brit. med. J.*, **1**, 309.
- Carter, A. B. (1959). *Quart. J. Med.*, **28**, 125.
- David, N. J., and Heyman, A. (1960). *J. chron. Dis.*, **11**, 394.
- Fisher, C. M. (1958). *Neurology*, **8**, 311.
- Hill, A. B., Marshall, J., and Shaw, D. A. (1960). *Quart. J. Med.*, **29**, 597.
- Lindgren, S. O. (1958). *Acta psychiat. scand.*, **33**, 343.
- McMichael, J. (1952). *Brit. med. J.*, **1**, 933.
- Marshall, J., and Shaw, D. A. (1959). *Ibid.*, **1**, 1614.
- Merrell, M., and Shulman, L. E. (1955). *J. chron. Dis.*, **1**, 12.
- Pincock, J. G. (1957). *Ann. intern. Med.*, **46**, 925.
- Robinson, R. W., Cohen, W. D., Higano, N., Meyer, R., Lukowsky, G. H., McLaughlin, R. B., and MacGilpin, H. H., jun. (1959). *J. Amer. med. Ass.*, **169**, 1149.
- Smirk, F. H. (1957). *High Arterial Pressure*. Blackwell, Oxford.