annual incidence of leprosy in this population of child contacts, in the absence of vaccination, was 4.62 per 1,000 children per year.

At the time when this estimate was made a total of 4,263 children (all in Grade O, I, or II initially) had been admitted to the unvaccinated group. According to the estimate 98 cases of leprosy would be expected to develop among them during a period of follow-up of five years. It was not known whether the population of child contacts was stationary, but it was suspected that, as a result of the treatment of known cases, the risk of contracting leprosy might be falling. In addition it was uncertain how effectively the participants could be traced for follow-up examinations, and whether it would be possible to continue these for as long as five years. In the circumstances it was safer to assume that perhaps only about half of the above total of 98 cases would develop and be detected in the course of the trial. If, say, 50 cases were found in the unvaccinated group, then it would not be permissible to claim a clear benefit from B.C.G. vaccination unless 25 or fewer cases were found in a randomly allocated vaccinated group of equal size (any lesser difference could be attributed to chance). Since it was important to be able to detect a reduction in leprosy incidence due to B.C.G.

vaccination, if it occurred, which was less than 50%, it was decided to increase the number of participants in the trial, and the intake was continued.

The final total of children in the unvaccinated group (Grade O–II) was 8,152. According to the same estimate of incidence a total of 75 cases of leprosy would have been expected to develop among these children during an average period of follow-up of two years. This may be compared with the total of 77 cases actually found in this group during the period of the first follow-up (the other 12 of the 89 cases shown in Tables IV and V had suspicious lesions which were not confirmed as leprosy until the second follow-up). Because of the various uncertainties and assumptions associated with the incidence estimate, it is clear that the agreement with reality is very much closer than could reasonably have been expected. It suggests, however, that the approach described in this appendix was not unrealistic, and represented a useful method of assessing when the intake to a trial of a prophylactic measure for a chronic disease was sufficiently large, from information obtained in the course of the intake. The approach has been placed on record in the hope that it may be useful to other workers in similar circumstances.

Hypertension and Cerebral Infarction

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Cerebrovascular disease provides many problems, but none is more puzzling than the reversal in the incidence of cerebral infarction and cerebral haemorrhage during the past four decades. Thirty years ago cerebral haemorrhage caused death in three times the number of cases as did cerebral infarction; to-day the latter is in excess of the former. This change has been brought about by a slight fall in the incidence of cerebral haemorrhage and a steep rise in that of cerebral infarction. The immediate explanation that springs to mind is that there has been a change in the fashion of death certification. This explanation is not tenable, however, for Yates (1964) has shown the same reversal to be present in a large series of cases proved at necropsy.

An alternative explanation for this phenomenon is that many hypertensive patients who would formerly have died from cerebral haemorrhage have been prevented from doing so by hypotensive therapy; these patients may have survived only to become the victims of cerebral infarction. Leishman (1963) has indeed provided evidence that hypotensive therapy reduces the mortality from an early stroke due to cerebral haemorrhage but has little influence upon the long-term risk of dying from a stroke associated with the progressive development of atherosclerosis. On the other hand, both Hodge, McQueen, and Smirk (1961) and Marshall (1964) have found that hypotensive therapy reduces the incidence of all types of stroke in hypertensive patients.

The elucidation of this problem is hampered by the considerable gaps in our knowledge of the causes of cerebral infarction. The widespread use of the term "cerebral thrombosis" to describe the clinical picture commonly associated with the pathological lesion of infarction reflects this, for as long ago as 1951 Hicks and Warren pointed out that it is uncommon to find evidence of arterial thrombosis in cases of cerebral infarction, an observation which has been repeatedly confirmed.

Alternative explanations for cerebral infarctions have therefore been advanced; these include occlusion by emboli which have subsequently fragmented, arterial spasm, the failure of collateral supply because of systemic hypotension (Denny-Brown and Meyer, 1957), and stenosis or occlusion of the carotid and vertebral arteries in the neck by atheroma (Hutchinson and Yates, 1957).

