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CLINICAL ASPECTS OF MALIGNANT PHASE HYPERTENSION

A thesis presented to the University of Glasgow, Faculty of Medicine,
for the degree of Doctor of Medicine by

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My interest in malignant hypertension began when I worked as a Junior House Officer in the MRC Blood Pressure Unit in Glasgow. As a registrar this interest was encouraged in the Blood Pressure Unit, and again in Dumfries and at the Royal Infirmary in Glasgow. It then took me to Johannesburg for a year when I had the opportunity to observe many cases of malignant hypertension in the urban black population of that city. On my return from South Africa I rejoined the Blood Pressure Unit and also worked in the Renal Unit in the Western Infirmary, Glasgow, where I gained further experience in the assessment and management of the disease.

I am responsible for most of the work presented in this thesis, which includes two studies (Study 2 and Study 4) conducted by junior colleagues under my supervision. I also wrote most of the papers. Certain aspects of the thesis lay outwith my area of expertise however, and I should like to thank in particular Dr GD Murray for statistical advice, Ms BM Rankin who did the tests of haemostasis, Dr JWK Robertson for computing help and Dr J Clarke who provided the control data from the Strathclyde population.

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SUMMARY

This thesis is a report on nine studies of patients with malignant hypertension who were seen in Glasgow between 1968 and 1983 (Studies 1-5, 7-9) and in Johannesburg in 1983 and 1984 (Study 6).

1. Clinical features of 139 patients with malignant hypertension.

The first study is a description of 139 patients with malignant hypertension (70 males, mean age 45 years) who were admitted to the Blood Pressure Unit in Glasgow between 1968 and 1983 (108 cases) or to the Renal Unit at the Royal Infirmary in Glasgow between 1979 and 1983 (31 cases). Average initial blood pressure was 233±27/145±18 (SD) mmHg. All patients had bilateral retinal haemorrhages and exudates, thus satisfying the WHO criteria for the diagnosis of malignant hypertension. Ninety-six also had papilloedema. Fifty-six (40%) patients had a possible underlying cause for their hypertension, particularly renovascular disease (19), chronic glomerulonephritis (13) and interstitial nephropathy (12). All but three patients had symptoms, the commonest of which were headache and visual upset. Other clinical features included serum creatinine >120 µmol/l in 79%, electrocardiographic evidence of left ventricular hypertrophy in 86%, cardiac failure in 30% and neurological complications in 17%. We conclude that malignant hypertension should be suspected in severely hypertensive patients who complain of symptoms, particularly headache and visual upset. Having confirmed the diagnosis by fundal examination, a full diagnostic evaluation, including renal arteriography, is indicated.

2. Retinal changes in the diagnosis of malignant hypertension.

The second analysis concerns the importance of different retinal changes in the diagnosis of malignant hypertension. It is in two parts. Four observers reviewed 56 photographs of fundi from patients with severe

hypertension and grade III or IV retinopathy. Complete agreement on the presence or absence of haemorrhages and exudates was recorded in 93% and 95% of cases respectively. Opinion on papilloedema was divided, however, with agreement between all four observers in 61% of cases only. In the second part of the study, the relation between different retinal changes and survival was examined by life tables. Ten year survival was 46% in patients with bilateral haemorrhages and exudates alone (n= 43) and 48% when papilloedema was present as well (n= 96). Multivariate analysis confirmed that papilloedema was not related to survival in these patients. These results suggest that papilloedema is an unreliable physical sign, and that it does not adversely affect prognosis in hypertensive patients who already have bilateral retinal haemorrhages and exudates.

3. Cigarette smoking may predispose to malignant hypertension.

The third analysis tests the possibility that cigarette smoking may predispose to the malignant phase in susceptible subjects. The smoking habits of 82 patients with malignant hypertension were compared with those of subjects in three control groups matched for age and sex. Sixty-seven (82%) patients with malignant hypertension were smokers, compared with 41 (50%) and 71 (43%) patients in two control groups with non malignant hypertension, and 43 people (52%) in a general population survey. The excess of smokers in the malignant phase group was significant for both sexes separately and together, for all forms of smoking combined and for cigarette smoking alone. It is concluded that hypertensive patients who smoke are more likely to develop the malignant phase than those who do not.

4. Relation between oral contraceptives and malignant hypertension.

The fourth paper examines the relation between the oral

contraceptive pill and malignant hypertension in women of childbearing age. Thirty-four of the women in the main analysis were aged 15-44 years, and of these 11 were taking oral contraceptives at presentation. All had normal blood pressure before starting the pill. In four, the interval between the start of oral contraceptives and the diagnosis of malignant phase was less than 4 months, and in 8 no other cause for the hypertension was found. Underlying renal disease and renal failure were less common among pill users than among non-users with malignant hypertension who were of similar age. No pill user became normotensive after withdrawal of the pill, but blood pressure was well controlled (diastolic <90 mmHg) in three patients on one drug only. By contrast, all 23 non-users needed two or more antihypertensive drugs to control blood pressure. Ten year survival was 90% among pill users and 50% among non-users. These results suggest that oral contraceptives may be a common cause of malignant hypertension in women of childbearing age. If the pill is stopped and underlying renal disease can be excluded, the long-term prognosis for such patients is excellent.

5. Abnormal haemostasis and malignant hypertension.

The fifth analysis is a test of the hypothesis that low grade coagulopathy is a necessary step in the transition from the benign to malignant phase. Eighteen patients with malignant hypertension, 18 healthy controls and 18 patients with non-malignant hypertension were studied. Both groups of controls were matched for age, sex and smoking habit with patients in the malignant phase, and the hypertensive controls were selected in addition to have similar blood pressure, serum creatinine and renal pathology. Malignant hypertensives had higher levels of fibrinogen, α2 macroglobulin and plasminogen than non-malignant hypertensives, and both groups of hypertensives had significantly increased plasma viscosity, blood viscosity, fibrinogen, factor VIIIc and beta-thromboglobulin together with

significantly decreased haematocrit, anti-thrombin III and platelet counts than healthy controls. These results are consistent with the hypothesis that low grade coagulopathy is important in the pathogenesis of the malignant phase, but also raise the possibility that abnormal coagulation may be a consequence of the disease.

6. Slow release nifedipine and atenolol as initial treatment for malignant hypertension.

The sixth study was a trial of treatment. It was conducted in the Non-European Hospital in Johannesburg where 20 consecutive black patients with untreated malignant hypertension were randomised to receive either slow release nifedipine 40mg at 0 and 12h, or atenolol 100mg at 0h only. Baseline blood pressure was 233/142 mmHg in patients given nifedipine and 226/141 mmHg in patients given atenolol. The rate of fall of pressure was greater after nifedipine, whose maximum hypotensive effect occurred 4-5 h after each dose. Blood pressure decreased more slowly and more enduringly after atenolol, although the extent of the fall was the same: Δ BP 5h after first dose nifedipine was 67/41 mmHg; Δ BP 16 h after atenolol was 64/40 mmHg. There were no precipitous falls of pressure, and no patient developed focal neurological signs during treatment. These results support recommendations that most patients with malignant hypertension can be managed without recourse to parenteral therapy.

7. Malignant hypertension presenting with acute renal failure.

The seventh analysis documents the clinical features and outcome of 7 consecutive patients presenting to the Renal Unit at the Royal Infirmary in Glasgow with malignant essential hypertension and acute renal failure. Only one of these patients was known to have been hypertensive previously, 4 were oligo-anuric when first seen, and all 7 needed dialysis. Good control

of blood pressure was associated with significant recovery of renal function in 5 of the 7 patients after 10-44 days of dialysis. Mean serum creatinine when last measured was 248 µmol/l (range 125-350 µmol/l) after an average of 24 months (range 15-62 months) follow up. The only feature which appeared of value in predicting recovery of renal function was the presence of tubular regeneration on renal biopsy. This was present in 4 of 5 biopsies from patients who recovered, but in neither of the two who did not. These results confirm previous reports of recovery of renal function in patients presenting with malignant essential hypertension and acute renal failure. We have also shown that the proportion of patients who improve may be higher than has been recognised, and that recovery may last several years.

8. Renal outcome in malignant hypertension.

To determine whether there were other circumstances in which long-term improvement of renal function may occur, we examined serial changes in serum creatinine concentration in the main analysis of 139 patients. End-stage renal disease occurred commonly during long-term follow-up in patients with chronic glomerulonephritis (13/13) and interstitial nephropathy (9/12), irrespective of blood pressure control, and in patients with essential hypertension who presented with serum creatinine >300 µmol/l but did not require dialysis immediately (11/15). By contrast, renal function tended to remain stable or improve slightly in the majority of patients with renovascular disease, and in patients with malignant essential hypertension whose serum creatinine was <300 µmol/l when first measured. The most striking improvements in renal function were seen in the 5 patients in this series with malignant essential hypertension and acute renal failure, 4 of whom showed significant reduction in serum creatinine after dialysis and control of their blood pressure. The implications of these findings are that in glomerulonephritis and interstitial nephropathy, deterioration of renal

function represents the natural history of a progressive underlying disease; and that in malignant essential hypertension, irreversible renal damage will usually have occurred by the time the serum creatinine concentration exceeds 300 μmol/l unless acute renal failure is superimposed.

9. An analysis of survival in malignant hypertension.

The purpose of the ninth analysis was to determine the extent to which the mortality of the 139 patients with malignant hypertension exceeded that of controls with non-malignant hypertension and the general population from which they were derived. Overall survival among patients with the malignant phase was 63% at 5 years and 47% at 10 years. Patients with malignant hypertension were twice as likely to die as non-malignant hypertensives who attended the Glasgow Blood Pressure Clinic and were matched for age, sex and initial diastolic pressure, who in turn had a much reduced life expectancy when compared with an age and sex matched general population from the Strathclyde Region. Further analyses showed that initial serum creatinine was strongly related to outcome in patients with malignant phase, and that, proportionately, renal deaths were 3 and 9 times more common among patients with malignant hypertension than controls from the clinic and the general population respectively. Despite improved survival compared with previous years, renal failure remains the most serious manifestation of patients with this disease.

PUBLICATIONS

As a result of the work described in this thesis, Studies 2,3,4,5,6,7 and 9 have been published:-

Study 2. McGregor E, Isles CG, Jay JL, Lever AF, Murray GD. Retinal changes in malignant hypertension. Br Med J 1986; 1: 233-234.

Study 3. Isles CG, Brown JJ, Cumming AMM et al. Excess smoking in malignant phase hypertension. Br Med J 1979; 1: 581-583.

Study 4. Lim KG, Isles CG, Hodsman GP, Lever AF, Robertson JWK. Malignant hypertension in women of childbearing age and its relation to the oral contraceptive pill. Br Med J 1987; 1: 1057-1059.

Study 5. Isles CG, Lowe GDO, Rankin BM et al. Abnormal haemostasis and blood viscosity in malignant hypertension. Thromb Haemostas 1984; 52: 253-255.

Study 6. Isles CG, Johnston AOC, Milne FJ. Slow release nifedipine and atenolol as initial treatment in blacks with malignant hypertension. Br J Clin Pharm 1986; 21: 377-383.

Study 7. Isles CG, McLay A, Boulton-Jones JM. Recovery in malignant hypertension presenting as acute renal failure. Q J Med 1984; 53: 439-452.

Study 9. Isles CG, Lim KG, Boulton-Jones JM et al. Factors influencing outcome in malignant hypertension. J Hypertension 1985: 3: (Suppl 3) S405-S407.

Photostat copies of these papers are included at the end of the thesis.

INTRODUCTION

Clinicians who manage patients with malignant hypertension have witnessed some remarkable changes in recent years. The incidence of the disease appears to have fallen, at least in the United Kingdom and other western countries (1). Reduction of blood pressure within minutes by parenteral therapy, common practice in the 1950's and 1960's, is no longer recommended as a routine procedure, as it is now recognised that initial management is best achieved by one or two drugs given orally (2). Survival has improved as a result of more effective antihypertensive drug therapy and the increasing availability of renal dialysis and transplantation (3-6).

Despite these encouraging trends, some difficult areas remain. Malignant hypertension continues to be a major problem in developing countries and is thought likely to stay so for some time (7). As the disease becomes less common in the West, too few doctors see enough of its complications, especially hypertensive encephalopathy, to gain expertise in managment (2). Moreover, despite improved survival overall, the prognosis for patients with impaired renal function remains poor (3-6).

My thesis is concerned primarily with clinical aspects of malignant hypertension. It is in two parts. The first is a review of the literature, and the second is a report on nine studies of patients with malignant hypertension who were seen in Glasgow between 1968 and 1983, and in Johannesburg in 1983 and 1984.

LITERATURE SURVEY

Introduction

In this literature survey, I shall review the diagnosis, pathology, pathogenesis, clinical features, management and prognosis of malignant hypertension with particular reference to recently published work.

Diagnostic criteria

The new WHO criteria are probably the most useful, namely that patients should have severe hypertension with bilateral retinal haemorrhages and exudates (8). Diastolic blood pressure is usually greater than 130 mmHg but there is no absolute level above which malignant hypertension always develops and below which it never occurs. Lower pressures are said to be characteristic of patients with renal failure (9) and of patients with eclampsia and acute glomerulonephritis (10), although the latter are both uncommon in the UK today. Conversely, patients are frequently seen with pressures greater than 130 mmHg but without malignant hypertension (11). Other features of the disease such as microangiopathic haemolytic anaemia (MAHA) and renal failure are not always present.

Pathology

Although fibrinoid arteriolar necrosis is usually regarded as the histological hallmark of the acute stage of the disease, it is not necessarily the most significant finding (11,12). Subintimal cellular proliferation of the interlobular arteries of the kidney is seen more commonly and could be important in its own right as intimal thickening in these small arteries may be so great as to occlude their lumina (Fig 1). It is likely that vessel damage of this type plays a major part in causing the chronic renal ischaemia, and thus the chronic renal failure, which so often accompanies malignant hypertension (11). Neither fibrinoid arteriolar necrosis nor subintimal cellular proliferation are pathognomonic for malignant hypertension however, and one or other (and sometimes both) may be seen

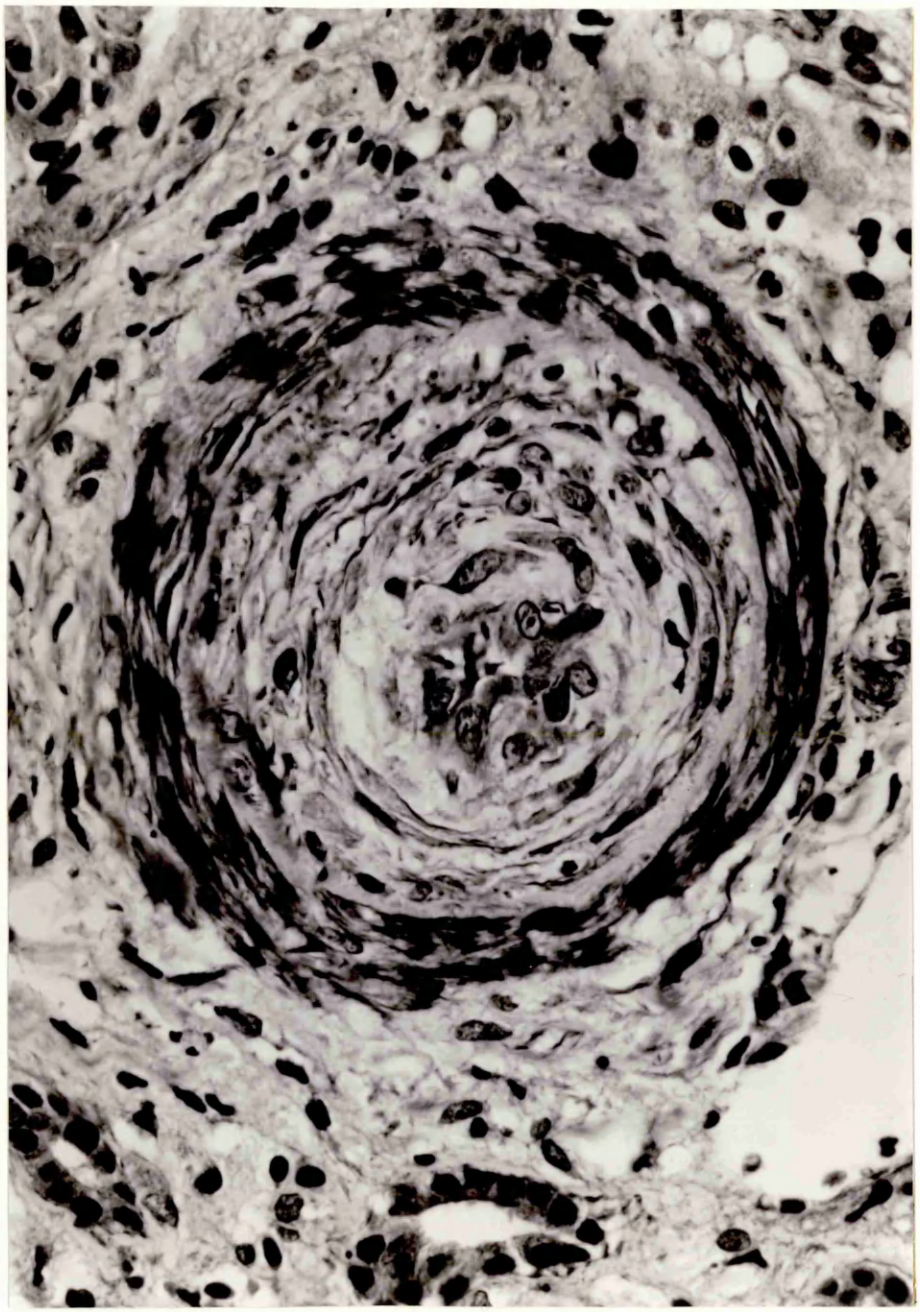

FIGURE 1 Renal biopsy in a patient with malignant hypertension showing marked subintimal cellular proliferation of an interlobular artery. The vessel lumen appears to have been completely occluded by the thickened intima.

in progressive systemic sclerosis, accelerated graft rejection, postpartum acute renal failure, haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura (13).

Pathogenesis

The events leading to these pathological changes are still not fully understood. Most accept that increased arterial pressure is a necessary feature and that the rate of rise of pressure is more important than the actual level achieved, but opinion then divides on whether there are other factors capable of determining which patients will enter the malignant phase. Some have argued that increased pressure is the only factor (14), others that important roles are played by immunological changes (15), intravascular coagulation (16,17), cigarette smoking (18-21), the oral contraceptive pill (22-30) and vasoactive agents (31,32).

