THE EFFECT OF ANTIHYPERTENSIVE THERAPY ON THE COURSE OF CEREBRAL VASCULAR DISEASE*

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WITHIN a remarkably short time of the introduction of hexamethonium,[1] the benefits of antihypertensive therapy in reducing the mortality from certain complications of hypertension were becoming defined. Thus by 1953 Morrison[2] could demonstrate an improved prognosis in respect of the malignant phase and this was quickly confirmed by Rosenheim,[3] Schroeder,[4] and McMichael and Murphy.[5] Simultaneously, Smirk[6] could claim that hypertensive heart failure, formerly considered responsible for between 40 and 50% of deaths among untreated hypertensive subjects, had been virtually eliminated as a cause of death among treated patients.

However, the effect of antihypertensive therapy upon the course of cerebral vascular disease remained in confusion for many years. The early ganglion-blocking agents were characterized by erratic and inadequate absorption from the alimentary tract,[7] and the control of hypertension with these drugs was characterized by erratic and considerable fluctuation in the level of blood pressure, so that profound, unexpected, and undesirable falls in blood pressure were not uncommon and, following such profound episodes of hypotension, some patients developed manifestations of cerebral thrombosis. In consequence many

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physicians developed a strong prejudice against the use of antihypertensive drugs; they maintained that such treatment caused strokes. I do not believe that there is yet any evidence to support the view that reduction in blood pressure, unless excessive, causes stroke, but for many years the prognosis in hypertension associated with stroke remained uncertain, until Leishman,[8, 9] by comparing consecutive groups of patients, provided convincing proof of the improved prognosis attributable to the effects of antihypertensive therapy given to such patients.

In considering the influence of antihypertensive therapy upon the course of cerebral vascular disease, therefore, two main questions require discussion: first, does the treatment cause development, or accelerate the progression, of the disease, and second, is there any evidence to show that the treatment will reduce the development, or retard the progress, of the disease, i.e., does antihypertensive therapy cause or prevent strokes? Unfortunately much of the confusion which initially produced so much uncertainty in the minds of many physicians still remains, and while I suspect that I shall do little to resolve this confusion, I trust that I shall not provoke further uncertainty.

We have recently analyzed the results of treatment 653 patients with severe hypertension[10] maintained on treatment for periods ranging from four months to 10 years. All were referred on account of high arterial pressure or some complication of hypertension, and the need for treatment was determined solely by the severity of the disorder or of its complications. A variety of treatments have been used—that used for any individual being the drug, or combination of drugs, which maintained the most adequate control of the blood pressure with the production of the minimum of symptoms. Thiazides alone were used in maintaining 223 of the patients; the remaining 430 required more potent therapy: either a blocking agent, methyldopa used alone or, more usually, in conjunction with a diuretic.

Of these 653 patients, 106 had suffered a stroke before the introduction of antihypertensive therapy. All had made a considerable objective recovery so that, at the time of starting treatment, none showed sufficient physical or mental impairment of function as to interfere with treatment, i.e., all had suffered a "clean stroke."[11] Of these 106 patients only 40 have suffered a further stroke while on treatment; 18 of the strokes were fatal. Seven more patients died from coronary thrombosis, i.e., there was a total mortality of 25 patients.

Seventeen patients with hypertensive encephalopathy were admitted; this diagnosis has frequently been abused.[12] All presented with epileptiform fits proceeding to coma, 13 developed focal neurological signs, all made a complete objective recovery within 36 hours of admission to the hospital, and none showed blood-stained or xanthochromic cerebrospinal fluid. While the nature of such attacks might be questioned[13] the therapeutic value of reducing blood pressure has been amply demonstrated.[14] Of these 17 patients in our own series, five died, all from stroke within 12 months of starting treatment in two patients; the other three patients died after two, three, and seven years of treatment. The remaining 12 patients of this group still survive, although two have suffered, and survived, a further stroke.

Thus in these two groups, 47 of 123 patients have suffered a further stroke—an incidence of 38% recurrence.

A 10-year follow-up of 1,018 patients admitted to a hospital in Worcester, Mass., following cerebral thrombosis[15] gave an initial mortality of 21%. Of the survivors, 59% died within five years; this contrasted with an expected mortality of 29%, recurrent cerebral thrombosis accounted for 53% of all deaths; 85% of all deaths were due to vascular disease. These results are comparable to those of Pierson and Hoobler,[16] who reported a 60% recurrence of cerebral vascular disease in their series of 71 patients.

An incidence of 38% recurrent stroke among these patients treated for hypertension certainly compares favorably with the above series, and does suggest that the antihypertensive treatment has not accelerated the progression of the cerebral vascular disease. But these figures do not support the claim that the therapy has retarded its progression.

