STUDIES ON RENOVASCULAR HYPERTENSION

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

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PUBLICATIONS AND COMMUNICATIONS

The research described in this thesis was conducted at the Medical Research Council, Blood Pressure Unit, Western Infirmary, Glasgow, between November 1978 and December 1980. During this period a number of papers relating to this work were published or submitted for publication, and a number of communications were delivered.

Publications.

Mackay A, Brown JJ, Cumming AMM, Isles C, Lever AF, and Robertson JIS. Smoking and renal artery stenosis. British Medical Journal 1979; 2: 770.

Mackay A, and Cumming AMM. Renal artery stenosis with severe hypertension: a rare case with detailed assessment of the renin-angiotensin system before and after the development of the lesion. British Heart Journal 1979; 42: 480-482.

Davies DL, McIlroy K, Atkinson AB, Brown JJ, Cumming AMM, Fraser R, Leckie BL, Lever AF, Mackay A, Morton JJ, and Robertson JIS. Exchangeable sodium and blood pressure in patients with hypertension. Clinical Science 1979; 57: 69s-75s.

Mackay A, Cumming AMM, Brown JJ, Lever AF, and Robertson JIS. Ischaemic heart disease in young hypertensive women. British Heart Journal 1980; 43: 80-87.

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Mackay A. Recovery of renal function after renovascular surgery. Scottish Medical Journal - in press.

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Carr D, Mackay A, and Atkinson AB. Does inhibition of prostaglandin synthesis increase the diagnostic accuracy of the intravenous urogram in renal artery stenosis? Submitted for publication.

Mackay A, Boyle P, Brown JJ, Cumming AMM, Forrest H, Graham AG, Lever AF, Robertson JIS, and Semple PF. The decision on surgery in renal artery stenosis. Submitted for publication.

Mackay A. Blood pressure changes after excision of the clipped kidney in rats with two-kidney hypertension. Submitted for publication.

Communications.

Factors influencing the decision to operate in patients with renal artery stenosis. Scottish Society of Physicians, Inverness, October, 1979.

Comparison of ^{123}I-hippuran renography and bilateral ureteric catheterisation studies in the measurement of renal plasma flow of patients with renal artery stenosis. 2nd International Conference on secondary forms of hypertension, Montecatini Terme, Italy, May 1980.

Hypertension as a consequence of renal trauma. Symposium on renal trauma, Blackburn, October 1980.

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STUDIES ON RENOVASCULAR HYPERTENSION

SUMMARY

Aspects of the pathogenesis, diagnosis, prognosis and management of renal artery stenosis have been studied in 86 hypertensive patients and in experimental animals.

PATHOGENESIS

Mean exchangeable sodium was normal in patients with unilateral renal artery stenosis compared with normotensive controls, but the relation between exchangeable sodium and blood pressure was significant and negative ($r = -0.62$, $p < 0.001$) in contrast to other forms of hypertension. Patients with the lowest exchangeable sodium had hyponatraemia, hypokalaemia, and secondary hyperaldosteronism - the "hyponatraemic hypertensive syndrome". Urinary sodium excretion from the unaffected kidney correlated positively ($r = +0.51$, $p < 0.01$) with arterial pressure, possibly reflecting the phenomenon of pressure natriuresis. Patients who responded least well to subsequent surgery excreted least sodium from the unaffected kidney for a given arterial pressure, and maintained this relationship after surgery. The findings suggest an important role for arterial pressure in the control of sodium balance in contrast to Conn's syndrome where the roles are reversed.

Before surgery arterial pressure was disproportionately high for a given plasma angiotensin II concentration in patients with unilateral renal artery stenosis in comparison with normal individuals infused with angiotensin II. After successful surgery this relation fell towards normal, consistent with a slow pressor action of angiotensin II in renovascular hypertension.

Cigarette smoking was found to be significantly commoner ($p < 0.001$) in patients with non-malignant hypertension and renal artery stenosis (84% smoked) than in age- and sex-matched controls with non-malignant hypertension without renal artery stenosis who were inpatients (46% smoked) or were attending the Glasgow Blood Pressure Clinic (44% smoked). The differences were significant for men and women separately, and for subgroups with renal artery occlusion, fibromuscular hyperplasia, and stenosis due to atheroma. 91% of patients with renal artery stenosis and malignant-phase hypertension at the time of presentation also smoked.

Fibromuscular hyperplasia is one cause of renal artery stenosis whose aetiology remains obscure. Of 23 patients with this condition 21 were women, but no relationship between fibromuscular hyperplasia and pregnancy could be established. The right renal artery was involved twice as often as the left, perhaps reflecting a greater degree of nephroptosis on that side.

DIAGNOSIS

The diagnosis of ischaemia due to renal artery stenosis in the present study was based on the demonstration of a narrowed lumen at arteriography, together with reduced urine flow and increased urinary concentration of creatinine and para-aminohippurate on the affected side at bilateral ureteric catheterisation studies. This pattern of ischaemia was quite distinct from the pattern of abnormality in hypertensive patients with unilateral small kidney but normal vasculature.

The value of intravenous urography in diagnosis was assessed in 37 patients who also underwent arteriography, renal vein sampling and ureteric catheterisation. There was considerable disagreement between six independent observers in the reporting of delay in the appearance of contrast and increased density of contrast in later films on the affected side. False negative reports of ischaemia occurred in 41% of patients with unilateral stenosis, but in no patient were all observers wrong; this emphasised the importance of more than one observer viewing the urogram of a hypertensive patient, and of following up even slight abnormalities by arteriography. Diagnostic accuracy was not enhanced either by the administration of a prostaglandin synthetase inhibitor before urography, or by further radiographs after an oral water load. False positive reports were common in a small group of patients with unilateral small kidney but normal vasculature. The

ratios of urine flow rate, and urinary creatinine and para-aminohippurate concentration correlated positively with delay and density differences, suggesting that the urographic appearances of stenosis could be explained in terms of how the ischaemic kidney handles non-reabsorbable solute. The renal vein renin ratio did not correlate with urographic abnormalities but did correlate with the ratio of para-aminohippurate clearances by the unaffected and affected kidneys ($p < 0.05$).

^{123}I-hippuran clearance and para-aminohippurate clearance measured on the same day were closely related ($r = 0.96$, $p < 0.001$). Divided renal plasma flow, measured using ^{123}I-hippuran and a gamma camera technique, also correlated well with divided para-aminohippurate clearance measured at ureteric catheterisation studies in both affected ($r = 0.77$, $p < 0.01$) and unaffected ($r = 0.81$, $p < 0.001$) kidneys of patients with unilateral renal artery stenosis. ^{123}I-hippuran renography was thus shown to be a rapid, accurate and non-invasive means of measuring divided renal plasma flow in comparison with ureteric catheterisation.

PROGNOSIS.

Of 39 patients with renal artery stenosis who underwent surgery, 21 (54%) had untreated blood pressure within one standard deviation of the age and sex-related mean values of a control population one year after surgery, while 18 (46%) failures did not. The definition of success and failure was arbitrary, and did not imply that failure was

total. A retrospective analysis failed to find any single prognostic test - based on clinical features, simple tests, peripheral plasma renin concentrations, renal vein renin ratios, infusions of the competitive angiotensin II antagonist, saralasin, ureteric catheterisation studies, or urinary sodium excretion by the unaffected kidney - any combination of tests or any discriminant function which uniformly separated success and failure preoperatively. However, all six patients who had a renal vein renin ratio of 2.0 or more had successful surgery while all six patients with bilateral renal artery involvement did not.

MANAGEMENT

The surgical success rate in this series was comparable to those of other large series with renovascular hypertension, and with other forms of surgically treated hypertension, such as Conn's syndrome. The inadvisability of pronouncing on cure in the early days after surgery was demonstrated in one-clip two-kidney hypertensive rats following excision of the clipped kidney - after initial hypotension blood pressure returned to significantly elevated levels in the weeks after surgery.

The superiority of reconstructive surgery over nephrectomy in terms of renal function was demonstrated in patients with normal preoperative renal function. One year after arterial reconstruction serum creatinine concentration had fallen by a mean of 13.3 μmol/l ($p < 0.01$) while after nephrectomy it had risen by a mean of 22.7 μmol/l ($p < 0.01$)

due partly to diminished function in the remaining kidney and partly to loss of the excised kidney.

Two major management decisions in hypertensive patients with renal artery stenosis were made. The first, whether or not to undertake further tests with a view to surgery, was influenced largely by the patient's age, fitness for elective surgery and the ease of blood pressure control with drugs, though none of these features was an absolute contraindication to further tests. The second, whether or not to recommend surgery on the basis of further tests, was difficult because of lack of an accurate prognostic index. Indeed had the decision to operate been based on age, the presence of other vascular disease and renal function alone, and had all special prognostic tests been ignored, the surgical success rate would have been similar though fewer patients would have come to surgery.

