# Cerebrovascular Diseases in West Central India

## A Report on Angiographic Findings from a Prospective Study

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**Summary: Cerebral angiographic findings in ischaemic stroke are described and discussed in detail. Though the Indian patients studied had altogether different social customs, living standards, and dietary habits from Western people, the relative incidence of various cerebral vascular lesions did not differ significantly. Irrespective of the poor nutritional status of the patients, thrombosis associated with atherosclerosis was chiefly responsible for a non-embolic cerebral infarction. Atherothrombosis in the young normotensive persons not showing any evidence of arteritis, diabetes mellitus, or hypercholesterolaemia was also identified.**

**The grave risks involved in cerebral angiography in cases of acute stroke are re-emphasized.**

**As to prognosis, the nutritional status, the type and territory of an ictal lesion, and the blood levels of sugar and cholesterol had no significant influence on the immediate survival after a non-embolic cerebral infarction. However, a significantly greater number of deaths were encountered in the hypertensive patients. Female patients and patients with a large cerebral infarction had a poor prognosis.**

### Introduction

The use of hospital material in epidemiology has limitations as well as potential applications (Masi, 1965). Nevertheless, in any region virtually devoid of reliable data—for example, strokes in India—a clinicopathological study can provide basic information. To fulfil this objective quickly attempts were first made to obtain a retrospective analysis of the stroke material derived from many hospitals in Bombay, but meaningful and valid information was not available from the routine hospital records containing unstandardized, incomplete, and unverifiable data. It was therefore considered desirable, as a first step, to initiate a prospective clinicopathological and cerebral angiographic study of all cases of acute stroke coming to one of the large general hospitals in Bombay. This paper is a preliminary report on angiographic findings based on this study.

### The Study

The city of Bombay (19° N, 73° E), with its population of 4,600,000 people, is one of the largest cities in India. All shades of Indian people with differing social customs and dietary habits reside here, but a major and significant proportion of the population come from the neighbouring regions of Maharashtra, Gujarat, and Goa.

The prospective study was undertaken at the B. Y. L. Nair Charitable Hospital, where on an average 22,000 patients are admitted every year, and where about 45% of all deaths are routinely necropsied. The hospital has a 24-hour emergency service, and admits acutely ill persons (including those with acute stroke) for free medical care at any hour and regardless of the hospital's total bed accommodation, or the age, community, and socio-economic status of the patient. The neighbouring population served consists mainly of labourers, mill and factory workers, and clerical staff of the lower economic groups.

A stroke (or cerebrovascular disease) was defined as a focal neurological deficit of sudden onset resulting from a vascular lesion other than trauma. A successful pilot study had preceded the proposed study. During the subsequent seven months of prospective observations 127 consecutive patients who had had a recent stroke (three weeks or less) were admitted to the 84-bed medical service. After all possible information on the clinical event of the ictus had been obtained, a complete physical examination was carried out personally and serially on every patient. From the criteria given in *Neurology* (1958) and from further clinical investigations 105 patients were diagnosed as suffering from ischaemic cerebrovascular disease and 22 had haemorrhagic cerebrovascular disease.

Apart from routine clinical investigations (haemogram, urinalysis, blood levels of sugar, cholesterol, and urea nitrogen, electrocardiography, serological tests for syphilis, cerebrospinal fluid examination, and other similar tests), 112 of the 127 patients were submitted to percutaneous cerebral angiography under local anaesthesia. The choice of the vessel to be studied first was based on the anatomy of the neurovascular syndrome (Fisher *et al.*, 1962).

Bilateral brachial-basilar angiography (Chase *et al.*, 1963), and a left-carotid study were routinely carried out in patients with a non-embolic cerebral infarction. The origins of brachiocephalic trunks were routinely visualized, and, when indicated, arch aortography was also performed. Persistent non-filling of an artery or its normal branch, accompanied by an avascular zone in the territory of its supply, with or without retrograde collateral circulation in that area, was taken as evidence of a complete occlusion. When an arterial segment was narrowed by 50% or more of its expected average lumen found patent proximally or distally it was called a partial occlusion. When no significant occlusive abnormality was detected it was termed a "normal" or a "negative" angiogram. Ectasia, kinking, tortuosity, focal or generalized luminal irregularities, and the speed of angiographic circulation were also recorded. Despite the progressive nature of some of the strokes, any major or minor neurological or systemic worsening within 24 hours of an angiographic procedure was considered an angiographic complication.

In view of the high natural mortality in embolic cerebral infarction (Carter, 1957), angiography was performed only in the ictal territory; another angiogram in that territory was also possible in some cases (Dalal *et al.*, 1965b). Angiography, however, was not performed in 6 of the 22 haemorrhagic and in 9 of the 105 ischaemic cerebrovascular disease subjects; 12 of them had died soon after admission to hospital, but necropsy confirmation of the diagnosis was available in 11; the other three recovered.

