

mittent treatment than with continuous (daily) treatment given in a comparable mean annual dose. The incidence of suspected and proved peptic ulceration was approximately the same in the two treatment groups. Sixteen patients (6%) died, seven from status asthmaticus and nine from other causes. The deaths from status asthmaticus were probably due to failure to increase the dose of corticosteroid when acute symptoms supervened. The death rate was no higher in patients on intermittent treatment regimens than in those given corticosteroids every day.

The results in 28 children were similar to those obtained in the 245 adults, but the children required a proportionately higher dose of corticosteroid, and were in consequence more liable to develop the stigmata of hypercorticism. More serious side-effects were uncommon, and no deaths were recorded. Intermittent treatment was effective less often in children than in adults, but complete withdrawal of corticosteroids was achieved more often in children (18%) than in adults (5%). Although growth had already been retarded in many children with severe chronic asthma before corticosteroids were given, it is possible that the administration of these agents was responsible for further retardation of growth in a few cases.

This investigation has shown that in suitably selected cases regimens of intermittent treatment with prednisolone are as

effective in controlling the symptoms of chronic asthma as continuous (daily) treatment. There are some indications that side-effects are less likely to be produced by intermittent than by continuous administration of prednisolone, but further studies will be required to confirm this tentative conclusion.

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Comparison of Mortality Rates in Elderly Hypertensive and Normotensive Hemiplegic Patients

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Some indications for antihypertensive treatment are categorical at any age (Rosenheim, 1962), but caution is necessary in attempts to lower blood-pressure in elderly hypertensive patients, especially if they have had transient ischaemic episodes or strokes. However, strict control of blood-pressure levels, by means of hypotensive drugs if necessary, has been recommended in the hypertensive hemiplegic on the grounds that hypertension considerably reduces the chances of survival in a patient with cerebrovascular disease (Marshall, 1963). Marshall (1964) believed that the risk of reactions to long-term hypotensive therapy was not to be compared with the risk of leaving hypertension untreated in patients with non-embolic cerebral infarction. Carter (1963, 1964) also experienced higher long-term mortality rates in hypertensive than in normotensive patients, and recommended lowering raised pressure in hypertensive hemiplegics because, besides the risks of cardiac, renal, or further cerebral complications, hypertension "accelerates the advance of atherosclerotic lesions in blood-vessels and drives the process into smaller vessels." Marshall's conclusions were drawn from a three-year review of progress in 39 patients receiving hypotensive therapy and 42 untreated patients, Carter's from a five-year follow-up of 178 hypertensive hemiplegics. Diastolic pressure of 110 mm. Hg and over was regarded as hypertensive by Marshall and Kaeser (1961); Carter's (1963) criteria were systolic greater than 200 mm. Hg and diastolic over 110 mm. Hg.

Since 1948 a series of 710 hemiplegics have been reviewed from time to time in Wakehurst House. Most of these patients

had cerebral thromboses—that is, non-embolic cerebral infarction. Age and sex distribution and results of treatment have been described elsewhere (Adams and Merrett, 1961; Adams, 1965), but the influence of blood-pressure on survival was not considered in the earlier statistical analysis because the casual pressures recorded did not conform strictly to a recognized standard method. However, by January 1965 there were only six male and 26 female survivors, and our systematic routine pressure recordings seemed to be at least as reliable as some of those used to condemn hypertension as an adverse factor in the prognosis of strokes. This paper is a study of mortality rates compiled for groups of male and female patients defined according to certain blood-pressure levels.

Methods

Elsewhere (Adams, 1965) it has been shown that pressure tends to be high at the onset of a cerebral vascular accident, falling gradually over the next eight weeks in those who survive, and then rising a little again. We have therefore limited this analysis to patients admitted or transferred to Wakehurst House not later than one month after the onset of their strokes; this accounted for 207 omissions from the analysis. Twelve patients were untraced, and 26 others with embolic cerebral infarction related to rheumatic heart disease are excluded, leaving 465 patients (211 men and 254 women). Survival has been estimated in months from the date of onset of the stroke until death, or until 1 January 1965.