Whichever of these hypotheses is true, the appearance of alternating bands of constriction and dilatation in arterioles (the so called "sausage-string" effect) probably heralds the onset of malignant hypertension (11). It is likely that the dilated segments represent focal failure of the vessel wall to resist a rapid rise in intraluminal pressure, and it has been shown that these areas are abnormally permeable to plasma proteins (33). Disruption of the vessel wall may then trigger the following changes: insudation of plasma leading to deposition of fibrin i.e. fibrinoid necrosis (33); platelet aggregation causing release of growth factors which could well cause the subintimal cellular proliferation (34); and activation of the coagulation system (16,17). The latter may promote further deposition of fibrin, not only in the vessel wall, but also within the microcirculation causing microangiopathic haemolytic anaemia (35).

Epidemiology

Malignant hypertension can occur at any age but rarely does so in patients older than seventy. For the reasons outlined above this may be

because malignant hypertension is most likely when severe hypertension develops rapidly. If instead, blood pressure increases gradually over many years to reach very high levels at an advanced age, vasculature may have time to adapt and so avoid the disruption which leads to subintimal cellular proliferation and fibrinoid necrosis (36).

Most studies (3,5,7,37,38) but not all (4,6) show a preponderance of male patients. Also, the disease seems commoner in blacks than whites (39,40). Indeed while many authors now consider malignant hypertension to be rare among whites (1) it remains a common problem in developing countries; in a recent report from Johannesburg no fewer than 2% of all admissions to the medical wards of the Non-European Hospital were as a consequence of malignant hypertension (7).

Underlying causes

It is well recognised that patients with malignant hypertension are more likely to have an identifiable underlying cause for their high blood pressure than are patients with non malignant hypertension. Renal and renovascular diseases are the causes most commonly found (3-6,41-43) although any cause of raised blood pressure can lead to the malignant phase if the hypertension is severe enough and if the blood pressure has risen so rapidly as to exceed the autoregulatory capacity of the retinal circulation. Even patients with Conn's syndrome, a condition previously thought to cause only mild or moderate hypertension, may develop the malignant phase (44,45).

Cigarette smoking

The relation between cigarette smoking and hypertension is an intriguing one. Epidemiological studies show an inverse relation between smoking and blood pressure (46), and yet the act of smoking causes a transient rise in pressure (47). The increased mortality rate among smokers with hypertension is also well known (48). That smoking may predispose to

malignant hypertension in patients who are already hypertensive, was first noted by our group in Glasgow (18) and by colleagues in Birmingham (19). Similar findings have subsequently been reported from other centres (20,21). Possible mechanisms involved are discussed on page 43 of this thesis.

Oral contraceptive pill

The oral contraceptive pill causes a small rise in blood pressure in most women and a large rise in pressure in a few (49). A number of case reports suggest an association between oral contraceptives and malignant hypertension (22-30). A causal association seems likely when patients who were previously known to be normotensive develop malignant hypertension within a few weeks or months of starting oral contraceptives, even if as is usually the case their blood pressure does not fall to normal when the pill is stopped. Although it is generally agreed that the risk of malignant hypertension is less with low oestrogen pills, we have seen a patient who was previously normotensive and who presented with malignant hypertension only eight weeks after starting a pill containing a low dose (20 μg) of ethinyloestradiol. No other cause for her hypertension was found (30).

Clinical features of maligant phase hypertension.

The wide variety of clinical features which may occur in malignant hypertension are well described in earlier reviews (37,38). Recent onset of headache and visual upset are the commonest complaints (37,38). The headache of malignant hypertension is said to be worse in the morning (50,51) and visual symptoms are generally related in degree to the severity of the retinal and optic nerve changes.

Renal failure is the most serious manifestation of malignant hypertension (3-7,52). Despite investigation it is often difficult to be certain in individual patients whether hypertension preceded and perhaps caused renal failure or whether an underlying renal disorder caused the hypertension. Exclusion of renovascular disease is important under these

circumstances since surgical intervention in selected cases may improve both blood pressure control and renal function (53). Otherwise, and in the majority of cases, the distinction between primary hypertension and primary renal disease may yield useful prognostic information (see later) but does not lead to a change in management.

The heart is commonly involved in malignant hypertension and breathlessness due to cardiac failure is a frequent clinical manifestation. By contrast, ischaemic chest pain occurs rarely (38). Left ventricular hypertrophy may be prominent (54) but is not a universal finding (55). When absent it is likely that malignant hypertension was of sudden onset and not preceded by a long period of non malignant hypertension.

A number of neurological complications may occur (56). The most serious of these is hypertensive encephalopathy (57-61) whose clinical hallmark is altered consciousness, ranging from agitation to coma. Other features include headache, nausea and vomiting, seizures and changing focal neurological signs. Fundal examination will show retinal haemorrhages, exudates and often papilloedema. Difficulty may occur in distinguishing hypertensive encephalopathy from cerebral haemorrhage, since severe hypertension and ischaemic retinopathy may be present in both conditions. As a general rule patients with major lateralising signs are more likely to have cerebral haemorrhage (59). The distinction is important because the rate at which blood pressure should be lowered depends on the specific clinical diagnosis.

Gastrointestinal symptoms including anorexia, nausea, vomiting, abdominal pain and weight loss occur commonly in malignant hypertension. The association of malignant hypertension and weight loss is not explained entirely by the degree of renal impairment (38). Abdominal pain due to acute pancreatitis (62) and small bowel infarction (63) has also been recorded.

Other well recognised features of malignant hypertension include microangiopathic haemolytic anaemia (MAHA) and secondary hyperaldosteronism. MAHA is thought to arise when red cells are fragmented by fibrin strands laid down within the microcirculation (35,64). The diagnosis is based on the presence of red cell fragmentation on the blood film and, when fully developed, MAHA is associated with low haemoglobin, low platelets and increased reticulocytes.

Secondary hyperaldosteronism occurs more frequently than MAHA in malignant hypertension, but again it is not a universal finding. Renal ischaemia secondary to unilateral renal artery disease, or to malignant hypertension per se, increases secretion of renin which, via angiotensin II, is the likely cause. Hypokalaemia will usually be present and is a useful clue to the diagnosis. A few patients develop hyponatraemic hypertensive syndrome, a vicious cycle in which high blood pressure causes pressure natriuresis from the unaffected kidney in unilateral renal artery stenosis. This leads to sodium depletion and further elevation of angiotensin II with worsening secondary hyperaldosteronism and symptoms of thirst, polyuria and weight loss (65-70).

Differential diagnosis of retinopathy

Usually the retinal haemorrhages of the malignant phase are flame-shaped, and the exudates "soft" (fig 2a). A particularly florid example is shown in fig 2b in which hard exudates, macular stars and papilloedema are also present. The pathogenesis of this form of hypertensive retinopathy has recently been reviewed (71). Although retinal haemorrhages and exudates are necessary features for the diagnosis of malignant hypertension, they are not pathognomonic. Similar appearances may be seen in diabetes mellitus (fig 2c), retinal vascular occlusion (figs 2d,2e), raised intracranial pressure (fig 2f), gastrointestinal haemorrhage and a number of haematological disorders including anaemia (fig 2g), polycythaemia, leukaemia and

2a

2b

2c

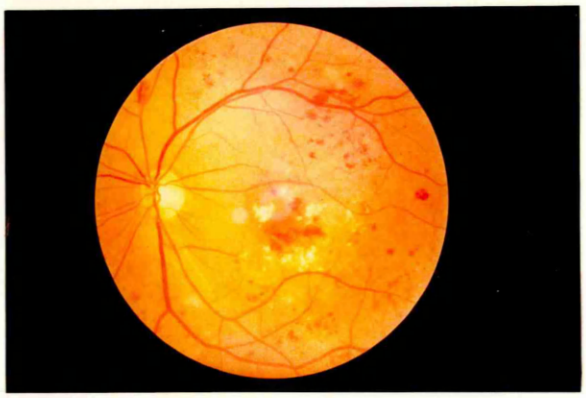

FIGURE 2 Differential diagnosis of hypertensive retinopathy:-
2a - malignant hypertension showing flame shaped haemorrhages and soft exudates.
2b - malignant hypertension: a particularly florid example showing flame shaped haemorrhages, hard and soft exudates, macular star and papilloedema.
2c - diabetic retinopathy: dot and blot haemorrhages and hard exudates are typical, but occasionally an ischaemic retinopathy indistinguishable from that of malignant hypertension may occur.

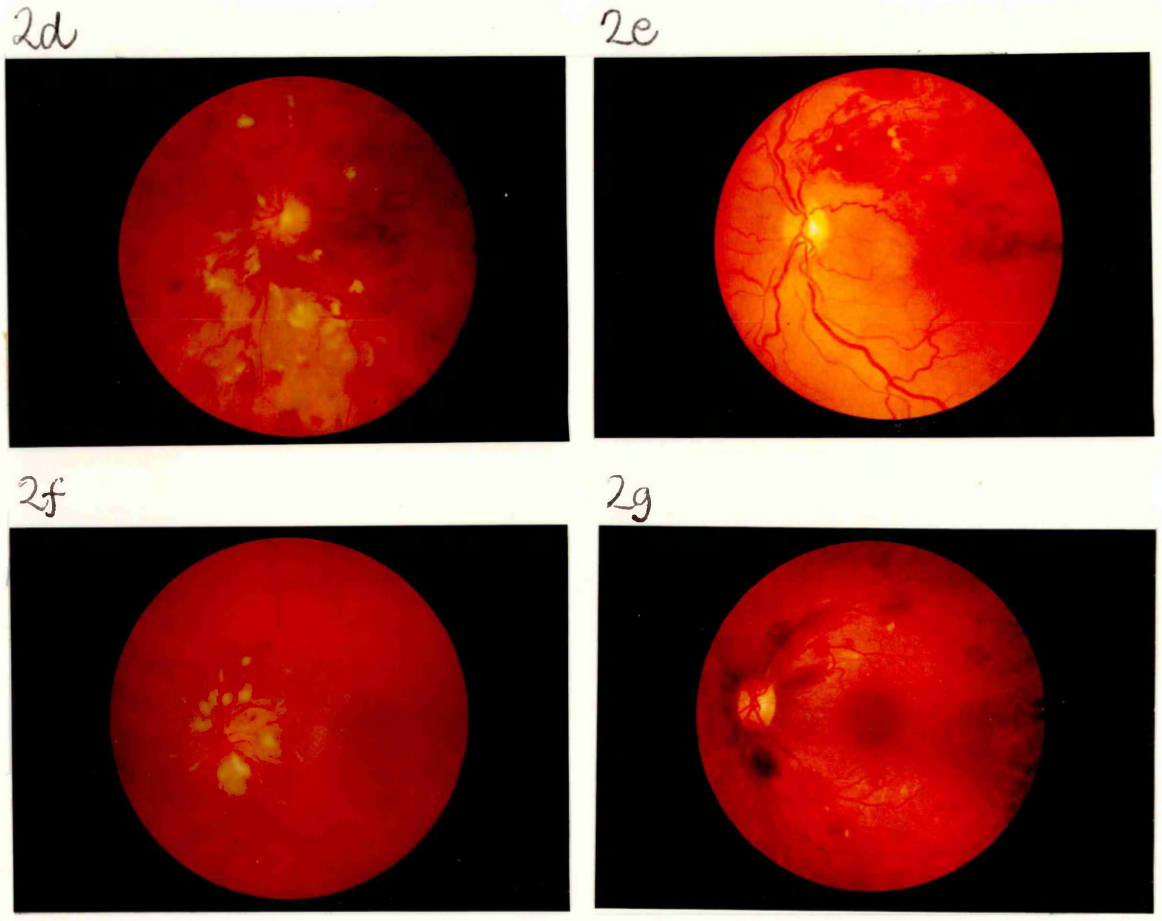

FIGURE 2 Differential diagnosis of hypertensive retinopathy (continued)
2d - central retinal vein occlusion: an engorged retina, with haemorrhage a prominent feature, is typical.
2e - branch retinal vein occlusion: haemorrhages and exudates are limited to the area of the affected vein.
2f - raised intracranial pressure: fundus appearance may be similar to that of malignant hypertension except that venous distension is greater.
2g - anaemia: haemorrhage is the main feature of this form of retinopathy, in this case due to pernicious anaemia.

Waldenstrom's macroglobulinaemia, all of which may produce an ischaemic retinopathy (72).

The occurrence of such similar retinal changes in these apparently unrelated conditions suggests a common pathogenesis which, Pears & Pickering have postulated, may be focal hypoxia (73). Thus it may be useful to consider the retina as having a limited range of responses to a variety of different insults. In the same way that proteinuria may be the end result of renal damage from drugs, toxins, immunological and multisystem disease, so may haemorrhages and exudates be the ultimate expression of hypertension, diabetes and other disorders which affect the retinal circulation. If correct, then this model may also explain the tendency for ischaemic retinopathy to develop at lower blood pressures when another disorder capable of causing ischaemic retinal damage is present. The increased incidence of exudates in diabetics who are hypertensive, may be an example (74), and the well-recognised tendency for ischaemic retinopathy to develop at lower pressures in renal patients (9) may be another, reflecting the combined insults of hypertension and anaemia.

Initial Management of malignant hypertension

The ideal rate of reduction of blood pressure in patients with malignant hypertension must be a balance between the risks of inadequate and too rapid reduction of blood pressure. Central to this is the phenomenon of autoregulation, the means by which an organ maintains a constant blood flow across a wide range of arterial pressures (fig 3a) (75); the brain in particular has little capacity to function properly without an adequate blood supply, and shows clear autoregulation of blood flow (76). In uncomplicated malignant hypertension and other forms of chronic hypertension, the range of cerebral autoregulation is reset upwards and patients may therefore be less able to compensate for a sudden fall in pressure (fig 3b). Neurological complications, particularly cerebral infarction

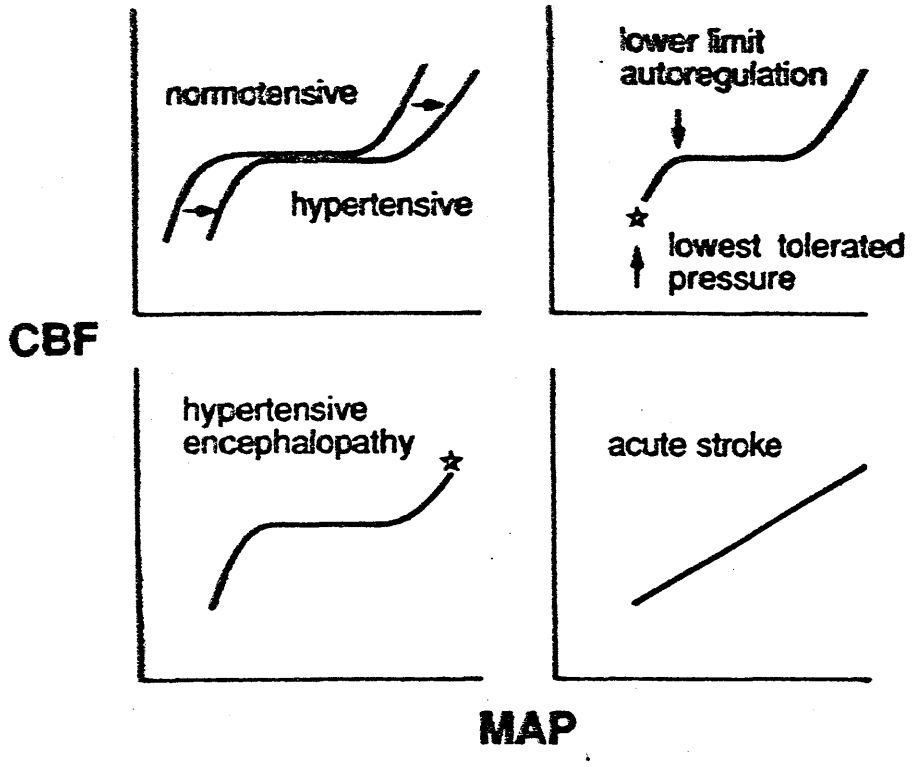

FIGURE 3 Relation between cerebral blood flow (CBF) and mean arterial pressure (MAP). In normotensive man CBF is maintained at 50ml/100g/min across a wide range of arterial pressure from 65-140 mmHg. In hypertension the curve is reset upwards (fig 3a). The lower limit of autoregulation is the point at which CBF begins to fall, and the lowest tolerated pressure the point at which symptoms of cerebral ischaemia are likely to develop. It follows that symptoms of cerebral ischaemia are more likely in hypertensive patients whose blood pressures are reduced too quickly (fig 3b). In hypertensive encephalopathy the rate of rise of blood pressure is thought to have been so rapid as to have exceeded the upper limit of autoregulation, causing hyperperfusion, cerebral oedema and, if untreated death (fig 3c). Cerebral autoregulation is lost in the area of an acute stroke so that CBF to the ischaemic area becomes pressure dependent (fig 3d).

in the watershed areas (so called boundary zone infarction) (77,78) and blindness (79-82) are well recognised. The kidney (83) and spinal cord (84) are also susceptible to ischaemic damage when blood pressure is lowered too quickly, as a result of which it has been suggested that abrupt forms of therapy, particularly injected drugs, be avoided in most cases.

Uncomplicated malignant hypertension

Despite their widespread use in the past, there is no evidence that parenteral drugs are required, and oral agents are usually quite satisfactory (85-87). Our current practice is to prescribe atenolol 50-100mg orally or nifedipine retard 20-40mg b.d., initially, and usually to add a diuretic on the second day. Some authors recommend a diuretic as part of the initial therapy (2), but this has yet to be tested in a clinical trial. In light of the upward shift in the autoregulatory curve it is probably unwise to attempt full control of pressure in the first week of treatment.

Malignant hypertension with renal failure

It used to be recommended that blood pressure be lowered cautiously in patients with malignant hypertension and renal failure (88) since acute loss of renal function resulting from rapid lowering of blood pressure was commonly fatal before dialysis became generally available. Opinion has since changed such that patients with and without renal failure are now treated similarly. The argument now is that renal failure will worsen unless the vessel changes can be made to heal, and that this will only happen if blood pressure is lowered (89).

Hypertensive heart failure

Hypertensive heart failure differs from other forms of cardiac failure in that drug treatment not only relieves symptoms, but also removes one of its underlying causes, increased afterload. It generally responds to conventional treatment with diuretics and vasodilators, such as oral nifedipine or hydralazine. Reflex tachycardia is rarely a problem since the

sympathetic nervous system is already maximally stimulated (90).

Hypertensive encephalopathy

Fortunately, hypertensive encephalopathy is extremely uncommon but as a consequence of this few doctors in Europe, America and Australia see sufficient patients to gain experience in management. The drug of choice is one with rapid onset of action, producing a predictable fall in blood pressure, having short duration of therapeutic effect and preserving cerebral blood flow. A drug which fulfils most of these criteria is nitroprusside (91). Although widely recommended, particular care has to be taken with this drug which is inactivated by light and must be given by constant intravenous infusion. The hypotensive effect of nitroprusside is so short lived that if the infusion is interrupted for any reason, blood pressure will very quickly return to baseline levels. Moreover nitroprusside has a toxic metabolite, thiocyanate, which is excreted by the kidneys. Experience in Glasgow with labetalol given by intravenous infusion suggests that this might be a useful alternative treatment for hypertensive encephalopathy (92). Intravenous hydralazine and diazoxide have also been recommended (93).