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Necropsy, with complete removal of major extracranial vessels, was possible in 45 of the 52 fatal cases, and after fixation a careful neurovascular and neuropathological examination was carried out.

## Results

General data on the stroke lesions are given in Table I. The age and sex distribution is analysed in Table II. The number and types of diagnostic angiographs are given in Table III, and the frequency of the occlusive arterial lesions found at angiography and necropsy is shown in Tables IV and V. The angiographic complications are summarized in Table VI.

TABLE I.—*General Data on 127 Unselected and Consecutive Cases Having a Recent Stroke (A Seven-month Prospective Study)*

| Final Diagnosis | No. of Cases | No. of Deaths | No. of Necropsies |
|---|---|---|---|
| Ischaemic cerebrovascular disease: | | | |
| Cerebral thrombosis | 66 | 20 (30·3%) | 17 |
| Cerebral embolism | 26 | 14 (53·8%) | 12 |
| Cerebral thorem* | 13 | 0 | 0 |
| Total | 105 (82·7%) | 34 (32·3%) | 29 |
| Haemorrhagic cerebrovascular disease: | | | |
| Hypertensive, spontaneous | 11 | 10 | 9 |
| Ruptured aneurysms | 4 | 3 | 2 |
| Ruptured angioma | 1 | 0 | 0 |
| Purpura, leukaemia, lymphoma | 3 | 3 | 3 |
| Massive tumour bleed | 2 | 2 | 2 |
| Undiagnosed source | 1 | 0 | 0 |
| Total | 22 (17·3%) | 18 (81·8%) | 16 |
| Grand total | 127 | 52 (40·9%) | 45 (86·5%) |

During this seven-month period 13,627 patients were admitted to the B.Y.L. Nair Charitable Hospital. Of the 2,789 medical cases (20·4%), 18 had a previous history of " stroke " in addition to the 127 new cases. Two patients who had had a recent stroke left the hospital immediately after their admission, and necropsy in a case of bacterial endocarditis showed multiple visceral and cerebral infarctions in addition; these three cases are not included in the stroke analysis here. Also excluded from this report are 40 cases of traumatic intracranial haemorrhage confirmed at necropsy.

* Thorem denotes *th*rombosis *or em*bolism.

## Ischaemic Cerebrovascular Disease

### Cerebral Thrombosis

Sixty-six ischaemic strokes were from a non-embolic cerebral infarction. Forty-seven of the patients were admitted to hospital within four days and 62 within two weeks of the ictus. Twenty subjects were aged 50 or below, whereas 46 were above that age ; the mean age for the group was 56.44 years. There was no significant difference in the frequency of cerebral thrombosis in various religious groups (Table II).

Thirty-four subjects were angiographed within four days, 50 within seven days, and 57 within two weeks of the ictus. Partial or total occlusion of major extracranial vessels in the

TABLE III.—*Number and Types of Angiograms of Patients, Mean Number of Angiograms, and Case Fatality Rate for Patients by Diagnosis*

| Final Diagnosis | Total No. of Cases | No. having Angiograms | No. of Angiograms | | | | Deaths in Patients Angiographed | |
|---|---|---|---|---|---|---|---|---|
| | | | Carotid | Brachial | Total | Mean No. per Patient | No. | % |
| Cerebral thrombosis | 66 | 64 | 123* | 93 | 216 | 3·3 | 18 | 28·1 |
| Cerebral embolism | 26 | 20 | 41 | 4 | 45 | 2·2 | 10 | 50·0 |
| Cerebral thorem | 13 | 12 | 31 | 6 | 37 | 3·1 | 0 | 0·0 |
| Total | 105† | 96 | 195 | 103 | 298 | 3·1 | 28 | 29·2 |

* 35 studies were retrograde right carotid injections to visualize innominate-vertebro-basilar circulation on that side.

† 6 of the 9 patients not examined by arteriography died, necropsy verification of the diagnosis being available in 5; the other 3 are alive and well. (For details see text.)