The last of these proposed causes of cerebral infarction raises further complex issues. Brice, Dowsett, and Lowe (1964) have shown that a stenosis of the internal carotid artery must reduce the lumen to 2 square millimetres before there is a significant effect upon blood flow. Most stenoses are not of this degree of severity. On the other hand, interference with blood flow may not be the only means by which a stenosis of the carotico-vertebral system produces a cerebral infarction. Gunning, Pickering, Robb Smith, and Ross Russell (1964) have produced good evidence that emboli formed on atheromatous plaques in the neck arteries may be responsible for such lesions. The incrimination of atheromatous lesions of the neck arteries in the causation of cerebral infarction seems possible therefore on two grounds: the stenosis may be sufficiently severe to interfere with blood flow, or it may provide a site for the formation of emboli; it may, of course, do both.

There is, however, a further aspect of carotico-vertebral stenosis which relates to the starting point of this discussion—namely, the reversal in the incidence of cerebral haemorrhage and cerebral infarction during recent decades. Schwartz and Mitchell (1961) have shown that there is an age-dependent factor involved in the causation of strokes which is not related to the state of the arteries in the neck. That this factor may be hypertension is suggested by the necropsy-controlled study of Low-Beer and Phear (1961), in which it was established that patients who die from cerebral infarction have on average a higher blood-pressure than the normal population of the same age and than patients with myocardial infarction.

These various strands of evidence suggest that among the several factors contributing to the genesis of cerebral infarction hypertension holds an important place. It has always been

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recognized that although the correlation between cerebral infarction and hypertension is by no means complete an interdependence between the two is undoubtedly present. The nature of the relationship has frequently been in dispute but few would deny that it exists. The purpose of the present study was to throw further light upon this relationship by examining the characteristics of a series of cases diagnosed clinically as suffering from cerebral infarction after they had been separated according to the height of the blood-pressure. The results are presented here.

Material

In a personal series of 700 cases of cerebrovascular disease there were 134 aged 55 years or less who had sustained what was diagnosed on clinical grounds to have been a cerebral infarction. A cerebrovascular incident was considered to have been due to cerebral infarction if the neurological deficit lasted more than 24 hours, there was no evidence of a source of emboli, and the cerebrospinal fluid was clear and colourless and not under raised pressure. This method of selection will admit occasional cases of intracerebral haemorrhage (McKissock, Richardson, and Walsh, 1959), but in the present state of knowledge this difficulty cannot be avoided.

The study was restricted to patients of 55 years and under, in order to give greater sharpness to clinical patterns which might emerge. Distinctions between the clinical picture of cerebral infarction due to one cause as against that due to another might well be blurred in older patients because of the simultaneous presence of several of these causes.

The patients were divided into two groups in accordance with the diastolic blood-pressure at the time of their admission with the last stroke. Seventy-one had a diastolic blood-pressure below 110 mm. Hg and will be referred to as the normotensive group, and 63 had a pressure of 110 mm. Hg or above and will be called the hypertensive group. It must be stressed that a sustained diastolic blood-pressure of 105 mm. Hg is not normal; the term normotensive is used solely for reasons of convenience. In only four patients did the blood-pressure reading on admission to hospital differ markedly from subsequent readings, being lower because of complicating factors. This coincides with the experience of Low-Beer and Phear (1961), who found that the blood-pressure at the time of the stroke did not differ significantly from the habitual blood-pressure of the patient except when complicating factors such as post-operative shock, haemorrhage, dehydration, heart failure, myocardial infarction, or hypotensive therapy were present. The four patients have been classified, in accordance with their habitual readings, in the hypertensive group.

The division of patients according to whether or not their diastolic blood-pressure falls below 110 mm. Hg is arbitrary. It has, however, been found to be a satisfactory dividing line in the past, and the continued use of this classification facilitates comparison with previous studies (Hill, Marshall, and Shaw, 1960, 1962). Moreover, its value has recently been confirmed in the study of Ross Russell (1963), who, using an identical method of selecting patients, found a specific cerebrovascular lesion (microaneurysms) in 94% of the hypertensive group but in only 26% of the normotensive group, substantive evidence that can rarely be offered to support any method of separating normotensive and hypertensive patients.

Results

The age and sex distribution of the patients in both normotensive and hypertensive groups is shown in Table I.

The distribution of the blood-pressure in the whole series in relation to that of the normal population of the same age and sex was first examined. This was done by subtracting from

the patient's blood-pressure the mean blood-pressure of the normal population of the same age and sex as given by Hamilton, Pickering, Roberts, and Sowry (1954) and dividing the result by the standard deviation of that mean. The frequency distribution of these results is given in the Fig. This shows that only a minority of patients had a normal blood-pressure; the remainder had raised blood-pressure to very varied extents.