CHAPTER 1

INTRODUCTION

Renal artery stenosis, the commonest potentially curable cause of hypertension in man, has been described by Kaufman and Maxwell (1964) as an "experiment of Nature". Unfortunately, in contrast to the ingenious animal experiments of Goldblatt, Floyer and many others, the protocol for this human experiment or series of experiments, is not available, and it is not possible to determine with accuracy the temporal relationship, if any, which exists between the development of a stenosis and the onset of hypertension. Four relationships are possible: the stenosis has caused the hypertension, and removal of the stenosis may or may not cure the hypertension; the hypertension has preceded, and may have contributed to, the stenosis; the hypertension has preceded the stenosis which then acts as a secondary cause and raises blood pressure further; and the stenosis and the hypertension are unrelated findings in the same patient. In practice any of the four may occur.

Investigation in hypertensive patients is therefore intended first to establish whether or not a stenosis is present and is raising blood pressure (diagnostic tests), and second to predict whether or not surgical treatment will restore blood pressure to normal (prognostic tests). This thesis presents an analysis of the management of 86 hypertensive patients with renal artery stenosis seen over

an 11 year period, and assesses the value of tests singly and in a variety of combinations in diagnosis and surgical prognosis. New observations on the pathogenesis of renal artery stenosis are also described, and the consequences of surgery assessed in man, and in rats with experimental hypertension.

CHAPTER 2

RENOVASCULAR HYPERTENSION - A REVIEW OF THE LITERATURE

2:1 The physician who, in seeking to determine the best way to manage a hypertensive patient whom he suspects may have renal artery stenosis, turns to the literature for guidance is faced with a vast, complex and daunting array of often contradictory advice about the investigation and treatment of his patient, not to mention the pathogenesis of the hypertension. The object of this literature review is to examine the development, and current status, of the investigation and management of renal artery stenosis in man, and to assess the role of the renin-angiotensin system in its pathogenesis.

2:2 HISTORICAL PERSPECTIVE.

I. The renin-angiotensin system. While the association between kidney disease and raised arterial pressure in man was first noted by Richard Bright in 1827, it was not until 1898 that relevant supportive experimental evidence began to be gathered. In that year, Tigerstedt and Bergman published their observations on the pressor activity of crude saline extracts of rabbit kidney following injection into other rabbits. They named the active extract renin. However, the importance of this extract was a matter of contention for over 30 years until

Goldblatt, Lynch, Hanzal and Summerville (1934) provided and easy and reliable model for the study of experimental hypertension. Goldblatt, by applying an adjustable silver clamp to the renal artery of a dog whose contralateral kidney was untouched, consistently produced a transient elevation in blood pressure. Clamping of the contralateral renal artery rendered the animal persistently and severely hypertensive, while constriction of the splenic or femoral arteries produced no pressor effect. Interestingly, as Kaufman and Maxwell (1964) point out, Goldblatt had "no prescience that such a constriction occurred frequently as an experiment of nature".

Nevertheless, the availability of this model stimulated considerable research into possible humoral or neural mechanisms responsible for the pressor response. Failure of local section of renal nervesto prevent the response (Page, 1935; Goldblatt, Gross and Hanzal, 1937) and the pressor and depressor effects of clipping and unclipping the artery to a kidney which had been transplanted to the neck of a dog (Blalock and Levy, 1937; Glen, Child and Heuer, 1937) pointed to a humoral mechanism being responsible. Further evidence was gathered in three laboratories where the pressor activity of kidney extracts was confirmed (Kohlstaedt, Helmer and Page, 1938; Pickering and Prinzmetal, 1938;

Braun-Menendez and Fasciolo, 1939).

Increasing purification of the pressor extract by Kohlstaedt et al (1938) led to the realisation that renin itself was not pressor, but that it became pressor following its incubation with a substance or substances in plasma. In 1940 Page and Helmer in the U.S.A. identified a substance which they named angiotonin formed by the interaction of renin with "renin activator"; with this they were able to raise the arterial pressure of a pithed cat. At the same time in Argentina, Braun-Menendez, Fasciolo, Leloir and Munoz isolated a pressor substance from the renal vein blood of acutely ischaemic kidneys and called it hypertensin. While the term renin substrate was generally accepted instead of renin activator in the 1940's, it was not until 1958 that the term angiotensin was coined as a compromise between angiotonin and hypertensin, which had been shown to be identical substances.

Further purification of angiotensin led to the recognition of three different forms - angiotensin I, a decapeptide (Skeggs, Marsh, Kahn and Shumway, 1954a; Elliott and Peart, 1956), angiotensin II, an octapeptide formed by cleavage of the dipeptide histidyl leucine from angiotensin I (Skeggs, Marsh, Kahn and Shumway 1954b) and angiotensin III, a heptapeptide - and to

synthesis of angiotensin II in 1957 (Bumpus, Schwarz and Page, 1957; Rittell, Iselin, Kappeler, Riniker and Schwyzer, 1957). Angiotensin II has been shown to be the principal active component in man, though angiotensin III may be of importance in other species (Semple, Boyd, Dawes and Morton, 1976; Brown, Casals-Stenzel, Cumming, Davies, Fraser, Lever, Morton, Semple, Tree and Robertson 1979a).

Current understanding of the renin-angiotensin-aldosterone cascade has been reviewed in detail by Pickering (1968), Page and Bumpus (1974) and Boucher, Rojo-Ortega and Genest (1977). Renin, synthesized stored and secreted mainly by the Lacis cells of the juxta-glomerular apparatus in the kidney, acts on its substrate, an α-2-globulin produced by the liver, to form angiotensin I. This reaction takes place in circulating blood and in vessel walls. Angiotensin I converting enzyme, found principally in the lungs, but also in circulating plasma and in the kidney, cleaves a dipeptide from angiotensin I to produce angiotensin II. Angiotensin II, apart from its direct pressor activity, has a number of actions reviewed by Atkinson, Brown, Fraser, Leckie, Lever, Mackay, Morton and Robertson (1980a): it stimulates aldosterone production, has direct renal actions modifying the excretion of water and electrolytes, acts on the sympathetic nervous system at a number

of levels, stimulates drinking, stimulates secretion of antidiuretic hormone from the posterior pituitary gland, and inhibits adrenocorticotrophic hormone secretion, while further interactions with prostaglandins and kinins and the internal distribution of sodium and potassium in smooth muscle cells remain to be fully clarified.

Recent work on renin has shown that it exists in several forms (Leckie, 1980) but principally those known as active and inactive renin, which are found within both the kidney and the circulation (Leckie, Millar, Morton and Semple, 1979). Activation by acid, trypsin or low temperatures (+5 to -5^{o}C) results in the cleavage of a 13,000 M.W. fragment from the inactive compound (M.W. 55-60,000) and recombination of the fragments results in the reformation of inactive renin (Leckie and McConnell, 1975). In the circulation of man an endogenous serine protease may be responsible for activation of inactive plasma renin (Leckie, 1978, Atlas, Laragh and Sealey, 1978; Derkx, Tan-Tjiong and Schalekamp, 1978) without much change in molecular weight, but with a change in iso-electric point.

Of great interest has been the recognition that activation of renin by acid, though not by trypsin, is dependent on factor XII (Hageman factor), pre-kallikrein and possibly plasmin. Since renin bound to the walls of

blood vessels may have an important physiological role (Swales, 1979) the connection between renin, coagulation mechanisms, and surface-mediated reactions leading to the formation of kinins may be of significance as a mechanism of blood pressure regulation.

Central to furtherance of understanding of the role of the renin-angiotensin system experimentally and clinically was the development of simple and accurate assay techniques for components of the system. Early bioassays of plasma renin activity (Helmer and Judson, 1963; Boucher, Veyrat, De Champlain and Genest, 1964) and plasma renin concentration (Brown, Davies, Lever, Robertson and Tree, 1964) were based mainly on the ability of angiotensin II to produce contraction of smooth muscle: while sensitive and reproducible, these assays were not convenient in terms of manpower requirements and the lack of standardization of the assays between different centres. The development of radioimmunoassay techniques (Berson and Yalow, 1959) was therefore of great importance. Angiotensin I, angiotensin II and aldosterone now may be measured readily using this technique, as detailed in Chapter 4:1. The availability of such assays, and synthetic angiotensin II for infusion, has also made possible the study of dose-response relationships between angiotensin II and blood pressure, and angiotensin II and

aldosterone, which have furthered insight into possible mechanisms in renovascular hypertension - see Chapter 2,4.

2:2 HISTORICAL PERSPECTIVE.

II. Renovascular hypertension in man. The early concept that renal abnormalities could be responsible for hypertension found its first clinical application in 1937 when Butler removed the pyelonephritic kidney of an 8 year old hypertensive boy and returned his blood pressure to normal. Unfortunately, rather indiscriminant nephrectomy in hypertensive patients with a variety of underlying pathologies, including renal artery stenosis, followed this exciting result (Figure 1): such was the enthusiasm that with hindsight Capelli, Wesson and Houssel (1973) have justly called this surgical activity the "rape of the nephros". However, Smith (1948 and 1956) critically reviewed the results of nephrectomy in hypertensive patients, proposed clear cut criteria for pre-operative hypertension (BP >140/90 mmHg), and surgical success (BP <140/90 mmHg at least one year after surgery) and demonstrated a distressingly low success rate in both series - 19% of 242 patients (1948) and 26% of 575 patients (1956). Reappraisal of the indications for surgery followed, and the operation rate fell dramatically (Figure 1).