Hypertension with acute stroke

Regrettably there are still no useful data to indicate how best to manage increased blood pressure in the presence of an acute stroke (2). Special considerations in the hypertensive stroke patient are that blood pressure is often labile and may fall spontaneously, also that the autoregulatory response is lost locally, causing cerebral blood flow to the ischaemic area to become pressure dependent (fig 3d). In patients with subarachnoid haemorrhage there is the additional risk of vasospasm. Moreover, as already discussed, the distinction between cerebral haemorrhage and hypertensive encephalopathy, can sometimes be difficult. Under the circumstances it would seem sensible to withhold antihypertensive drugs for at least 24-48 hrs if diastolic pressure is less than 120 mmHg.

Treatment should then be initiated cautiously with either a thiazide diuretic or a beta blocker. If diastolic pressure is greater than 120 mmHg initially then the correct course of action is unclear, although a single oral dose of atenolol 50 mg or nifedipine retard 20 mg would not seem unreasonable in the first instance. In the unconscious stroke patient, recourse to intravenous therapy may be necessary.

Effect of treatment on retinopathy and vision

The risk of precipitating or worsening visual loss when blood pressure is lowered too quickly in patients with malignant hypertension has already been discussed. In most patients, the retinal lesions clear and vision improves with effective treatment (71). Although a fully formed macular star may take a year to disappear (fig 4a,b) less severe retinopathy clears over a period of 3-6 months (fig 4c). Not every fundus returns completely to normal however and two late changes may occasionally be seen: optic atrophy and pipe stem sclerosis of the retinal arterioles (fig 4d). Patients who present with severe maculopathy or who develop optic atrophy may have residual visual impairment, but otherwise, and in the great majority the prognosis for vision is excellent.

Effect of treatment on renal function

It is useful to consider short term changes in renal function and long term renal outcome separately. Lawton (94) studied the short term course of renal function in malignant hypertensives with renal insufficiency, and concluded that when blood pressure is controlled initially renal function will stabilize in 10%, deteriorate progressively in 30% and deteriorate transiently before improving in the remainder. Lawton also showed that the latter group can usually be identified after two weeks of antihypertensive therapy and that in the short term, patients with primary renal parenchymal disease did not have a worse prognosis than those without primary renal disease. These findings are consistent with current knowledge of the effects of

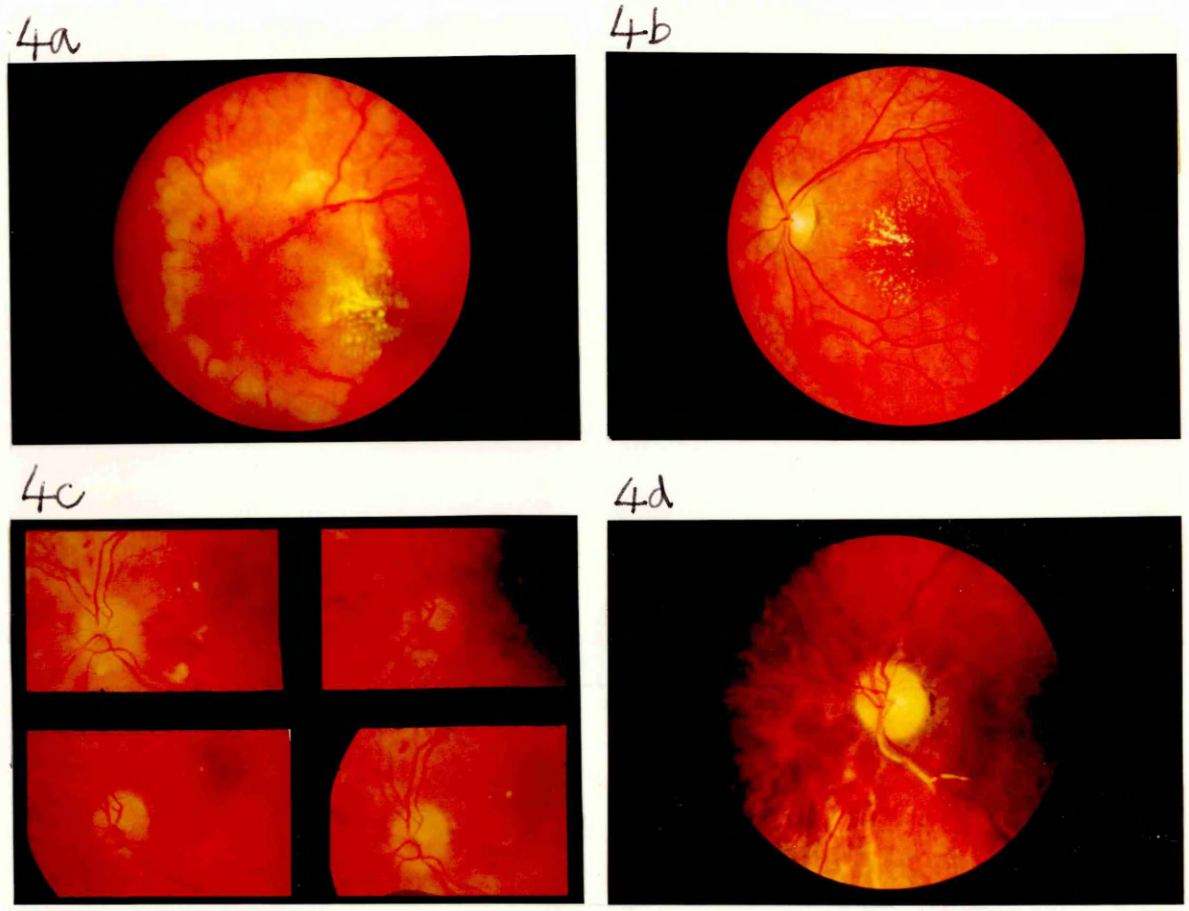

FIGURE 4 Changes that may occur in the retina during treatment:
4a and 4b - fundal appearances of a 15 year old girl with malignant hypertension, taken at presentation (fig 4a) and after nine months of treatment (fig 4b). Papilloedema had resolved completely by this time but the macular star was still present.
4c - resolution of fundal changes in a less severe case. Moving from top left in clockwise direction, these photographs were taken 3,5,8 and 16 weeks after presentation. By 16 weeks the papilloedema and most of the haemorrhage and soft exudate had disappeared, leaving only a small trace of hard exudate.
4d - optic atrophy and pipe stem sclerosis of the retinal arterioles, two years after successful treatment for malignant hypertension.

treatment on the hypertensive vascular lesions in the kidney and the possible adverse consequences of reducing renal perfusion pressure.

The question of whether renal function can be improved or maintained by treatment in the long term is perhaps more important. In Study 7, I describe seven patients with malignant essential hypertension and acute renal failure, five of whom showed substantial and prolonged improvement in renal function following a period of peritoneal dialysis and meticulous blood pressure control (95). From this experience and that of others (96-108) it seems likely that such patients represent a distinct syndrome, early recognition of which may allow a more reassuring prognosis than was previously considered possible.

For the larger number of patients with malignant hypertension who do not present with acute renal failure, it is now generally accepted that renal prognosis is determined by the level of serum creatinine concentration at presentation and the presence or absence of underlying renal disease (109-115). In Study 8, I describe our experience in Glasgow of the differences in renal outcome when malignant hypertension is superimposed upon renal parenchymal disease, renal vascular disease and essential hypertension.

Survival

In 1939 Keith et al published life tables showing that five year survival in untreated patients with malignant hypertension was as low as 1% (116). Similar findings were reported among untreated patients from the UK (38). With the advent and development of effective antihypertensive drug therapy, (52) and more recently the introduction and increasing availability of renal dialysis and transplantation, the prognosis of malignant hypertension has improved such that in 1979 Gudbrandsson and colleagues were able to report a five-year survival of almost 75% (3). Recently published data from other centres including Glasgow (4), Melbourne (5) and Leicester (6) support this view. All authors agree that the single most

important predictor of outcome is the degree of renal impairment at initial presentation, and it seems likely that differences in the proportion of patients with impaired renal function will account for many of the remaining differences in results. Survival of patients with renal function that is normal or only mildly impaired may be little different from that of non malignant hypertensives matched for age, sex and pressure (4).

AIMS OF STUDY

The nine analyses which follow were developed from points raised in this survey of the literature. The first is a general description, including clinical features, of 139 patients with malignant hypertension seen in Glasgow between 1968 and 1983. The second is of the importance of different retinal changes in the diagnosis of malignant hypertension. The third tests the possibility that cigarette smoking may predispose to the malignant phase in susceptible patients. The fourth examines the relation between the oral contraceptive pill and malignant hypertension in women of childbearing age. The fifth evaluates the role played by abnormal haemostasis in the pathogenesis of the disease. In study six the efficacy and safety of slow release nifedipine and atenolol as initial treatment for malignant hypertension are compared. The seventh and eighth analyses examine the changes that occur in renal function during treatment of malignant hypertension, and the ninth is a study of survival.

PATIENTS & METHODS

Malignant hypertension

Seven of the nine analyses presented in this thesis are based on a consecutive series of 139 patients with malignant hypertension who were admitted to the Blood Pressure Unit at the Western Infirmary in Glasgow between 1968 and 1983 (108 cases) or to the Renal Unit at the Royal Infirmary in Glasgow between 1979 and 1983 (31 cases). Seventy were men, mean age 45.5±11.0 (SD) years, 69 were women, mean age 42.3±15.8 years.

Selection was by case review of patients with hypertension and grade 3 or 4 retinopathy (n= 193), and a decision to include a patient based entirely on the appearances of the retinal fundus was taken by an observer (Dr AF Lever) who was unaware of the clinical course or outcome. The diagnosis of malignant hypertension was accepted if the attending physician had recorded the presence of haemorrhages and exudates in both fundi. If this information had not been given, but bilateral retinal haemorrhages and exudates were present in fundal photographs taken at the time of admission, the patient was also included in the study. Fundal photographs were available in 156 of the 193 patients.

In the remaining two studies, different sources of patients with malignant hypertension were used. Study 6 was a randomised controlled comparison of two drugs given orally to 20 consecutive black patients with malignant hypertension in Johannesburg. Malignant hypertension occurs too infrequently in the United Kingdom for such a trial to have been conducted in Glasgow. Study 7 was based on a series of 7 consecutive patients presenting to the Royal Infirmary in Glasgow with malignant essential hypertension and acute renal failure. Four of the 7 patients belonged to the main cohort of 139 patients, the remaining 3 were identified by review of Royal Infirmary files.

Controls

Comparisons were made with four control groups: with patients attending the Glasgow Blood Pressure Clinic who had non malignant hypertension (117), with healthy volunteers, with apparently healthy subjects identified during the course of an epidemiological survey of middle aged adults in Renfrew and Paisley (118-119), and with data derived from the general population of Strathclyde (120). The particular control population chosen for each analysis will be described in more detail with the report of that analysis, but it may be useful to discuss the two main control populations more fully here.

Control patients from the Glasgow Blood Pressure Clinic were from a pool of 3783 patients (1868 males, mean age 49 years) with non malignant hypertension who attended the clinic between 1968 and 1983 (117). These patients were often severely hypertensive and were referred to the clinic by their general practitioners or by other hospital doctors. All had diastolic blood pressure of 90 or more before treatment; average blood pressure at initial acceptance to the clinic was 183/110. Full details of the clinic and an analysis of mortality among patients attending the clinic have been reported (117). The main advantage to us of using clinic patients as controls was that these patients were seen in the same city, over the same period and often by the same doctors, as our patients with malignant hypertension. Also, computerisation of clinic data meant that it was a relatively simple procedure to match malignant hypertensives individually with non-malignant controls for whatever baseline characteristics (for example, age, sex, year of presentation and initial blood pressure) were considered necessary for a particular analysis.

For our second main control group, we used data derived from the general population of Strathclyde, since the majority of our patients came from the West of Scotland. To obtain these data we calculated the survival

expected of our 139 malignant hypertensives had they been subject to the all-cause average mortality rates of the Strathclyde population at the midpoint of the study in 1976 (120). In this way it was possible to compare survival of patients with malignant hypertension with that of the general population from which they were derived. We have used this technique in another analysis comparing benign phase hypertensives with Strathclyde controls (117).

STUDY I: CLINICAL FEATURES OF 139 PATIENTS WITH MALIGNANT HYPERTENSION

Introduction

Benign or non malignant hypertension is a common condition which occurs predominantly in middle aged or elderly men and women, the majority of whom have no underlying cause for their high blood pressure and do not complain of symptoms unless or until complications supervene (121). By contrast, malignant hypertension is rare and tends to effect a younger age group. Underlying causes for hypertension are frequently found and patients usually present with symptoms (37,38). To determine whether our 139 patients with malignant phase were typical of malignant hypertensives generally, a descriptive study of their clinical features was undertaken.

Methods

Clinical features were recorded prospectively using a standard proforma in 59 consecutive patients from 1979 to 1981, and retrospectively by case sheet review, collecting the same information where possible, in the remaining 80 patients. The quality of the retrospective data is likely to be high as complete case notes are kept and malignant hypertension is a special interest of the Blood Pressure Unit.

Results

Age, sex and race

The age distribution of patients was 20 to 66 years in men and 14 to 67 years in women. Twenty-five (18%) were 30 years or younger at the time of presentation with malignant hypertension. No patient was older than 70 years. This is in marked contrast with the age distribution of non malignant hypertension as determined by population surveys (fig 5) (122). Sex distribution was equal. 134 patients were white Caucasian; the remainder came from India (2), Pakistan (1), West Indies (1), Trinidad (1).

Underlying causes

The proportion of patients with malignant hypertension in Glasgow who were found to have an underlying cause for their hypertension is given in Table 1 where, for the purposes of comparison, the prevalence of secondary hypertension in other centres reporting their experience of malignant phase has also been shown. In Glasgow, a possible cause for hypertension was identified in 56 (40%) patients. The commonest was renovascular disease in 19 (14%), confirmed by renal arteriography in 17 cases and by autopsy in 2. Chronic glomerulonephritis was likely to have been responsible for hypertension in 13 cases. This diagnosis was confirmed in 4 cases by renal biopsy and was "probable" in the remaining 9 cases who gave a past history of acute nephritis, nephrotic syndrome or proteinuria with hypertension and were known to have had small smooth kidneys preceeding the onset of malignant phase. Ten patients had the radiological appearances of chronic pyelonephritis on IV urography. Two had consumed large quantities of analgesics and had radiological features suggestive of analgesic nephropathy. Six patients presented with serum creatinine greater than 500 µmol/l and in these a diagnosis of primary renal disease could not be confirmed nor could essential hypertension be excluded. They were classified as having chronic renal failure of undetermined cause therefore. A variety of other conditions may have been responsible for the hypertension in 6 patients: unilateral small kidneys in 2 not having renal arteriography, hydronephrosis (1), progressive systemic sclerosis (1), Takayasu's arteritis (1) and noradrenaline secreting paraganglioma (1).

The remaining 83 patients were considered to have essential hypertension by exclusion of other causes. Eighty-two had normal IV urography and 40 also had normal renal arteriography. Proteinuria greater than 1g/24hrs was present in 10 of these patients only. Additional pathological changes consistent with essential hypertension were found on

renal biopsy (7 cases), following bilateral nephrectomy (1 case) or at autopsy (5 cases). The possibility that the oral contraceptive pill may have precipitated the malignant phase in 11 patients is considered in study 4.

Sources of referral

Seventy-three patients were referred to us from the Glasgow area: 44 (60%) directly by their general practitioners, 21 (29%) by the Department of Ophthalmology at the Western Infirmary, Glasgow, and 8 (11%) by other physicians in the Western or Royal Infirmaries (3 urologists, 3 respiratory, 2 general physicians). After general practitioners, the ophthalmologists were the single most common source of locally referred patients in the study. This is likely to reflect the high prevalence of visual symptoms at presentation. Sixty-six (47%) patients were referred from physicians working in other hospitals in the West of Scotland and other parts of the United Kingdom.

Duration of hypertension

Eighty-six (62%) patients gave no past history of hypertension or had not had their blood pressure measured prior to the onset of the malignant phase. Twenty-seven (19%) were known to be hypertensive and claimed to be taking their treatment at the time of diagnosis. Twenty-six (19%) were known to be hypertensive but admitted they did not comply with therapy. Serial measurements of blood pressure prior to the development of malignant hypertension were only rarely available. Nevertheless, the longest interval between recognition of hypertension and malignant phase was 19 years in a male patient with essential hypertension, and the shortest period between a well-documented normal blood pressure and the malignant phase was 8 weeks in a 27 year old female following the introduction of the oral contraceptive pill.

Blood pressure on admission

Average initial blood pressure was $233 \pm 27/145 \pm 18$(SD) mmHg.

Diastolic blood pressure was greater than 130 mmHg in 128 (92%) of cases. There was, however, marked variation in initial blood pressure between patients, from 165 to 300 mmHg systolic and 110 to 190 mmHg diastolic. Patients who were allegedly taking long-term antihypertensive treatment at the time of their diagnosis (n=27) had slightly lower pressure (229/143 mmHg on average) than those whose malignant hypertension developed while untreated (236/147 mmHg). Another feature which may have contributed to the variation in blood pressure at presentation was renal failure. In a subgroup of 50 consecutive patients (28 male) who had not previously received antihypertensive treatment, there was a significant inverse correlation between initial mean arterial pressure (MAP) and $\log_{10}$ serum creatinine ($r = -0.37$, $p<0.01$ for maximum MAP, and $r=-0.41$, $p<0.01$ for average of all MAP before treatment began). One explanation of this finding is that renal failure lowers the threshold blood pressure at which malignant hypertension develops.

Retinal changes, cigarette smoking, oral contraceptive pill

All patients included in this analysis had bilateral retinal haemorrhages and exudates. Ninety-six had papilloedema as well. These fundal changes were confirmed by photography in each of 102 cases.

Adequate smoking histories were obtained in 138 patients. 109 (79%) were current smokers at the time of presentation, 5 (4%) were ex smokers and 24 (17%) had never smoked.

Thirty-four of 69 women in this analysis were of childbearing age (15-44 years) and of these 11 (32%) were taking the oral contraceptive pill when malignant hypertension was diagnosed. None of the 35 women aged 45 or more were taking oral contraceptives or other sex hormones.

More detailed analyses of retinal changes in malignant hypertension, of cigarette smoking and of the relation between the oral contraceptive pill and malignant hypertension in women of childbearing age are presented in

studies 2,3 and 4.

