A comparison of two groups of patients—one treated predominantly with insulin coma and E.C.T., and the other with chlorpromazine, modified insulin, and E.C.T.—shows a significant advantage for the latter group, and a reduction of the average stay from 10.7 to 6.3 weeks. A comparative follow-up also confirms the superiority of the results of treatment in the latter group.

The methods used and the advantages of treating selected schizophrenic patients in a general-hospital setting are also discussed.

Statistical Note.—The probabilities were calculated by chi-square to give some estimate of the differences, but as the original selection was not randomized the tests may not be fully appropriate. We are grateful to Dr. E. D. West for statistical advice on our figures.

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ANTICOAGULANT TREATMENT IN PROGRESSING STROKE*

BY

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It is probably agreed by most workers in the field of cerebral vascular disease that anticoagulants should not be used as a routine in the treatment of cerebral infarction, and that in the acute full-blown stroke they are contraindicated, as they are ineffective and may be dangerous. Moreover, in this type of lesion differentiation from intracerebral haemorrhage is particularly difficult and sometimes impossible. My initial experience suggested that if these acute strokes were excluded from the overall results, then treatment seemed beneficial, and so I decided to plan a controlled clinical trial of anticoagulants in patients suffering from the slower-onset type of cerebral infarction—the progressing stroke.

Selection of Patients

The patients for this trial were selected from consecutive "stroke" admissions to the Ashford Hospital, Middlesex, during the four years 1956 to 1959. The details of these are shown in Table I.

The selection of patients was made in two ways. The first was a positive selection which included patients with a pre-hospital history of progressing symptoms and patients who after admission to hospital showed increase in severity or in distribution of their disability. The second was a negative selection made by excluding from this first selected group patients in whom past experience had shown that anticoagulants might be dangerous. I had previously found that major haemorrhage was much more likely to occur during the treatment of patients with established cerebrovascular disease if they showed any of the following

features: (1) loss of consciousness at the time of commencing treatment; (2) severe hypertension, with a diastolic pressure reaching 120 mm. Hg. or above; (3) age over 70 years, with few exceptions; (4) evidence of past severe hypertension, such as cardiac enlarge-

TABLE I.—Analysis of Patients Admitted to Ashford Hospital Suffering from Acute Cerebral Vascular Lesions, Showing Sex and Aetiology

Year	No. of Patients	Male	Female	Embolism	"Thrombosis"	Haemorrhage
1956	140	67	73	9	63	68
1957	147	70	77	10	66	71
1958	147	72	75	8	72	67
1959	136	73	63	7	76	53
Total	570	282	288	34	277	259

ment, retinal changes with haemorrhages or oedema, and evidence of severe renal dysfunction; (5) xanthochromic or blood-stained cerebrospinal fluid; (6) evidence of hepatic disease or definite history of peptic ulceration, etc.

Analysis of Material

In the four years, 122 patients out of the 277 admitted with the diagnosis of cerebral thrombosis came into the category of progressing stroke. The above-mentioned contraindications to anticoagulant therapy reduced this number to 80, and this group of 80 patients formed the series for the trial. Patients were placed in the control or treated group by random selection, and, apart from anticoagulants, were treated in the same way. Of these 80, four had to be withdrawn from the trial owing to recognized mistakes of diagnosis—two, by chance, in each group. Three had cerebral gliomata, and one, who was fortunately in the control group, had an intra-cerebral haematoma. In the final trial, therefore, were 76 patients, and these have been analysed according to age and sex in Table II. The distribution is seen to

TABLE II.—Analysis of Series According to Age and Sex

Age	No. of Patients	Treated		Untreated	
		Male	Female	Male	Female
40-49	8	2	2	3	1
50-59	26	7	5	8	6
60-69	42	12	10	12	8
Total	76	21	17	23	15

be reasonably even between the groups; over half the patients are between 60 and 70, and the ratio of men to women is four to three.