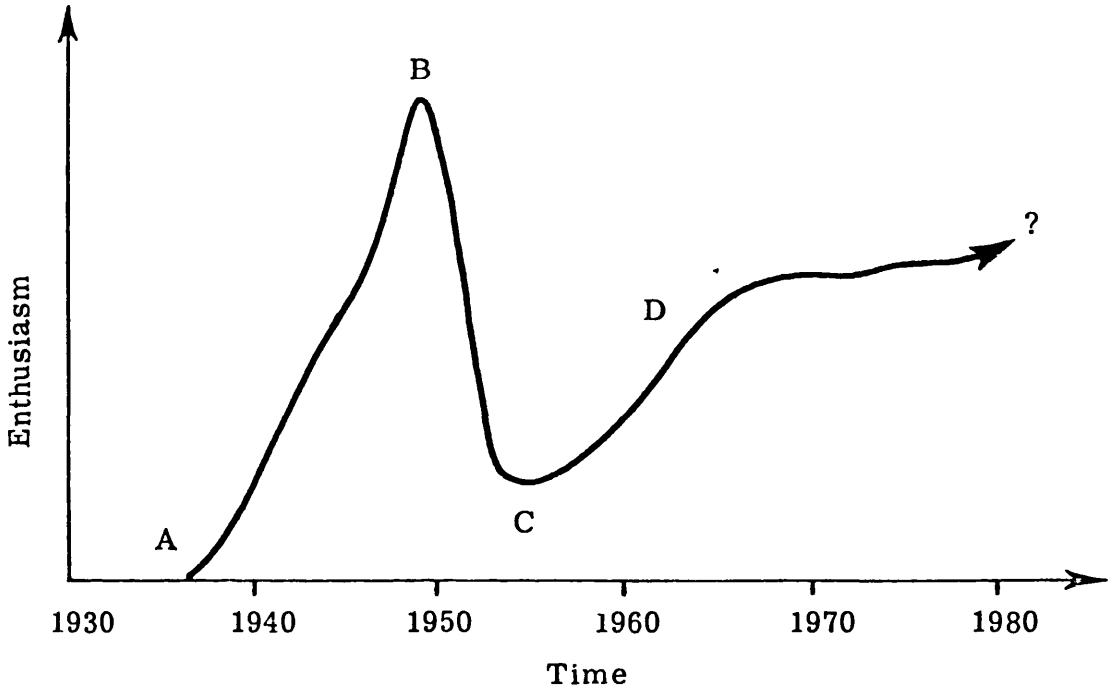


Figure 1: Oscillations in the surgical management of renal artery stenosis, 1937-1980 (after Laurence, 1973).

A. Butler, 1937.

B. Smith, 1948 "It may come about that from the smoke and noise of the battle ..... the urologist will emerge the hero when he proclaims 'well, I once had a case .... and I took one kidney out .... and I cured high blood pressure'. It is our task to calculate the probabilities of that happy event".

C. Smith, 1956

D. Stamey, 1963 "We are in an era of romance with renal artery stenosis. When the hue and cry is over, there will be far less enthusiasm for the surgical repair of even functionally significant atherosclerotic occlusions of the renal artery".

There followed in the 1950's and early 1960's "an era of romance" (Stamey, 1963) which saw the development of new investigative techniques aimed at improving diagnostic and prognostic accuracy, paralleled by the emergence of new techniques of reconstructive renal artery surgery, and operative management of renovascular hypertension began to re-expand on a more logical basis.

Central to this re-expansion was the development of new radiographic techniques. While characteristic appearances of renal artery stenosis were recognised on intravenous pyelography in the 1950's (Brown, Owen, Peart, Robertson and Sutton, 1960) the sensitivity of this indirect technique was low. Direct visualisation was for many years possible only using translumbar aortography (Smith, Rush and Evans, 1951), a technique with a high morbidity which was not readily undertaken. Then, in 1953, Seldinger described a new technique of aortography via femoral artery puncture under local anaesthesia with retrograde catheterisation of both aorta and, selectively, the renal arteries.

Major though this advance was, arteriography did not define abnormalities of function in a kidney whose artery was narrowed. However, work by Mueller, Surtshin, Carlin and White (1951) which demonstrated reduced excretion of water and sodium by the stenosed kidney in

Goldblatt two-kidney hypertensive dogs paved the way for the introduction of the split renal function studies (bilateral ureteric catheterisation studies) in man by Howard, Berthrong, Gould and Yendt in 1954. Hyperconcentration of non-reabsorbable solute (inulin and, less strictly, creatinine) on the affected side was also recognised (Birchell, Batson and Moore, 1958), and Brown et al (1960) and Stamey, Nudelman, Good, Schwencker and Hendricks (1961) using combinations of these tests demonstrated abnormalities characteristic of ischaemia in man.

However, because of the invasiveness and relative complexity of bilateral ureteric catheterisation studies, alternative tests of differential function were sought. To date none with the quantitative accuracy and richness of information of catheter studies has been found. Taplin, Meredith, Kade and Winter in 1956 developed the semi-quantitative technique of isotope renography using radioactively labelled hippuran, an analogue of the non-reabsorbable solute paraaminohippurate (PAH) used in bilateral ureteric catheterisation studies. The value of early results was limited largely by the lack of efficient counting equipment, but lately the development of computer-linked gamma cameras and the use of tracers such as ^{123}I-hippuran, which are particularly suited

for gamma camera imaging (O'Reilly, Herman, Lawson, Shield and Testa, 1977) have led to the possibility of a more quantitative approach.

A further approach to the assessment of deranged function concerned the 'endocrine kidney' (Selye and Stone, 1946). Most helpful among tests of endocrine function has been renal vein sampling. Houssay and Taquini (1938) first found that renal vein samples from dogs with experimental renal artery stenosis produced intense vasoconstriction when injected into the isolated vascular bed of the hind legs of toads, whereas renal vein blood from normal dogs did not. However, it was only with the development of fluoroscopic X-ray control, the use of the Seldinger technique for catheterisation of the femoral veins, and thereby retrograde catheterisation of the renal veins, and the ready availability of reliable assays for plasma renin concentration, that the assessment of differential endocrine pressor function by renal vein sampling became a practicable proposition in man. Judson and Helmer (1965) first established its place as a prognostic test in human renovascular hypertension, but now the ratio of plasma renin concentration from the affected to the unaffected renal vein is regarded by most investigators as the most useful single prognostic test (Marks and Maxwell, 1975). This is

discussed in greater detail below (Chapter 2:7).

Within the last 6 years a further in vivo means of assessing the role of the renin-angiotensin system in renovascular hypertension has become possible with the development of antagonists and inhibitors of the system. These have been reviewed in detail by Atkinson et al (1980a) and are discussed further below (Chapter 2:7). Most useful in man have been the parenteral competitive angiotensin II antagonist, saralasin (sarcosine-1-alanine-8-angiotensin II) and the oral angiotensin I converting enzyme inhibitor captopril (SQ 14225). Attempts to predict the response to surgery on the basis of a hypotensive response to saralasin have not been uniformly successful, though the long-term response to captopril may prove to be a more helpful prognostic test.

Thus the last 40 years have seen both the recognition of renal artery stenosis as a disease entity in man, and the development of tests of varying degrees of ingenuity for diagnosing the condition and assessing the prognosis should surgery be performed.

2:3 PATHOGENESIS.

The pathogenesis of renovascular hypertension is multifactorial, complex, and as yet incompletely understood. Two principal animal models have been developed.

In the first a constriction is applied to one renal artery while the contralateral kidney is not touched: this model is known as the one-clip two-kidney model, two-kidney hypertension, or Goldblatt 2-kidney hypertension. In the second, a constriction is applied to one renal artery while the contralateral kidney is excised: this is known as the one-clip one-kidney model, one-kidney hypertension or Goldblatt 1-kidney hypertension. The humoral, biochemical and blood pressure changes which occur with these procedures vary within the same species depending on the model used, and vary within the same model depending on the species of experimental animal used (Swales, Thurston, Queiroz, Medina and Holland, 1971). The one-kidney model has been thought of as a prototype for the hypertension in man accompanying chronic renal disease with volume excess as the primary mechanism (Kaplan, 1979) while the two-kidney model is the counterpart of renovascular hypertension with renin excess as the driving force (Davis, 1977). Dogs (Goldblatt et al, 1934; Bianchi, Tenconi and Lucca, 1970; Bianchi, Baldoni, Lucca and Barbin, 1972), rabbits (Pickering and Prinzmetal, 1938; Romero, Lazar and Hobler, 1970), rats (Wilson and Byrom, 1941; Floyer, 1951, 1957), sheep (Funder, Blair-West, Cain, Catt, Coghlan, Denton, Nelson, Scoggins and Wright, 1970) and

monkeys (Goldblatt, 1937) have all been used, but two-kidney hypertension in the rat is most akin to the situation in man (Davis, 1977).

Terms (Floyer, 1957) commonly used in descriptions of this model include 'untouched kidney' which denotes the contralateral kidney whose renal artery has not been narrowed - this does not imply normality in that kidney, merely freedom from surgical interference: 'clipped kidney' which signifies the kidney whose renal artery has been narrowed; and 'unclipped kidney' which signifies the kidney from whose artery a constriction has been removed.