Symptoms at time of diagnosis

Symptoms at the time of presentation were recorded prospectively using a standard proforma in 59 consecutive patients from 1979 to 1981, and have been summarised in Table 2. Recent onset of headache and visual upset were the commonest complaints, and also the commonest presenting symptoms. Headache was as likely to be frontal as occipital, and had no tendency to occur at any particular time of day. Impairment of vision preceding treatment was reported by 39 (66%) patients. Generally, visual symptoms related in degree to the severity of the retinal changes. One patient however experienced sudden loss of vision due to an associated central retinal vein thrombosis, and 2 presented with visual field defects due to small strokes. One patient only developed visual symptoms after treatment had been started: cortical blindness, which was transient, developed in a 19 year old girl whose blood pressure fell precipitously after intravenous diazoxide. Gastrointestinal symptoms, including weight loss and breathlessness due to cardiac failure, occurred in one-third to one-half of cases. Occasionally these symptoms were the presenting complaint at the time of diagnosis. One patient presented to the surgeons with abdominal pain, nausea and vomiting, another consulted his general practitioner solely on account of weight loss. Epistaxis, macroscopic haematuria, thirst and polyuria and fits were much less common but provided unusual sources of referral. None of the 59 patients in this analysis had chest pain due to myocardial ischaemia. Three patients denied having any symptoms at all: their malignant phase hypertension was discovered on routine clinical examination.

Other clinical features

Serum creatinine concentration was raised in 79% of patients, and moderate to severe renal impairment (serum creatinine >300 μmol/l) was

present in 33% (Table 3). More detailed analyses of renal function and its relation to outcome will be presented later in this thesis.

Electrocardiographic evidence of left ventricular hypertrophy, as judged by standard criteria (SV1or2 + RV5or6 > 35mm or R in aVL > 13mm) was present in 86% of our patients. Just under one-third had clinical or radiological evidence of heart failure at presentation. This took the form of a congestive cardiac failure in every instance, there being no case of acute pulmonary oedema in our study.

Neurological complications occurred in 24/139 (17%) patients. Seven of these presented with a recent stroke: hemiparesis in 4, hemianopia in 2 and an upper motor neurone 7th nerve palsy in one. Symptoms suggestive of transient cerebral ischaemia were present in 4 patients; these included transient loss of consciousness in 2, transient blindness in one and migraine-like visual aura in one. One patient presented with a lower motor neurone facial palsy. Fourteen of the 24 patients with neurological complications were considered to have hypertensive encephalopathy: 5 of these had grand mal seizures. In all of these patients, neurological features were present before the start of effective antihypertensive therapy.

107/139 (77%) patients had an examination of blood films during the first week of their illness, and of these 30 (28%) had red cell fragmentation. In no instance was there clinical evidence of an abnormal bleeding tendency. Moreover, conventional coagulation screens, where performed, were always normal. The results of other haematological tests which were measured in 18 patients are presented in study 5.

Plasma active renin concentration was measured in 37 of the 108 patients not on treatment at presentation. Elevated values (>50μU/ml) were found in 28 (76%). The remainder had normal plasma renin. Increased renin was of no value in differentiating the cause of the hypertension in these patients, nor was it of any prognostic significance,

there being no tendency for patients with higher renin values to have higher mortality.

Discussion

Although the incidence of malignant hypertension is said to be declining in much of Europe and North America (1) we were nevertheless able to identify 139 patients in Glasgow in only 15 years, most of whom were seen in one unit. We cannot say, however, whether malignant hypertension is particularly common in the West of Scotland, as direct comparison of our data with that of other centres is not possible. Leaving aside the debate on diagnostic criteria (see Study 2) factors other than the incidence of the disease may also have influenced the rate of referral in this study. It is possible, for example, that some of our patients were referred because the Blood Pressure Unit has an interest in malignant hypertension. Alternatively, the wider availability of effective antihypertensive drugs may have reduced the rate of referral, as physicians in other centres became more confident in the use of these drugs. Because the survival of locally-referred patients was similar to that of patients referred from other centres (Study 9) it is unlikely that patient selection had an important influence on our results, and I shall consider all 139 patients together in the analyses which follow.

The clinical features of our 139 patients are similar to those reported elsewhere (37,38). Nearly all patients with malignant hypertension have symptoms, in contrast to patients with non malignant hypertension which is usually a symptomless condition. Headache and visual upset were the commonest symptoms at presentation in the Glasgow series, but were not always present, and the diagnosis of malignant hypertension should be borne in mind when assessing patients with breathlessness, weight loss, epistaxes, haematuria, thirst and polyuria, and fits.

The prevalence of other clinical features in the Glasgow series is

shown in Table 2. Impaired renal function was one of the most common and, as will be seen in later analyses, the most serious manifestation of patients with this disease. Hypertensive encephalopathy, while serious, occurred less frequently as did heart failure and MAHA. Increased plasma renin concentration, although frequent, did not appear to have any bearing on outcome.

Another feature distinguishing malignant from non-malignant hypertension in our own experience (123) and that of others (124-126) is that underlying causes for high blood pressure are frequently identified in the former but not in the latter. However, the proportion of patients with malignant hypertension who have an underlying cause varies from centre to centre (table 1). In Glasgow, underlying causes were found in 40% of patients with malignant hypertension, and the commonest of these was renovascular disease (4). In Melbourne, 80% of patients had secondary hypertension, which was usually parenchymal in nature (5). By contrast, most of the cases seen among urban blacks in Johannesburg were considered to be idiopathic or essential (7), an observation which has been supported by autopsy data from that city (127). These differences are likely to reflect real differences in the prevalence of some diseases (e.g. analgesic nephropathy which is particularly common in Australia) as well as the enthusiasm of the diagnostic search, and the specific interests of individual units. Generally speaking, when patients present with malignant phase hypertension, a thorough search for an underlying cause is indicated.

TABLE 1 UNDERLYING CAUSES IN MALIGNANT HYPERTENSION

	GLASGOW	MELBOURNE	LEICESTER	JOHANNESBURG BLACKS	VANDERBILT WHITES
Period of study	1968-83	1979-85	1974-83	1979-80	1964-77
Number of patients	139	83	100	62	76
Essential	60	20	68	82	?
Renal	18	46	19	5	?
Renovascular	14	13	6	3	32
Other	9	21	7	10	?

Table shows percentage of patients with possible underlying causes for malignant hypertension in different centres. The data for the Vanderbilt series is uncompleted except for the group with renovascular disease.Detailed references are given in the text.

TABLE 2 SYMPTOMS AT DIAGNOSIS IN 59 PATIENTS

	NO. IN WHOM SYMPTOM PRESENT	MAJOR SYMPTOM AT PRESENTATION
Headache	37 (63%)	17
Visual upset	39 (59%)	20
GI symptoms	29 (49%)	3
Weight loss	22 (37%)	1
Breathlessness	21 (36%)	9
Epistaxis	8	1
Haematuria	2	2
Thirst/polyuria	3	2
Fits	1	1
None	3	3

The prevalence of symptoms in this table was estimated prospectively by questionnaire in 59 consecutive patients between 1979 and 1981.

TABLE 3 OTHER CLINICAL FEATURES

Mild renal impairment (serum creatinine 115-300 µmol/l or blood urea 7-15 mmol/l)	64/139	46%
Severe renal impairment (serum creatinine >300 µmol/l or blood urea >15 mmol/l)	46/139	33%
LVH by voltage criteria	118/138	86%
Cardiac failure	42/139	30%
Neurological complications	24/139	17%
Encephalopathy	14/139	10%
Microangiopathic haemolytic anaemia	30/107	28%
Secondary hyperaldosteronism	28/37	76%

The value for microangiopathic haemolytic anaemia is derived from 107 having patients having blood films within a week of presentation, and the estimate for secondary hyperaldosteronism was based on 37 previously untreated patients in whom plasma active renin concentration was measured. All other values in this table are based on all 139 patients in the Glasgow series.

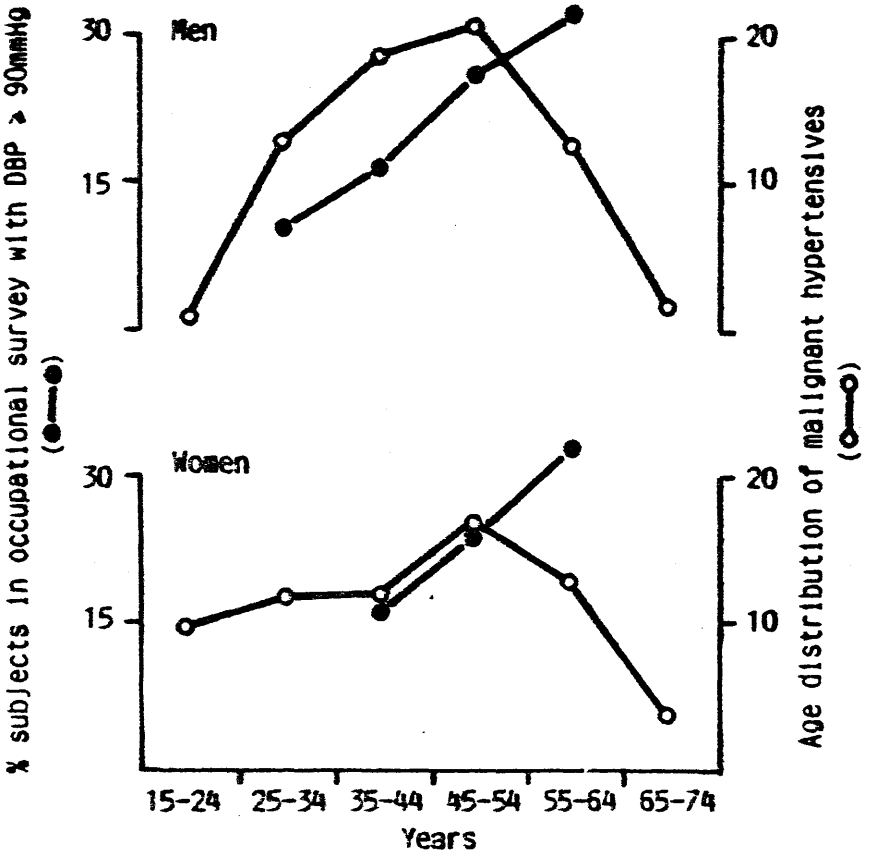

FIGURE 5 Age distribution of malignant (O) and non malignant (●) hypertension. Patients with non malignant hypertension were detected during an occupational survey on apparently healthy men and women in the West of Scotland (Greaves 1973).

STUDY 2: RETINAL CHANGES IN THE DIAGNOSIS OF MALIGNANT HYPERTENSION

Introduction

Despite recommendations by the World Health Organisation that the criteria for malignant hypertension should include hypertensive patients with bilateral retinal haemorrhages and exudates alone (8), some clinicians insist that papilloedema should also be present (37,38,51). To try to resolve this issue we assessed the importance of papilloedema in severe hypertension in a two part study. The study has been published (128) and an outline of the main points is given below.

Methods

The first part of the study was a test of observer error in which four observers (a consultant ophthalmologist, a consultant general physican and two junior hospital doctors working in the Blood Pressure Unit) were presented with 56 photographic slides of the retinal fundus showing a variety of features including haemorrhagic or exudative retinopathy, and were asked whether haemorrhages, exudates or papilloedema were present or absent. The second was an analysis of survival, comparing prognosis at five and ten years of those patients judged to have bilateral haemorrhages and exudates alone with that of patients in whom papilloedema was present as well.

The relation between presence of papilloedema and survival was determined firstly by life table analysis and, secondly, by Cox's proportional hazards model (129) to control for the possible influence of age, sex, smoking habit, underlying diagnosis, initial serum creatinine concentration, and initial and achieved blood pressure. We assessed the proportional hazards model graphically by stratifying separately for each co-variate and examining plots of the log-log survival function.

Results

The results are shown in figs 6 & 7. Agreement between observers was close when haemorrhages and exudates were being assessed, but there was frequent disagreement on papilloedema. As expected, florid papilloedema was recognised correctly by all observers. Disagreement was greatest when changes were mild. In the second part of the study, 10 year survival was 48% in patients with and 46% without papilloedema. The lack of an association between papilloedema and survival was confirmed by multivariate analysis using the Cox proportional hazards model (fig 7).These results suggest that papilloedema, unless florid, is an unreliable physical sign, and that it has no influence on survival when bilateral retinal haemorrhages and exudates are already present.

Discussion

A heated debate has been conducted over the years concerning the severity of the fundal changes necessary to establish the diagnosis of malignant hypertension. At one extreme, the view has been expressed that "one large exudate convicts" (121). Others have argued that hypertension should not be classified as malignant unless papilloedema is present (37,38,51), prefering to use the term "accelerated" hypertension to describe patients with retinal haemorrhages and exudates alone (51). It is our view, that of Pickering (121) and the WHO (8) that papilloedema need not be present in malignant hypertension and in support of this, fibrinoid arteriolar necrosis, the pathological hallmark of the malignant phase, has been detected in hypertensive patients with haemorrhages and exudates alone (130); soft exudates and papilloedema share a similar pathogenesis (131); and papilloedema is not constantly present even when malignant hypertension causes acute oliguric renal failure, one of the most malignant of all presentations of hypertension (132). To these reasons we now add the finding that papilloedema is of no additional prognostic importance in

patients treated for hypertension who already have bilateral haemorrhages and exudates (128). Colleagues in Birmingham have conducted a similar study and have reached similar conclusions (133).

This longstanding argument will, it is hoped, now be settled. Agreement on the diagnosis of malignant hypertension is important for epidemiological purposes, and for the reasons outlined above the WHO criteria have been adopted in Glasgow. In practice, hogever, one would never wait for the full syndrome to occur, and the development of fresh haemorrhages or soft exudates in a hypertensive patient, either de novo or when blood pressure is poorly controlled, signifies an urgent need for treatment.

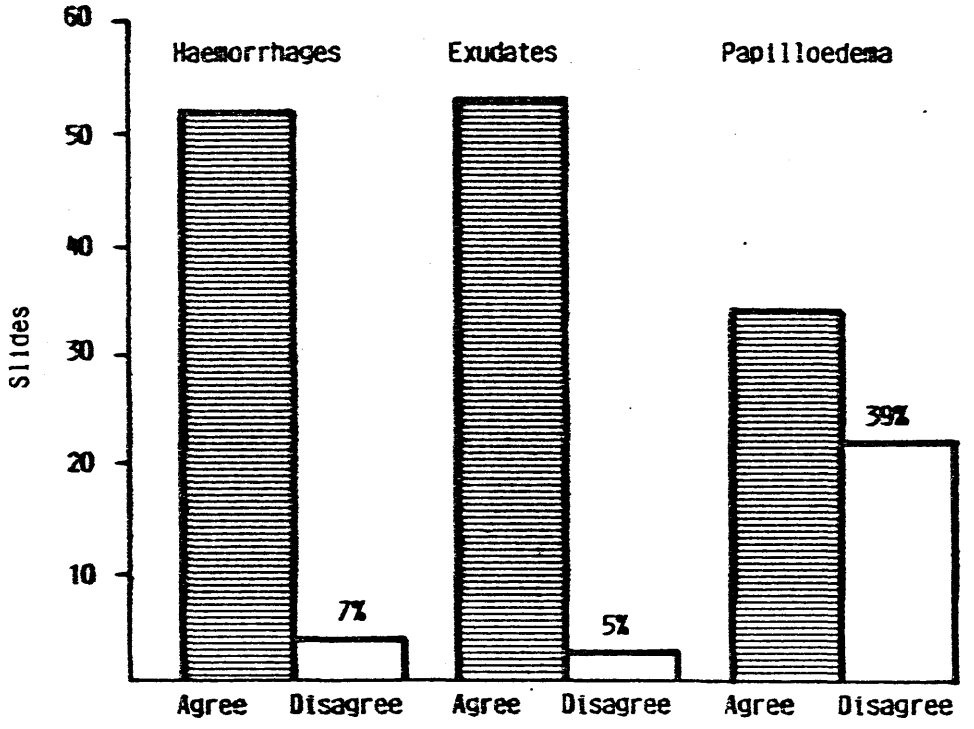

FIGURE 6 The four observers agreed that haemorrhages were present or absent in 52 of 56 slides, and disagreed in 4 (7%) cases. A similar consensus was obtained for exudates, with disagreement in 3 (5%) cases. Opinion on papilloedema, however, was divided, the observers agreeing in only 34 of the 56 cases.

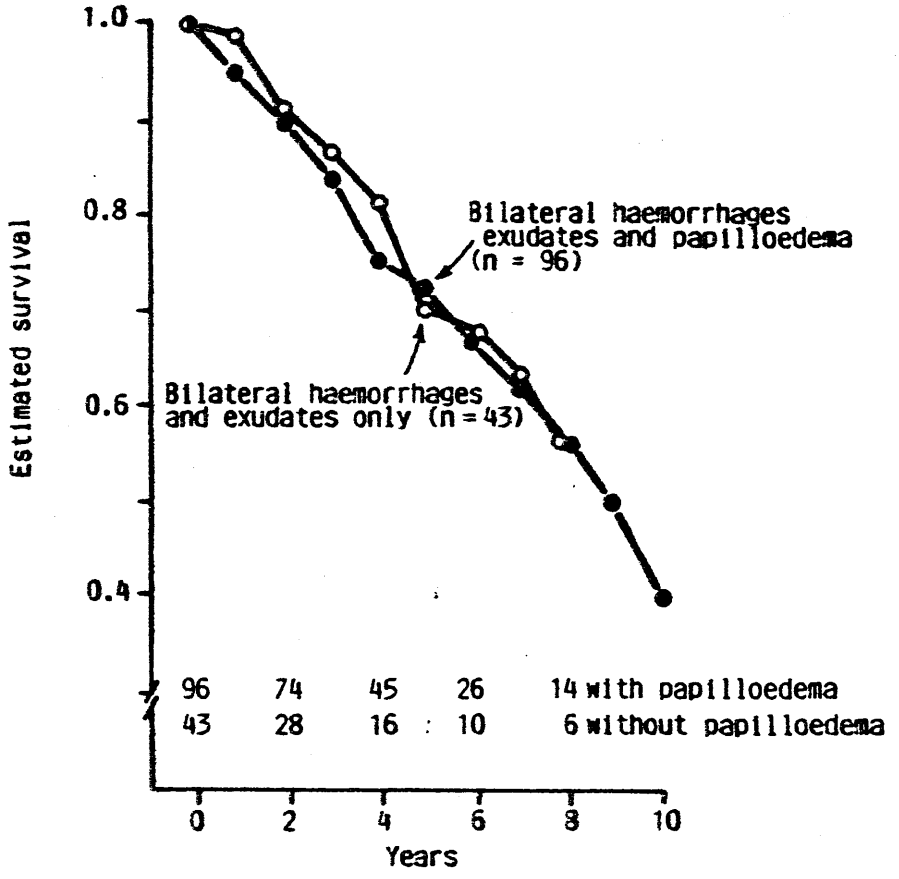

FIGURE 7 Relation between papilloedema and survival in 139 hypertensive patients with bilateral retinal haemorrhages and exudates after controlling for age, sex, smoking habit, underlying diagnosis, initial serum creatinine concentration, and initial and achieved blood pressures by multivariate analysis. Numbers of patients observed at beginning of each time interval are given. After 8 years there were no deaths among 6 remaining patients without papilloedema. Failure of papilloedema to influence prognosis was confirmed by likelihood ratio test (chi-squared = 0.89, 1df, p= 0.34).