TABLE I.—Age and Sex Distribution of the Patients

Age (Years)	Normotensive Group			Hypertensive Group		
	Males	Females	Total	Males	Females	Total
26-30	—	1	1	—	—	—
31-35	1	2	3	1	1	2
36-40	2	2	4	6	—	6
41-45	8	5	13	4	4	8
46-50	13	10	23	14	6	20
51-55	16	11	27	14	13	27
Total	40	31	71	39	24	63

The patients were then divided into the arbitrarily named normotensive and hypertensive groups. The distribution between the two groups of features commonly associated with hypertension—namely, changes in the fundi, electrocardiographic evidence of left ventricular hypertrophy or strain, and radiographic evidence of cardiac enlargement—is shown in Table II. Five of the patients in the hypertensive group had evidence of malignant hypertension with papilloedema. One of these had a blood urea of 78 mg. per 100 ml.; in the remaining four it was below 60 mg. per 100 ml. There were two diabetics in each group.

TABLE II.—Distribution of Fundal Changes, Electrocardiographic and Radiological Abnormalities

	Normotensive Group			Hypertensive Group		
	Males	Females	Total	Males	Females	Total
Fundi						
Normal ..	30	28	58	13	5	18
Grade I ..	8	0	8	9	7	16
" II ..	2	3	5	11	9	20
" III ..	0	0	0	2	2	4
" IV ..	0	0	0	4	1	5
E.C.G.						
Normal ..	18	9	27	7	5	12
Left ventricular hypertrophy or strain ..	4	1	5	22	12	34
Radiograph						
Normal ..	28	20	48	24	12	36
Cardiac enlargement	6	2	8	11	10	21

History of Previous Strokes

There was a history of a previous stroke prior to the time at which the patient came under observation in 26 patients.

Nine of these occurred among the 71 normotensive patients, making a total of 80 infarcts; and 17 among the 63 hypertensive patients, giving the same total of 80 infarcts. This difference falls just short of the 5% level of significance (χ^2 test).

Transient Ischaemic Attacks Before Onset

Episodes of neurological disturbance lasting less than 24 hours, commonly referred to as transient ischaemic attacks (T.I.A.s), occurred before 19 of the 75 infarcts about which there was information on this point in the normotensive group, and before 14 of 69 infarcts in the hypertensive group. The difference is not significant.

Mode of Onset

In the normotensive group 34 of the 64 patients for whom the information was available were engaged in activity at the time of onset of their stroke. In the hypertensive group 34 out of 56 patients were similarly active. Although strokes occurred slightly more frequently in the hypertensive group during activity, the difference is not significant. Forty-seven of the strokes in the normotensive group developed suddenly and 28 had a gradual onset; in the hypertensive group the figures were 33 and 36 respectively. Again the difference is not significant.

The two groups were also examined for the incidence of headaches, convulsions, unconsciousness, and vomiting. Convulsions did not occur in either group. In the normotensive group 25 had headache at the onset, 19 vomited, and 10 became unconscious; in the hypertensive group the figures were 19, 12, and 6 respectively, the differences not being significant. Thus the features surrounding the onset of the stroke did not differ materially between the two groups.

Clinical Features

There was no difference between the groups vis-à-vis the site of the lesion, 73% of the lesions in both groups being diagnosed as sited in the cerebral hemispheres, with an equal distribution between the dominant and non-dominant hemispheres.

The incidence of dysphasia in the dominant hemisphere lesions in the two groups was, however, strikingly different, this sign being present in 23 of 28 lesions in the normotensive group as against 15 of the 29 in the hypertensive group; this difference is significant at the 5% level (χ^2 test).

The severity of the stroke in terms of the immediate disability was likewise the same in the two groups, but the degree of recovery was very different. In the normotensive group 21% of the 67 survivors showed little or no recovery as against only 6% of the 60 survivors in the hypertensive group. This difference is also significant at the 5% level.