I. The role of the renin-angiotensin system.

This has been reviewed in detail by Brown, Fraser, Lever, Morton, Robertson and Schalekamp, 1977; Davis, 1977; and Brown, Lever and Robertson, 1979b. The last named authors have divided the response to unilateral renal artery clipping in two-kidney hypertensive animals into three phases. First there is an early phase after clipping when blood pressure and plasma renin (Bianchi et al, 1970) and angiotensin II concentrations (Caravaggi, Bianchi, Brown, Lever, Morton, Powell-Jackson, Robertson, and Semple, 1976) rise acutely and in parallel. Secondly, there is a transitional phase when blood pressure remains high or rises further in the face of decreasing plasma renin concentrations. During both this phase and the

early phase unclipping or nephrectomy of the clipped kidney returns blood pressure to normal. Eventually a late phase supervenes when blood pressure remains elevated despite a normal circulating plasma renin concentration, and unclipping or nephrectomy fails to restore normal blood pressure.

i. Early phase. In this phase the contention that the renin-angiotensin system is solely responsible for producing the hypertension is supported by two main pieces of evidence. Firstly, Caravaggi et al (1976) showed that graded intravenous infusions of angiotensin II to trained conscious dogs produced increments in plasma angiotensin II concentration and blood pressure. In the same animals 2 to 4 weeks later, progressive narrowing of the renal artery also produced increments in plasma angiotensin II concentration and blood pressure. The regression equations for plasma angiotensin II concentration against blood pressure were closely similar on the two occasions.

Secondly, infusion of competitive angiotensin II antagonists in the early phase restores normal blood pressure in both the rat (Pals, Masucci, Denning, Sipos and Fessler, 1971) and dog (Miller, Samuels, Haber and Barger,1975; Davis, 1975).

ii. Transitional phase. In this phase sustained blood pressure elevation in the face of falling plasma renin and angiotensin II concentrations has been well documented in dogs by Bianchi et al (1972). Furthermore, in patients (Cuesta, Bianchi, Brown, Caravaggi, Davies, Deheneffe, Fraser, Lever, Morton, Oelkers, Robertson and Schalekamp, 1976) and rats (Hutchinson, Matthews, Dax and Johnston, 1975) arterial pressure in this phase is higher for a given plasma angiotensin II concentration than in normal subjects (or animals) infused acutely with angiotensin II. The implication of these observations is that the direct pressor effect of angiotensin II is not solely responsible for the blood pressure elevation in this phase. The direct effect is partly responsible, in proportion to the circulating plasma angiotensin II concentration; immediate blood pressure reduction by infusion of saralasin at this stage (but not to normal levels) have been shown to be related directly to the pre-infusion plasma angiotensin II concentration (Pals et al, 1971; Brown, Brown, Fraser, Lever, Morton, Robertson, Agabiti-Rosei, Tree and Trust, 1976). However, one or more alternative pressor mechanisms must be involved.

Slow action of angiotensin II.

While McDonald, Boyd and Peart (1975) and Davis, Freeman, Watkins, Stephens and Williams (1976) suggest

that factors other than angiotensin II must be involved, a convincing body of evidence has grown that a slow pressor action of angiotensin II may be the responsible agency in the transitional phase. The main supportive evidence for this contention is:-

1) Prolonged infusion of angiotensin II at constant sub-pressor rates in rabbits (Dickinson and Lawrence, 1963) and dogs (McCubbin, De Moura, Page, and Olmsted, 1965; Cowley and De Clue, 1976; Bean, Brown, Casals-Stenzel, Fraser, Lever, Millar, Morton, Petch, Riegger, Robertson, and Tree, 1979) leads to a slow but progressive rise in arterial pressure. Furthermore, after several days the rate of infusion required to maintain a constant increase in blood pressure gradually declines (Ames, Borkowski, Sicinski, and Laragh, 1965). Also Bean et al (1979) by superimposing short incremental angiotensin II infusion on top of a prolonged angiotensin II infusion in dogs have shown that angiotensin II is capable of modifying its own dose-response curve.

2) A parallel situation in man of prolonged angiotensin II infusion may be found in patients with a renin-secreting tumour. In one such patient Brown, Fraser, Lever, Morton, Robertson, Tree, Bell, Davidson, and Ruthven (1973) demonstrated an abnormal relationship between blood pressure and plasma angiotensin II

concentration similar to that in patients with chronic renovascular hypertension and higher than in normal subjects acutely infused with angiotensin II. The normal relationship was restored by nephrectomy. In a similar French patient (Mimran, Leckie, Fourcade, Baldet, Navratil and Barjon, 1978) an acute saralasin infusion preoperatively led to a fall in blood pressure but not to normal levels. Six weeks after nephrectomy plasma renin and angiotensin II concentrations were normal and blood pressure was lower than during saralasin. Two years postoperatively blood pressure was normal for the patient's age and sex. While the partial agonist action of saralasin means that the preoperative data must be interpreted with caution, the evidence does support an altered angiotensin II-blood pressure relationship before surgery and a gradual recovery of the normal relationship after surgery.

3) Angiotensin II infusions preoperatively and 9 days and 16 weeks postoperatively in a severely hypertensive patient with a renal artery occlusion (Brown et al, 1979b) showed a gradual return to normal of the angiotensin II-blood pressure dose-response curve after unilateral nephrectomy. This contrasts with the gradual upward resetting of the angiotensin II-blood pressure relationship after clipping the renal artery of a conscious trained dog (Brown et al, 1979a). Also, in support of this gradual resetting is the

rapid (1-2 hours) return to hypertensive levels in two-kidney rats after reclipping a renal artery, unclipped 2 days before, in contrast to a slow (1 week) return to hypertensive levels when unclipping had taken place 21 days before (Skulan, Brousseau and Leonard, 1974). 4) Intravenous infusion of converting enzyme inhibitor (teprotide, SQ 20881) over several days of renal artery constriction prevents the development of chronic reno-vascular hypertension in one-kidney dogs (Miller et al, 1975). In two-kidney rats of 28-60 days standing (Riegger, Lever, Millar, Morton and Slack, 1977) 11 hour infusions of saralasin at 10 μg/kg/min produced two effects: firstly, a rapid initial blood pressure fall in direct proportion to the pre-infusion plasma renin concentration; secondly, a further gradual fall in blood pressure over 11 hours not related to the pre-infusion plasma renin concentration. Similar infusion into normal rats did not alter arterial pressure, nor did dextrose infusion into two-kidney hypertensive rats, while saralasin infused into rats made hypertensive by desoxycorticosterone acetate administration produced a further rise in blood pressure (Morton, Casals-Stenzel, Lever, Millar, Riegger and Tree, 1979). A similar return of blood pressure to normal in two-kidney hyper-tensive rats has followed infusion of converting enzyme inhibitor (Riegger et al, 1977; Morton et al, 1979)

and oral captopril (Bengis and Coleman, 1979). Again the fall in blood pressure was not closely related to pretreatment plasma renin levels. Atkinson et al (1980) have shown that long-term administration of captopril to patients with unilateral renal artery stenosis produced an initial (2 hour) fall in blood pressure related to pretreatment plasma angiotensin II concentrations, followed by a more gradual fall over 6 weeks, not directly related to plasma angiotensin II levels.

Lately several workers (Sen, Smeby, Bumpus, and Turcott, 1979; Thurston, Bing, Marks and Swales, 1980) have restudied the reversal of two-kidney hypertension in rats by using antagonists and inhibitors of the renin-angiotensin system. Sen et al (1979) described a return to normal pressures in rats who had been clipped for 36 weeks, after regular intramuscular administration of captopril for 3 days, and also described a fall in blood pressure with renin inhibitor; by contrast the competitive angiotensin II antagonist, sar-1-Thr-8-angiotensin II, given by regular subcutaneous injection for 3 days, or by continuous subcutaneous infusion for 5 days, failed to lower blood pressure. Similarly, Thurston et al (1980) working with rats which had been hypertensive for 4 months found that captopril administered orally for

1 day produced a marked fall in blood pressure, while infusion of sar-1-ala-8-angiotensin II for 10-12 hours failed to lower blood pressure. These findings do not contradict those supporting a slow pressor action of angiotensin II in the transitional phase, since they refer to rats which have passed from the transitional to the chronic phase (p.50) as evidenced by persistent hypertension in comparable rats after excision of the clipped kidney (Thurston et al, 1980). A possible explanation of the efficacy of captopril in these animals is that captopril potentiates bradykinin activity (Thurston et al, 1980).

There is thus sound evidence that a slow component of the action of angiotensin II may be responsible along with the direct pressor effect for producing hypertension in the transitional phase of two-kidney hypertension.

Role of sodium in the transitional phase.