Most of the patients were transferred from general medical wards in the third or fourth week of convalescence after surviving the onset of their strokes (Adams and Merrett, 1961).

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Blood-pressure were recorded at least once a week either by the medical staff or by senior nurses responsible for these routine records. The level used in this analysis was the highest resting pressure noted, usually at the beginning of this convalescent period.

Results

Results are presented separately for males and females; within each sex patients have been classified according to their arterial pressure in four ways, as shown in the column headings of Tables I–IV, which deal with diastolic pressures, systolic pres-

TABLE I.—Diastolic Blood-pressure

No. of Months after Stroke	< 110 mm. Hg (L)		110 + mm. Hg (H)		Difference in Death Rates (H)–(L)
	n	Death Rate	n	Death Rate	
Males					
0	124	25.81	87	21.84	-3.97 ± 5.92
2	92	20.65	68	20.59	-0.06 ± 6.47
12	73	16.44	54	33.33	16.89* ± 7.74
24	61	22.95	36	22.22	-0.73 ± 8.77
36	47	19.15	28	17.86	-1.29 ± 9.24
48	38	18.42	23	26.09	7.67 ± 11.11
60	31	12.90	17	35.29	22.39 ± 13.06
72	27	22.22	11	36.36	14.14 ± 16.56
84	21	38.10			
96	13	30.77			
Females Aged < 70 Years at Stroke					
0	41	19.51	67	14.93	-4.58 ± 7.57
2	33	6.06	57	15.79	9.73 ± 6.37
12	31	6.45	48	20.83	14.38 ± 7.34
24	29	10.34	38	26.32	15.98 ± 9.11
36	26	19.23	28	7.14	-12.09 ± 9.13
48	21	14.29	26	19.23	4.94 ± 10.87
60	18	5.56	21	14.29	8.73 ± 9.35
72	17	11.76	18	11.11	-0.65 ± 10.77
84	15	6.67	16	0.00	-6.67 ± 13.51
96	14	14.28	15	18.75	4.47 ± 13.51
Females Aged 70+ Years at Stroke					
0	86	44.19	60	20.00	-24.19* ± 7.44
2	48	20.83	48	27.08	6.25 ± 8.69
12	38	28.95	35	20.00	-8.95 ± 9.99
24	27	22.22	28	25.00	2.78 ± 11.44
36	21	28.57	21	33.33	4.76 ± 14.25
48	15	20.00	14	21.43	1.43 ± 15.06
60	12	16.67	11	36.36	19.69 ± 18.06
72	10	10.00			

In this and subsequent tables: n = Number of patients alive at the beginning of the stated period. Death rate = Number of patients who died during the stated period expressed as a percentage of the number alive at the beginning of the same period. The standard error of the difference in the death rates follows the ± sign in the last column of the table.

* Indicates that the difference in death-rates is significantly different from zero at the P < 0.05 level.

sures, a combination of both, and pulse pressures respectively. Preliminary investigation showed significant differences (at P < 0.05 used throughout) in age distribution of females in the pressure groups compared in Tables I and III. These differences did not occur in any analysis of male patients, and there were no differences for either sex in Tables II and IV. Consequently it was necessary to calculate mortality rates for females for two age groups: under 70 years of age and 70 years or over at onset of the stroke (Tables I and III).