STUDY 3: CIGARETTE SMOKING MAY PREDISPOSE TO MALIGNANT HYPERTENSION

Introduction

Our study on the association between cigarette smoking and malignant hypertension was prompted by the observation that diabetics who smoked were more likely to develop proliferative and haemorrhagic retinopathy than diabetics who did not (134). Malignant hypertension is characterised by another form of ischaemic retinopathy, but as far as we were aware, the smoking habits of patients with the condition had not been reported. Our findings, which were published in 1979 (18), are summarised below.

Methods

The prevalence of cigarette smoking in malignant hypertension was determined by case review of 82 consecutive patients admitted to the Blood Pressure Unit with this diagnosis between 1968 and 1978, and comparisons were made with 3 control groups. The first control consisted of 82 patients with non-malignant hypertension who had been admitted to our wards during the same period, and who were matched individually for age and sex with the index group. The second control comprised 164 patients with non-malignant hypertension obtained from the files of the Glasgow Blood Pressure Clinic. Two control subjects were matched individually for age and sex with each patient in the malignant phase. For our third control we used 82 subjects in the general population who had been screened during the course of an epidemiological survey of 15000 apparently healthy middle-aged men and women in Renfrew and Paisley between 1972 and 1976. Each patient with malignant hypertension was matched by computer with a person of the same age (where possible) and sex from Renfrew and Paisley.

The proportion of smokers among patients and controls was compared using the chi-squared test and Yates's continuity correction. The relative risk of smokers having the malignant phase was determined by the odds

ratio.

Results

Sixty-seven (82%) of the patients with malignant hypertension were smokers compared with 41 (50%) non malignant hypertensives from the ward, 71 (43%) non malignant hypertensives from the clinic and 43 (52%) of the general population in Renfrew and Paisley. Differences between the malignant phase and control groups were significant for both sexes separately and together, for all forms of smoking combined and for cigarette smoking alone (Table 4). There were no significant differences between the control groups. Hypertensive patients who smoked were on average 4.3-6.9 times more likely to be in the malignant phase than hypertensive patients who did not smoke (Table 4).

Discussion

The main finding of our study was a large excess of smokers among patients with malignant hypertension. The excess is a feature of the malignant phase, not of hypertension generally. Colleagues in Birmingham came to the same conclusion (19) and similar findings have subsequetly been reported from other centres (20,21). An interesting exception to this trend is the study from Johannesburg (7) in which cigarette smoking was not a feature of urban blacks with the malignant phase in whom, as described previously, the disease appears to be particularly common.

Clearly then smoking may predispose to malignant phase hypertension but it is not the only precipitant. Smoking could act as a trigger in susceptible subjects, and it may exert its effect by promoting intravascular coagulation (135). Alternatively smoking may be a marker for some other variable which is itself a cause of malignant hypertension. Hypertensives with negative attitudes to health may be more likely to default from clinical attendance and less likely to comply with therapy, and may thus be predisposed to develop the malignant phase (135a). Such patients may also

be more likely to smoke. This is an area which deserves further study.

TABLE 4 No.(%) SMOKERS IN EACH GROUP AND RELATIVE RISK (ODDS RATIO) WITH 95% CONFIDENCE INTERVALS OF SMOKERS HAVING MALIGNANT HYPERTENSION COMPARED WITH NON SMOKERS

	MALIGNANT HT	NON MALIG HT FROM WARD	NON MALIG HT FROM CLINIC	RELATIVE RISK (MALIG v ALL NON MALIG)		GEN. POP. FROM RENFREW/ PAISLEY	RELATIVE RISK (MALIG. V GEN. POP.)	
	%	%	%	RR	95% CI	%	RR	95% CI
Men and women (all forms of smoking)	67 (82)	41 (50)	71 (43)	5.3	(2.8,9.9)	43 (52)	4.1	(1.7,9.6)
Men (all forms of smoking)	34 (87)	21 (54)	37 (47)	6.9	(2.5,19.1)	25 (64)	3.8	(1.2,12.2)
Men (cigarette smoking)	29 (74)	14 (36)	33 (42)	4.3	(1.6,11.6)	22 (56)	2.2	(0.8,5.9)
Women (all forms of smoking)	33 (77)	20 (47)	34 (40)	4.6	(1.7,12.1)	18 (42)	4.6	(1.8,11.9)

STUDY 4: RELATION BETWEEN THE ORAL CONTRACEPTIVE PILL AND MALIGNANT HYPERTENSION.

Introduction

Although malignant hypertension is a well recognised complication of the oral contraceptive pill (22-29), most reports of its occurrence have been limited to case studies of selected patients only, and as such the clinical features and outcome of the malignant phase in pill users had never been fully defined. This was the main purpose of our study (30).

Methods

The case records of the 69 women in the main analysis (Study 1) were reviewed to determine whether they had been taking the oral contraceptive pill or other sex hormones at the time of diagnosis of their malignant hypertension. If this information had not been recorded in the notes, the patients or their general practitioners were contacted. In these ways a drug history was established for all but 2 patients, who were considered to be non users. Following initial assessment, blood pressure, drug therapy, renal function and other events were monitored to 1.4.84. If death occurred in the United Kingdom, record linkage with the Registrar General ensured that the data and certified cause of death was notified in each case.

The differences in the clinical features of pill users and non users with malignant hypertension were assessed by t-tests. Survival in the two groups was by life table analysis, and comparison of the survival curves by the log rank test.

Results

Relation of malignant hypertension to pill, and type of pill

Thirty-four of the 69 women were of childbearing age (arbitrarily 15 to 44 years) and of these 11 (32%) were taking oral contraceptives at the time of presentation with malignant hypertension. None of the women aged

45 or more was taking oral contraceptives or other sex hormones. The mean age of the pill users was 31 years. Blood pressure was known to be normal immediately before starting the pill in 6 women and within 3 years of starting the pill in a further 3. In the remaining 2 women, normal blood pressure had been recorded 13 and 21 years before the pill, but more recent measurements were not available. Four women developed malignant hypertension within 4 months of starting the pill, while in the others malignant hypertension did not develop for 14 months to 8 years. The commonest preparations were those containing 50 µg or oestrogen or more (8 cases). Two patients developed malignant hypertension while taking 30 µg of oestrogen, and 1 presented within 8 weeks of starting a 20 µg oestrogen pill. Blood pressure in this patient was 110/70 mmHg immediately before treatment began. Apart from the oestrogen component, preparations taken included 4 different progestagens (Norethisterone, Levonorgestrel, Lynoestrenol, Ethynodiol), two of which (Norethisterone, Levonorgestrel) were present in different doses.

Clinical features and prognosis

The clinical features and prognosis of the 11 women who developed malignant hypertension while taking the oral contraceptive pill, were compared with those of the 23 women who were also of childbearing age but who were not taking the pill (Table 5). Other details in four of the pill users have been reported elsewhere (28). Age, initial blood pressure and smoking habits were similar in the two groups. 73% of pill users, and 74% of non users smoked cigarettes, a higher than usual proportion than in the Scottish population and in women attending the Glasgow Blood Pressure Clinic with non malignant hypertension (18). Pill users had less underlying renal disease and less renal failure than non users. The level of blood pressure achieved during treatment was similar in the two groups. No pill user became normotensive following withdrawal of the pill, but diastolic

blood pressures consistently less than 90 mmHg were recorded during follow-up in 3 patients while taking one antihypertensive drug only. By contrast all 23 non users required two or more drugs to control blood pressure. Ten year survival was 90% among pill users but only 50% among non users (Table 5). This was related at least in part to the higher incidence of renal failure in non users, 8 of whom eventually developed end stage renal failure requiring dialysis.

Discussion

There are several mechanisms by which the contraceptive pill could cause malignant hypertension. Malignant hypertension may develop as a consequence of the known pressor effects of oestrogens and/or progestagens. Thus, the rapid rise in blood pressure which occurs in malignant hypertension may be an extreme example of the varied increase in pressure noted when most women are given the pill (49). Alternatively, malignant hypertension may be a consequence of some other property of oral contraceptives. It is known that oral contraceptives activate the coagulation system (136) and that in-situ thrombosis causes other cardiovascular complications of the pill. As will be discussed in Study 5, abnormalities of blood coagulation are well recognised in malignant hypertension not associated with oral contraceptives. It is possible therefore that in-situ thrombosis involving either the main (137) or the intrarenal (138) arteries could contribute to the pathogenesis of malignant hypertension in pill users.

Clinically, the most striking difference to emerge between the pill users and controls in the study, was that pill users had less underlying renal disease and less renal failure than non users. By contrast, 6 of 9 previously recorded patients in the literature had appreciable renal impairment (23,25,26). Whether our findings reflect more accurately the natural history of pill associated malignant hypertension, or merely the fact that women

who are known to be hypertensive or unwell for other reasons are less likely to be given the pill, is not clear. Certainly, selection bias may have determined the high prevalence of renal impairment among the patients described in previous reports, many of whom were admitted to renal units.

As the degree of renal impairment at presentation is the single most important predictor of outcome in patients with malignant hypertension (4) it is perhaps not surprising that most of our patients did well. Although a return of blood pressure to normal after withdrawal of the pill is the exception rather than the rule (occurring in 2 of 9 patients in previous reports and in none of our 11 patients), blood pressure was well controlled in most of our cases and 10-year survival was 90%. This result compares favourably with the 10-year survival of only 50% among the women with malignant hypertension who did not take the pill. The higher prevalence of renal disease and renal impairment among the non users seems the likely explanation.

TABLE 5 COMPARISON OF WOMEN TAKING PILL WITH THOSE NOT TAKING PILL

	Women taking the pill (n=11)	Women not taking the pill (n=23)
Age (years):		
Mean (SD)	31 (8)	30 (9)
Range	19-43	15-44
No (%) current smokers	8 (73)	17 (74)
Mean (SD) initial blood pressure (mmHg)	233 (25)/149 (13)	230 (28)/151 (20)
No. with underlying renal disease:		
Renovascular disease	2	2
Chronic pyelonephritis	1	6
Chronic glomerulonephritis		1
Chronic renal failure of undetermined cause		1
Phaeochromocytoma		1
Mean (SD) initial serum creatinine (μmol/l)	116 (26)	334 (386)
Mean (SD) blood pressure at 1/4/84 or death (mmHg)	156 (64)/88 (22)	154 (31)/94 (19)
Survival (%) to 1/4/84:		
5 years	89.5	62.3
10 years	89.5	49.8

Differences in age, smoking habit, initial and final blood pressure, and initial serum creatinine concentration not significantly by unpaired t test.

STUDY 5: ABNORMAL HAEMOSTASIS AND MALIGNANT HYPERTENSION

Introduction

The deposition of fibrin within blood vessels of the kidneys of patients with malignant hypertension suggests that disordered coagulation may be a feature of the disease. In a previous study from Glasgow, Gavras and colleagues (16) found abnormalities of haemostasis suggestive of low grade coagulopathy in a group of patients with malignant hypertension, but not in non-malignant controls. As a result of these findings, it was postulated that abnormal haemostasis was a necessary step in the transition from the benign to malignant phase. More recently it has been shown that patients with renal disease who do not have malignant hypertension may also have high levels of fibrinogen, factor VIIIc, fibrinolytic inhibitors and FDP and decreased platelet counts. To examine the relation between malignant hypertension, renal failure and haemostasis in more detail, a further study was undertaken. A report of our findings has been published (17).

Methods

Haemostatic and haemorheological variables were measured in three groups of subjects: Group 1 comprised 18 consecutive patients with malignant hypertension admitted for investigation in 1979-1980. Group 2 consisted of 18 healthy volunteers, and Group 3 of 18 non-malignant hypertensives attending hypertension and renal clinics. Groups 2 and 3 were matched for age, sex and smoking habit with patients in Group 1, and Group 3 patients were selected in addition to have comparable levels of blood pressure and serum creatinine as well as similar renal pathology (Table 6).

Blood was taken with minimal occlusion from a forearm vein, and anticoagulated with trisodium citrate (0.129 mol/l, 9:1 v:v). Platelet-poor

plasma was obtained by centrifugation for the following coagulation tests - fibrinogen (Dade Fibrometer and Standards), factor VIIIc by a one-stage assay (139), antithrombin III activity (with heparin) and fast antiplasmin activity on chromogenic substrates (Chromozym, Boehringer), plasminogen by a caseinolytic assay (140), and alpha$_2$-macroglobulin antigen by radial immunodiffusion (Behringwerke antiserum). Plasma beta-thromboglobulin (BTG) was measured by radioimmunoassay (Radiochemical Centre, Amersham). Serum FDP was measured by tanned red cell haemagglutination inhibition immunoassay (Wellcome FDP kit). Serum creatinine was measured by Technicon Autoanalyser. Blood was anticoagulated with dry edetic acid (EDTA, 0.004 mol/l) for measurement of blood viscosity at a high shear rate (94 s^{-1}) and at a low shear rate (0.94 s^{-1}) in a Contraves LS 30 rotational viscometer, 37°C; haematocrit by Hawksley microcentrifuge (13,000 g for 5 mins); platelet count (Coulter Thrombocounter); and plasma viscosity (BS M3 capilliary viscometer obtained from Poulten, Seiz and Lee, Wickford, Essex UK; 37°C). Blood viscosity was corrected to a standard haematocrit of 0.45, using regression equations for each shear rate obtained from 200 samples of widely varying haematocrit. Red cell deformability was assessed as the filterability of red cells in plasma, haematocrit 0.45, through special quality Nuclepore polycarbonate filters (pore diameter 5 µm), correcting for plasma viscosity as described by Buchan (141). Blood films were reviewed by a consultant haematologist unaware of the clinical diagnosis for red cell fragmentation (evidence of MAHA). Differences in means were analysed by Wilcoxon's rank sum test, and correlations determined by the method of least squares.

Results

Compared to healthy controls (Group 2), both groups of hypertensives had significantly increased plasma viscosity, blood viscosity, fibrinogen, factor VIIIc and beta-thromboglobulin, and significantly decreased

haematocrit, antithrombin III and platelet count. Fast antiplasmin and alpha2-macroglobulin were elevated in Group 1, but not in Group 3. Plasminogen was decreased in Group 3. Both groups of hypertensives had a non significant increase in serum FDP. Red cell deformability was the same in all three groups.

When the two groups of hypertensives were compared with each other, patients with malignant hypertension (Group 1) had higher levels of fibrinogen ($p<0.05$), alpha$_2$-macroglobulin ($p<0.01$) and plasminogen ($p<0.05$). Fast antiplasmin was also raised in Group 1 but not significantly so.

Several variables were significantly correlated ($r=0.3-0.5$) with serum creatinine. Plasma viscosity, fibrinogen, factor VIIIc, FDP and beta-thromboglobulin showed positive correlations with creatinine; while haematocrit, antithrombin III and platelet count showed negative correlations.

Three patients in Group 1 had evidence of red cell fragmentation on blood films; their results were not obviously different from those of the other 15 patients.

Discussion

This study confirms the findings of Gavras et al (16) that patients with malignant hypertension (Group 1) have several abnormalities of haemostasis: decreased mean platelet count, and increased mean levels of fibrinogen, factor VIIIc and FDP (although the increase in FDP was not statistically significant). Patients with malignant hypertension also had a decreased mean level of antithrombin III, for which Gavras et al had insufficient samples to analyse (16), and elevated levels of beta-thromboglobulin. These haemostatic abnormalities are consistent with activation of haemostasis. Furthermore, we have shown increased levels of plasma viscosity and blood viscosity (corrected for haematocrit), which might contribute to disordered tissue perfusion in malignant hypertension.

Red cell deformability was normal after correction for the influence of plasma viscosity, and was not different in the patients with evidence of MAHA.

However, similar abnormalities were also found in patients who did not have the retinal changes of malignant hypertension, but who were carefully matched for age, sex, smoking habit, renal pathology and levels of blood pressure and serum creatinine (Group 3). Most variables correlated with serum creatinine, and it is possible therefore that low grade coagulopathy may be a consequence of renal failure, rather than a necessary step in the pathogenesis of malignant hypertension. An alternative explanation is that both hypotheses are true, namely that malignant hypertension causes renal damage which activates haemostasis, which in turn promotes further renal damage. In this context it should be noted that there is morphological evidence of intravascular coagulation in several renal disorders other than malignant hypertension (13).

A weakness of both the present study and the original study (16) as a test of the coagulation hypothesis is that the blood pressure of patients with malignant hypertension was lower at the time of blood sampling than at presentation. Malignant hypertension requires urgent treatment and it was not possible to obtain blood prior to starting treatment. The reported haemostatic changes may have been different to those present initially. However, all patients still had bilateral haemorrhages and exudates at the time of sampling, and in 11 patients repeat sampling one week later showed little change in results. It seems unlikely therefore that these variables alter rapidly during the first weeks after presentation.

TABLE 6 CLINICAL DETAILS OF PATIENTS (MEAN±SEM)

	GROUP 1 Malignant hypertension	GROUP 2 Healthy controls	GROUP 3 Non-malignant hypertension
No	18	18	18
Male sex	13	13	13
Smokers	11	11	11
Age (years)	38±3	40±3	40±3
Blood pressure (mmHg)			
- systolic	165±6	121±4	173±9
- diastolic	102±4	75±3	99±5
Creatinine (µmol/l)	435±83	79±5	399±69
Renal pathology			
- glomerulonephritis	5	0	5
- other renal disease	5	0	5
- no renal disease	8	18	8
Micro-angiopathic haemolytic anaemia	3	0	0

TABLE 7 RESULTS OF BLOOD STUDIES IN PATIENT GROUPS (MEAN ± SEM)

	GROUP 1 Malignant hypertension	GROUP 2 Healthy controls	GROUP 3 Non-malignant hypertension
Fibrinogen (g/L)	4.87±0.36**	2.90±0.21	3.89±0.32**
Factor VIIIc (μ/ml)	2.32±0.32**	1.31±0.08	2.06±0.26**
Antithrombin III (μ/ml)	15.7±0.6**	18.8±0.7	14.5±0.9**
Fast antiplasmin (U/ml)	3.9±0.5**	2.4±0.3	3.0±0.4
$Alpha_2$-macroglobulin (% normal pool)	131±8**	104±5	92±4
Plasminogen (casein U/ml)	2.8±0.2	2.7±0.1	2.1±0.2*
Fibrin degradation products (μg/ml)	7.8±1.6	4.5±0.7	7.3±1.7
Beta thromboglobulin (ng/ml)	85±8**	42±3	69±5**
Platelet count (x 10^9/L)	233±18*	282±18	233±11*
Plasma viscosity (mPa-s)	1.36±0.03**	1.24±0.02	1.35±0.03**
Haematocrit	0.359±0.022**	0.445±0.006	0.370±0.018**
Blood viscosity (mPa-s)			
High shear	5.91±0.25**	4.92±0.14	5.75±0.14**
Low shear	21.4±0.7**	18.5±0.6	20.4±0.06**
Red cell deformability (ml/minute)	0.44±0.03	0.44±0.01	0.44±0.01

Asterisks indicate signficiant differences from Group 2 (healthy controls).
*$p<0.05$, **$p<0.001$

STUDY 6: SLOW RELEASE NIFEDIPINE AND ATENOLOL AS INITIAL TREATMENT FOR MALIGNANT HYPERTENSION

Introduction

Since precipitous falls in pressure in patients with severe hypertension may cause ischaemic damage to brain (77,78), eye (79-82), kidney (83) and spinal cord (84) it has been recommended that parenteral therapy be avoided where possible (2) and that initial treatment should be with one or two drugs given orally instead. In this study the efficacy and safety of slow release nifedipine and atenolol were compared in 20 consecutive black patients with malignant hypertension. The study was conducted at the Non European Hospital in Johannesburg between June 1983 and February 1984. Malignant hypertension occurs commonly among urban blacks (7) and is a frequent cause for admission to the Non European Hospital.