In contrast to one-kidney hypertensive rats whose exchangeable sodium is on average 10% higher than in normal rats, exchangeable sodium in established two-kidney hypertensive rats does not differ significantly from normal (Tobian, Coffee and McCrea, 1969). Furthermore, Swales, Thurston, Queiroz and Medina (1972) showed that a slightly negative sodium balance occurred in two-kidney hypertensive rats whose contralateral kidneys were untouched, but that contralateral nephrectomy

resulted in a progressive positive sodium balance. However, there is good evidence in dogs and rats that a degree of sodium retention occurs during the early stages of two-kidney hypertension (Conway,1968; Bianchi et al, 1970, 1972; Liard, Cowley, McCaa, McCaa and Guyton, 1974; Mohring, Mohring, Naumann, Philippi, Honsy, Orth, Dauda, Kazda and Gross, 1975). These observations can only be explained in terms of a resetting of the normal relationship between arterial pressure and urinary sodium excretion described by Selkurt in 1951, whereby a small increment in arterial pressure is accompanied by a large increment in sodium excretion. Kaloyanides, DiBona and Raskin (1971) confirmed in isolated dog kidneys that this phenomenon was mediated by increased peritubular capillary pressure leading to decreased proximal tubular sodium reabsorption. Thus, without a resetting severe sodium depletion must ensue: in some cases both in rats (Mohring et al, 1975) and humans (Atkinson, Brown, Fraser, Leckie, Lever, Morton and Robertson, 1979a) where the hypertension is particularly severe and rapidly developing, sodium depletion may occur - the hyponatraemic hypertensive syndrome. However, Thompson and Dickinson in 1973 demonstrated that resetting, or a shift to the right, of the pressure natriuresis curve was common in the perfused kidneys of rabbits with renovascular hypertension, while Guyton, Cowley, Coleman, Liard, McCaa, Manning, Norman and Young (1973) have presented a detailed theoretical

explanation of resetting in man.

Brown et al (1977, 1979b) have proposed that similar resetting of the pressure-natriuresis relationship must also occur in patients with renovascular hypertension and have suggested that three effects may contribute to this: firstly, the direct sodium retaining action of angiotensin II (Brown and Peart, 1962); secondly, the stimulant effect of angiotensin II on aldosterone (Davis, 1962); thirdly, increased sodium reabsorption in the clipped kidney caused by reduced renal perfusion (Selkurt, 1951) or perhaps by an intrarenal effect of angiotensin II (Krahe, Orth, Mikshe and Gross, 1972; McGregor, Briggs, Brown, Chinn, Gavras, Lever, MacAdam, Medina, Morton, Oliver, Paton, Powell-Jackson, Robertson and Waite, 1973).

Thus, in the development of two-kidney hypertension an equilibrium is reached between the actions of angiotensin II and sodium retention but with the balance set in favour of a predominant role for angiotensin: indeed sodium status has been shown to be relatively normal (Tobian et al, 1969; Swales et al, 1972).

Mechanism of the slow action.

A variety of intriguing mechanisms may be wholly or partly responsible for the way angiotensin II and sodium interact to raise arterial pressure in the transitional phase. These have been reviewed by Brown et al,(1977, 1979b):-

1) Angiotensin II has been shown to stimulate the sympathetic nervous system at a number of levels in the brain, particularly the area postrema in the brain stem (Joy and Lowe, 1970) at infusion rates which did not raise blood pressure when given intravenously (Dickinson and Yu, 1967). This subject has been reviewed by Ferrario, Gildenberg and McCubbin (1972). Evidence supporting alternative sites and mechanisms of action within the adrenal medulla and sympathetic ganglia have been reviewed by Zanchetti and Bartorelli (1977). However, an intact sympathetic system is not necessary for the development of chronic renal hypertension as shown in rats whose sympathetic system had been ablated by adrenal demedullation and chronic guanethidine administration (Douglas, Johnson, Heist, Marshall and Needleman, 1976).

2) Structural changes in resistance vessels by leading to an altered wall:lumen ratio (the 'geometric hypothesis') might result in an augmented vasoconstrictor response to angiotensin II (Folkow, 1971, 1978).

3) The vasoconstrictor response to angiotensin II might be heightened because of accumulation of sodium in vascular tissue (Tobian, Janecek, Tomboulan and Ferreira, 1961). Against this Simon (1980) has found that the sodium content of thoracic aorta in one-kidney hypertensive rats did not differ from normal. However, Bohr (1974) has suggested that vascular smooth muscle responsiveness

could be enhanced in renovascular hypertension irrespective of the sodium content of the vessel walls.

4) Alterations in the distribution of sodium and water within tissue compartments secondary to changes in the compliance of the extravascular space may be more important than the total sodium content (Brown et al, 1979b). Lucas and Floyer (1974) have provided some evidence for altered (reduced) interstitial space compliance in one-kidney hypertensive rats.

5) Prolonged exposure of the adrenal cortex to high levels of angiotensin II leads to an increased release of aldosterone for a given plasma angiotensin II concentration (Oelkers, Brown, Fraser, Lever, Morton and Robertson, 1974). It has been suggested that arterial pressure would rise to counteract the ensuing sodium retention.

6) Sodium retention in the early phase and first part of the transitional phase may produce expansion of plasma volume and extracellular fluid volume (Ledingham and Cohen, 1963). This in turn may raise cardiac output, lead to overperfusion of the tissues and autoregulatory vasoconstriction (Guyton, Coleman, Cowley, Scheel, Manning and Norman, 1972).

7) Upward resetting of baroreceptors observed in dogs by Cowley and DeClue (1976) during prolonged angiotensin II infusion may also be a contributary mechanism. These workers also demonstrated that during angiotensin II

infusion in dogs an initial decrease in cardiac output was succeeded by the fifth day of infusion by a 38% increase, whereas blood volume was unchanged.

All these effects have been demonstrated experimentally. Whether some or all contribute wholly or in part to the slow action in the clinical situation has yet to be clarified.

iii. The late phase. In this phase attempts to correct the hypertension by nephrectomy of the clipped kidney or by unclipping are unsuccessful. Plasma renin and angiotensin II concentrations are not usually elevated and long-term infusions of saralasin do not return blood pressure to normal, though captopril may do so, perhaps by potentiation of bradykinin activity (Sen et al, 1979; Otsuka, Carretero, Albertini and Binia, 1979; Thurston et al, 1980). Thus, while renin and angiotensin may have been instrumental in bringing about the late phase, alternative mechanisms must then be responsible (Otsuka et al, 1979). From the work of Byrom and Dodson (1949) and Floyer (1951) it is clear that where the late phase has been reached histological evidence of vascular damage in the contralateral 'untouched' kidney is consistently found. In patients with renovascular hypertension coming to nephrectomy damage to the contralateral kidney with a plasma flow of less than 200 ml/min was recognised by Stamey (1966) as an important predictor of surgical failure. The

mechanism or mechanisms by which hypertension is sustained at this stage are not fully understood, though Floyer (1957) felt that extrarenal factor(s) were responsible, probably involving retention of water and sodium.

II. The role of alternative pressor mechanisms.

The presence of renal pressor agents, other than renin was proposed in 1966 by McPhaul, McIntosh, Williams, Gritti and Grollman in man, and Grollman and Krishnamurty (1971), having identified this pressor agent in the dog and rat, named it nephrotensin. However, Schweikert, Carey, Liddle and Island (1972) by chemical, immunological, and electrophoretic studies identified nephrotensin as angiotensin I bound to an α_2-globulin. Recently Skeggs, Kahn, Levine, Dorer and Lentz (1976, 1977) have reopened the question of a non-renin pressor substance in kidney extracts having found that active immunisation of chronic one-kidney hypertensive rabbits with a protein from a non-renin fraction of kidney extracts resulted in lowering of blood pressure. Further developments in this direction are awaited.

III. The role of antihypertensive factors.

The influence of prostaglandins and the kallikrein-kinin system in modifying the hypertension associated with renal artery constriction remains to be fully elucidated. These fields of study are rapidly expanding ones, but because of big species differences extrapolation of data

to man with renal artery stenosis must be guarded at present. The present status of prostaglandins has been reviewed by Dunn and Hood (1977), Dunn (1979) and Hollenberg (1979). The place of the renal kallikrein-kinin system has been reviewed by Levinsky (1979), Margolius and Buse (1979), and Hulthen (1980). Davis (1977) has assessed the role of these agents in experimental hypertension. These subjects are large in themselves and it is not proposed to discuss them further here. It is true, however, (Levinsky, 1979) that many complex interrelationships exist between the renin-angiotensin system, prostaglandin system, and kallikrein-kinin system in the modulation and control of renal perfusion, blood pressure and perhaps sodium homeostasis, though continuing work seems likely to confirm that the pressor activity of angiotensin II is the dominant force in renovascular hypertension.

2:4 PATHOLOGY.

The 'experiment of nature' (Kaufman and Maxwell, 1964) which results in narrowing or occlusion of the renal artery in man is more of a series of experiments than one definitive experiment. Goldblatt's clamp (Goldblatt et al, 1934) applied extrinsic pressure to the renal artery: though the pathophysiological consequences are the same, renal artery stenosis in man is principally caused by internal narrowing of the vessel

by atheroma or fibromuscular hyperplasia.

