Presymptomatic Diagnosis of Hypertension

by M Hamilton MD FRCP
(*Chelmsford & Essex Hospital, Chelmsford*)

Within a remarkably short time of the introduction of hexamethonium it was possible to demonstrate an improved prognosis in respect of many of the complications of hypertension. Thus, by 1953, Morrison claimed that 4 out of 7 patients with malignant hypertension had maintained a normal life for up to fifteen months. The following year, Rosenheim as well as Schroeder confirmed these observations, and by 1955 McMichael & Murphy considered that the life extension in their series had already become statistically significant.

Simultaneously, an improved prognosis in respect of other complications of hypertension was being demonstrated as attributable to the effects of blood pressure reduction. In 1953 Smirk stated that 'hypertensive heart failure and cardiac asthma as causes of death are almost eliminated', and this opinion was confirmed later by Smith & Fowler (1955); this confident and authoritative view referred to that complication which alone has accounted for between 40% and 50% of deaths among untreated hypertensives.

By 1959 Leishman could demonstrate an improvement in the overall mortality of hypertension as a result of treatment, so that within ten years of the first introduction of an effective antihypertensive chemotherapeutic agent a reduced mortality from all the major complications of the disease was definitely established.

If, therefore, such benefit can be derived from the treatment of the established disease, even in the presence of serious complications, will any further benefit follow presymptomatic diagnosis of hypertension? The principal benefit of presymptomatic diagnosis of any disorder surely lies in the application of treatment at this stage, in order to prevent the development of complications of the disease, and permit the subject to follow a normal active life, subject only to any restrictions imposed by such treatment.

In the treatment of hypertension certain principles must be accepted: (1) That most drugs used for the control of high blood pressure cause side-effects, some of which are merely unpleasant, others being potentially dangerous. (2) That, once started, with very few exceptions treatment must be continued for the rest of the patient's life. (3) That the more time and consideration given by the physician, and the more co-operative the patient, the better will be the results obtained by treatment.

Thus one not only commits the patient to a lifetime of drug administration, often productive of some symptomatic side-effects, but also commits oneself to a lifetime of supervision of that patient, and in order to justify these principles benefits of such treatment must be clearly established. I hope to demonstrate that despite such inconvenience the presymptomatic diagnosis of hypertension is desirable and to be encouraged.

The first favourable aspect of such diagnosis concerns the ætiology of the raised arterial pressure. In a small proportion of subjects in whom the arterial pressure is raised, investigation discloses the presence of a remediable lesion responsible for the raised pressure, e.g. unilateral renal disease, phæochromocytoma, aortic coarctation. Therefore the first advantage of early diagnosis lies in the early discovery of such a lesion and its successful correction or removal with the chances of reversion of the blood pressure to a normal level and subsequent maintenance at this level. Once the hypertension is firmly established, of long duration, and with complications, the removal of the ætiological cause offers little prospect of return of blood pressure to within the normal range. But the proportion of hypertensive subjects in whom a remediable cause can be demonstrated is small, and if this were to constitute the sole case for presymptomatic diagnosis, I should be hard pressed to make the case favourable. Fortunately, this is not so, and the greater bulk of evidence justifying presymptomatic diagnosis concerns the fate of the patient receiving treatment late in the course of established, usually complicated, hypertension and also, the role of early blood pressure reduction in the prevention of such complications.

I have recently analysed the results of treatment in 396 patients with severe hypertension. This is a highly selected series, for all these patients have received treatment with drugs more potent than thiazide diuretics alone, i.e. all have received ganglion- or adrenergic-blocking agents, or drugs causing noradrenaline depletion either alone or in conjunction. Therefore they have been selected by virtue of the severity of the hypertension in that the presence of complications demanded such potent therapy from the outset, or alternatively, thiazides alone had proved incapable of maintaining an adequate reduction of blood pressure. These patients have been under treatment for periods of up to eight years, during which time I have lost contact with 16, so that the analysis concerns the remaining 380.

In 37 of these patients the hypertension was in the malignant phase, and a further 87 showed Grade 3 retinal changes (Keith *et al.* 1939), i.e. showed the presence of exudates and/or hæmorrhages. The ætiology of the raised pressure in

Table 1
Ætiology of 380 cases of hypertension in respect of retinal grading

Retinal grade	*No. of cases*	*Sex* *M*	*F*	*Essential hypertension*	*Chronic pyelo-nephritis*	*Chronic nephritis*	*Renal artery stenosis*	*Polycystic kidneys*
4	37	24	13	19	13	3	2	
3	87	41	46	61	21	2	1	2
2	256	99	157	192	48	2	10	4
Total	380	164	216	272	82	7	13	6

relation to retinal grading is shown in Table 1. In addition to these 124 patients with an established retinopathy, there were many other complications present at the start of treatment, consisting of angina in 80, previous stroke in 67, cardiac failure in 40, encephalopathy in 15, and subarachnoid hæmorrhage in 2 (Table 2), making a total of 328 complications among 380 subjects undergoing treatment.