Methods

Twenty consecutive black patients with untreated malignant hypertension whose diastolic pressure remained greater than 120 mmHg after 3 hours bed rest, were randomised to receive either slow release nifedipine 40 mg at 0 and 12 h, or atenolol 100 mg at 0 h only. None had received antihypertensive drugs during the 48 h before admission to hospital.

Patients remained supine throughout the study. Blood pressure was measured at 15 minute intervals from -3 to 24 h by a semi automatic recorder (Omega 1000) the accuracy and reproducibility of which were checked against a standard mercury sphygmomanometer at monthly intervals.

Results

Average blood pressure in the 10 patients given nifedipine was 233/142 mmHg immediately prior to the first dose (baseline pressure), 185/112 mmHg at 1h, and reached its lowest value of 166/100 mmHg after 5 h (fig 8). Thereafter blood pressure rose gradually to 191/119 mmHg at 12 h. A second trough level, 157/94 mmHg was recorded 4 h after the

second dose. Mean blood pressure at the end of the study in the nifedipine group was 188/114 mmHg.

Baseline blood pressure in the atenolol group was 226/141 mmHg. One hour after atenolol, mean blood pressure had fallen to 210/132 mmHg. Blood pressure continued to fall, reaching its lowest value of 162/100 mmHg at 16 h, before rising gradually to a mean of 173/112 mmHg at 24 h.

Whereas the rate of reduction of blood pressure after nifedipine was greater than after atenolol (Δ BP at 1h nifedipine = 52/31 mmHg, Δ BP at 1h atenolol = 22/11 mmHg, $p<0.001$ for systolic and diastolic pressure), the duration of action of a single dose of atenolol was longer than that of nifedipine and the extent of the fall was the same (Δ BP 5h after first dose nifedipine = 67/41 mmHg, Δ BP 16h after atenolol = 64/40 mmHg).

No patient developed focal neurological signs at any time during admission to hospital, nor was heart failure precipitated by either form of treatment. The lowest MAP recorded in any patient was 53% of baseline MAP (figure 9). This occurred 3.5 h after nifedipine in one patient, 16h after atenolol in another. The most rapid decline in MAP was to 67% of the baseline value within 30 min of the first dose of nifedipine. Since acute reduction of pressure to a value not less than 45% of baseline is unlikely to cause symptoms of cerebral ischaemia (142), both drugs appear to have been safe in this trial.

Discussion

Nifedipine has been shown previously to be highly effective as initial therapy in blacks with malignant hypertension (7) and in whites with severe, including malignant hypertension (86,143) although the very rapid onset of action of the capsule form has led to concern regarding its safety. We were interested, therefore, to test the slow release preparation of the drug. Transient retinal ischaemia has been reported after 20 mg capsule nifedipine (144) but this complication was considered to be due to a steal phenomenom

and was not associated with a precipitous fall in pressure; we know of no other neurological complications following the use of nifedipine alone. Indeed, in one small study cerebral blood flow increased in 4 of 5 patients with severe hypertension who were given 10-20 mg capsule nifedipine orally (86) suggesting that nifedipine, like other drugs in this class e.g. nimodopine (145) has cerebral vasodilator properties. Our results confirm the more gradual onset of the slow release preparation and that it possesses the advantage of a more prolonged action.

Atenolol is also effective when given as initial therapy in whites with malignant hypertension (85) but its use has not been described in blacks with this disease, despite a higher prevalence of malignant hypertension among black people (7). This may reflect a view that beta adrenoceptor blockers are less effective in blacks than whites (146). While this is probably true when beta adrenoceptor blockers are used as first line therapy in blacks with non malignant hypertension (147) blacks with malignant hypertension may respond to these drugs since high renin values are common in the malignant phase in both races (130,148). Hence or otherwise, atenolol was found to be as effective overall as nifedipine, the effects of a single oral dose of 100 mg persisting for up to 24 h. Of equal interest, we believe, was the more gradual reduction of blood pressure achieved by atenolol in the study. Review of the literature indicates that there have been no reports of neurological complications in malignant hypertension following the use of atenolol alone.

In summary, both slow release nifedipine and atenolol lowered blood pressure in black patients with malignant hypertension. The maximum reduction in blood pressure was the same in the two groups although the rate of fall of pressure was greater for nifedipine and the duration of action longer for atenolol. There were no precipitous falls in pressure. These results support recommendations that most patients with malignant

hypertension can be managed without recourse to parenteral therapy.

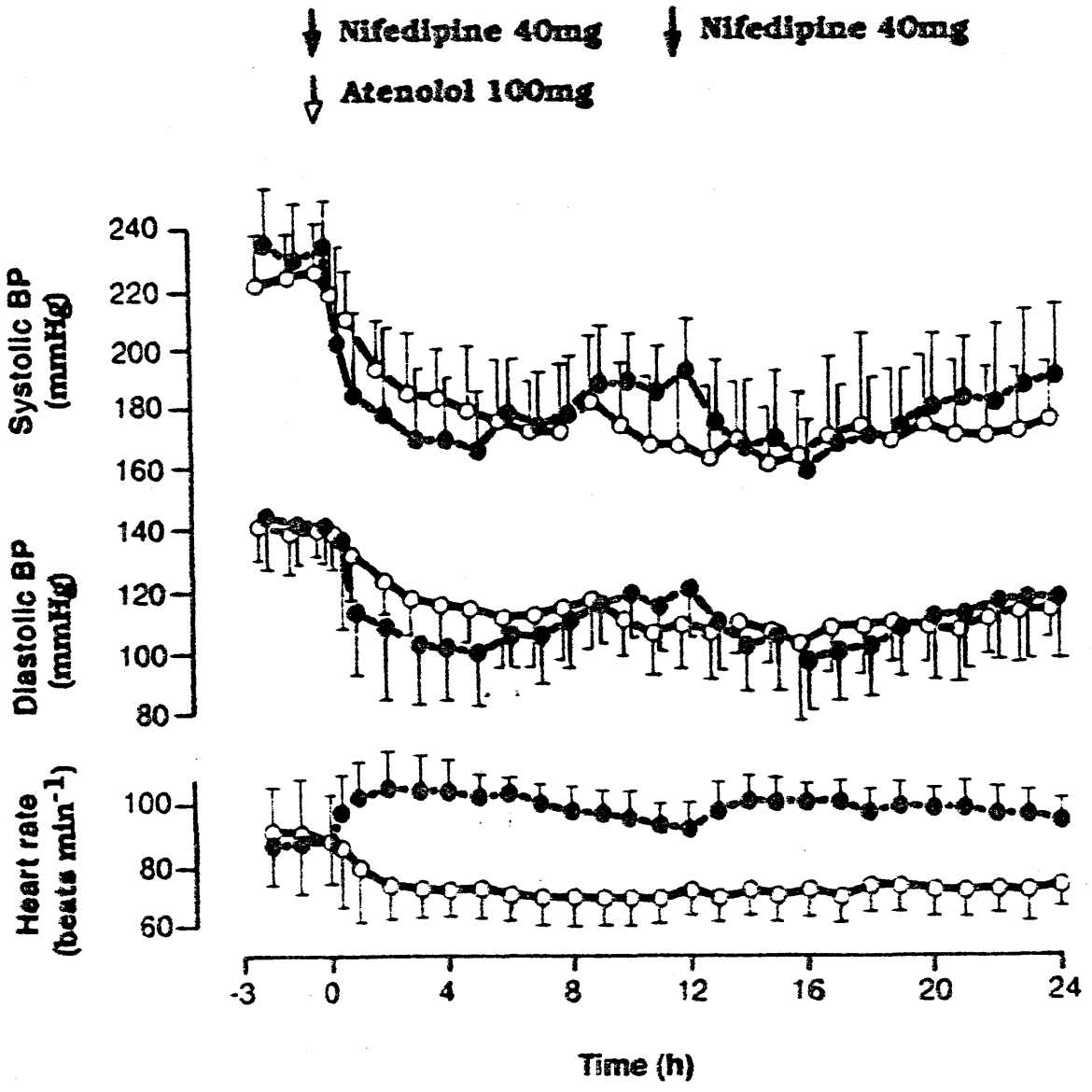

FIGURE 8 Blood pressure (mean±SD) and heart rate after slow release nifedipine (●) and atenolol (O). Each value represents the mean of the half hourly readings in each treatment period for each patient. The fall in systolic and diastolic pressure, and the change in heart rate, was significant ($p<0.01$) at all times after 1h in both treatment groups.

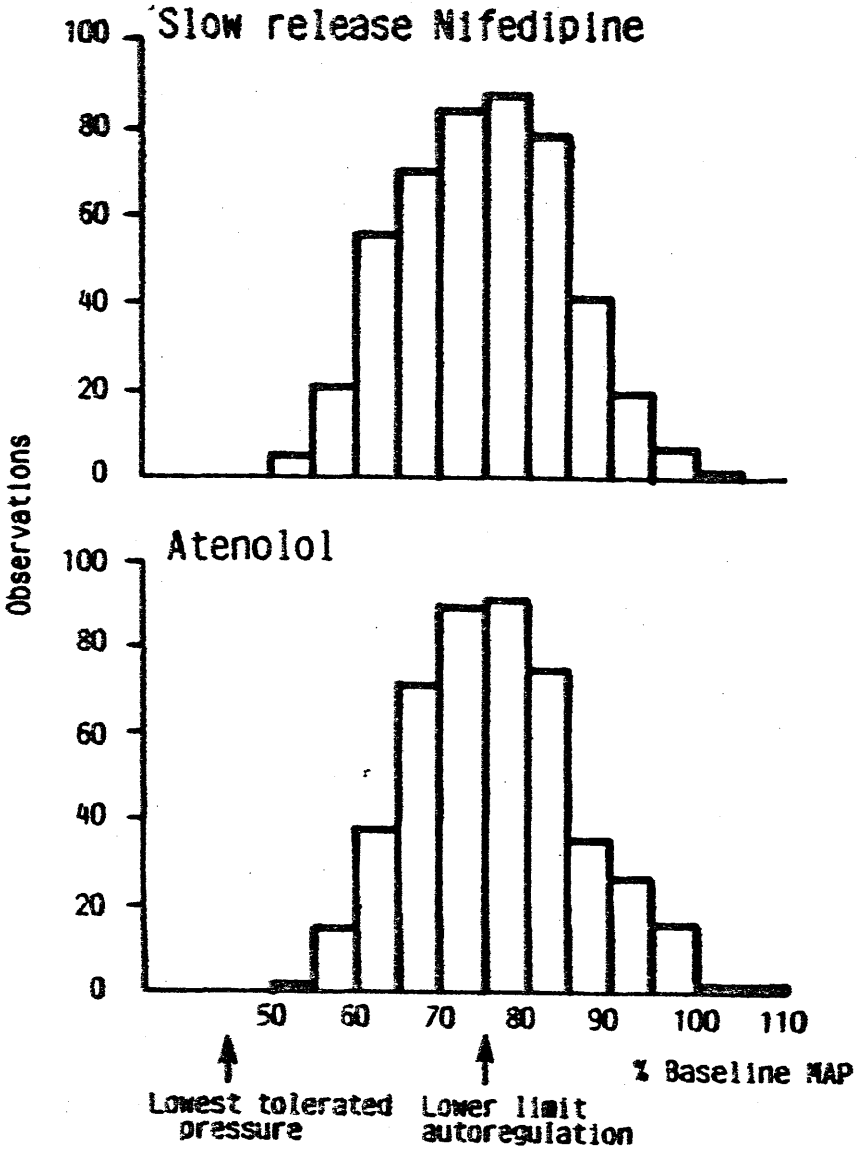

FIGURE 9 Histogram showing changes in mean arterial pressure after slow release nifedipine and atenolol as a percentage of baseline mean arterial pressure. The estimates of the lower limit of autoregulation (75% of initial MAP) and the lowest tolerated pressure (45% of initial MAP) are from Strandgaard (1976) and suggest that no patient had a dangerous fall of pressure in this study.

STUDY 7: MALIGNANT HYPERTENSION PRESENTING WITH ACUTE RENAL FAILURE

Introduction

Recovery of renal function in malignant hypertension complicated by severe renal insufficiency is uncommon particularly in the presence of underlying renal disease (109,111). A rare but important exception is the patient with malignant hypertension who presents with acute renal failure (96). The purposes of this analysis were two fold. First, to review the clinical and histological features of 7 patients presenting with malignant hypertension and acute renal failure between 1977 and 1981 all of whom received peritoneal dialysis and hypotensive therapy. Significant recovery of renal function occurred in 5 patients and the progress of each has since been followed for up to 5 years. Second, to identify the reason for such a high recovery rate in this group of patients. A report of this analysis was published in 1984.

Methods

The case records of 7 patients who presented to the Renal Unit of the Royal Infirmary in Glasgow with malignant essential hypertension and acute renal failure between 1977 and 1981 were reviewed. The diagnosis of malignant essential hypertension was based on WHO criteria (1978) and was confirmed by renal biopsy in each case. The progress of the 7 patients over a period ranging from 15 to 62 months (mean 42 months) was documented, and the clinical and histological features of the five in whom renal function recovered were compared with the two in whom it did not.

Results

Details of these patients histories and investigations are shown in Table 8. All were white and all smoked. Their age range (20-67 years) was typical of malignant hypertension. Only one was known to have been hypertensive (for 6 weeks) before presentation. All satisfied the criteria for

the malignant phase having severe hypertension with bilateral retinal haemorrhages and exudates: 3 had papilloedema was well. MAHA was present in the 6 patients in whom it was sought. All 7 patients had acute renal failure requiring immediate dialysis, and 4 were oligo-anuric. Six patients had other complications of malignant hypertension including congestive cardiac failure and hypertensive encephalopathy.

The managment of these patients consisted of control of blood pressure and peritoneal dialysis. Four of the 7 were resistant to a combination of beta blockers, hydralazine, methyldopa and frusemide and required minoxidil before their diastolic pressure fell consistently below 90 mmHg. In 5 patients renal function recovered sufficiently to stop peritoneal dialysis after 10-44 days. Serum creatinine fell gradually for up to 12 months and thereafter remained stable at a mean of 248 µmol/l (range 125-350 µmol/l) after an average 42 months follow up (15-62 months). Two patients did not recover renal function despite adequate control of blood pressure. One patient (patient 3) had only 16 days dialysis, which we would now consider an inadequate trial. However, his biopsy showed more extensive changes than any other, and he was unfit for regular dialysis. He died of renal failure. The other patient (patient 6) remains well on CAPD 28 months after presentation with no sign of renal recovery.

Examination of the biopsies of these 7 patients showed that all had significant vascular damage with marked subintimal cellular proliferation, oedema and fibrosis. Fibrinoid arteriolar necrosis and intraluminal fibrin thrombi were present in patient 2 only; this patient's illness may have been triggered by the oral contraceptive pill. Varying degrees of tubular dilatation, interstitial fibrosis and inflammatory infiltrate were seen: tubular regeneration was present in 4 out of 5 biopsies of patients who recovered but in neither of the two who did not. By contrast the glomeruli were relatively normal showing ischaemic changes only, as judged by tuft

collapse, wrinkling of the basement membrane and focal necrosis.

Examination of the biopsies by electron microscopy and immunofluorescence excluded primary glomerular pathology in all but one patient. This was again patient 2 whose biopsy showed weak linear deposition of IgG. There was no clinical evidence of pulmonary abnormality. The light microscopic and ultrastructural changes were in keeping with microvascular disease and her subsequent history was most unlike anti-GBM nephritis. For these reasons we have included her in the study.

Discussion

Malignant hypertension was first recognised as a cause of acute renal failure in 1931 (149) but it was not until 1971 that the first report of short term recovery was published (96). That report described transient improvement in renal function in 3 out of 10 patients but, within two years, nine of the patients had died and the tenth was on dialysis. The most striking feature of the series was failure to achieve more than temporary control of blood pressure. With the introduction of more potent antihypertensive drugs and the wider availability of dialysis, several reports have since confirmed the potential for significant and sustained improvement of renal function in these patients (97-108).

Although uncommon, the diagnosis should be considered in all patients with malignant hypertension and renal failure, especially if oliguric. Characteristic features include normal sized kidneys as seen on high dose urography, and marked vascular changes with well preserved glomeruli on renal biopsy (99). Good control of blood pressure is essential if improvement of renal function is to follow. Peritoneal dialysis allows a smoother control of blood pressure than haemodialysis and may be preferable therefore when acute renal failure complicates malignant hypertension (105). Dialysis should be continued for a period of several

months before concluding that recovery of renal function will not occur (99-102,104).

On retrospective review of all available clinical and histological material, the only feature which appeared to be of value in predicting recovery of renal function was the presence of tubular regeneration, the hallmark of acute tubular necrosis, on renal biopsy. This was found in 4 out of 5 patients who recovered, but was absent in the 2 who did not. On the basis of this observation we propose the following model for the development of acute renal failure in malignant hypertension. First, intimal proliferation and oedema leads to narrowing of the lumen of the small renal arteries. This in turn causes a reduction in glomerular blood flow and filtration rate. If this occurs very quickly, acute tubular necrosis and oliguria result. Such a lesion should be reversible. If, on the other hand, the reduction in glomerular blood flow occurs more slowly, then unidentified adaptive changes may prevent the development of acute tubular necrosis, thus prolonging the time before the patient presents and increasing renal parenchymal destruction. Such patients would be less likely to recover renal function.