Atheroma in the renal artery, as is the case with atheroma in other large vessels, is most marked at, or just distal to, the origin of the vessel from the aorta or at the bifurcation of the main renal artery. Thus, a stenosis occurring in the proximal third of the renal artery of an older patient, more commonly male, who has evidence of vascular disease at other sites is more likely to be atheromatous than not. 63% of all stenoses are caused by atheroma deposition (Genest, Boucher, Rojo-Ortega, Roy, Lefebvre, Cartier, Nowaczynski and Kuchel, 1977).

Fibromuscular hyperplasia by contrast affects principally the middle and distal two-thirds of the main renal artery and often extends into segmental branches, afflicts younger patients, particularly females (80%), who, generally speaking, have less concurrent vascular disease at other sites and accounts for 32% of all renal stenoses (Genest et al, 1977). While the disease process may affect mesenteric, iliac, carotid or even coronary vessels, the principal clinical manifestation of fibromuscular hyperplasia is hypertension secondary to renal artery stenosis.

Convenient as it is to think of fibromuscular hyperplasia as a single disease entity, it is in reality constituted by a number of affections of the renal artery. A classification of these proposed by the Mayo

and Cleveland Clinics (Harrison and McCormack, 1971) divides dysplasias on the basis of the part of the artery wall principally affected - intimal (1%), medial (98%) and adventitial or periarterial (<1%). The commonest types are medial fibroplasia with mural aneurysm formation (64%) and perimedial fibroplasia (20%). In the former, thickened ridges of fibromuscular tissue alternate with areas of thinning of the vessel wall in which the media is entirely absent. These areas are responsible for the characteristic 'string of beads' arteriographic appearance. In perimedial fibroplasia dense collagen replaces the outer half of the media in a circumferential manner, but since the collagen deposition is not necessarily uniform, a beaded appearance may again be apparent arteriographically. Nevertheless, it is important to realise that all varieties of fibromuscular hyperplasia may cause a single smooth stenosis of a renal artery so that arteriographic appearances are not pathognomonic. The histological appearance of the above two forms of dysplasia, together with the less common form - medial hyperplasia (10%) and medial dissection (5%) - are detailed in reviews by Harrison, Hunt and Bernatz (1967) and by Youngberg, Sheps and Strong (1977).

Despite the fact that fibromuscular hyperplasia was first described over 40 years ago (Leadbetter and Burkland, 1938), and a multiplicity of ingenious theories

of causation by congenital factors, abnormalities of pressure-wave conduction, associations with pregnancy, body habitus and excessive mobility of the kidneys (Twigg and Palmisano, 1965; Youngberg et al, 1977) have been developed, no clear understanding of the aetiology of this group of diseases has been reached as yet.

Extrinsic pressure. More akin to Goldblatt's original experiment is a variety of factors producing narrowing of the renal artery by extrinsic pressure. Among these are fibrous bands extending from the crura of the diaphragm, sympathetic chains (Sutton, Brunton Foot and Guthrie, 1963) haematomata or cysts (Kaplan, 1973), aneurysms of the renal artery (Poutasse, 1974), fistulae (Weir and Milliken, 1968) and neoplasia such as phaeochromocytomata (Agabiti et al, 1976). Trauma, as well as causing stenosis by extrinsic haematoma formation, may result in renal artery occlusion secondary to intimal damage (Von Knorring, Fyhrquist, Ahonen, Lindfors and Bonsdorff, 1976).

2:5 RELATIONSHIP BETWEEN RENAL ARTERY STENOSIS AND HYPERTENSION IN MAN.

Crucial to a reasoned approach to the management of renal artery stenosis in man is the realisation that the presence of a stenosis and high blood pressure in a particular patient does not necessarily imply a cause

and effect relationship, though this may be the case. The possible relationships which have been outlined by Genest et al (1977), and Brown et al, (1979b) are:-

1) The stenosis has caused the hypertension and removal of the stenosis will cure the hypertension. Definition of these ideal circumstances for surgical correction is the object of investigation. Unfortunately as betokened by failure rates of 19-34% (Capelli et al, 1973; Foster, Maxwell, Franklin, Bleifer, Tripple, Julian, DeCamp and Varady, 1975) the ideal is not fully realised.

2) The stenosis has caused the hypertension but removal of the stenosis will not cure the hypertension. As indicated in Chapter 2:3 damage to the 'untouched' kidney may be instrumental in sustaining the hypertension, but removal of that 'untouched' kidney at a second operation after failure of unclipping the ischaemic kidney to cure hypertension, may render the animal normotensive (Floyer, 1951). Comparable procedures in man have been reported in only two cases (Thal, Grage and Vernier, 1963; Miller and Phillips, 1968) with unsuccessful reconstructive surgery as the primary procedure and curative contralateral nephrectomy as the secondary procedure. McAllister, Michelakis, Oates and Foster (1972) have described a further case where ipsilateral reconstruction and contralateral nephrectomy were bravely performed at the same operation, but the interpretation of their data is less certain.

3) Renal artery stenosis and hypertension are coincidental findings in the same patient. Certainly, clinical and autopsy studies have shown stenoses in 46% of normotensive patients (Dustan, Humphries, De Wolfe and Page, 1964; Holley, Hunt, Brown, Kincaid and Sheps, 1964). Genest et al (1977) maintain that 'true' renovascular hypertension does not occur until a pressure gradient is present across the stenosis of at least 30 mmHg, corresponding to a reduction in cross-sectional area of the lumen of 55-65% (Gupta and Wiggers, 1951; Haimovici, 1954).

4) Hypertension by contributing to atheroma formation may help to generate an atheromatous renal artery stenosis. That stenosis may then become functional and exacerbate the hypertension. Under these circumstances technically excellent surgery will only lower blood pressure to the originally elevated level.

Faced with a hypertensive patient with renal artery stenosis the clinician has thus a complex set of circumstances to unravel in order to determine which explanation is correct: he also must be clear whether each piece of clinical information and each test which the patient undergoes is providing information about abnormal anatomy or abnormal function (i.e. diagnostic tests) or the likely outcome of surgery (i.e. prognostic tests). The place of each is discussed below.

2:6 CLINICAL FEATURES.

Many detailed studies (Brown et al, 1960; Peart, 1966; Simon, Franklin, Bleifer and Maxwell, 1972; Hunt, Sheps, Harrison, Strong and Bernatz, 1974; and others) have failed to identify distinctive symptomatology or findings on clinical examination in the great majority of patients with renovascular hypertension.

In a few patients the sudden onset of loin pain with or without haematuria may be indicative of a renal artery embolus or occlusion, and a history of abdominal trauma followed rapidly by hypertension may be suggestive of traumatic renal artery thrombosis (Von Knorring et al, 1976). There are also a few patients with the hyponatraemic hypertensive syndrome secondary to renal artery stenosis or occlusion who may present with severe secondary hyperaldosteronism and may complain of polyuria, polydipsia, weight loss and salt-craving. Typical examples of such a presentation are described by Barraclough (1966) and Atkinson et al (1979a). Milder degrees of nocturia may be found in 35-40% of all patients with renovascular hypertension (Genest et al, 1977).

On examination, a systolic or continuous bruit heard over the umbilical region with radiation to one side or loin may suggest a renal artery stenosis on that side. Shapiro, Perez-Stable, Scheib, Bron, Moutsos, Berg and Misage (1969) have gone as far as to suggest

that such a continuous bruit heard over the loin posteriorly may be specific for renal artery stenosis. Simon et al (1972) found abdominal bruits in 48% of patients in their series; Hunt et al (1974) similarly found bruits in 58% of their patients with an even higher incidence (73%) in patients with fibromuscular hyperplasia. However, because abdominal bruits may occur in patients with essential hypertension who have aortic atheroma and because patients with renovascular hypertension form only a small percentage of the total hypertensive population, the finding of a bruit in a hypertensive patient is more likely to be an incidental finding than otherwise (Capelli et al, 1973). Also, since the absence of a bruit could result from a stenosis where the lumen is reduced by more than 78% (Gupta and Wiggers, 1951), as well as no stenosis at all, bruits are a non-specific and unreliable finding.

In the absence of all these features where a young patient (less than 30 years) presents with hypertension, or a patient presents with the retinal changes of malignant phase hypertension, or where there has been a sudden deterioration in blood pressure control, the possibility of a renal artery stenosis being responsible should be entertained (Genest et al, 1977). Genest et al (1977) also estimate that up to 20% of patients with renal artery stenosis present with malignant phase hypertension.

Rare associations of renal artery stenosis which may be helpful clinically are the nephrotic syndrome (Berlyne, Tavill and De Baker, 1964) and polycythaemia (Luke, Kennedy, Barr-Stirling and McDonald, 1965). Haematocrit is also raised in renal artery stenosis, but the relationship between renin, erythropoietin and haematocrit is not close (Bourgoigne, Gallagher, Perry, Kurz, Warnecke and Donati, 1968; Takacs, Albert and Vajda, 1976).

Shapiro et al (1969) found frank diabetes mellitus in 20% of their patients with renovascular hypertension, but other studies have failed to confirm this high incidence. Shapiro also report bacteriuria in 18% of patients; Simon et al (1972) also found bacteriuria to be twice as common in patients with renal artery stenosis as in age-matched essential hypertensives. While interesting this finding is not helpful from the diagnostic point of view.

2:7 INVESTIGATIONS.