Distribution of Infarction

The distribution of cerebral infarction was commonly in the middle cerebral territory, and of the 76 patients 65 were in this group. Of the others, 8 were in the vertebral-basilar territory with brain-stem lesions, two showed occlusion of the posterior cerebral and one occlusion of the anterior cerebral artery. This proportion of six middle cerebral infarctions to one elsewhere is close to the seven to one for all types of infarction (Murphy, 1954; Glynn, 1956; Carter, 1960) but greater than the series of Adams (1958), who in a series of 58 patients over a five-year period found middle cerebral, 22; vertebral basilar, 22; posterior cerebral, 4; lateral medullary syndrome, 3; and uncertain, 7. This surely must have been a very selective group.

*An address given on January 5, 1961, at the Third International Conference on Cerebrovascular Disease at Princeton, New Jersey, U.S.A.

Method of Treatment

As soon as anticoagulant treatment was indicated the patients in the treated group received 125 mg. of heparin intravenously and 200 mg. of phenindione by mouth. Two further similar doses of heparin were given intramuscularly at six-hour intervals, and during the second 24 hours 150 mg. of phenindione in divided doses, and thereafter sufficient to keep the prothrombin time between two and three times the normal, for three weeks. In the fourth week the dose was slowly reduced to prevent rebound thrombotic episodes. One patient showed sensitivity, with diarrhoea and generalized erythematous rash, and the phenindione was replaced by ethylbiscoumacetate. I now use phenindione as my oral anticoagulant because I found dicoumarol was more difficult to control and I had some unfortunate experiences with regard to major haemorrhage. I therefore abandoned it in 1954 and have not used it since.

Results

Assessment

The patients were followed up for six months and then an assessment was made by clinical examination, dividing them into four groups: recovered, improved, not improved, and died.

Recovered.—This meant that the patient noticed slight or no disability and was able to resume normal life without help and to return to full work. Some loss of fine-movement dexterity in the hand was regarded as compatible with full "recovery" if the above criteria were fulfilled. Probably all patients with initial complete hemiplegia continue to show slight pyramidal signs permanently.

Improved.—This meant some useful movement was possible at the elbow and wrist and that the patient required only slight assistance to get about and live a useful life. Some work was possible and walking with a stick was reasonably well tolerated.

Not Improved.—This implied no return of arm movement below the shoulder and a poor recovery in the leg so that considerable assistance was needed for the patient to get about. Return to work was not possible, and this group included the bedridden patient.

Analysis

In the control group half the patients had recovered or were substantially improved at the end of six months. Table III shows that prognosis worsens with age. In the group 40–49 years 3 out of 4 showed a good result, in the group 50–59 years 8 out of 14, and in the group 60 to 69 years 8 out of 20, although the groups are not numerically comparable. Treatment improved the recovery figures from 50 to 70% (Table IV), but this may well have

TABLE III.—Results in Untreated Series

Age	No. of Patients	Recovered	Improved	Not Improved	Died
40–49	4	2	1	1	0
50–59	14	5	3	4	2
60–69	20	4	4	7	5
Total	38	11 (29%)	8 (21%)	12 (32%)	7 (18%)

TABLE IV.—Results in Treated Series

Age	No. of Patients	Recovered	Improved	Not Improved	Died
40–49	4	2	2	0	0
50–59	12	5	4	2	1
60–69	22	6	7	7	2
Total	38	13 (34%)	13 (34%)	9 (24%)	3 (8%)

arisen by chance, the odds being only ten to one against ($P=0.1$). However, this was encouraging enough to make me look at these patients a little more carefully. I first thought that the time of evolution of the stroke might be the key factor, and that those taking longer to develop might respond better to treatment. This, however, was not so. I finally found that if I separated the patients into those whose neurological deficit, although of slow onset, was clinically complete when treatment was begun, and those whose deficit was incomplete but progressing, then, although there was no prognostic difference in the controls, there was statistically significant improvement with treatment in the latter group ($P<0.05$). This, then, showed that anticoagulants seem to improve the prognosis if given before infarction becomes clinically complete (Tables V, VI, VII).