TABLE IV.—*Final Summary* of Arterial Lesions in the Ictal Territory of 101 Consecutive Patients with a Recent Stroke.*

| Category of Lesions | Sex | | Age in Years | | | | | | | Religion | | | Total Cases |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | 11–20 | 21–30 | 31–40 | 41–50 | 51–60 | 61–70 | 71–85 | H | M | C | |
| Cerebral thrombosis | 51 | 15 | 0 | 2 | 6 | 12 | 23 | 17 | 6 | 43 | 13 | 10 | 66 |
| Cerebral embolism | 13 | 13 | 6 | 3 | 2 | 4 | 6 | 4 | 1 | 17 | 3 | 6 | 26 |
| Cerebral thorem | 7 | 6 | 0 | 1 | 2 | 0 | 8 | 1 | 1 | 12 | 1 | 0 | 13 |
| Total | 71 | 34 | 6 | 6 | 10 | 16 | 37 | 22 | 8 | 72 | 17 | 16 | 105 |
| Haemorrhagic stroke | 14 | 8 | 3 | 1 | 4 | 4 | 7 | 2 | ?1 | 12 | 4 | 6 | 22 |
| Total cases | 85 | 42 | 9 | 7 | 14 | 20 | 44 | 24 | 9 | 84 | 21 | 22 | 127 |

H = Hindus. M = Muslims. C = Christians and others.

TABLE IV.—*Final Summary* of Arterial Lesions in the Ictal Territory in 101 Consecutive Cases of Ischaemic Cerebrovascular Disease*

| Territory of Lesion | Cerebral Thrombosis | | Cerebral Embolism | | Cerebral " Thorem " | | Total Cases |
|---|---|---|---|---|---|---|---|
| | No. of Lesions | No. of Cases | No. of Lesions | No. of Cases | No. of Lesions | No. of Cases | |
| " Normal " angiogram | — | 27 (40·9%) | — | 3 (13·0%) | — | 3 | 33 |
| Intracranial lesions | | (19·7%) | | (65·2%) | | | |
| Anterior cerebral: complete occl. | 2 (1) | 2 | 3†+0 | 0 | 0 | 0 | 2 |
| Middle cerebral: | | | | | | | |
| Partial occl. | 2†+5 (3) | 5 | — | — | — | — | 26 |
| Complete occl. | 5†+1 (2) | 1 | 14 | 14 | 2†+6 | 6 | |
| Posterior cerebral: complete occl. | 1†+3 (2) | 3 | 1 | 1 | — | — | 4 |
| Basilar: | | | | | | | |
| Partial occl. | 1 | 1 | — | — | — | — | 2 |
| Complete occl. | 1 | 1 | — | — | — | — | |
| Extracranial lesions | | (39·4%) | | (21·8%) | | | |
| Innominate: | | | | | | | |
| Partial occl. | 1 (1) | 1 | — | — | — | — | 2 |
| Complete occl. | 1 | 1 | — | — | — | — | |
| Common carotid: | | | | | | | |
| Partial occl. | 1 (1) | 1 | — | — | — | — | 2 |
| Complete occl. | 1 | 1 | — | — | — | — | |
| Internal carotid: | | | | | | | |
| Partial occl. | 1†+9 (8) | 9 | — | — | 2 | 2 | 25 |
| Complete occl. | 1†+8 (3) | 8 | 5 | 5 | 1 | 1 | |
| Subclavian: | | | | | | | |
| Partial occl. | 0 (1) | — | — | — | — | — | — |
| Complete occl. | 0 (3) | — | — | — | — | — | |
| Vertebral: | | | | | | | |
| Partial occl. | 1†+4 (2) | 4 | — | — | — (2) | — | 5 |
| Complete occl. | 1 (2) | 1 | — | — | — | — | |
| Total | 50 (29) | 66 | 23 | 23 | 11 (2) | 12 | 101 |
| No information | — | — | — | 3 | — | 1 | 4 |

Occl. = Occlusive lesion.

* Based on angiographic and necropsy findings.

† Lesions found in continuation or association of a proximal lesion responsible for the ictus. Figures in parentheses denote lesions in non-ictal territory only

TABLE V.—*Final Summary of All Arterial Lesions in* 101 *Consecutive Patients with Recent Ischaemic Cerebrovascular Disease*

| Category of Lesion | Cerebral Thrombosis | | Cerebral Embolism | | Cerebral Thorem | | Total Cases |
|---|---|---|---|---|---|---|---|
| | No. of Lesions | No. of Cases | No. of Lesions | No. of Cases | No. of Lesions | No. of Cases | |
| "Normal" angiograms .. .. | — | 18 (27·3%) | — | 3 (13·0%) | — | 2 (16·7%) | 23 (22·8%) |
| Intracranial lesions .. .. .. | 29 | 15 (22·7%) | 18 | 15 (65·2%) | 8 | 6 (50·0%) | 36 (35·6%) |
| Extracranial lesions .. .. .. | 50 | 33 (50·0%) | 5 | 5 (21·8%) | 5 | 4 (33·3%) | 42 (41·6%) |
| Total .. .. | 79 | 66 | 23 | 23 | 13 | 12 | 101 |

All arterial lesions include stenoses and occlusions in the ictal and non-ictal territory.

ictal territory was seen in 26, and in only 13 was an occlusive lesion noted in the intracranial vessels. In all, 50 occlusive lesions were found in the ictal territory in these 39 cases; in 15 of them 19 additional lesions were also detected in the non-ictal territory. In the remaining 27 cases no major angiographic abnormality was noted in the ictal territory, but in nine of them 10 occlusive lesions were present in the non-ictal territory (Tables IV and V).