Ten separate tests have been, or are being, used in the preoperative evaluation of patients with renal artery stenosis. Each is considered in this section, greater emphasis being given to those most commonly employed.

1. Intravenous urography.

The intravenous urogram, a description of which is given in Chapter 4:5, is probably still the most widely used screening test in patients with suspected renovascular hypertension. The classical appearances of renal artery stenosis are of two sorts (Brown et al, 1979b). Where the stenosis is of mild or moderate severity the three most important signs (Bookstein, Abrams, Buenger, Lecky, Franklin, Reiss, Bleifer, Klatte and Maxwell, 1972a) are an increase in density due to hyperconcentration of contrast on the affected side in later films, disparity in the size of the kidneys (remembering that the right may normally be up to 1.5 cm smaller than the left kidney), and delay in the appearance of contrast on the affected side. Other signs (Saxton, 1969) include a small renal pelvis, calyceal narrowing (Brown et al, 1960) and scalloping of the upper ureter by collaterals. On the other hand, where the renal artery narrowing is more marked and glomerular filtration markedly reduced, contrast may fail to appear on the affected side. Thus, depending on the severity of the stenosis, greater density may be present on the affected or the unaffected side (Brown et al, 1960), a fact which may lead the unwary to imperil the healthy kidney.

An explanation for these appearances has been proposed on the basis of data obtained at bilateral ureteric catheterisation studies (Brown et al, 1960; Stamey, 1961; Schreiber, Sarles, Herring and Remmers, 1964), where on the affected side there is increased tubular reabsorption of water and sodium, and hyperconcentration of non-reabsorbable solute, be this endogenous (creatinine) or exogenous (PAH or inulin). In mild or moderate stenosis glomerular filtration is not markedly reduced (Zweig, Rapoport, Wilson, Ranking, and Husdan, 1972; DeForrest, Davis, Freeman, Watkins, and Stephens, 1978), and modern radiographic contrast media are filtered at the glomerulus, and not reabsorbed by the tubules (Fry and Cattell, 1979). Diminished urine flow and increased reabsorption of water would then result in delayed appearance and late hyperconcentration of contrast on the affected side. This explanation has not been verified quantitatively.

Modifications of the intravenous urogram have been introduced with the object of improving its diagnostic yield. Maxwell, Gonick, Wiita, and Kaufman (1964) and Bookstein, Abrams, Buenger, Lecky, Franklin, Reis, Bleifer, Klatte, Varady, and Maxwell (1972b) have shown the value of multiple early or 'minute sequence' films in identifying delay in the appearance of contrast. Concentration differences may be enhanced by an oral water load

(Sutton, Brunton, and Starer, 1961) while an infusion of solute, usually urea, has been claimed by some (Amplatz, 1962; Schreiber et al, 1964) to improve diagnostic accuracy and act as a modified split function study: others have failed to confirm its usefulness.

Hazards attached to intravenous urography include hypersensivity reactions, and the syndrome of renal failure induced by contrast media, a problem more worrying in diabetics and in patients with underlying renal impairment (Harkonen and Kjellstrand, 1977; Lancet, 1979).

Estimates of the sensitivity of the intravenous urogram have ranged from 72% (Wilson, Dustan, Page, and Poutasse, 1963) to 93% (Maxwell et al, 1964), while specificity has been estimated at 83% (Maxwell et al, 1964), 88.6% (Bookstein et al, 1972b) and 92% (Wilson et al, 1963). Lack of specificity may be attributed to spurious causes of asymmetry such as overlying gas or faeces, and true causes, such as ureteric obstruction, outlined by Saxton (1969).

Further criticism has surrounded the place of the intravenous urogram in screening populations; this criticism is more or less justified depending on the population involved. In hypertensive patients picked up in a survey of the general population (Brown et al, 1979b) or referred to hypertension clinics (Atkinson and Kellett, 1974; Bailey, Evans, and Fleming, 1975) the

intravenous urogram is rarely positive, whereas in a specialist unit a high yield of abnormal results may be found (Brown et al, 1979b).

Thus the intravenous urogram is a helpful but far from ideal diagnostic test, whose value in screening selected populations has been established.

2. Isotope renography.

Recent methodology of this test is described in Chapter 4:10. Introduced by Taplin, Meredith, Kade, and Winter in 1956 as a semi-quantitative non-invasive alternative to bilateral ureteric catheterisation studies, and reviewed by Winter (1963) and Britton and Brown (1971), renography is based on the handling by the kidney of an analogue of PAH - ortho-iodohippurate or hippuran. This hippuran which has been labelled with a radioactive isotope of iodine - either ^{125}I (Ram, Evans, and Chisholm, 1968), ^{131}I (Tauxe, Maher, and Taylor, 1971) or ^{123}I (Short, Glass, Chisholm, Vernon, and Silvester, 1973) - is 20% filtered at the glomerulus, 80% secreted by the proximal tubule, and not reabsorbed (Brodkey, Schlegel, and Derouen, 1979). Its handling by the kidney is monitored by external counting and a graph of radioactivity over the renal areas against time is obtained. Improvements in the accuracy of this technique by making allowances for the activity of tracer present in the blood in the renal background areas - a technique known as CABBS, or computer assisted blood background subtraction

renography, reviewed in detail by Britton and Brown (1971) - permits definition of a characteristic pattern of abnormality in unilateral stenosis in which the slope of the activity-time curve is less steep on the affected side, the peak activity is delayed, and the clearance of isotope is slower on the affected side.

Renography has a place in the diagnosis (Luke, Briggs, Kennedy, and Barr-Stirling, 1966) of renovascular hypertension and as a screening test in the population should this be considered a worthwhile exercise (Britton and Brown, 1971). However, its sensitivity (70% (Genest et al, 1971) - 85% (Winter, 1963)) and specificity (70% (Doig, Lawrence, Philp, Tothill, and Donald, 1963; Sandler and Rickards, 1966)), as for intravenous urography, are far from ideal. Luke et al, 1966 have suggested that the IVU and the renogram be used together as a screening procedure for renovascular hypertension, and McNeil, Varady, Burrows, and Adelstein (1975) have confirmed that this combination of tests gives a better diagnostic yield than either alone. Farmelant, Sachs, and Burrows (1970) and Norman, Sundsfjord, and Stiris (1975) have claimed that renography may be valuable as a test of surgical prognosis, but most workers have not been able to confirm this.

With the development of more efficient computer-linked counting equipment in the 1970's, came the possibilty of greater quantitative accuracy being achieved by renography. This subject has been reviewed by Britton (1979) and is investigated in Chapter 8:5.

3. Arteriography.

Renal arteriography, described in Chapter 4:6, is necessary to establish the existence of a renal artery stenosis or occlusion. It allows definition of the site and extent of lesion, the likely nature of the lesion, the presence and degree of aneurysmal dilatation, the distribution and extent of collateral vessels, the presence and patency of accessory vessels and, to some extent, the intrarenal vasculature, the presence of fistulae or infarcts, and recognition of alternative pathology such as renal carcinoma or phaeochromocytoma (Brown et al, 1960; Bookstein, Abrams, Buenger, Reiss, Lecky, Franklin, Bleifer, Varady, and Maxwell, 1972c). Since urographic and renographic diagnosis are based mainly on a comparison of the two kidneys, arteriography alone will define the presence of bilateral stenoses. Arteriography is necessary in planning the nature and feasibility of corrective surgery. However, none of the arteriographic features outlined above reliably predict surgical outcome (Bookstein et al 1972c), but since it is a test of anatomy and says little of function this is not surprising.

Erikson, Hemmingsson, Ljungstrom, and Aberg (1975) have advocated that arteriography be used as a screening procedure for renal artery stenosis in all hypertensive patients, but few, if any, would support this contention. Nevertheless, using the Seldinger (1953) technique the procedure is comparatively safe. In the co-operative study of renovascular hypertension (Reiss, Bookstein, and Bleifer, 1972) a morbidity of less than 1% was found. Complications included haematoma formation at the arterial puncture site, thrombosis, embolism (affecting the cerebral circulation more often if the brachial rather than the femoral artery has been catheterised) and renal failure.

4. Bilateral ureteric catheterisation studies.

Bilateral ureteric catheterisation studies, as described in Chapter 4:8, are a composite of several tests of water and solute handling which have been recognised over the years to differ from ischaemic to non-ischaemic kidneys. The classical pattern of ischaemia, exemplified in the first case report in Chapter 5, is of increased water and sodium reabsorption in the proximal tubules of the ischaemic kidney (Kaloyanides et al, 1971), leading to reduced urine flow rate and urinary sodium concentration, and to increased urinary concentration of non-reabsorbable solutes - endogenous creatinine and infused PAH. As Zweig et al, (1972) and DeForrest et al (1978) have demonstrated glomerular filtration rate and effective

renal plasma flow are relatively well maintained despite these other abnormalities until the degree of narrowing of the artery becomes marked. A considerable amount of useful information on total and differential renal function is thus available, allowing a further step in diagnosis, that of functional impairment, to be made.