TABLE II.—Systolic Blood-pressure

No. of Months after Stroke	< 185 mm. Hg (L)		185 + mm. Hg (H)		Difference in Death Rates (H)–(L)
	n	Death Rate	n	Death Rate	
Males					
0	113	26.55	98	21.43	-5.12 ± 5.87
2	83	22.89	77	18.18	-4.71 ± 6.37
12	64	15.63	63	31.75	16.12* ± 7.42
24	54	16.67	43	30.23	13.56 ± 8.65
36	45	20.00	30	16.67	-3.33 ± 9.05
48	36	22.22	25	20.00	-2.22 ± 10.58
60	28	14.29	20	30.00	15.71 ± 12.20
72	24	25.00	14	28.57	3.57 ± 14.96
84	18	27.78	10	60.00	32.22 ± 18.75
96	13	30.77			
Females					
0	112	38.39	142	17.61	-20.78* ± 5.60
2	69	15.94	117	19.66	3.72 ± 5.74
12	58	20.69	94	19.15	-1.54 ± 6.69
24	46	15.22	76	9.78	5.46 ± 7.26
36	39	30.77	57	14.04	-16.73 ± 8.71
48	27	7.41	49	24.49	17.08* ± 7.95
60	25	20.00	37	13.51	-6.49 ± 9.78
72	20	5.00	32	15.63	10.63 ± 8.06
84	19	5.26	27	7.41	2.15 ± 7.19
96	18	16.67	25	16.00	-0.67 ± 11.44

There was no evidence that the side of brain involved by the cerebrovascular accident differed significantly between "pressure" groups of any table for any tabulated age and sex group.

Mortality rates for successive years after the stroke have been tabulated for each of the "pressure"-sex-age groups shown in the tables. In the first year the rates are given separately for the first two months and the last 10 because of the heavy mortality experienced by these patients soon after their admission. Death rates based on fewer than 10 patients are omitted. When the "pressure" groups are compared a negative difference in mortality rates indicates greater mortality in the lower-pressure group and a positive difference indicates greater mortality in the higher-pressure group. The number of survivors after

TABLE III.—Systolic and Diastolic Blood-pressures Combined

No. of Months after Stroke	Diastolic < 110 mm. Hg and Systolic < 185 mm. Hg (I)		Diastolic 110+ mm. Hg or Systolic 185+ mm. Hg (II)		Diastolic 110+ mm. Hg and Systolic 185+ mm. Hg (III)		Difference in Death Rates		
	n	Death Rate	n	Death Rate	n	Death Rate	(II)–(I)	(III)–(I)	(III)–(II)
Males									
0	98	24.49	41	34.15	72	18.06	9.66 ± 8.59	-6.43 ± 6.28	-16.09 ± 8.68
2	74	22.97	27	14.81	59	20.34	-8.16 ± 8.40	-2.63 ± 7.17	5.53 ± 8.61
12	57	14.04	23	30.43	47	31.91	16.39 ± 10.64	17.87* ± 8.21	1.48 ± 11.76
24	49	18.37	16	31.25	32	25.00	12.88 ± 12.78	6.63 ± 9.44	-6.25 ± 13.89
36	40	20.00	11	18.18	24	16.67	-1.82 ± 13.24	-3.33 ± 9.89	-1.51 ± 13.90
48	32	18.75			20	25.00	6.25 ± 11.89	21.79 ± 13.69	
60	26	11.54			15	33.33	8.26 ± 16.85		
72	23	21.74			10	30.00			
84	18	27.78							
96	13	30.77							
Females Aged < 70 Years at Stroke									
0	29	24.14	25	20.00	54	11.11	-4.14 ± 11.28	-13.03 ± 9.02	-8.89 ± 9.07
2	22	9.09	20	5.00	48	16.67	-4.09 ± 7.83	7.58 ± 8.15	11.67 ± 7.26
12	20	5.00	19	21.05	40	17.50	16.05 ± 10.54	12.50 ± 7.74	-3.55 ± 11.12
24	19	15.79	15	6.67	33	27.27	-9.12 ± 10.56	11.48 ± 11.41	20.60* ± 10.09
36	16	12.50	14	28.57	24	4.17	16.07 ± 14.64	12.86 ± 14.40	-24.40 ± 12.74
48	14	7.14	10	20.00	23	21.74	12.86 ± 14.40	14.60 ± 11.02	7.14 ± 15.30
60	13	7.69			18	11.11	3.42 ± 10.46		
72	12	8.33			16	12.50	4.17 ± 11.49		
84	11	9.09			14	0.00	-9.09 ± 9.22		
96	10	10.00			14	14.29	4.29 ± 13.32		
Females Aged 70+ Years at Stroke									
0	59	50.85	38	26.32	49	20.41	-24.53* ± 9.66	-30.44* ± 8.69	-5.91 ± 9.18
2	29	20.69	28	21.43	39	28.21	0.74 ± 10.80	7.52 ± 10.42	10.59 ± 10.59
12	23	26.09	22	31.82	28	17.86	5.73 ± 13.51	-8.23 ± 11.67	-13.96 ± 12.29
24	17	17.65	15	20.00	23	30.43	2.35 ± 13.86	12.78 ± 13.32	10.43 ± 14.10
36	14	42.86	12	25.00	16	25.00	-17.86 ± 18.20	-17.86 ± 17.09	0.00 ± 16.54