Electroencephalography

Electroencephalography was performed on 85 of the patients during the acute stage. The results are given in Table III, which shows that a normal E.E.G. occurred much more commonly in the hypertensive group than in the normotensive

TABLE III.—*Electroencephalographic Findings*

E.E.G.	Normotensive Group	Hypertensive Group
Normal	6 (14.5%)	12 (27.3%)
Bilateral abnormalities without asymmetry	10 (24.5%)	12 (27.3%)
Mild asymmetry	9 (22%)	12 (27.3%)
Marked "	16 (39%)	8 (18%)
Total	41	44

group, the difference being largely due to the preponderance of cases showing marked asymmetry in the normotensive group.

Angiography

Forty-seven patients in the normotensive group and 30 in the hypertensive group were examined by means of angiography, 81 extracranial vessels being outlined in the former group and 50 in the latter. The lesions demonstrated were classified as occlusion or stenosis, no attempt being made to subdivide the latter according to the degree of stenosis.

The results are given in Table IV. This shows a clear difference between the two groups, 22 of the 81 extracranial arteries examined in the normotensive group being abnormal as against 3 out of 50 in the hypertensive group. A similar difference was found with regard to the intracranial arteries. In terms of patients, 20 out of 47 in the normotensive group had extracranial lesions against 3 of the 30 patients in the hypertensive group. These differences are significant at the 1% level (χ^2 test).

TABLE IV.—*Results of Arteriography*

	Normotensive Group	Hypertensive Group
No. of patients examined	47	30
" " extracranial arteries visualized	81	50
Normal	59	47
Occluded	14	—
Stenosed	8	3
Intracranial arteries occluded	11	1
" " stenosed	6	1

Serum Cholesterol

The mean serum cholesterol was 228.8 mg. per 100 ml. in the normotensive group and 209.8 mg. per 100 ml. in the hypertensive group, this difference falling just short of the 5% level of significance.

Necropsy Findings

In the normotensive group there were four deaths in the acute stage, three necropsies being obtained (Table V). In the hypertensive group there were three deaths in the acute stage with necropsy in each case. In addition, necropsies were obtained on three patients in the hypertensive group who died later, one from myocardial infarction, one from ventricular fibrillation, and the third from bronchopneumonia. Two of the patients in the hypertensive group were found to have an intracerebral haemorrhage which had been misdiagnosed clinically as an infarction. The remaining four cases in the hypertensive group had small cystic softenings deeply situated in the cerebral hemisphere. In contrast, all three cases in the normotensive group had large infarctions in the hemisphere.

TABLE V.—*Necropsy Findings*

Normotensive Group			
C.V. No.	Sex	Age	Result
195	F	37	Large infarction in middle cerebral territory
344	F	41	Massive infarction in anterior and middle cerebral territories
665	M	52	Massive infarction right hemisphere
Hypertensive Group			
208	F	52	Intracerebral haemorrhage
396	M	44	Softening 1.2 cm. $\times$ 0.5 $\times$ 1.5 cm. in region of internal capsule
213	M	39	Intracerebral haemorrhage
Died Later			
91	F	42	Small cystic softenings in central white matter
270	M	48	Macroscopic changes in region of internal capsule
132	F	44	Small area of softening in region of internal capsule

Discussion

Before discussing the differences between the two groups we should note that the distribution of blood-pressure in the whole series was higher than that in the normal population as given by Hamilton, Pickering, Roberts, and Sowry (1954). This confirms the findings of Low-Beer and Phear (1961) in their necropsy-controlled series and conflicts with the widespread belief that cerebral infarction is commonly associated with low blood-pressure. This confusion may well have arisen from the failure to distinguish between those patients in whom cerebral infarction occurs as an isolated event and those in whom it occurs in association with such conditions as gastro-intestinal haemorrhage and myocardial infarction, which produce a fall of blood-pressure. In the former group the blood-pressure at the onset of the stroke does not differ from the habitual blood-pressure, and is on average higher than in the normal population. In the latter group low blood-pressure readings are commonly found. It is essential to distinguish these two groups among the general mass of cases of cerebral infarction if our knowledge of the causation of strokes is to advance. The importance of this distinction from the therapeutic standpoint needs no emphasis.