Six more patients were admitted following a subarachnoid hemorrhage, no aneurysm was demonstrated on carotid angiography, and all maintained a raised arterial pressure following recovery from the hemorrhage. With control of the blood-pressure level, none developed further manifestations of cerebral vascular disease, although the treatment has been maintained for less than two years in four of these patients.

Whether antihypertensive therapy will reduce the incidence of stroke is more difficult to determine. By comparing consecutive series of patients, Leishman[8, 9] provided convincing evidence of an improved prognosis in this respect, but a study of consecutive cases is always open

to some doubt. In an attempt to resolve this prognostic dilemma, my colleagues and I[17] conducted a therapeutic trial, the object of which was to determine whether the control of high blood pressure did influence the incidence of complications, including strokes, in patients with severe benign essential hypertension. Although published some years ago the results of this trial have only recently been confirmed;[18] I therefore think its reproduction is justifiable.

It was essential to include in such a trial only patients who were hypertensive but in whom arterial disease was not a dominant feature of the condition. Thus all subjects included in the trial were under 60 years of age. None had symptoms of arterial disease; i.e., all denied angina, claudication, rest pain in the limbs, or episodes suggesting cerebral vascular insufficiency. In all subjects the carotid and femoral pulses were palpable, none had a bruit audible over the femoral or carotid arteries, and none showed cardiographic change of infarction. As it was obviously essential that all should show a sustained manometric hypertension, all subjects maintained a minimum diastolic pressure of 110 mm. Hg over a period of at least three months' outpatient observation; this entailed a minimum of three visits to the clinic.

It would have been indefensible to have included in such a trial any patient whose disorder was of such severity as to require early treatment. Thus all patients had been referred to the outpatient clinic because of symptomless hypertension, which in all was diagnosed as essential hypertension, known causes of raised arterial pressure had been excluded by an investigation undertaken during the three-month period of outpatient observation. Further, no patient showed evidence of complications of a raised arterial pressure in that none showed retinal changes, or clinical, radiological, or cardiographic changes of ventricular hypertrophy, and none had albumin or casts in the urine. All had a normal level of serum urea.

Thus all subjects included in the trial were under 60 years of age, with symptomless, uncomplicated, benign essential hypertension. All received a minimum of two and a maximum of six years' treatment or observation.

After clinical examination and investigation to exclude the need for early treatment of the hypertension and the presence of some lesion known to be associated with a raised arterial pressure, patients were admitted to the trial and allocated to the treated or control group alter-

nately in order to maintain an even number in both groups. Three were ultimately rejected from the trial, one on account of age, and two because of suspect etiology of the hypertension, so that the numbers of cases in the two groups do not exactly balance. No indication was made in the patients' notes of their inclusion in the trial in order to avoid prejudice regarding the introduction of treatment at any time during the course of it.

Sixty-one patients—22 men and 39 women—who satisfied all the above criteria were included in the trial. There was no significant difference for either sex between the treated and control group in respect of age, weight, or blood pressure.

In assessing the degree of control of the blood pressure, the following criteria were maintained: 1) good control, implying a diastolic pressure consistently below 100 mm. Hg; 2) fair control, implying a diastolic pressure consistently below 110 mm. Hg; and 3) poor control, implying a diastolic pressure consistently over 100 mm. Hg.

Of the 22 men, 10 were in the treated and 12 in the control group. In all the treated cases adequate control was maintained over the blood pressure; it was good in 9 and fair in one. None suffered a stroke or other complications of the disease. Four of the 12 untreated cases suffered a stroke from which two made a complete objective recovery, one was left with a residual speech defect and arm weakness, and one died from cerebral hemorrhage proved by autopsy. Although there was apparently a high incidence of stroke, the numbers in the two groups are small, and these four strokes do not constitute a statistically significant difference from the treated group. However, among the remaining eight patients in this group four developed other complications: a coronary thrombosis in one, clinical and cardiographic changes of ventricular hypertrophy in two, and headaches of increasing intensity that required reduction of blood pressure for their relief in one other. Thus eight of 12 subjects in the control group developed complications of a raised arterial pressure as compared with no complications in the 10 treated subjects; this difference is highly significant at the 2.5% level.

There were 19 women in the control group, of whom three suffered a stroke; one died from a ruptured intracranial aneurysm 15 months after starting treatment introduced for the successful relief of headaches of increasing severity; two others made a full objective recovery from a presumed cerebral thrombosis. Other complications arose

in four other patients: coronary thrombosis in two, and increasing left ventricular hypertrophy in three. Thus eight of 19 patients developed complications.