seven years was small, so that their death rates are unreliable, and as standard errors relating to them are large it is difficult to estimate statistical significance in the later years even when differences in death rates are considerable.

Table I shows the mortality rates for the diastolic-pressure groups; of the 25 comparisons only two were significant. One, in the second year after stroke among males, favours the low-pressure group; the other, in the first two months after stroke among females aged 70 and over, favours the high-pressure group. Similarly, in Table II, comparing systolic pressures, only three differences were significant. For males, in the second year after stroke, mortality was significantly greater in patients with higher pressures, as was mortality in females in the fifth year. However, patients of either sex with high pressures appeared to do better in the first two months, although only one of the differences (among women) was significant.

Comparison of mortality between the three groups of patients classified by a complex of systolic and diastolic pressure is given in Table III. There were only four significant differences: males with both high systolic and diastolic pressures had a significantly greater mortality in the second year after stroke than males with both pressures low; female patients aged less than 70 years at the onset of strokes with both high systolic and diastolic pressures had a significantly greater mortality in the third year after the stroke than if only one pressure was high; and for females aged 70 years and over the mortality in the first two months after the stroke was significantly lower in patients with both pressures raised than in either of the other two pressure groups.

There was only one significant difference between the two pulse-pressure groups (Table IV): female patients with high pulse pressures had a significantly higher mortality in the fifth year after stroke than females with low pulse pressures.

TABLE IV.—Pulse Pressures

No. of Months after Stroke	< 80 mm. Hg (L)		80+ mm. Hg (H)		Difference in Death Rates (H)-(L)
	n	Death Rate	n	Death Rate	
<i>Males</i>					
0-	106	29.25	105	19.04	-10.21 ± 5.85
2-	75	24.00	85	17.65	-6.35 ± 6.44
12-	57	22.81	70	24.29	1.48 ± 7.56
24-	44	36.36	53	26.42	-9.94 ± 9.45
36-	36	25.00	39	12.82	-12.18 ± 8.99
48-	27	22.22	34	20.59	-1.63 ± 10.59
60-	21	9.52	27	29.63	20.11 ± 10.87
72-	19	21.05	19	31.58	10.53 ± 14.18
84-	15	33.33	13	46.15	12.82 ± 18.42
96-	10	30.00			
<i>Females</i>					
0-	99	31.31	155	23.87	-7.44 ± 5.78
2-	68	14.71	118	20.34	5.63 ± 5.67
12-	58	20.69	94	19.15	-1.54 ± 6.69
24-	46	19.57	76	22.37	2.80 ± 7.55
36-	37	24.32	59	18.64	-5.68 ± 8.69
48-	28	3.57	48	27.08	23.51 ± 7.31
60-	27	22.22	35	11.43	-10.79 ± 9.64
72-	21	9.52	31	12.90	3.38 ± 8.79
84-	19	10.53	27	3.70	-6.83 ± 7.92
96-	17	17.65	26	15.38	-2.27 ± 11.64

Discussion

Although so few differences were significant, mortality in the first two months after stroke was almost always higher in patients with low pressures than in those who appeared to be hypertensive. Throughout the rest of the tables there were so few significant differences, and there was such a conspicuous lack of predominantly positive differences favouring low-pressure groups, that there is no evidence from this analysis to show that hypertension, as defined here, adversely affects mortality after cerebral infarction.

