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CEREBROVASCULAR DISEASE: TRIAL OF LONG-TERM ANTICOAGULANT THERAPY

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A trial of long-term anticoagulant therapy in patients with cerebrovascular disease was started in October, 1957, and progress during the first 20 months to June, 1959, was reported by Hill, Marshall, and Shaw in 1960. At that stage there was no evidence that anticoagulants were reducing either the mortality or the recurrence rate of cerebrovascular accidents; indeed, the data suggested an adverse effect, particularly in hypertensive patients. The trial was therefore modified by withdrawing those who were hypertensive, and we report here the further progress of the trial in its modified form to its conclusion in October, 1961.

The design of the trial, the selection of patients, and the methods of treatment and control were described in detail in the original report (Hill, Marshall, and Shaw, 1960). All the patients included were under 70 years of age and had suffered one or more disturbances of neural function lasting more than 24 hours and attributed to non-haemorrhagic cerebral, carotid, or vertebral arterial disease. Admission to the trial was permissible any time after 14 days had elapsed since the last acute episode. The usual contraindications to anticoagulant therapy were observed and patients were included in the trial only if it seemed likely that their personal, occupational, and geographical situations would permit regular attendance and adequate co-operation. Patients admitted to the trial were differentiated by sex and allotted by pairs to high-dosage (treatment) or low-dosage (control) groups by a random method. The former group received tablets containing 50 mg. phenindione ("dindevan") in a dosage aimed at maintaining the prothrombin time, estimated by the Quick one-stage test (human brain thromboplastin), at a level of two to two and a half times the control value. The low-dosage control group received apparently identical tablets containing 1 mg. phenindione, and their management otherwise did not differ from that of the high-dosage group. All patients were seen and had blood taken for prothrombin estimation at least once every four weeks. Many of the criteria adopted for selection and control were based on the plan of the Medical Research Council (1959) trial of anticoagulant therapy in coronary thrombosis, to which access was kindly granted.

By the end of 20 months—that is, at the time of the last report—142 patients had been admitted to the trial,

71 (47 men and 24 women) to the high-dosage group and 71 (47 men and 24 women) to the low-dosage group. Analysis of the groups in respect of age distribution, clinical diagnosis, frequency of previous attacks, and incidence of hypertension showed them to be comparable. Table I reproduces the summary of results to

TABLE I.—Summary of Results October, 1957 to June, 1959*

	High-dosage Group			Low-dosage Group		
	M	F	Total	M	F	Total
Total number of patients	47	24	71	47	24	71
Non-fatal cerebrovascular accidents	3	2	5	4	—	4
Fatal cerebrovascular accidents	2	2	4	—	—	—
Deaths possibly attributable to treatment	1	—	1	—	—	—
Deaths from other causes	2	1	3	1	—	1
Progressive deterioration	—	1	1	1	—	1
Defaulters	—	—	—	1	1	2

* Hill, A. B., Marshall, J., and Shaw, D. A. (1960). *Quart. J. Med.*, **29**, 597, reproduced by permission of the editorial board.

June, 1959. There was little difference between the groups in the rate of recurrence of non-fatal cerebrovascular accidents or in the incidence of deaths not related to the disease or its treatment. But four patients had died from cerebral haemorrhage in the high-dosage group, whereas no deaths had occurred from this cause in the low-dosage group. Another patient in the high-dosage group had died suddenly and at necropsy had been found to have a haemopericardium. Thus five deaths possibly attributable to anticoagulant treatment had occurred in one group as against none in the other; and while this difference did not reach the conventional significance level the odds against such a distribution occurring by chance are about 17 to 1.