In 17 randomly selected subjects with an occlusive lesion in the carotid middle cerebral axis another angiographic study later showed no significant change in that lesion; the data in four additional cases were incomplete. Thus spontaneous clot lysis, so frequently observed in cerebral embolism (Dalal *et al.*, 1965a), was not encountered in cerebral thrombosis.

The occurrence of thrombotic cerebral infarction in nine young normotensive subjects not showing any evidence of arteritis, diabetes mellitus, hypercholesterolaemia, or cardiovascular diseases was of great interest, since in six of them angiographic evidence of atherosclerosis was present. Our findings regarding stroke in young adults are discussed elsewhere (Dalal, 1968); other findings are being reported separately.

## Immediate Survival after Cerebral Thrombosis

Twenty of the 66 cases in this group died during the acute phase of the illness. Of 64 submitted to angiography 18 died,

TABLE VI.—*Angiographic Complications in Ischaemic Cerebrovascular Disease* (195 *Carotid and* 103 *Brachial-basilar Studies in* 96 *Cases*)

| | No. of Complications* | No. of Cases | Procedure | |
|---|---|---|---|---|
| | | | No. | Type |
| Focal or generalized seizures .. .. | 5 | 5 | 5 | Carotid |
| Focal seizures with transient increase in neuro-deficit .. .. .. | 2 | 2 | 2 | Carotid |
| Increase in neuro-deficit: | | | | |
| Transient .. .. .. | 1 | 1 | 1 | Carotid |
| | 1† | 1 | 1 | Brachial |
| Permanent .. .. .. | 2 | 2 | 2 | Carotid |
| Death within 24 hours of angiography‡ | 1 | 1 | 2 | Carotid |
| Local complications: | | | | |
| Thrombophlebitis .. .. .. | 1 | 1 | 1 | Brachial |
| Loss of arterial pulse .. .. | 1 | 1 | 1 | Brachial |
| Total .. .. .. | 14 | 14 | 15 | |

* Excluding pain and tenderness from local swelling as well as feeble pulse (temporary) after the procedure; local swelling (haematoma) in 5 carotid cases was big enough to cause watchful concern but resolved without causing any systemic or neurological worsening.

† This was one of the patient's typical episodes of transient cerebral ischaemia that occurred (? by chance) during the course of angiography.

‡ Death from pulmonary embolus within 24 hours of angiography without any increase in neuro-deficit.

the mean number of angiographs performed per patient being 3.3 (Table III). The influence of various prognostic factors on the immediate survival is analysed in Table VII. The most striking finding was a significantly high ($P<0.01$) number of deaths in hypertensive subjects. Hypertensive females also fared worse; 9 out of 12 died as compared with 8 out of 27 hypertensive males. Moreover, 19 of the 54 elderly subjects died as compared with only one of 12 young subjects; a rising trend in general mortality seen with advancing age was again significantly higher in the hypertensive group.

There was statistically no significant difference in the case fatality rates in those having hemispheral or brain-stem signs, but subjects suspected of having a large cerebral infarct had a poor prognosis; 7.6% of the normotensive subjects with a small infarct died as against 14.3% with a larger infarct, and in the hypertensive group 28.5% with a smaller infarct died as against 52.0% with a larger cerebral infarct.

The influence of a previous stroke on survival was also studied. Thirty-five of the 66 cases had a previous history of stroke—19 in the ictal territory (three died) and 16 in the non-ictal territory (eight died). In the normotensive group 1 out of 12 who had had previous lesion and 2 of 15 who had not had such a lesion died, as compared with 7 deaths among the 16 hypertensives without a previous stroke and 10 of the 23 with a recurrent stroke. Furthermore, in hypertensives with a recurrent stroke another lesion in the non-ictal territory proved more often fatal (63.6%) as compared with a similar lesion in the ictal territory (25.0%).

Among other prognostic factors studied, the nutritional status, the type of ictal onset and the territory of infarction, and the blood levels of cholesterol and sugar did not significantly influence the survival rate.

## Cerebral Embolism

Twenty-six ischaemic strokes were from embolic cerebral infarction. The strict criteria used in the clinical and necropsy diagnosis of embolic cerebral infarction, as well as the number and the types of lesion found by angiography, were discussed in detail in our earlier report (Dalal *et al.*, 1965b). Spontaneous lysis of the embolic plug was a frequent finding (Dalal *et al.*, 1965a, 1966).