Smirk (1964) has shown that the ultimate prognosis following treatment is greatly influenced by the condition of the patient at the time of starting such treatment, i.e. the greater the number of complications present before treatment the worse will be the results obtained by treatment, and my results will support this very logical opinion.

Out of these 380 patients with serious complications of the disorder 50 have died, 62% of the deaths occurring within the first three years and 26% occurring within the period four to twelve months after starting treatment. These cases are further selected by including only those who survived the first four months of treatment, so that many of the most severely ill patients have already been excluded by such selection. The majority of deaths have been due to cardiovascular causes: Stroke 23; coronary thrombosis 10; cardiac failure 9; renal failure 3; aortic dissection 2; pneumonia 1; carcinoma of breast 1; post-operative 1.

This mortality, of only 50 deaths among 380 patients with advanced complicated arterial hypertension, constitutes a favourable response to treatment. However, in addition to these 50 deaths, a further 73 have developed serious, although not fatal, complications during the course of treatment: Stroke 21; coronary thrombosis 27; onset of angina 14; progressive impairment of renal failure 11. Thus of 380 patients treated, 123 have developed complications of the disease, 50 of these complications proving fatal.

I find this result disappointing, for of these patients, all suffering from serious complicated hypertension, almost one-third developed further serious complications during the course of treatment. Surely, in view of such results, it is preferable to introduce treatment at an early stage in the course of the disease, in order to prevent or delay the advent of such complications if such a desirable end can be achieved.

In order to determine whether or not this was possible my colleagues and I (Hamilton *et al.* 1964) started a therapeutic trial in an attempt to demonstrate whether blood pressure reduction would influence the incidence of complications, including strokes, among subjects with previously uncomplicated benign essential hypertension.

It was essential to include in such a trial only such 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, 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 mmHg over a period of at least three months' outpatient observation, entailing 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 sufficient severity to require early treat-

Table 2
Incidence of complications, other than retinopathy, before starting treatment

	Retinal changes			
Complication	*Grade 4*	*Grade 3*	*Grade 2*	*Total No.*
Stroke	9	14	44	67
Angina	6	17	57	80
Heart failure	7	16	17	40
Encephalopathy	2	1	12	15
Subarachnoid hæmorrhage	1		1	2

ment. 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 having been excluded by investigation undertaken during the three-month period of outpatient observation. Furthermore, 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 alternately in order to maintain an even number in the two. Three were ultimately rejected from the trial, one on account of age, and 2 because of suspect ætiology 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 so as to avoid prejudice regarding the introduction of treatment at any time during the course of it.

There were 61 patients who satisfied all the above criteria, and who were therefore included in the trial. 22 were men and 39 women, and 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 mmHg. (2) Fair control, implying a diastolic pressure consistently below 110 mmHg. (3) Poor control, implying a diastolic pressure consistently over 110 mmHg.

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, being 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 2 made a complete objective recovery, one was left with a residual speech defect and arm weakness, and one died from cerebral hæmorrhage proven by autopsy. Although apparently a high incidence of stroke, the numbers in the two groups are small, and these 4 strokes do not constitute a statistically significant difference from the treated group. However, among the remaining 8 patients in this group, 4 developed other complications, consisting of a coronary thrombosis in one, clinical and cardiographic changes of ventricular hypertrophy in 2, and headaches of increasing intensity, requiring reduction of blood pressure for their relief, in one other. Thus, 8 out of 12 subjects in the control group developed complications of a raised arterial pressure, compared with no complications in the 10 treated subjects, and this difference is highly significant at the 2·5% level.

There were 19 women in the control group, of whom 3 suffered a stroke; one died from a ruptured intracranial aneurysm fifteen months after starting treatment introduced for the successful relief of headaches of increasing severity; 2 others made a full objective recovery from a presumed cerebral thrombosis. Other complications arose in 5 further patients, consisting of coronary thrombosis in 2, and increasing left ventricular hypertrophy in 3. Thus, 8 out of 19 patients developed complications.

Of 20 women in the treated series, 5 developed complications, consisting of 3 strokes (one fatal cerebral hæmorrhage, and 2 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 4 in whom the control of blood pressure was considered to be poor, i.e. the diastolic pressure was never maintained below 110 mmHg, which was 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 consisting of increasing heart size. Contrast with this the 23 with inadequate control of blood pressure (19 of the control group plus 4 inadequately treated) of whom 12 developed complications, including 6 strokes. Both the overall incidence of complications, and that of strokes alone, represents a highly significant increase among the group receiving inadequate or no treatment.