It was therefore decided that the trial could not be continued in its existing form. It is generally held that hypertension increases the hazard of anticoagulant therapy, and authors experienced in this field have supported this view (Carter, 1957). As three of our four patients who had died of cerebral haemorrhage had had diastolic blood-pressures greater than 110 mm. Hg (mean of six readings at rest), it seemed likely, although not proved statistically, that anticoagulant therapy carried particular hazard in patients with cerebrovascular disease who were also hypertensive. Accordingly the trial was modified by withdrawing patients with hypertension, a mean diastolic pressure of

110 mm. Hg being arbitrarily chosen as the critical level. There were 24 patients in each of the two treatment groups with readings at this level or greater who were withdrawn from the trial. This modification did not materially upset the balance of the treatment and control groups, nor did it in any way invalidate the basic design of the trial. The 94 remaining patients with no hypertension continued treatment without interruption according to their original grouping and all patients subsequently added to the trial had mean diastolic pressures below 110 mm. Hg. By December, 1960, a further 37 had been admitted, making 131 in all. Thereafter no more were admitted, but the defined treatment was continued until October, 1961. The analysis of the results for these 131 patients is based on the whole four-year period from the start of the trial in October, 1957.

Case Material

Of the 131 patients included in the modified trial, 66 (49 men and 17 women) were in the high-dosage group and 65 (47 men and 18 women) were in the low-dosage group. Table II shows the age-and-sex distributions. The average age was 57.0 years in each group, with standard deviations of 6.8 in the high-dosage group and 7.4 in the low-dosage group. The diagnoses in terms of the anatomical site of the lesion are shown in Table III. Cerebral angiography was carried out

TABLE II.—Age-and-Sex Distribution

Age (Years)	High-dosage Group				Low-dosage Group			
	M	F	Total	%	M	F	Total	%
35-44	3	1	4	6.1	1	1	2	3.1
45-54	12	7	19	28.8	15	5	20	30.8
55-64	29	6	35	53.0	20	11	31	47.7
65-69	5	3	8	12.1	11	1	12	18.4
Total	49	17	66	100.0	47	18	65	100.0

TABLE III.—Clinical Diagnosis

Site of Lesion	High-dosage Group				Low-dosage Group			
	M	F	Total	%	M	F	Total	%
Hemisphere focal	35	15	50	75.8	32	11	43	66.0
diffuse	3	—	3	4.5	2	—	2	3.1
Brain stem	9	2	11	16.7	10	5	15	23.2
Internal carotid	2	—	2	3.0	3	2	5	7.7
Total	49	17	66	100.0	47	18	65	100.0

in 20 of the high-dosage patients and in 22 of the low-dosage. When there was a history of more than one previous acute episode the diagnosis was based on the most recent. Table IV gives the frequency of previous attacks in the two groups and Table V compares their duration of treatment, the average being 28 months for the high-dosage group and 31 months for the low-dosage group. Examination of these data shows no material differences between the composition of the high-dosage and low-dosage groups, so that comparison between them is valid in the assessment of the influence of anticoagulant treatment.

TABLE IV.—Frequency of Previous Attacks

No. of Previous Attacks	High-dosage Group				Low-dosage Group			
	M	F	Total	%	M	F	Total	%
1	34	13	47	71.2	35	15	50	76.9
2	10	4	14	21.2	6	2	8	12.3
3 or more	5	—	5	7.6	6	1	7	10.8
Total	49	17	66	100.0	47	18	65	100.0

TABLE V.—Duration of Treatment

Months	High-dosage Group				Low-dosage Group			
	M	F	Total	%	M	F	Total	%
0-6	6	—	6	9.1	2	1	3	4.6
6-12	4	—	4	6.0	1	3	4	6.1
12-18	4	1	5	7.6	2	—	2	3.1
18-24	2	3	5	7.6	4	1	5	7.7
24-30	11	1	12	18.2	10	3	13	20.0
30-36	8	5	13	19.7	9	3	12	18.5
36-42	9	4	13	19.7	12	5	17	26.1
42-48	5	3	8	12.1	7*	2	9	13.9
Total	49	17	66	100.0	47	18	65	100.0

* For 2 patients the duration was slightly over 48 months.