Of 20 women in the treated series five developed complications: three had strokes (one fatal cerebral hemorrhage and two presumed thromboses), one coronary thrombosis, and one increasing heart size. Clearly the difference between these two groups is neither impressive nor significant. But among the treated group there were four in whom the control of blood pressure was considered to be poor, i.e., the diastolic pressure was never maintained below 110 mm. Hg—the original criterion for inclusion in the trial. If therefore the women in this trial are considered not in respect of treatment but in respect of the adequacy of that treatment, a different result emerges. There were 16 with adequate control of blood pressure with only one complication: increasing heart size. Contrast this with the 23 with inadequate control of blood pressure (19 of the control group plus four inadequately treated) of whom 12 developed complications, including six strokes. Both the over-all incidence of complications and that of strokes alone represents a highly significant increase among the group that received inadequate or no treatment.

The recent trial of 143 male hypertensive patients with hypertension of similar severity conducted by the Veterans Administration Co-operative Study Group in Washington, D.C.,[18] reached similar conclusions based on a very similar outcome of the trial. These trials therefore certainly give rise to optimism regarding the role of antihypertensive therapy in the prevention of stroke; they suggest that deaths from stroke should diminish in hypertensive patients maintained on treatment. The results obtained in the treatment of large numbers of hypertensive subjects is therefore somewhat disappointing. In our own series of 653 patients, 36 of a total of 81 deaths were due to stroke, 36 other patients survived a stroke during the course of treatment, i.e., 11% of the patients suffered a stroke within 10 years of treatment.

This discrepancy, I think, can be explained simply by considering the nature of the disease from which the 653 patients suffered at the time of starting treatments (Tables I and II). It will be seen that there were 532 complications present at the time of starting treatment in 653 severely hypertensive subjects, i.e., the majority of these patients had established vascular disease at the time of starting treatment and the subsequent

TABLE I. ETIOLOGY, IN RELATION TO RETINAL GRADING, OF 653 PATIENTS UNDER TREATMENT FOR HYPERTENSION

	Essential	*Chronic pyelo-nephritis*	*Chronic nephritis*	*Renal artery stenosis*	*Polycystic kidney*	*Total*
Retinal grade 4	24	13	3	2	0	42
3	103	31	3	2	3	142
2	369	74	3	18	5	496
	496	118	9	22	8	653

TABLE II. COMPLICATIONS, INCLUDING RETINOPATHY, AT THE START OF TREATMENT

Complications	*Treatment with* *Thiazide alone*	*Blocking agents*	*Total*
Stroke	35	71	106
Angina	59	85	144
Cardiac failure	32	47	79
Encephalopathy	2	15	17
Subarachnoid hemorrhage	—	2	2
	128	220	348
Retinopathy	Gd. 4 42	Gd. 3 142	184
		Total complications	532

TABLE III. FATAL COMPLICATIONS AMONG 653 TREATED HYPERTENSIVE PATIENTS

Stroke	36	Renal failure	4
Coronary thrombosis	27	Pneumonia	1
Cardiac failure	9	Carcinoma of breast	1
Aortic dissection	2	Postoperative	1

TABLE IV. NONFATAL COMPLICATIONS THAT DEVELOPED DURING TREATMENT OF 653 HYPERTENSIVE PATIENTS

Stroke	36
Coronary thrombosis	45
Cardiac failure	4
Onset of angina without ECG evidence of infarction	18
Intermittent claudication	2
Progressive impairment of renal function	12

development of further vascular complications (Table IV) is merely a manifestation of the progression of the disease.

Only 11% of the deaths were due to cardiac failure—a striking reduction from the incidence of fatal cardiac failure in untreated hypertensive subjects. It is now accepted that many patients are prevented from dying from heart failure, only to die subsequently from other complications—the two most prominent are cerebral and coronary thrombosis. The same argument applies, although to fewer cases, to the reduced mortality from the accelerated phase as a result of antihypertensive therapy, which permits an increased survival of these patients also who die later of arterial disease.

Is treatment, then, influencing the course or incidence of arterial disease? The therapeutic trials reported suggest that over a short period of time the mortality from stroke is significantly reduced in patients free from recognized stigmata of arterial disease. One notable reduction is that of cerebral hemorrhage in patients with adequate control of blood pressure. The changing nature of the cerebral vascular complications of hypertension are well illustrated by Leishman.[8] In his untreated series of patients, cerebral hemorrhage accounted for 70% of the deaths from stroke, and 31% of the over-all mortality. Of the subsequent patients treated for hypertension by sympathectomy, or by antihypertensive drugs, or both, cerebral hemorrhage accounted for 37% of deaths from stroke, and only 12% of the over-all mortality. This can be attributed to the reduced incidence of intracerebral aneurysms, originally described by Charcot and Bouchard[19] and more recently beautifully illustrated by Ross Russell,[20] who correlated their presence with severity and duration of the raised arterial pressure and leaves no doubt regarding their role in the etiology of cerebral hemorrhage. Control of hypertension must be preventing either the development or the rupture of these intracerebral aneurysms, and this accounts for the reduced incidence of cerebral hemorrhage among adequately treated patients.