Within the group of cerebral infarctions unassociated with any complicating condition it is possible to make a further distinction, as the present study has shown. This distinction is based primarily upon the level to which the blood-pressure is raised, the dividing line in the present series being at 110 mm. Hg diastolic. Although there is nothing in the mode of onset to separate these two groups, there are distinguishing features to be found subsequently. In the so-called normotensive group the frequency of marked asymmetry in the electroencephalogram, the high incidence of dysphasia when the lesion is in the dominant hemisphere, and the proportion of patients who show little recovery all suggest the presence of a large lesion of cortical or subcortical distribution. In the hypertensive group, on the other hand, the frequency with which either a normal E.E.G. or one showing bilateral abnormalities is found, the low incidence of dysphasia in the dominant hemisphere lesions, and the high degree of recovery favour small deeply situated lesions. These differences in the clinical picture are associated with a high incidence at angiography of stenotic or occlusive lesions of the extracranial or intracranial arteries in the normotensive group and a virtual absence of these lesions from the hypertensive group.

The number of necropsies was too small to enable a firm correlation to be established between the clinical features and the pathological findings in these two groups. The evidence, in so far as it goes, is, however, extremely encouraging. Thus, of the three patients in the normotensive group who came to necropsy, one had a large infarct in the territory of the middle cerebral artery and the second a massive infarct involving the territory of both the anterior and middle cerebral artery, and the third a massive hemisphere infarct associated with occlusion of the internal carotid artery. In the hypertensive group two patients had intracerebral haemorrhages misdiagnosed as infarcts. This finding emphasizes once again how difficult it is to be certain of the pathological cause of a stroke. This point has been made in the past (Dalsgaard-Nielsen, 1956) but is worthy of stress, for as long as this uncertainty in diagnosis persists, so long will therapeutic advances be handicapped.

Four of the patients in the hypertensive group (three of whom died later from other causes) had small cystic softenings deeply situated in the region of the internal capsule. This type of lesion accords well with the clinical picture described. Lesions of this kind have previously been described in association with strokes showing a considerable degree of recovery. Hughes, Dodgson, and MacLennan (1954) studied a series of 51 hypertensive patients who presented primarily with dementia. The evolution of the dementia had, however, been preceded, or accompanied, by frequent strokes, many of which

showed considerable recovery. Necropsies were available on 15 patients, who showed multiple small ischaemic softenings in the caudate nucleus, the putamen, and the thalamus in the territory of the perforating arteries. More recently Ross Russell (1963) has demonstrated a high incidence of miliary aneurysms on the cerebral arteries of hypertensive subjects. The normotensive subjects he examined had a much lower incidence. These aneurysms were found most commonly upon the small perforating arteries and also showed a tendency to thrombose, a process which sometimes extended to affect the parent vessel with the production of a small area of ischaemic softening in the distribution of the vessel. There was often no evidence of present or past haemorrhage in the area of the aneurysm.

It seems not unreasonable to suggest, therefore, that a stroke in a subject with a high diastolic pressure in association with a clinical picture suggestive of a small, deeply placed lesion in the cerebral hemisphere and unassociated with angiographic evidence of extracranial or intracranial stenosis or occlusion may well be due to the development of one or more of these areas of softening in relation to a miliary aneurysm on the perforating arteries, whereas the stroke in the subject whose blood-pressure, though raised, does not exceed 110 mm. Hg diastolic and who shows signs of a large hemisphere lesion and angiographic evidence of stenosis or occlusion of extracranial vessels is likely to be due to a large cortical and subcortical infarct.

The implications of this distinction as far as the therapy of the acute stage is concerned are not immediately clear. Suffice it to say that therapeutic advance can only be based upon accurate diagnosis of the lesion to be treated and sound understanding of its pathogenesis. Every clarification of the obscurities which at present exist in relation to the clinical syndrome we call "a stroke" will therefore ultimately contribute to the amelioration of this frequent and increasing affliction.

Summary

One hundred and thirty-four patients with a clinical diagnosis of cerebral infarction were studied; 71 had a diastolic blood-pressure below 110 mm. Hg and 63 a diastolic pressure of 110 mm. Hg or above. The former group presented a picture of a large cortical and subcortical lesion and showed a high incidence of stenotic and occlusive lesions at angiography; the degree of recovery was poor. The latter group presented a picture of a small deeply situated lesion. There was a low incidence of arteriographic lesions and the patients were left with little disability. The importance of distinguishing between these two groups is stressed.

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