Results

The results are summarized in Table VI. There was little difference in the recurrence rate of non-fatal cerebrovascular accidents in the two groups. In the high-dosage group there were 17 recurrences in 12 patients, and in the low-dosage group there were 18 in 10 patients. However, there were five fatal cerebrovascular accidents in the high-dosage group as

TABLE VI.—Summary of Results

	High-dosage Group			Low-dosage Group		
	M	F	Total	M	F	Total
Total number of patients	49	17	66	47	18	65
Non-fatal cerebrovascular accidents	10	7	17	14	4	18
Fatal cerebrovascular accidents	5	—	5	—	1	1
Deaths possibly attributable to treatment	1	—	1	—	—	—
Deaths from other causes	6	—	6	3	—	3
Defaulters	1	—	1	1	1	2
Moved away	1	—	1	1	1	2

against one in the low-dosage. Necropsies were performed on three of these patients, all in the high-dosage group, and in each case the cause of death was cerebral haemorrhage. In the other three patients, who were not examined post mortem, there was no doubt clinically that death was due to a cerebrovascular accident, but its precise nature in pathological terms must remain uncertain. The one death regarded as attributable to treatment was in the patient, previously described, in whom a haemopericardium was found at necropsy. A clinical diagnosis of myocardial infarction had been made but was not confirmed; nor was there evidence of spontaneous haemorrhage elsewhere, and the prothrombin time was within the therapeutic range.

Clearly, anticoagulant treatment has failed to reduce mortality. Once again the figures suggest an adverse trend, although the difference in the incidence of fatal cerebrovascular accidents in the two groups (5 deaths to 1) does not reach the conventional significance level. If we add to these fatal cerebrovascular accidents the death possibly attributable to treatment we have mortality rates of 9.1% in the high-dosage group (6 deaths) and 1.5% in the low-dosage group (1 death). The difference of 7.6% has a standard error of 3.9 and therefore very closely approaches the conventional significance level.

Of the deaths due to causes other than cerebrovascular accident or complication of treatment, there were six in the high-dosage group and three in the low-dosage. The former included three deaths from myocardial infarction, one from cardiac aneurysm and failure, one from suicidal carbon-monoxide poisoning, and one from congestive heart failure. All but the last were confirmed at necropsy. The three deaths in the low-dosage group

were all attributed to myocardial infarction although post-mortem confirmation was not obtained.

Three patients defaulted from regular out-patient attendance, but their progress was followed by almoner's visit. One was in the high-dosage group, and he had two further non-fatal cerebrovascular accidents; of the two in the low-dosage group, one died of myocardial infarction. Three patients, one in the high-dosage group and two in the low-dosage group, went to live in other parts of the country, but contact was maintained with them by post and no further incidents were reported.

The complications of treatment are shown in Table VII. In eight of the 12 instances of haemorrhage it was possible to resume treatment within 28 days, but

TABLE VII.—Complications of Treatment

	High-dosage Group			Low-dosage Group		
	M	F	Total	M	F	Total
Total number of patients	49	17	66	47	18	65
Haemorrhage; treatment interrupted	4	4	8	—	—	—
Haemorrhage; treatment abandoned	4	—	4	—	—	—
Hypersensitivity; treatment abandoned	—	1	1	—	—	—
Intercurrent illness; treatment abandoned	2	—	2	3	3	6

in 4 patients anticoagulant treatment was abandoned. They were all followed up by post or by out-patient or almoner's visit, as were the 9 patients in whom treatment was abandoned because of intercurrent disease or sensitivity to phenindione. Thus complete follow-up was achieved of all patients who left the trial before its completion for any reason other than death. Including the defaulters and those who moved away, enumerated above, they number 19, and Table VIII

TABLE VIII.—Patients Withdrawn, Defaulted, or Moved Away

	High-dosage Group			Low-dosage Group		
	M	F	Total	M	F	Total
Survived { No further cerebrovascular accident	5	—	5	2	5	7
Survived { Further cerebrovascular accident	2*	1	3	—	—	—
Died { Intercurrent illness	1	—	1	3	—	3
Died { Cerebrovascular disease	—	—	—	—	—	—
Total number of patients—19	8	1	9	5	5	10

* One patient had two cerebrovascular accidents.

analyses the follow-up of this group. Taking the figures in conjunction with those contained in the summary of results (Table VI), it can be seen that inclusion of data on patients subsequent to their withdrawal from the trial does not materially influence the main analysis.