Cerebral thrombosis, however, is based on a different change in the vessel passing under a variety of names: atheroma, atherosclerosis, or nodular arteriosclerosis,[21, 22] and discussed and clarified more recently by Pickering.[23] It is this lesion which is responsible for the occurrence of thrombosis in the cerebral and coronary arteries, an event that accounts for 144 thrombotic incidents, of which 63 proved fatal among my own series of 653 patients. Further, 22 other complications (Table

IV) were attributable to this same disease, i.e., more than 25% of the patients developed severe manifestations of thrombotic arterial disease during the 10-year period under review. I do not believe that this is an expression of failure of treatment, but rather an indication that treatment was introduced too late in the course of the disease. As illustrated in Table III, the majority of patients already showed manifestations of arterial disease at the time of starting treatment. Had treatment been introduced earlier in the course of the disease, before the development of arterial disease, could this high incidence of cerebral and coronary thrombosis have been prevented? There is still no evidence available on this point, and such evidence must await the outcome of therapeutic trials now in progress involving younger patients with mild hypertension. The results of these trials will take many years to produce definitive conclusions, and until then the full extent of the effect of antihypertensive treatment on the course of cerebral vascular disease must necessarily remain obscure.

Summary

There is no evidence to suggest that antihypertensive therapy causes stroke.

Such therapy has produced a reduced mortality from cerebral hemorrhage, possibly owing to the reduced incidence of intracerebral aneurysms.

There remains a high incidence of cerebral thrombosis in treated patients, and the exact role of antihypertensive therapy in the prevention of stroke must await the outcome of further therapeutic trials, involving young patients with mild hypertension.

REFERENCES

1. Paton, W. D. M. and Zaimis, E. J. *Nature 161*:718, 1948.
2. Morrison, B. *Brit. Med. J. 1*:1291, 1953.
3. Rosenheim, M. L. *Brit. Med. J. 2*:1181, 1954.
4. Schroeder, H. A. *Amer. J. Med. 17*: 540, 1954.
5. McMichael, J. and Murphy, E. A. *J. Chronic Dis. 1*:527, 1955.
6. Smirk, F. H. *New Zeal. Med. J. 52*:325, 1953.
7. Harrington, M. *Proc. Roy. Soc. Med. 55*:283, 1962.
8. Leishman, A. W. D. *Brit. Med. J. 1*: 1361, 1959.
9. Leishman, A. W. D. *Lancet 1*:1284, 1963.
10. Hamilton, M. *New Zeal. Med. J. 67*: 275, 1968.
11. Turner, R. W. D. In: *Symposium on the Clinical Management of Hypertension*, p. 79, 1956.
12. Hamilton, M. In: *Symposium on Hypertension and Cerebral Artery Disease,*

Chelmsford, England. Fryer, J. H., ed. London, Pitman Med. Pub., 1961, p. 32.

13. Byrom, F. B. In: *International Symposium on Antihypertensive Therapy,* Siena, Italy. Gross, F., ed. Berlin, Springer-Verlag, 1966, pp. 125-31.
14. Jellinek, E. H., Painter, M., Prineas, J. and Ross Russell, R. *Quart. J. Med. 33*:239, 1964.
15. Robinson, R. W., Cohen, W. D., Higano, N., Meyer, R., Lukowsky, G. H., McLaughlin, R. B. and MacGilpin, H. H. *J.A.M.A. 169*:1149, 1959.
16. Pierson, E. C. and Hoobler, S. W. *Univ. Mich. Med. Bull. 23*:446, 1957.
17. Hamilton, M., Thompson, E. N. and Wisniewski, T. K. M. *Lancet 1*:235, 1964.
18. Veterans Administration Cooperative Study Group in Antihypertensive Agents. *J.A.M.A. 202*:1028, 1967.
19. Charcot, J. M. and Bouchard, C. *Arch. Physiol. 1*:110, 643, 1868.
20. Russell, R. W. R. *Brain 86*:425, 1963.
21. Councilman, W. T. *Trans. Assoc. Amer. Phys. 6*:179, 1891.
22. Peabody G. L. *Trans. Assoc. Amer. Phys. 6*:154, 191.
23. Pickering, G. W. In: *High Blood Pressure.* London, Churchill, 1968, p. 296.