The difference between our findings and those of others who have studied blood-pressure in relation to prognosis of strokes may be attributable to age and sex differences, to inconsistencies in definitions of hypertension, or to discrepancies in methods and times of recording blood-pressure. However, there are

other possibilities. The risk of a cerebrovascular accident as a complication of hypertension, and the limiting effect of hypertension on life expectancy after a stroke, are separate propositions, and patients with hypertension who have not had strokes and those who have had them may represent different populations with different mortality risks (Adams, 1965). Incidence and mortality of cerebrovascular accidents complicating hypertension have been studied in detail (Pickering, 1955; Hodge *et al.*, 1961; Smirk and Hodge, 1963; Leishman, 1963; Hamilton *et al.*, 1964), but studies of the hemiplegic population comparable to those of the hypertensive population have yet to be made. In his five-year follow-up of patients with severe hypertension Leishman (1963) has shown that most deaths in untreated severe hypertension occur from uraemia and stroke, and the protective effect of blood-pressure lowering is made evident by prevention of these; but of 22 deaths from stroke in treated patients 12 occurred in patients with well-controlled pressures. These he regarded as victims of cerebral atherosclerosis, and control of hypertension could not be expected to protect them from the effects of this.

The relationship between atheroma and hypertension is still far from clear, although Carter (1964) believes that hypertension promotes it and extends it to the smaller vessels. McKeown (1965), in a most thorough study of 1,500 necropsies in elderly subjects, states: "Hypertension accentuates the development of atheroma in the cerebral vessels as well as in the aorta and coronary arteries, but this effect is much less apparent in the aged than in younger individuals, perhaps because of the natural tendency for atheroma to increase in severity of its own accord with advancing years, and for patients with significant hypertension to fail to survive to old age. Hyaline arteriosclerosis when occurring in the brain has little or no relationship to hypertension, and if present in the aged is regarded as a normal age change. Some degree of medial hypertrophy and fibrosis in large and smaller cerebral vessels, with perhaps capillary fibrosis, are the only vascular changes which may be attributed to hypertension."

Another source of differences may be in the timing of blood-pressure readings. Pickering (1955) observed that "arterial pressure may be at any level in cerebral thrombosis," but in most patients there seems to be a well-marked rise in blood-pressure at the onset of cerebral infarction, followed in the first few weeks of convalescence by a gradual fall, and then by a slight rise again in the later weeks (Adams and Merrett, 1961; Adams, 1965). Some patients may be labelled hypertensive at the time of onset, and the spontaneous fall in pressure that follows may then be credited to unnecessary antihypertensive therapy. Others are troubled by symptoms of relative hypotension in convalescence. Investigating 100 people over 70 years of age, Johnston *et al.* (1965) noted falls in systolic blood-pressure of as much as 60 mm. Hg, provoked by sitting up (in 11%) and by standing (in 17%). All of those with falls in systolic pressure of more than 20 mm. Hg had evidence of cerebrovascular disease, and the hypotension induced in these patients by postural changes, illnesses, or drugs—for example, chlorpromazine—could provoke vertigo, drowsiness, or more serious side-effects such as loss of consciousness and the risk of further cerebral catastrophe.

Low-Beer and Phear (1961) investigated blood-pressure in 109 patients with cerebral infarction, comparing levels at the time, or within hours, of the onset of the stroke with readings made before the onset and more than three weeks after. They concluded that hypertension is more common and reaches higher levels in cerebral than in myocardial infarction, and that there were two groups of patients with cerebral infarction—those whose pressures were high at the onset, rising from the lower levels noted beforehand, and those whose pressures were low at the onset because they had been predisposed to a fall at the time of the stroke by complications such as coronary infarction, operation, haemorrhage, dehydration, severe infection, or hypotensive therapy.