Discussion

The final results show trends similar to those found in the early stages before the hypertensive patients were withdrawn. In the two groups each of 24 patients with hypertension who were withdrawn in June, 1959, we saw three deaths from cerebrovascular accident in the high-dosage group and none in the low-dosage group. In the present groups of non-hypertensive patients (66 and 65) we have seen five deaths from cerebrovascular accident in the high-dosage group and one in the low-dosage group. Again it has been felt impossible to pursue the trial to the point of formal statistical significance, but certain conclusions can be drawn. It is clear that no protection against recurrence of cerebro-

vascular accidents is afforded by phenindione, given in accordance with generally accepted therapeutic practice to patients of the type included in this trial. This last stipulation must be emphasized because obviously no inference can be drawn regarding the possible effectiveness of anticoagulant drugs in the treatment of certain clinical subgroups of cerebrovascular disease inadequately represented in the present series. For example, no evidence is presented regarding the response of patients with "transient ischaemic attacks," the frequently recurring disturbances of function sometimes associated with carotid or vertebro-basilar disease, which have been shown to be preventable in many instances by anticoagulant drugs (Siekert, Millikan, and Whisnant, 1961). But such patients are rare in comparison with the great number who present with the familiar "stroke" syndromes, and it was the treatment of these common forms of cerebrovascular disease, encountered daily in general medical practice, that the trial was originally designed to evaluate.

While confirming the failure of long-term anticoagulants to benefit patients who have had a stroke, the trial also helps to some extent to put the problem of treatment in perspective. Knowledge is inadequate regarding the natural history of cerebrovascular disease, but studies such as the present one suggest that in many instances the prognosis is less grave than might be expected. Consider the control group on its own. Out of a total of 65 patients observed on the average for just over two and a half years, 11 (17%) suffered recurrent cerebrovascular accidents during the four-year period of the trial. In seven there was more than one recurrence, but in only one was the outcome fatal. Considering the duration of the follow-up and the fact that many of these patients had their original cerebrovascular accident some time before they were admitted to the trial, the mortality and recurrence rates are surprisingly low. Certainly it would require a highly effective form of treatment to reduce them by an amount that would be detectable by the usual methods of clinical trial unless such trial included very large numbers of patients and was continued for a prolonged period of time. A trial of such dimensions usually demands the collaboration of several different medical centres, and this dispersal immediately raises both administrative and clinical difficulties.

Although quantitative grading is notoriously fallible in clinical studies, it is of interest to try to assess the morbidity involved in the recurrent cerebrovascular accidents. Of the 17 non-fatal recurrences in the high-dosage group and 18 in the low-dosage group, only two, one in each group, were florid "strokes" resulting in severe and permanent disability. More than half were very minor and transient disturbances, while the remainder produced moderately severe deficit from which good recovery was ultimately made. Again the impression has been that the disease, at least in the selected case material studied, runs a more benign course than might be anticipated.

The same relatively benign course of the disease was not observed in the hypertensive patients who were withdrawn from the trial but who were nevertheless followed up. They are not included in the present analysis, but their greatly reduced survival as compared with the normotensive group was described by Marshall and Kaeser (1961). There is therefore a much greater need for an effective form of treatment for hypertensives

with cerebrovascular disease. As anticoagulants are ineffective and probably increase the risk of cerebral haemorrhage, it is suggested that vigorous hypotensive therapy might be employed more extensively in this situation.