TABLE V.—Results in Untreated Incomplete Lesions

Age	No. of Patients	Recovered	Improved	Not Improved	Died
40–49	2	1	1	0	0
50–59	7	2	2	2	1
60–69	11	2	2	4	3
Total	20	5 (25%)	5 (25%)	6 (30%)	4 (20%)

TABLE VI.—Results in Treated Incomplete Lesions

Age	No. of Patients	Recovered	Improved	Not Improved	Died
40–49	2	2	0	0	0
50–59	7	2	4	1	0
60–69	13	4	5	3	1
Total	22	8 (36%)	9 (41%)	4 (18%)	1 (5%)

TABLE VII.—Composite Results

Year	No. of Patients	Treated				Untreated			
		Lesion Incomplete		Lesion Complete		Lesion Incomplete		Lesion Complete	
		Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
1956	22	5	2	3	1	4	3	1	3
1957	18	5	1	2	1	2	2	2	3
1958	20	4	1	3	2	2	4	3	1
1959	16	3	1	1	3	2	1	3	2
Total %	76 100	17 22	5 7	9 12	7 9	10 13	10 13	9 12	9 12

Group A—Recovered or improved. Group B—Unimproved or died.

Pathological Material

There were seven deaths in the untreated series, five occurring in the age-group 60–69, and three deaths in the treated series with two occurring in the patients over 60. Eight necropsies were obtained out of these 10 deaths, as two of the untreated patients died at home. These deaths were sudden, occurred in bedridden patients, and, on the clinical evidence, might well have been due to pulmonary infarction. Of the five untreated patients pulmonary infarction was the cause of death in three, diffuse bronchopneumonia in one, and complete basilar occlusion in one. One of the three patients dying of pulmonary infarction had a complete carotid occlusion and the other two had mid-cerebral thrombi. Of the three treated patients coming to necropsy one had a massive infarction of the brain with no obvious thrombus but with gross atheroma of the cerebral vessels, one had a small occluding thrombus in the mid-cerebral artery with a rather haemorrhagic infarction beyond, and the third showed carotid stenosis and an unsuspected carcinoma of the bronchus.

These findings, although few in number, confirm my previous experiences (Carter, 1960) that anticoagulants may reduce the death rate in patients suffering from cerebral infarction by protecting them from pulmonary infarction, and this protection in patients over the age of 50 is in agreement with recent experience in traumatic surgery (Sevitt and Gallagher, 1959).

Discussion

It appears from these results that anticoagulants have improved the natural history of progressing cerebral infarction in selected patients and have done no obvious harm in this particular series. In spite of this I still feel a sense of uneasiness when using anticoagulants for patients with established cerebrovascular disease. This feeling seems to stem from three uncertainties which I cannot ignore. The first is an uncertainty of whether my diagnosis is always correct, the second is an uncertainty of whether I am increasing the risk of cerebral haemorrhage by my treatment, and the third is the uncertainty of my knowledge regarding the mechanism by which anticoagulants can improve the effects of cerebral infarction. These three problems are worthy of some discussion.

The problem of diagnosis is in my opinion more difficult than has been commonly supposed, and I doubt very much if we possess a truly reliable and harmless method of differentiating cerebral infarction from small intracerebral haemorrhages. I have seen patients with proved intracerebral haematoma whose cerebrospinal fluid has contained fewer than 5 red blood-cells per ml.

The risk of cerebral haemorrhage must, I think, be increased by anticoagulant therapy, and the question is: Does this danger outweigh the advantages? My own experience has so far been fortunate, and is in accordance with that of Irving Wright and McDevitt (1954), Miller Fisher (1958), and Wells (1959). Other workers, notably de Morsier and Tissot (1957) and Vastola and Frugh (1959), have reported disturbing series; in one of these four fatal cerebral haemorrhages occurred in 55 treated patients. Perhaps the careful selection of patients as I have suggested may reduce this risk, and, indeed, I am now tending to narrow this selection even further than in this series and to exclude, for example, patients whose diastolic pressure is above 100 mm. Hg.