TABLE VII.—*Analysis of Various Prognostic Factors in* 66 *Unselected Cases of Cerebral Thrombosis*

| Survival | Age in Years | | Sex | | Nutrition | | | Onset† | | | Angio. Lesion‡ (Cases) | | | B.P. | | Coronary Heart Disease | | Cholesterol | | Blood Sugar | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <46 | 46+ | M | F | Poor* | Average | Obese | TIA | TIE | AI | No | ICA | VB | High§ | Normal | Yes | No | >250 mg. | <250 mg. | High‖ | Normal |
| No. of Cases | 12 | 54 | 51 | 15 | 24 | 29 | 13 | 2 | 32 | 32 | 27 | 29 | 10 | 39 | 27 | 20 | 43 | 8 | 47 | 13 | 48 |
| Alive (46) .. | 11 | 35 | 40 | 6 | 18 | 20 | 8 | 2 | 23 | 21 | 22 | 18 | 6 | 22 | 24 | 11 | 33 | 5 | 38 | 8 | 33 |
| Died (20) .. | 1 | 19 | 11 | 9 | 6 | 9 | 5 | — | 9 | 11 | 5 | 11 | 4 | 17 | 3 | 9 | 10 | 3 | 9 | 5 | 15 |
| Tests of significance | N.S. | | P<0·01 | | N.S. | | | N.S. | | | N.S. | | | P<0·01 | | N.S. | | N.S. | | N.S | |

* Those below the lowest expected standard weight for their height, body-frame, and sex.

† TIA = Transient ischaemic attacks; TIE = thrombosis in evolution; AI = accomplished infarct.

‡ Angio Lesion: Occlusive lesion not visualized; ICA = lesion seen in carotid-middle-anterior cerebral territory; VB = lesion in the vertebral-basilar-posterior cerebral territory.

§ Persistent rise of diastolic reading above 90 mm. Hg and left ventricular hypertrophy on E.C.G.

‖ High = fasting venous blood sugar above 120 mg./100 ml. or a similar level 2 hours after a glucose load or an abnormal glucose tolerance curve (Folin and Wu method); normal = between 80 and 120 mg./100 ml.

N.S. = Not significant.

### Cerebral Thorem

Because of the rigid criteria used in the diagnosis of thrombosis and embolism, 37 of the 105 cases, to begin with, had remained unclassified as "thorem," or thromboembolism. However, with supplementary information on the clinical events of the ictus, further clinical events—for example, recurrence of transient symptoms in that territory, etc.—and biopsy of the lesion during surgical repair or at necropsy, 24 of these cases have since fulfilled most of the diagnostic criteria for thrombosis and are grouped under cerebral thrombosis. The remaining 13 cases, though satisfying some of the criteria for thrombosis, still remain unclassified as thorem; for example, in three cases of internal carotid thrombosis in the neck a "local embolism" to the distal middle cerebral branches appeared to be the most likely cause of the ictus.

In this group of seven men and six women the mean age of our patients was 53.0 years. One of these, a 54-year-old hypertensive and diabetic subject with ischaemic infarction in the basilar territory, refused permission for angiography and other tests. The other 12 had clinically a lesion in the carotid middle cerebral axis, and this was confirmed by angiography in nine; in the remaining three cases, where no major angiographic abnormality was noted, occlusive disease of the smaller blood vessels appeared most likely. The location and configuration of these angiographic lesions in nine subjects showed no change when compared with another angiogram obtained a few weeks later.

In this group one subject was obese, eight were averagely nourished, and four were undernourished. Of the nine hypertensive subjects two were diabetic in addition to two having hypercholesterolaemia; of the four normotensive subjects one was diabetic and one had a raised serum cholesterol level. All 13 are alive.

### Haemorrhagic Cerebrovascular Disease

In the hypertensive haemorrhage group there were seven men and four women; their average age was 55.7 years and the mean arterial blood pressure of the group was $135.7 \pm 13.8$ mm. Hg. The site of intracerebral haematoma was putaminal in seven, thalamic in two, pontine in one, and parietal white matter in one. Only one subject survived the ictus, giving a case fatality rate of 91%.

The non-hypertensive group consisted of seven men and four women, their average age being 35.8 years. In four cases a ruptured aneurysm (anterior communicating one, posterior communicating one, middle cerebral one, and basilar artery one) was responsible for a fresh haemorrhage, and in one case a middle cerebral angioma had bled recently. In five other cases there was evidence of severe blood dyscrasia in three, and in two massive bleeding within a tumour mass was apparent. In the remaining case, despite pancerebral angiography, the cause of bleeding was undetermined. Eight of these 11 subjects died; necropsy confirmation of the diagnosis was available in seven (Table I).