These inquiries suggest that if treatment to influence blood-pressure is necessary at all after cerebral infarction the measures most likely to do good are those that maintain or raise blood-pressure rather than those that lower it, and the patients who most need treatment are the old people with disproportionately low pressures who suffer from symptoms of postural hypotension.

We support the statement that the intensity of the pressure rise for the individual is the important thing, not an arbitrary level used to define hypertension regardless of age, sex, and other factors that influence it (Pickering, 1955), and believe that a more precise study than any at present available should be made of the systemic blood-pressure in the survivors of cerebral infarction, and that the relationship of this pressure to life expectancy after stroke should be reassessed.

Summary

Comparison of mortality in survivors of strokes classified by systolic blood-pressure alone, diastolic blood-pressure alone, a complex of systolic and diastolic pressures, and pulse pressure alone, failed to provide convincing evidence of an adverse effect of hypertension on mortality after cerebral infarction. (The pressure levels accepted as hypertensive were systolic 180 mm. Hg or more, diastolic 110 mm. Hg or more). There is some

evidence, however, that patients with high pressures have a lower mortality in the first two months after stroke than patients with low pressures.

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Herpes Simplex Virus Skin Infection in Man Treated with Idoxuridine in Dimethyl Sulphoxide. Results of Double-blind Controlled Trial

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The satisfactory results of Kaufman's experiments with idoxuridine in the treatment of herpetic keratitis in rabbits, and subsequent double-blind controlled treatment trials in acute herpetic keratitis in humans, indicated that this substance might be effective in treating other manifestations of herpes simplex virus infection in man if it could be brought to act in adequate concentrations at suitable times in the cycle of replication of the virus without damaging unaffected cells in adjacent or other tissues or organs.

Reports of failure to increase the normal rate of healing of skin lesions (cold sores) by application of 0.5% idoxuridine in ointment (Burnett and Katz, 1963; Juel-Jensen and MacCallum, 1964) showed that other methods were required to facilitate the action of idoxuridine on virus in cells of the skin. Percutaneous inoculation of a 0.1% aqueous solution of idoxuridine in a fine spray by means of a pressure-jet gun achieved a modicum of success (Juel-Jensen and MacCallum, 1965), but only a single treatment was practicable, and obviously this did not reach all infected cells. The increased rate of recovery was assumed to be due to a combination of a reduction in the number of virus-infected cells and the action of antibody. When recurrences subsequently occurred in several treated patients the lesions appeared at new sites—an uncommon happening in the natural history of the disease.

Iodoxuridine is very insoluble in watery solution, and it therefore seemed that a solvent which would provide a higher con-

centration and/or allow greater powers of penetration of the drug through the skin to the affected cells was required. We chose dimethyl sulphoxide. After this work began reports appeared of the use of a solution containing equal parts of 50% polyethylene glycol 4000 and water to obtain 0.9% idoxuridine for treatment of experimental keratitis in rabbits (Jawetz *et al.*, 1965), and more recently Corbett *et al.* (1966) reported on the use of 0.1% idoxuridine in 1.4% polyvinyl alcohol in treatment of herpetic skin lesions in man.

The results of experiments in which primary herpes simplex virus intradermal infections in guinea-pigs were treated with varying concentrations of idoxuridine in different dilutions of dimethyl sulphoxide (Tomlinson and MacCallum, 1965) suggested that 5% idoxuridine in undiluted dimethyl sulphoxide might be effective in the treatment of recurrent herpetic skin lesions (cold sores) in volunteers. A double-blind controlled trial was organized in the same manner as our previous two trials.

Methods

The patients in the trial were drawn from the medical students of the Clinical School and from the staff of the Radcliffe Infirmary. Herpes sufferers reported as soon as possible and not later than 24 hours after the onset of the first symptoms. A careful history was taken, including information about the duration of previous attacks. A swab from the lesion was taken into virus transport medium and sent to the laboratory within an hour, and a sample of blood for antibody studies was collected.

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