Other observations support this hypothesis. First, Kerr (103) has stated that in the absence of "reversible" factors such as vomiting and cardiac failure (which may predispose to acute tubular necrosis), recovery does not occur. Second, Mamdani et al (99) suggest that oliguria at presentation may favour a good prognosis. Our findings support his observation. Four of our patients were oliguric at presentation or became so shortly afterwards; all have recovered. Three were never oliguric; 1 recovered and 2 did not. Oliguria may herald the development of acute tubular necrosis, and thus be an indication of a reversible component of the renal failure. Third, the period during which our patients required peritoneal dialysis before recovery was similar to that of patients with

simple acute tubular necrosis. A second phase of slower recovery, which lasted up to twelve months, may have been due to the healing of the arterial lesions (150) and increasing perfusion and hypertrophy of the remaining nephrons.

The final observation in support of a two stage pathogenetic mechanism is the fate of the patients with malignant essential hypertension who are described in the next study. Most of these patients presented with malignant hypertension and renal failure which was not severe enough to require immediate dialysis. The changes in their serum creatinine over a period of at least eighteen months are shown in Figure 11. Whereas a serum creatinine of less than 300 µmol/l was usually associated with a good prognosis, patients with initial creatinine of more than 300 µmol/l faired badly. This experience is broadly similar to that of others (3,7,94,111) and suggests that in malignant hypertension, irreversible renal damage probably occurs by the time the creatinine concentration has risen above 300 µmol/l unless acute renal failure is superimposed. Thus, the five patients who recovered renal function in our series may have had renal failure caused by hypertension up to this level and thereafter developed acute tubular necrosis and oliguria. This speculation is supported by the degree of recovery which occurred since all patients had a creatinine of 350 µmol/l or less at their last visit.

TABLE 8 MALIGNANT HYPERTENSION AND ACUTE RENAL FAILURE

Patient	1	2	3	4	5	6	7
Date	Nov 77	Jan 78	Sep 78	Sep 79	Jun 80	Aug 80	Oct 81
Age/sex	45 M	20 F	67 M	53 F	45 F	47 F	49 M
Previous BP	?	Normal (Nov 77)	?	?	?	?	130/70 (1976)
BP at onset	250/130	220/130	250/130	195/120	240/150	220/135	185/140
Papilloedema	+	-	-	+	-	+	?
MAHA	+	+	?	+	+	+	+
Initial creatinine (µmol/l)	1680	1080	945	956	839	1180	1004
Oliguria	+	+	-	+	+	-	-
Heart failure	-	-	+	+	-	+	-
Encephalopathy	-	-	-	+	+	-	+
Type of dialysis	PD	PD	PD	PD	PD	PD	PD
Duration of dialysis (day)	44	27	16	40	35	29 mo	47
Duration of follow-up(months)	62	60	1	40	31	29	15
Final creatinine (µmol/l)	300	125	Died	220	245	CAPD	350

STUDY 8: RENAL OUTCOME OF MALIGNANT HYPERTENSION: DIFFERENCES BETWEEN PATIENTS WITH ESSENTIAL HYPERTENSION, RENAL VASCULAR AND RENAL PARENCHYMAL DISEASE

Introduction

The previous paper described the changes in renal function during follow-up of 7 patients who presented with malignant essential hypertension and acute renal failure. Four of these patients belonged to the main cohort of 139 malignant hypertensives, and 3 were identified by case sheet review of other patients at the Royal Infirmary in Glasgow. Five of the 7 showed significant and sustained improvement in renal function following a period of dialysis and meticulous control of blood pressure. To determine whether there were other circumstances in which long term improvement of renal function may occur, we examined the changes in renal function of all other members of the cohort.

Methods

Patients included in this analysis were those in whom a confident diagnosis of essential hypertension, renovascular disease, chronic glomerulonephritis or interstitial nephropathy had been made, and for whom serial measurements of serum creatinine were available. Patients whose follow-up was less than one year were excluded, unless advancing renal failure had led to their death.

Results

The renal outcome of patients with renal parenchymal disease was poor despite treatment with antihypertensive drugs (Fig 10). Nine of 12 patients with interstitial nephropathy and all 13 patients with chronic glomerulonephritis progressed to end stage renal failure during the course of the study. By contrast, those who presented with malignant hypertension and who had arteriographic evidence of renovascular disease were more

likely to maintain renal function during treatment. Only 3 of 17 patients had evidence of progressive renal failure: a 51 year old man with bilateral renal artery stenosis who died of congestive cardiac failure with serum creatinine 884 µmol/l, a 61 year old mana also with bilateral renal artery stenosis who died of a stroke with serum creatinine 600 µmol/l, and a 48 year old woman whose cause of death was meningitis after a stormy course on peritoneal dialysis.

Of the 83 patients with malignant essential hypertension, 70 fulfilled the criteria for this analysis (Fig 11). Five of these had acute renal failure (4 of the 5 were considered in more detail in Study 7). Fifteen had serum creatinine greater than 300 µmol/l but did not require dialysis immediately, and 50 had serum creatinine less than 300 µmol/l when first seen. The renal outcome of these patients has been shown in figure 11. Deterioration of renal function to long term dialysis or death occurred in 1 (20%) patient with acute renal failure, 11 (73%) patients who did not require dialysis immediately and 4 (8%) patients with initial serum creatinine <300 µmol/l, respectively. These data suggest there may be three groups of patients with the malignant phase of essential hypertension, whose renal prognosis is quite different.

Discussion

Renal function of patients with malignant hypertension does not necessarily deteriorate during treatment, unless associated with underlying renal disease or with significant renal impairment at presentation. This was first established by Woods & Blythe in (109), and has since been confirmed by a number of other authors (110-115). In the series reported by Pohl et al (111) effective antihypertensive therapy improved renal function in patients who had survived for six months, whose initial creatinine clearance was >8 mls/min and in whom there was no intrinsic progressive renal disease. Follow-up extended to 43 months in this study

and the improvement in renal function was maintained during this time. Herlitz et al (115) evaluated renal function in a group of 24 patients with malignant essential hypertension presenting between 1969 and 1979. Renal function deteriorated in 5 of 6 patients whose initial serum creatinine was >300 µmol/l, but improved or remained stable in 16 of 18 patients whose creatinine was <300 µmol/l when first seen.

Our own results are similar in many respects. The renal function of patients with renal parenchymal disease almost invariably deteriorated during long term follow-up, irrespective of blood pressure control, such that all patients with glomerulonephritis and most with interstitial nephropathy had developed end stage renal failure by the end of the study. It seems likely that deterioration of renal function in these patients simply represents the natural history of a progressive underlying disease. By contrast, renal function in malignant hypertension associated with renovascular disease deteriorated in 3 of 17 patients only (Fig 10). Overall survival in these patients was no better, however, than in the renal parenchymal group (see Table 9, Study 9), presumably as a result of widespread atheromatous disease affecting not only the renal but also the coronary and cerebral circulations.

The renal outcome of patients considered to have the malignant phase of essential hypertension is shown in Figure 11, in which there appear to be three groups of patients, each with a different renal prognosis. First, patients who have serum creatinine concentration below 300 µmol/l at the time of presentation, most of whom do well with effective antihypertensive therapy. Second, patients who present with chronic renal failure but do not require dialysis immediately. These patients are less likely to maintain or recover renal function except possibly in the short term (94) and progression to end stage renal failure is common. Third, there is a small group with acute renal failure (as discussed in Study 7). These patients rarely give a

past history of renal impairment. The only certain way to establish the diagnosis, and to exclude underlying renal disease, is by renal biopsy. In this series of 70 consecutive patients with malignant essential hypertension, five presented with acute renal failure, and in four of these renal function improved significantly following a period of dialysis and meticulous blood pressure control. The implication of these findings is that in malignant essential hypertension, irreversible renal damage will usually have occurred by the time the serum creatinine concentration exceeds 300 μmol/l, unless acute renal failure is superimposed.

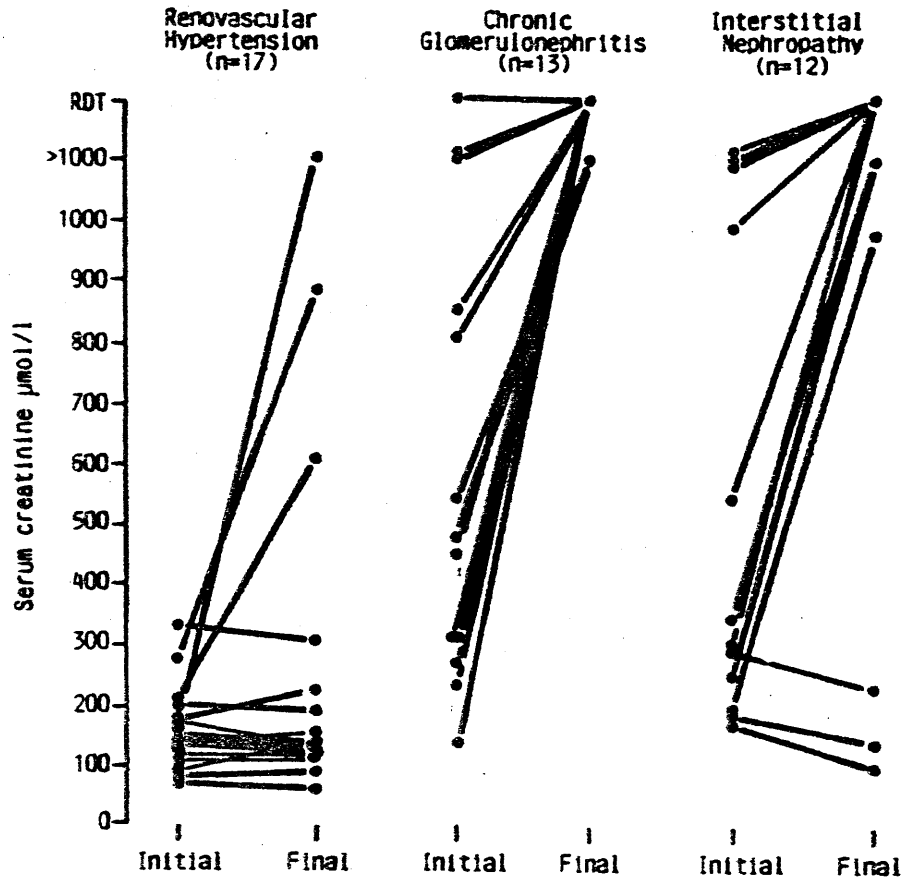

FIGURE 10 Changes in renal function during follow-up of malignant hypertension in patients with renovascular disease, chronic glomerulonephritis and interstitial nephropathy. The values shown are initial and final serum creatinine concentration. At least 1 year separates each pair of measurements except when rapidly advancing renal failure led to a patients death. These data represent long term rather than short term changes in renal function therefore.

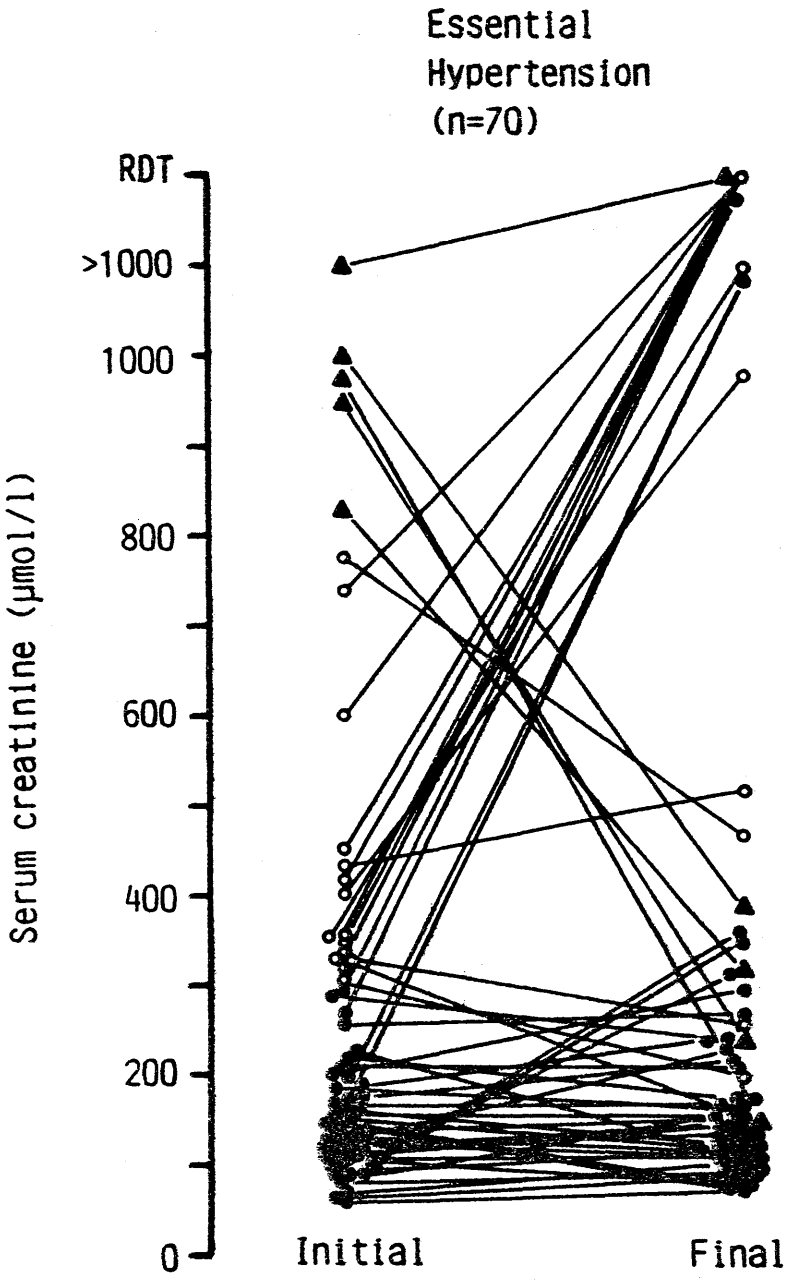

FIGURE 11 Changes in renal function during follow-up of patients with malignant phase of essential hypertension. Criteria for inclusion were as for figure 10. Closed circles represent patients whose serum creatinine was below 300 µmol/l at time of presentation (n=50). Open circles represent patients with renal failure who did not require dialysis immediately (n=15). Closed triangles are patients with syndrome of malignant hypertension and acute renal failure (n=5).

STUDY 9: AN ANALYSIS OF SURVIVAL IN MALIGNANT HYPERTENSION.

Introduction

The prognosis for patients with malignant hypertension has improved considerably since the advent of effective antihypertensive therapy (3,52,116) but the extent to which their mortality still exceeds that of matched controls, and the cause of that excess mortality, has never been determined. A preliminary report of our study has been published (4).

Methods

The study was in three parts. In the first part, factors influencing mortality among patients with malignant hypertension were assessed both by univariate analysis and by multivariate analysis using the Cox proportional hazards model (129).

In the second part, survival of the 139 malignant hypertensives from diagnosis to 1.4.84 was calculated by life table analysis, and was compared with that of two control populations: with 139 non malignant hypertensives who attended the Glasgow Blood Pressure Clinic (117) during the same period and were matched individually for age, sex, initial blood pressure and year of presentation, and with data derived from the general population of Strathclyde (120) at the mid-point of our study in 1976. Record linkage of both groups of hypertensive patients with the Registrar General in Scotland ensured that when death occurred, the date of death was notified in each case even if patients were no longer attending a hospital clinic, but providing that death occurred within the United Kingdom.

In the third part of the study, the cause of death among patients with malignant hypertension, as given by the Registrar General on the death certificate, was compared with that of the 139 matched non malignant hypertensives from the Glasgow clinic and also with an unmatched group consisting of all 3783 non malignant hypertensives who attended the Glasgow

clinic between 1968 and 1983. The average diastolic blood pressure at referral to the clinic was rather lower in this group (111 mmHg). Using the 9th revision of the ICD codings, we analysed causes of death in the following categories:

1.	IHD	ICD CODES 410-414
2.	CVD	430-438
3.	Other vascular	390-456 excluding above.
4.	Renal .	403-404, 580-599.
5.	All other causes	All other ICD codes

Results

Univariate analyses

Since the prognosis for men and women was similar (Table 9) the results for both sexes were combined in all the analyses which follow. Five year survival for the Glasgow patients with malignant hypertension is shown in figure 12 together with that of selected historical controls. Survival in Glasgow was better in the second than in the first half of our study, and better when compared with that of patients studied in an earlier period. Part of the improvement may have been due to the greater use of dialysis and transplantation, and part to more effective control of blood pressure. When the data were reanalysed on the assumption that dialysis was not available and that a patient requiring dialysis would have died, five year survival was reduced from 63% to 51%.

The benefit of good blood pressure control may be even greater. Five year survival in patients whose achieved blood pressure was better than average was 85%, and worse than average 29%, although this does not exclude the possibility that patients likely to die have pressure which is more difficult to control. Also the form of our analysis has the drawback that the assessment of blood pressure achieved during treatment was based on the last measurement of blood pressure before death, or before 1.4.84.

An alternative would be to assess blood pressure control at fixed intervals from the time of presentation for each patient, but since 17 of the 54 deaths among malignant hypertensives occurred within 6 months, and 22 within 1 year of presentation, there are objections to this approach also.

Mortality was increased in patients with secondary hypertension, in the presence of renal failure and in smokers (Table 9), but not by papilloedema when bilateral retinal haemorrhages and exudates were already present (Study 2). Women whose malignant hypertension was thought to have been precipitated by the oral contraceptive pill survived longer than women who were not taking the pill at presentation (Study 4). Survival was not related to the source of referral: local patients had a similar outcome to those referred to us from outside Glasgow (Table 9).

Multivariate analyses

Multivariate analyses were then performed using the Cox proportional hazards model to examine the possibility that a risk identified by univariate analysis might be related only indirectly to outcome. It was possible for example that the blood pressure of patients presenting before 1976 was less well controlled by drugs than that of those who developed malignant hypertension after 1976: an association between survival and year of presentation might simply reflect a stronger association between survival and blood pressure therefore.

Multivariate analysis of data available at diagnosis indicated that the single most useful predictor of risk was initial serum creatinine ($p<0.001$) (Table 10). The higher the serum creatinine at the onset of malignant phase, the more likely were patients to die. Patients presenting before 1976, those with secondary hypertension and, as expected, those who were older also had significantly increased mortality. By contrast, there was no evidence that male sex, cigarette smoking, papilloedema or the height of the initial blood pressure affected prognosis adversely after controlling for

the factors mentioned above.

When the multivariate analysis was repeated to include blood pressure achieved during treatment (Table 10), only pressure during treatment and initial serum creatinine were related independently to outcome. After controlling for these factors, year of presentation, underlying cause and age ceased to be of importance prognostically.