### Discussion

The present report deals only with some general observations on subjects who had had a recent stroke and came to a city hospital in Bombay, India. In this prospective study on consecutive cases there was, by intention or otherwise, no selection of patients in respect to age, sex, race, religion, socio-economic status, severity of the disease, or associated illness; nor was the policy of the administration restrictive in regard to admission of cases of acute stroke. It was our impression, however, that all subjects with transient symptoms and those dying quickly from a stroke were probably not reaching the hospital, and patients with better economic status (representing only a small fraction of the resident population in this area) were mostly seeking private medical care. These data, therefore, do not represent the epidemiology of strokes in sick persons in the community, nor do they denote the population at risk.

### Hospital Incidence

In our series 4.5% of all medical admissions and about 1% of all hospital cases were acute stroke (Table I). Such a low hospital incidence of strokes may to some extent be due to the short life-span of Indians in general; the average life-span of an Indian is reported to be under 50 years. Moreover, the mean age (56.44 years) of our patients with cerebral thrombosis was in no way different from that in countries in the West. It is possible, therefore, that with longevity increasing through the peak years of occurrence of stroke (55 to 65 years) the general incidence of strokes in Indians would rise further.

Of our cases, 82.7% had ischaemic disease and only 17.3% had a haemorrhagic lesion. This finding may be somewhat at variance with the expected hospital incidence of about 75% ischaemic and 25% haemorrhagic strokes. The fact that some of the stroke subjects died rapidly from intracranial bleeding and were not reaching the hospital may in part explain this difference. When judged by clinical findings alone, an ischaemic stroke is often indistinguishable from a haemorrhagic intracerebral lesion (Bull *et al.*, 1960; Silverstein, 1965a), and in many of our cases the diagnosis leading to admission was also in error. However, after examination of the cerebrospinal fluid and cerebral angiography, error in the final clinical diagnosis occurred only once. Furthermore, the final diagnosis was also verified by necropsy in 45 fatal cases. The possibility, therefore, that some of the survivors of hypertensive strokes (11 cases) in the ischaemic group who had shown a clear cerebrospinal fluid and a "normal" angiographic circulation in the ictal territory may have been examples of occult intracerebral haematoma is less likely but most difficult to refute, and can be verified (?) only by a later necropsy.

### "Negative" Angiogram in Ischaemic Stroke

The reported incidence of "negative" or "normal" angiograms in occlusive cerebrovascular disease has ranged from 19% (Newton *et al.*, 1964) to 51% (Silverstein, 1965b). With us, a normal angiogram in the ictal territory was obtained in 33 of the 101 (32.7%) cases in the ischaemic category.

In cerebral embolism the occluding plugs often migrated from their initial point of arrest and fragmented frequently, thereby restoring a normal angiographic circulation (Dalal *et al.*, 1965a, 1966); so that, late in the course of the disease, the number of normal-looking angiographs increased from an initial figure of 15% to 55% (Dalal et al., 1965b). We therefore believe that a negative angiogram in the ictal territory in cerebral embolism often denotes recanalization of the vessels in the zone of infarction resulting from migration or dissolution of a previously held up embolic plug (Dalal, 1967). On the other hand, immediate recanalization from lysis of a thrombotic plug was not observed in unequivocal cases of cerebral thrombosis. In the latter group, despite multiple angiograms with adequate visualization of the origins of all vessels in the ictal territory, a normal angiogram was obtained in 27 out of 66 (40.9%) cases; in five of them, coming to necropsy later, thrombotic occlusion of the smaller (penetrating) arteries, accompanied by an ischaemic infarction, was identified in each case. Thus a negative or normal angiogram in the ictal territory in non-embolic cerebral infarction is more suggestive of an occlusive disease in the blood vessels too small to be visualized by angiography.

Like Silverstein (1965b), we were unable to detect a statistically significant difference in the group characteristics (age, sex, previous stroke, hemispheral or brain-stem signs, hypertension, diabetes mellitus, heart disease, lesions by timings of

angiography, etc.) of those having a normal angiogram as against those having an abnormal angiogram.

## Extracranial Lesions in Ischaemic Stroke

In routine hospital necropsies the incidence of extracranial (carotid and non-carotid) obstructive arterial lesions, including complete occlusions and stenoses (more than 50% narrowing), has been in the vicinity of 40% (Martin *et al.*, 1960 ; Schwartz and Mitchell, 1961 ; Torvik and Jörgensen, 1964 ; Fisher *et al.*, 1965). A similar incidence, however, in selected necropsies with clinical findings suggestive of "cerebral ischaemia," was noted to be 58% (Yates and Hutchinson, 1961). On the other hand, in cases of cerebrovascular disease, where four-vessel angiography was performed, the incidence varied from 40 to 50% (Blaisdell *et al.*, 1962 ; Lindner *et al.*, 1962 ; Pribram, 1965), and the involvement of multiple vessels in the same subject was also a frequent finding (Bauer *et al.*, 1962 ; Newton *et al.*, 1964).