The third problem is the mechanism of treatment. I presume that benefit must arise in one of three ways. First, spread or propagation of the thrombus if present may be restricted either distally or centrally; and since this spread often involves anastomotic vessels anticoagulants may thus keep the infarcted area from enlarging. Secondly, they may prevent the formation of a thrombus if the infarction is caused by atheromatous narrowing without thrombosis. Thirdly, they may prevent the distal embolism of small thrombi or platelet clumps.

My own feeling is that anticoagulants do most good when large vessels are occluded or stenosed—such as the carotid, vertebral, basilar, subclavian, etc. This belief has up to now no true scientific basis, although my results in the treatment of carotid and vertebral stenosis have been better than those in the treatment of known intracerebral occlusions. The numbers have been insufficient to draw definite conclusions, and therefore this remains a clinical impression. If this is true, then the important mechanism of treatment is likely to be the prevention of embolization of microscopic

or macroscopic particles arising at the point of stenosis or occlusion, and the stepwise rather than smooth course of untreated progressing cerebral infarction gives a clinical blessing to this pathological concept.

Another good reason for believing this to be the main method of benefit is that anticoagulants do not appear to prevent thrombosis recurring. We have all had the mortifying experience of seeing a major thrombosis occur while the patient was adequately controlled with a so-called effective prothrombin time. I have also noticed that when a patient has been stabilized on a maintenance dose of phenindione he may occasionally begin to need much more for no apparent reason in order to keep his prothrombin time right, and I have thought that this has more often than not preceded further thrombosis, but I have no figures to support this theory.

Conclusion

The results of anticoagulant treatment in a selected series of patients with the clinical diagnosis of cerebral infarction suggest that the progressing type of infarction in a normotensive patient responds best to this treatment. It seems that reduction in death rate may be associated with prevention of pulmonary infarction, and in this series the treatment has not appeared to carry much risk. In spite of this, caution is needed as diagnosis is occasionally uncertain, treatment potentially dangerous, and the mechanism by which any benefit accrues is unknown.

Summary

A series of 277 consecutive patients with the clinical diagnosis of cerebral infarction were seen at the Ashford Hospital, Middlesex, during the four years 1956 to 1959.

From these patients 80 were selected for a controlled clinical trial of short-term anticoagulant therapy. Four were withdrawn from the trial owing to errors in diagnosis.

The selection was made by including only those patients under 70 years of age with a pre-admission history or with clinical signs of a progressing disability, and by excluding those who showed loss of consciousness, severe hypertension with a diastolic pressure reaching 120 mm. Hg or more, xanthochromic or blood-stained C.S.F., or evidence of hepatic disease or past peptic ulceration.

The results after six months have been analysed and tabulated and suggest that in this series anticoagulant therapy has improved the natural history of progressing cerebral infarction, particularly when the lesion is incomplete at the beginning of treatment. Protection from pulmonary infarction by anticoagulants appears to be established, and this treatment in selected patients seems to be without serious risk.

The mode of action of heparin and phenindione in helping these patients is not yet understood, but it appears that large-vessel stenosis or occlusion responds better than small-vessel lesions, thus probably making this treatment more valuable when infarction is due to disease of extracranial arteries.

Caution is necessary in using anticoagulants for patients with cerebral infarction, as diagnosis is more difficult than is commonly supposed, the method of action of the drugs is not fully understood, and the treatment is potentially dangerous. However, it would seem that this treatment is not entirely valueless if patients are selected with care.

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SURVIVAL AFTER NON-HAEMORRHAGIC CEREBROVASCULAR ACCIDENTS

A PROSPECTIVE STUDY

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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