Comparison with control populations

Figure 13 shows that despite the improved prognosis of patients with malignant hypertension, mortality still exceeds that in non malignant hypertensives matched for age, sex, initial diastolic blood pressure and year of presentation, by a factor of approximately two; also that non malignant hypertensives of this severity have a much reduced life expectancy when compared with the general population from which they are derived. This comparison was the basis of another study of mine (117) which is not detailed in this thesis as it concerned mainly non malignant hypertension.

Patients with the malignant phase of essential hypertension and initial serum creatinine less than 300 µmol/l had a relatively good prognosis (80% 5-year survival, 60% 10-year survival) approaching that of non malignant hypertensive controls. This observation is important because nearly half of our patients (n=64) belonged to this good prognosis category.

Analysis of the cause of death

Fifty-four patients with malignant hypertension (27 males) and 34 age, sex and pressure matched controls from the Glasgow Blood Pressure Clinic with non-malignant hypertension (21 males) died between presentation and 1.4.84. Between 1968 and 1.1.83, 750 (450 male) of 3783 non-malignant hypertensives attending the Glasgow clinic died. The principal cause of death among each of these groups, classified according to the Registrar General code, is shown in Table 11. Renal failure was the commonest certified cause of death among patients with malignant hypertension.

Stroke was the commonest cause among severe but non-malignant hypertensives, and myocardial infarction the commonest among non-malignant hypertensives generally. Proportionately, renal deaths were 3 and 9-times more common among patients with malignant hypertension than their control groups respectively. Case record review showed that uraemia itself was not the usual cause of death in these patients, confirming that most patients die with renal failure but not directly because of it. However, if the cause of death was assumed to be "renal failure" when the serum creatinine was greater than 1000 μmol/l, or the patient had been accepted for dialysis or transplantation, then the proportion of malignant hypertensives dying with renal failure was greater, not less, than that given by the analysis of their death certificates. No fewer than 29 (54%) of malignant hypertensive decedents fulfilled one or other of these criteria. These data are consistent with the observation (Table 10) that high initial serum creatinine concentration affects prognosis adversely.

Discussion

This analysis of survival in malignant hypertension is based on a series of 139 cases seen in 15 years. Record linkage with the Registrar General ensured completeness of mortality data, and comparison with a matched group of non malignant hypertensives was possible because of the existence of a computerised blood pressure clinic, the Glasgow Blood Pressure Cllinic (117) in the same city at the same time. Thus we had an unusual opportunity to assess factors influencing mortality in patients with malignant hypertension, and to determine how far mortality in our patients exceeded that of the hypertensive population from which they were derived.

Renal failure has long been regarded as the most serious manifestation of malignant hypertension (52,109-115) and our findings suggest that this statement is as true now as it was before the advent of effective antihypertensive drugs and renal dialysis. Of the other factors examined by

step-wise multiple regression, only blood pressure achieved during treatment appeared to bear any relation to subsequent mortality. Surprisingly, neither cigarette smoking nor the presence of papilloedema were related independently to outcome. The former is interesting since we (18) and others (19-21) have shown that patients with malignant hypertension are more likely to smoke. The latter supports recommendations (8) that the definition of malignant hypertension should include patients whose fundi show bilateral retinal haemorrhages and exudates only. Our findings also suggest that the improved survival in patients developing malignant hypertension during the second half of the study was due to improved blood pressure control, since the relationship between year of onset of malignant hypertension and mortality disappeared after controlling for achieved pressure.

Comparison of survival at 5 and 10 years by life table analysis showed that patients with malignant hypertension were still twice as likely to die as non malignant controls matched for age, sex, initial pressure and year of presentation. While improved survival may be the result of more effective antihypertensive drugs and the wider use of renal dialysis, the persistently high mortality is likely to reflect patients with underlying renal disease or significant renal impairment when first seen. These conclusions are supported by an analysis of the causes of death in patients with malignant hypertension and controls. Fortunately the majority of patients with malignant hypertension have the malignant phase of essential hypertension and renal function that is only mildly or moderately impaired, and in these a 10 year survival of at least 60% may be expected.

TABLE 9 LIFE TABLE ANALYSIS: FACTORS INFLUENCING OUTCOME IN 139 PATIENTS

Survival (%±SEM)	1 YEAR	2 YEARS	5 YEARS	10 YEARS
Men	81.4±4.6	77.1±5.0	62.0±6.4	36.8±12.1
Women	87.0±4.1	78.0±5.0	63.6±6.2	52.0±8.2
All patients	84.2±3.1	77.5±3.6	62.8±4.4	46.7±6.9
To dialysis or to death	73.4±3.7	67.5±4.0	50.8±4.5	37.5±5.9
Achieved MAP better than average (<119 mmHg)	95.4±2.2	90.7±3.1	85.3±4.2	71.2±8.7
Achieved MAP worse than average (>119 mmHg)	66.0±6.7	55.7±7.1	29.0±6.7	26.0±6.6
Chronic glomerulonephritis	92.3±7.4	76.3±11.8	48.5±14.7	
Renovascular disease	73.7±10.1	62.3±11.3	53.4±12.7	26.7±19.9
Chronic pyelonephritis	91.7±8.0	75.0±12.5	54.1±15.2	
Essential hypertension	86.7±3.7	85.5±3.9	72.4±5.2	55.1±8.1
All causes, serum creatinine <300 µmol/l	89.2±3.2	83.8±3.8	70.8±5.0	52.2±7.8
All causes, serum creatinine >300 µmol/l	73.9±6.5	64.7±7.1	46.0±8.3	
Smokers	81.7±3.7	75.1±4.2	58.8±5.1	38.0±8.1
Non and ex smokers	96.6±3.4	89.4±5.8	80.5±7.9	80.5±7.9
Local referral	83.3±4.4	76.3±5.0	64.4±5.9	54.8±7.3
Referral from other hospitals	86.4±4.2	80.1±4.9	61.9±6.6	36.1±12.1

TABLE 10 STEPWISE MULTIPLE REGRESSION OF FACTORS INFLUENCING MORTALITY IN MALIGNANT HYPERTENSION

	DATA AVAILABLE AT DIAGNOSIS OF MALIGNANT HYPERTENSION	INCLUSION OF BLOOD PRESSURE ACHIEVED DURING TREATMENT
Age	$p<0.01$	NS
Male sex	NS	NS
Presentation before 1976	$p<0.001$	NS
Smoking	NS	NS
Papilloedema	NS	NS
Initial blood pressure	NS	NS
Secondary hypertension	$p<0.05$	NS
Initial serum creatinine	$p<0.001$	$p<0.05$
Achieved blood pressure	-	$p<0.001$

Multivariate analysis of data available at the onset of malignant hypertension indicated that initial serum creatinine was the single most useful predictor of outcome. Older patients and those with secondary hypertension also had significantly increased mortality. When multivariate analysis was repeated to include blood pressure achieved during treatment, only treated pressure and initial serum creatinine were related independently to outcome.

TABLE 11

CLASSIFICATION OF DEATHS

	MALIGNANT HYPERTENSION	NON MALIGNANT HYPERTENSION (MATCHED FOR AGE, SEX & PRESSURE)	NON MALIGNANT HYPERTENSION (GLASGOW BP CLINIC)
	n (%)	n (%)	n (%)
n	139	139	3783
Age	45	45	49.1
Average initial DBP (mmHg)	145	142	111
IHD (ICD 410-414)	11 (20)	9 (26)	288 (38)
CVA (ICD 430-438)	8 (15)	11 (32)	172 (23)
Other vascular (ICD 390-456)	4 (8)	5 (15)	100 (13)
Renal (ICD 430-404, 580-599)	20 (37)	4 (12)	31 (4)
Miscellaneous (all other codes)	11 (20)	5 (15)	159 (22)
All deaths	54 (100)	34 (100)	750 (100)

The category of renal deaths includes hypertensive renal disease, hypertensive heart and renal disease, chronic renal failure and specific renal diseases.

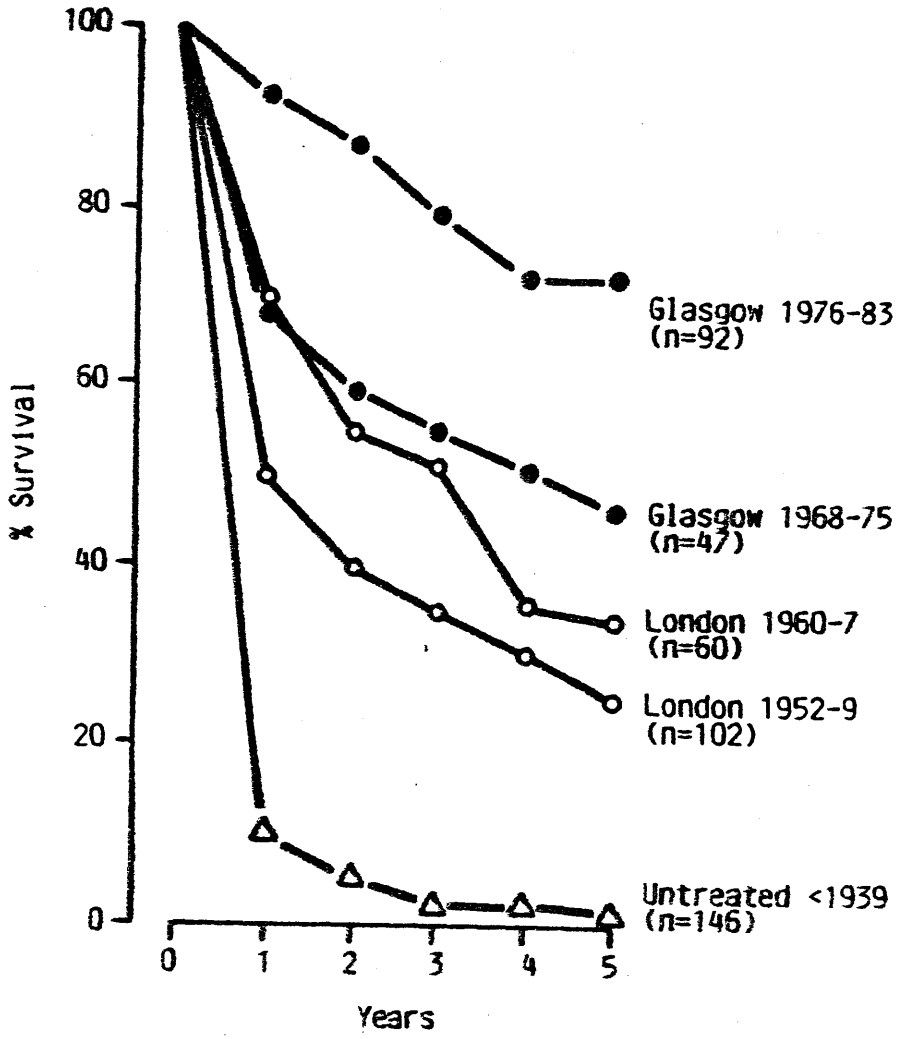

FIGURE 12 Five year survival in different studies of malignant hypertension showing a progressive improvement in outcome with time. The untreated survival curve is from Keith et al (1939), the London data from Breckenridge et al (1970) and the Glasgow data from Isles et al (1985).

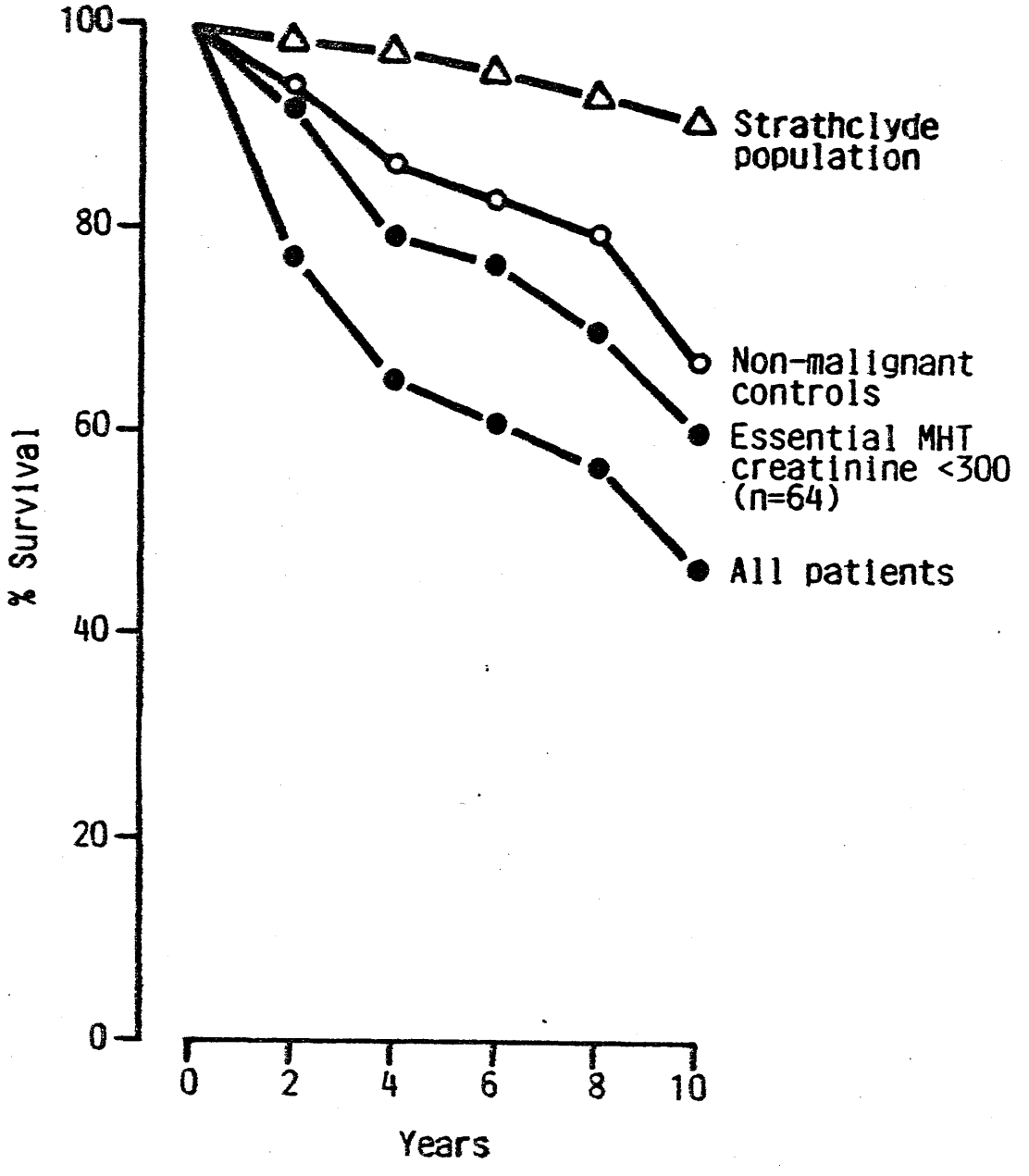

FIGURE 13 Ten year survival in all patients with malignant hypertension; in the subgroup with malignant essential hypertension and initial serum creatinine <300 µmol/l; in age, sex and pressure matched non malignant hypertensives from the Glasgow Blood Pressure Clinic; and in age and sex matched controls derived from the general population of Strathclyde.

CONCLUSIONS

Despite suggestions that the incidence of malignant hypertension is declining in Europe and North America (1), this study suggests that it is not yet a rare disease in the West of Scotland. Indeed its persistence in these parts has permitted us to conduct a number of analyses which would not have been possible had the number of new cases presenting each year been less.

The first analysis was an assesssment of retinal changes showing that papilloedema is of no additional prognostic importance in hypertensive patients who already have bilateral retinal haemorrhages and exudates. Hopefully this will settle the old argument concerning the degree of retinopathy required to establish a diagnosis.

The association of malignant hypertension with cigarette smoking had not been described before. We are unable to say on this evidence alone, whether smoking predisposes to the malignant phase in patients who are already hypertensive, or whether some other factor predisposes both to smoking and to malignant hypertension. Further studies will be required to resolve this question. There is plentiful evidence to show that smoking does not cause benign phase hypertension.

The nature of the association between the oral contraceptive pill and malignant hypertension is clearer, particularly in patients who were known to be normotensive before starting the pill and developed the malignant phase shortly afterwards. Thus, our results suggest that oral contraceptives may be a relatively common cause of malignant hypertension in women of childbearing age in whom the condition is otherwise rare. Fortunately, if the pill is stopped and underlying renal disease can be excluded, the long term prognosis for such patients can be excellent.

The fifth analysis was a test of the hypothesis that low grade coagulopathy is a necessary step in the transition from the benign to

malignant phase. Our finding that carefully matched controls had similar haemostatic abnormalities indicates there may be an alternative explanation, namely that abnormal coagulation may also be a consequence of the malignant phase.

The remaining four analyses were concerned primarily with treatment and outcome. Atenolol and nifedipine retard were compared in a randomised trial of treatment in 20 black patients with malignant hypertension, and both were found to be effective and safe when given as initial therapy. These results re-emphasize that most patients with malignant hypertension can be managed without recourse to parenteral therapy.

The two studies on renal outcome in malignant hypertension suggest that the heterogeneity of the renal response to treatment is determined primarily by the underlying renal pathology. Thus, in glomerulonephritis and interstitial nephropathy, deterioration of renal function during long term treatment is likely to represent the natural history of a progressive underlying disease. By contrast, in patients with the malignant phase of essential hypertension, renal failure is an uncommon outcome unless the initial serum creatinine exceeds 300 µmol/l.

An important exception to this general rule is the patient with malignant essential hypertension and acute renal failure. Many of such patients will show significant improvement in renal function following treatment with antihypertensive drugs and peritoneal dialysis. This diagnosis should be considered therefore in oliguric patients with marked vascular changes but well preserved glomeruli on renal biopsy.

In the final analysis of this thesis, malignant hypertensives were shown to have an improved survival compared with similar patients studied in an earlier period, but a higher mortality than non-malignant hypertensives matched for age, sex, initial pressure and year of presentation. Improved

survival may be, at least in part, the result of more effective antihypertensive drugs and the wider use of renal dialysis, while the persistently high mortality is likely to reflect underlying renal disease or significant renal impairment when patients are first seen.

What then of the future? The reason why some patients with diastolic pressures greater than 130 mmHg enter the malignant phase, while others do not has still to be determined. So too has the relative importance of genetic and socioeconomic factors in the pathogenesis of the disease. Not enough is known of the effects of different antihypertensive drugs on cerebral blood flow at different arterial pressures for a confident conclusion concerning the ideal rate of reduction of pressure when patients are first seen. It is also unclear whether further improvements in survival for patients with significant renal impairment can be expected. The problem in the United Kingdom is that we no longer see enough malignant hypertension, even in the West of Scotland, to answer these questions. The burden of work must then inevitably fall on units that do see it, probably those in Africa and South America (2).

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