In 101 of our cases with an ischaemic stroke, where nearly complete information was available by angiography or necropsy in the ictal and non-ictal territory (Table V), 42 had significant stenoses and occlusions in the extracranial vessels ; in 66 cases of cerebral thrombosis, 33 (50%) had similar lesions. There was no significant difference in the frequency of these lesions in the malnourished and well-nourished subjects, nor was any correlation found with the level of serum cholesterol ; our patients were from lower economic groups, and the principal source of their nutrition was a vegetarian diet. Thus, in an ethnologically different group in the East having altogether different social customs and dietary habits, and irrespective of their nutritional status, the angiographic incidence of extracranial lesions associated with ischaemic stroke showed no significant difference from that seen in the West. These observations are gaining further support from another comparative study of cerebral atherosclerosis in consecutive and routine necropsies at this hospital and at another in Minnesota, U.S.A. Here a preliminary analysis has shown that despite obvious ethnologic, socio-economic, and nutritional differences in these two samples, the atherosclerotic process on the whole appeared more relative to the advancing age and was probably more severe in hypertensive subjects. Further analysis of a larger experience, however, is awaited.

It is noteworthy that in cases of cerebral thrombosis 39.4% had ictal lesions extracranially, and in only 19.7% were the obstructive lesions found in the intracranial vessels (Table IV) ; in cerebral embolism, on the other hand, only 21.8% had extracranial lesions as against 65.2% showing ictal lesions intracranially. Thus, in those series (for example, Riishede, 1957 ; McDowell *et al.*, 1959 ; Eiken, 1963) where the incidence of extracranial and of intracranial lesions in embolic and thrombotic cases have been given together, the general incidence would be lower for extracranial lesions and higher for intracranial lesions.

The precise role of extracranial obstructive lesions alone in the pathogenesis of cerebral infarction found at a distance has been much debated. In our 26 cases showing a significant extracranial lesion proximal to a presumed cerebral infarct (confirmed by necropsy in 11), a similar significant obstructive lesion was also present on the opposite side in 11, and in six of these an unfavourable anomaly of the circle of Willis was present as well. In two other cases, also having an anomalous Willisian circle, the stenotic lesion had progressively become a complete occlusion. In these 13 cases even a temporary haemodynamic crisis could have significantly reduced the blood flow in its territory and predisposed them to infarction. In nine additional cases intracranial extension of a proximal lesion was found, and was thought to be primarily responsible for cerebral infarction. In three diabetic subjects with a symmetrical circle of Willis and in one hypertensive patient having a circle anomaly, obstructive lesions elsewhere were not found, and here the cause of infarction was difficult to explain ; though we have no supportive evidence, "local embolism" by platelet-fibrin masses from the proximal thrombus may have been responsible for the ictus. It is more logical to suppose that apart from the severely stenosed arterial lesions there are many other factors, such as inadequacy of collateral circulation, haemodynamic crisis, anoxia, and local embolism, operating in the pathogenesis of these infarctions.

## Angiographic Risks and Case Fatality

The reported incidence of angiographic complications in occlusive cerebral vascular disease has ranged from 2.2 to 20% per patient or 2 to 13% per procedure (Silverstein, 1966). In our series, 14.5% of all angiographed cases or 5% of all procedures were accompanied by an untoward reaction ; neurological complications were higher (5.6%) in the carotid studies than in the brachial studies (0.97%).

Apart from the skill of the angiographer and the use of relatively non-toxic contrast media, the number of complications in any series would depend on how thoroughly they were sought for. With us, some members of the staff were highly critical about angiography in the acute stroke, and there may have been an overcritical assessment ; however, the number of complications pointed out was in good agreement with that noted by us.

Our team has been well trained in angiography, and these complications occurred despite special preventive care both during and after the procedure. It is worth noting that the above complications were observed only in elderly subjects (aged 55 to 75 years), and nearly all of them had some systemic disease like hypertension, coronary heart disease, and diabetes mellitus. As technical faults such as intimal tear or extraluminal injections or accidental embolization had not occurred in these cases, and vasospasm or systemic hypotension was not recorded, their precise mechanism is an enigma to us.