The results of this trial show no evidence of a protective influence of anticoagulants against further strokes, so that in this particular context the problem of hazards and complications of treatment ceases to be relevant. However, as there are particular situations in which it may be desirable to use anticoagulant drugs in patients with cerebrovascular disease, the question remains one of some importance. In this particular series, as stated above, there were five fatal cerebrovascular accidents in the high-dosage group as against one in the low-dosage group. It is known that three of those in the high-dosage group were due to cerebral haemorrhage, but the exact pathological nature of the other three is unfortunately not known. While it is not possible to make a valid statistical assessment of the hazard of cerebral haemorrhage in patients with cerebrovascular disease who are treated with anticoagulants, there can be no doubt about its existence, and a small but appreciable incidence is to be found in most of the trials published. The trials most closely resembling the present one are those of the National Institutes of Health and the Veterans Administration in the United States, described together by Baker (1960). Among 133 treated patients, who were followed up on average for approximately 12 months, there were six fatal cases of cerebral haemorrhage; in addition there were four other fatal haemorrhages from other sites. It was felt that the treatment had provided no protection from recurrent cerebral infarction, although the number of patients experiencing transient ischaemic attacks and extracerebral thrombo-embolic episodes was thought to have been reduced. In their recent account of the surgical treatment of internal carotid stenosis Edwards and Gordon (1962) mentioned the deaths from cerebral haemorrhage of five patients who were on anticoagulant therapy. Such figures are fairly representative of the large number of clinical studies in which this complication has been encountered.

We would ourselves conclude that the use of anticoagulants in patients who have suffered a stroke is attended by a small but definite risk of cerebral haemorrhage; that this risk is not counterbalanced by adequate protection against the occurrence of further strokes; and that these drugs are therefore not to be recommended in chronic cerebrovascular disease except in the particular case of patients at risk of cerebral embolism or suffering from frequently recurring transient ischaemic attacks.

Summary

The final results of a controlled trial of long-term anticoagulant therapy in patients with cerebrovascular disease are presented. The trial has run over a period of four years and has included 66 treated patients and 65 controls with an average duration of treatment of approximately two and a half years. It has shown that, in patients of the type included, anticoagulant treatment fails to afford protection against recurrent cerebrovascular accidents and it adds further evidence of the risk of cerebral haemorrhage when patients with cerebrovascular disease are treated with anticoagulant drugs.

We are grateful to all the physicians and surgeons who referred patients to us and to the medical committees of the West Middlesex and North Middlesex Hospitals, where anticoagulant clinics were held; also to Professor J. N. Cumings and Dr. W. H. McMenemy, in whose laboratories prothrombin estimations were made. We are indebted to Evans Medical Limited for supply of tablets and to the Nuffield Foundation for generous financial support.

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USE OF RADIOACTIVE XENON FOR STUDIES OF REGIONAL LUNG FUNCTION*

A COMPARISON WITH OXYGEN-15

BY

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In lung disease and in heart disease there may be marked changes in the distribution of gas and blood in the lungs. These changes can be of diagnostic importance and can cause widespread change in bodily function. Often they can be detected by clinical examination with the help of radiography. But these methods alone are no substitute for more exact measurements, and they may be misleading and fail to detect gross changes in local blood or gas distribution. If the more complicated radiographic procedures (such as fluoroscopy, densitometry, tomography, and angiography) are used then these changes in distribution to different regions of the lungs can be detected more precisely, but the methods do not give a truly quantitative measure of local blood or gas flow.

The development of bronchospirrometry with the Carlens catheter allowed the comparative ventilation and blood flow to the two lungs to be measured. But—with the exception of using a triple-lumened catheter for isolating the right upper lobe (Mattson and Carlens, 1955)—no information about smaller units than a whole lung can be obtained, and unless the technique is in very skilled hands it is liable to error and can be distressing for the patient. By using a mass spectrometer for continuous gas analysis and with special sampling techniques during bronchoscopy, the ventilation to all the different lobes of the lung can be measured and some idea of their individual ventilation and blood-flow balance found (Hugh-Jones and West, 1960). But again

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