Thus there is no doubt that early treatment of severe uncomplicated essential hypertension significantly reduces the incidence of complications including stroke. But the patients included in this trial, although symptomless, nevertheless were severely hypertensive, with a sustained diastolic pressure in the region of 130 mmHg. Is it justifiable to ignore milder grades of hypertension, or will any benefit follow the treatment of a young person, in the second or third decade of life,

who maintains only a mild manometric hypertension, with a diastolic blood pressure of 90–100 mmHg? I have as yet little evidence to offer on this aspect of prophylactic treatment, apart from a limited experience in the treatment of hypertension in pregnancy (Hamilton 1966), when I believe that early reduction of blood pressure does greatly increase the chances of procuring a live infant, and provides a further instance of a situation in which presymptomatic diagnosis of hypertension is necessary in order to prevent complications.

REFERENCES

Hamilton M (1966) *Postgrad. med. J.* **42**, 195
Hamilton M, Thompson E N & Wisniewski I K M (1964) *Lancet* i, 235
Keith N M, Wagener H P & Barker N W (1939) *Amer. J. med. Sci.* **197**, 332
Leishman A W D (1959) *Brit. med. J.* i, 1361
McMichael J & Murphy E A (1955) *J. chron. Dis.* **1**, 527
Morrison B (1953) *Brit. med. J.* i, 1291
Rosenheim M L (1954) *Brit. med. J.* ii, 1181
Schroeder H A (1954) *Amer. J. Med.* **17**, 540
Smirk F H
(1953) *N.Z. med. J.* **52**, 325
(1964) *N.Z. med. J.* **63**, 413
Smith K S & Fowler P B S
(1955) *Lancet* i, 417

DISCUSSION[1]

Dr J M G Wilson (*London*) drew attention to the difficulty of translating the results of experimental work, yearly suggesting the possibility of practical preventive measures, into public health administrative action. He suggested that there was need to try to work out the proportion of the national medical effort that it was reasonable to allocate to various preventive measures, for instance the type of screening clinic methods for ischæmic heart disease referred to by Dr Oliver. As an example of the practical difficulties he cited a calculation made by Professor E S Perkins for the practical implications of screening for chronic simple glaucoma by tonometry. If this form of screening were applied to all persons over the age of 40 in England and Wales, each consultant ophthalmologist would need to carry out a full ophthalmological follow-up examination on some 4,500 persons, an enormous task which, with repeat examinations, would keep them busy for the rest of their lives.

Dr Wilson thought it was necessary to consider very closely how actual forms of preventive treatment for ischæmic heart disease should be carried out with the maximum provision against waste of effort. For instance, it was well known that overweight was an important factor in ischæmic heart disease, but there were considerable practical problems in persuading people actually to reduce their weight. Overweight people constituted a high risk group and, if they could be given sufficient motive, they could be effectively treated preventively. However, there was a danger, in putting a good deal of effort into this type of prevention but failing to carry it through to a successful conclusion, with consequent waste of resources.

[1]The general discussion has been considerably abridged

Dr M F Oliver (*Edinburgh*) in reply to a question said he did not think that nowadays it was acceptable to challenge the enormous volume of epidemiological data, which were exceedingly refined, showing that hypercholesterolæmia and ischæmic heart disease were positively correlated in developed and developing countries. There was much to support the view that hypercholesterolæmia and other forms of hyperlipidæmia were not environmentally determined in developed countries, but that they were genetically determined particularly in the younger age groups.

Dr Oliver suggested that in the United Kingdom, and in the United States, people ate far too much in terms of calories and fat. Their dietary intake was well above a threshold level and the excess of dietary fat consumed was probably unimportant so far as ischæmic heart disease was concerned, once this threshold had been exceeded. The question could, however, be put another way round, by asking why it was that only 30% developed ischæmic heart disease. Why did everyone not develop ischæmic heart disease since we were all eating more or less the same diet? There were important individual differences, often genetically based, which decided whether ischæmic heart disease developed. The whole epidemic proportions of ischæmic heart disease were really contained in two factors: in hyperlipidæmia and in hypertension. Without these two risk factors little else was left.

Dr Wilson had raised an extremely important point. He had asked what effort should be put into the detection of disease in relation to the yield. This was at present imponderable but much expense and time could be wasted by launching major disease detection surveys too soon. Further progress was needed before surveys to uncover occult ischæmic heart disease were warranted. Dr Oliver suggested that the decision of when such surveys should be carried out should wait until certain rather carefully defined preventive trials had been completed, so that it could be known, for example, whether the control of cigarette smoking, hyperlipidæmia, hyperglycæmia or hypertension produced the desired yield.