In the entire series studied by angiography the overall case fatality rate was 29.2% (Table III). We found no significant correlation between the case fatality rate and the number of angiographs performed in any particular group. Moreover, in another series at this hospital, when the cases of stroke were not angiographed, the case fatality rate was 28.6%. The degree of difference between 28.6% in a non-angiographed series and 29.2% in an angiographed series is well within the variation due to chance, the two series being nearly alike except for angiography. It was our feeling, therefore, that cerebral angiography *per se* did not appear to have a major detrimental effect on the outcome so far as the alive-and-dead status was compared. On the other hand, we found a significant correlation between hypertension and immediate case mortality (Table VII). The well-established observations that in hypertensive subjects there is an increased risk of a non-embolic cerebral infarction (Kannel, 1966), a high immediate mortality (our data), and a decreased life expectancy after immediate survival (Marshall and Kaeser, 1961) strongly suggest that prevention as well as early and rigid control of hypertension will prove very rewarding.

We wish to emphasize that cerebral angiography, even though of very great assistance in the diagnosis of acute stroke, carries grave risks in elderly subjects, and particularly in those having a systemic disease. It should be performed only when a surgically remediable lesion is suspected, in atypical cases where the diagnosis is in doubt, and when the therapy to be prescribed—for example, anticoagulants or fibrinolytic agents, etc.—demands an accurate diagnosis. Cerebral angiography is never indicated unless a centre is well equipped both for angiography and for vascular surgery, and has the technical proficiency to provide the required information with minimal risks.

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# Treatment of House Dust Allergy*

## A Report from the Research Committee of the British Tuberculosis Association

*This report was prepared on behalf of the Research Committee by Dr. P. Forgacs and Mr. A. V. Swan. Dr. Forgacs also co-ordinated the trial.*

*Brit. med. J.*, 1968, **3**, 774–777

**Summary: A controlled trial of the treatment of asthma by injections of a commercially produced extract of house dust is reported on 96 patients. The patients were allocated at random to two groups. One group received extract of house dust in a carbol saline solution, the other a carbol saline solution only. Some patients in both groups were advised on dust control in their houses.**

**Results were available for comparison from 70 patients, 33 treated and 37 controls. Neither the treatment with house dust extract nor advice on dust control was found to give any advantage.**

### Introduction

Many asthmatics become more wheezy when exposed to house dust, and some of them say that it is the main cause of their attacks. When this history of specific house dust sensitivity can be confirmed by a skin test it is reasonable to attempt desensitization with house dust extracts. Although this treatment is widely used, published reports about its value are scanty and contradictory.

In the earliest controlled trial (Bruun, 1949) 78% of the patients treated with house dust extract were improved or free from symptoms compared with 22% of the control group. In a more recent controlled study McAllen (1961) found that house dust extract by injection was ineffective, while treatment by inhalations of an aerosol of house dust extract gave good though short-lived results.

In the hope of resolving the uncertainty about the value of this treatment the Research Committee of the British Tuberculosis Association began in 1966 a controlled trial in which the effect of injection of a house dust extract and that of a control substance were compared. This study also offered an opportunity to assess the value of the advice usually given to patients on reducing the amount of house dust in their homes. A comparison between the progress of patients who received such advice and those who did not was included in the design of the trial.

### Selection of Patients

Patients of both sexes from 7 years upwards were accepted if they gave a history of paroxysmal dyspnoea or wheezing, however mild, at least once a week, if the physician attributed these symptoms to house dust, and if there was a positive immediate wealing reaction to a prick test with house dust extract. Patients with seasonal rhinitis or asthma due to pollen or moulds or with respiratory allergy to animal dander or food were excluded from the study. Positive skin reactions to moulds or pollens in addition to house dust were ignored if there was no appropriate history of seasonal aggravation of symptoms. The same rule applied to skin reactions to animal danders or food if the patient was not likely to encounter the allergen in question. Physicians taking part in the study were

The following took part in the study: Dr. L. Burkeman, Dr. L. H. Capel, Dr. K. M. Citron, Dr. J. A. Crocket, Dr. R. Davies, Dr. R. H. Elphinstone, Dr. H. S. Fraser, Dr. S. Z. Kalinowski, Dr. P. O. Leggat, Dr. M. K. McAllen, Dr. N. Macdonald, Dr. G. P. Maher-Loughnan, Dr. R. S. Bruce Pearson, Professor J. Pepys, Dr. J. Brian Shaw, Dr. J. Morrison Smith, Dr. D. A. Williams, Dr. D. G. Wraith.

The subcommittee responsible under the chairmanship of Professor J. Pepys for the planning and conduct of the study included all the above physicians, as well as the following members: Dr. P. Forgacs (co-ordinator), Dr. Wallace Fox, Dr. M. Pike (M.R.C. Statistical Research Unit), and Mr. A. V. Swan (M.R.C. Clinical Research Centre Statistics Division).

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