Critics of the technique (Genest et al, 1977) are quick to point out its invasiveness (a spinal anaesthetic and instrumentation of the urinary tract are necessary), its requirements in terms of theatre time and resources, the technical difficulties, particularly leakage of urine past ill-fitting ureteral catheters, and its morbidity in terms of urinary tract infection, dysuria and haematuria (Hunt, Maher, Greene, and Sheps, 1966) and transient renal failure (Turman, Foster, Oates, Rhamy, Klatte, Pettinger, Burko, Younger, and Scott, 1970). However, with experienced staff these problems may be minimized. Techniques are reviewed by Stamey et al (1961) and Capelli et al (1973).

Problems in interpretation of the results of bilateral ureteric catheterisation studies are associated not so much with the existence of a pattern of ischaemia (diagnostic test) (Brown et al, 1960: 1979b) as with the degree of abnormality necessary for an accurate prediction of the outcome of surgery (prognostic test). The lack of unanimity among workers is reflected in Table 1, and the diversity of results cannot be explained merely in terms of lack of standardisation of the technique between

centres. Not only is there a large variety of prognostic criteria for 'significant' unilateral stenosis, but other criteria (Stamey et al, 1961) have been proposed for a potentially correctable segmental stenosis. However, bilateral stenoses of equal severity may not be identified by the technique.

A further important prognostic distinction (Brown et al, 1979b) may lie between features favouring a good outcome after nephrectomy as against reconstructive surgery. A good response to nephrectomy will depend on the function of the contralateral kidney: Stamey (1966) has emphasised that a PAH clearance of less than 200 ml/min by the 'untouched' kidney is associated with a poor prognosis. On the other hand, prognosis after arterial reconstruction will depend on the function not only of the 'untouched' kidney but of the unclipped kidney also. Realisation that prognostic criteria differ depending on the surgical procedure offers a partial explanation of the variations in Table 1.

5. Peripheral plasma renin concentration.

Elevated peripheral plasma renin concentration may be associated with renal artery stenosis, and mean plasma renin concentration has been found to be higher in a group of patients with renovascular hypertension than in a group with essential hypertension (Brown, Davies, Lever, and Robertson, 1965). However, overlap between the two groups was marked and the majority of patients with

TABLE I.

BILATERAL URETERIC CATHETERISATION STUDIES:
CRITERIA FOR A POSITIVE TEST.

Author.	Criterion.
Rapoport (1960)	Tubular rejection fraction ratio* for sodium >1.6 = R.stenosis, <0.6 = L.stenosis.
Howard and Connor (1964)	Volume 50% ↓ + Na conc. 15% ↓ + creatinine conc. 200% ↑ in urine.
Birchell et al (1964)	$U_{Na}/U_{Creat.}$ of affected : unaffected kidney >1:1.6.
Guedon et al (1965)	$\Delta Vol \leqslant -50\% + \Delta U_{creat.} \geqslant 30\%$
Stamey (1966)	Volume 50% ↓ + creat. conc. 200% ↑ + contralateral PAH clearance ⩾ 200 ml/min
Suzuki et al (1967)	Rapoport criterion + urine potassium/sodium ratio differing from 1.0
Capelli et al (1973)	PAH excretion rate ischaemic : non-ischaemic <0.65
Fournier et al (1973)	$\Delta U_{Creat.} \geqslant 20\%$ on the diseased side

$$^{*}\text{Tubular rejection fraction ratio}_{Na} = \frac{U_{Na}^{L}}{U_{creat}^{L}} \times \frac{U_{creat}^{R}}{U_{Na}^{R}}$$

with renal artery stenosis have plasma renin concentrations within the normal range (Meyer, Ecoiffier, Alexandre, Devaux, Guize, Menard, Biron, and Milliez, 1967). Such a finding is not unexpected in view of the animal studies described above (Bianchi et al, 1970) where plasma renin concentration falls in the face of a consistently elevated or rising blood pressure in the transitional stage after clipping of a renal artery. Plasma renin concentration is more often raised in renal artery stenosis which is associated with malignant phase hypertension (Capelli et al, 1973), but plasma renin concentration is also elevated in malignant phase hypertension where no renal artery stenosis is present (Brown et al, 1979b). Laragh, Letcher, and Pickering (1979) have claimed that plasma renin concentration in relation to 24 hour urinary sodium excretion has value as a screening procedure for renovascular hypertension, but few others would support this contention. However, where plasma renin concentration is elevated further investigation is certainly indicated.

6. Peripheral plasma angiotensin II concentration.

For the same reasons as have been cited for plasma renin concentration, it would not be expected that peripheral plasma angiotensin II concentrations would be elevated in the transitional or late phases of renovascular hypertension. Using a bioassay technique Kotchen, Lytton,

Morrow, Mulrow, Shutkin, and Stansel (1970) failed to demonstrate elevated plasma angiotensin II concentration in any of a series of 49 patients with renal artery stenosis. However, in many series a small percentage of patients, particularly those with malignant phase hypertension, do have raised levels.

7. Renal vein sampling - renal vein renin ratio.

The ratio of plasma renin concentration in renal venous blood from the affected to the unaffected kidney has been widely claimed to be the single most useful prognostic test in renovascular hypertension (Genest et al, 1977). However, the ratio above which surgical success is predicted and below which surgery would not be performed varies widely: part of the variation reflects a lack of standardisation of the techniques for measuring renin. though the introduction of an agreed renin standard should be helpful (Bangham, Robertson, Robertson, Robinson, and Tree, 1975), while part reflects a lack of standardisation of the conditions under which renal vein sampling is carried out. Most workers perform the test on sodium-replete supine patients off medications, while stimulation of renin release at the time of renal vein sampling by hydrallazine (Mannick, Huvos, and Hollander, 1969) or frusemide with or without dietary sodium restriction (Genest et al, 1977) had been claimed to improve the prognostic accuracy. However, even where sampling and

assay conditions have been relatively uniform, the selected ratio has ranged from 1.5 (Michelakis, Foster, Liddle, Rhamy, Kuchel, and Gordon, 1967), to 1.6 (Bourgoignie, Kurz, Catanzaro, Serirat, and Perry, 1970) to 2.0 (Gunnells, McGuffin, Johnsrude, and Robinson, 1969) and even to 2.5 (Amsterdam, Conch, Christlieb, Harrison, Crane, Dobrzinsky, and Hickler, 1969).

Marks and Maxwell (1975) in reviewing the subject have pointed out that the higher the ratio the greater the confidence of surgical success - confidence limits of 81% exist with a ratio of 1.5 or more while 95% confidence exist with a ratio of 1.96 or more. They also reviewed 21 published series where renal vein renin ratios were used to identify 'lateralisation': accepting the criterion of each study they found that 94% of 286 patients with lateralisation were 'improved' (not cured) by surgery, but that 51% of 126 patients without definitive lateralisation who came to surgery also experienced improvement. Thus, helpful as the renal vein renin ratio is, it is not an ideal test: it is important that in seeking to improve the success rate of surgery, potentially curable patients should not be excluded from surgery on the basis of this test. Ratios as low as 1.12 (Atkinson, Brown, Davies, Leckie, Lever, Morton, and Robertson (in press) where technically excellent sampling has been performed have not precluded successful surgery. However, some low

ratios may be due to faults in sampling technique, including incorrect siting of the sampling cannula, dilution of renal vein blood by gonadal vein blood on the left, or the presence of accessory veins (which arise from 20-28% of right kidneys) (Paster, Adams, and Abrams, 1974; Marks and Maxwell, 1975).

The mechanism of a positive result, i.e. a high renal vein renin ratio, is less certain than the prognostic implication. Many workers hold that a high ratio reflects an increased renin secretion rate by the affected kidney but others for sound theoretical reasons reviewed in detail elsewhere (Brown et al, 1979b) conclude that increased renin release can only elevate the ratio to 1.5, but that in ratios above this removal of renin from the circulation by the 'untouched' kidney and/or reduction in blood flow through the ischaemic kidney more than the 'untouched' kidney are important mechanisms.

Suppression of renin release in the 'untouched' kidney has been found to be a good prognostic test in its own right. Stockigt, Collins, Noakes, Schamelan, and Biglieri (1972) found that a renal vein renin ratio greater than 1.5 plus a ratio of contralateral renin vein renin concentration to peripheral plasma renin concentration less than 1.3 was highly predictive of surgical success.

8. Angiotensin infusion test.

This test was first described by Kaplan and Silah (1964) and depended on the assumption that endogenous plasma angiotensin II concentration was high in patients with renal artery stenosis who would in consequence be relatively resistant to the pressor effects of infused angiotensin II. Subsequent studies failed to confirm the value of this test (Breckenridge, 1965; Morgan, 1965).

Nevertheless, as has been indicated above, angiotensin II infusions have proved a most useful research procedure in relating plasma angiotensin II concentration to blood pressure and plasma aldosterone concentration in many forms of hypertension (Brown et al, 1979a).

9. Use of antagonists and inhibitors of the renin-angiotensin system.

This subject has been reviewed in detail elsewhere (Atkinson et al, 1980). A hypotensive response during short-term incremental infusions of saralasin, the competitive angiotensin II antagonist, has been found by Brunner, Gavras, Laragh, and Keenan (1973) and Streeten, Anderson, Freiberg, and Dalakos (1975) to be an excellent test of 'true' renovascular hypertension and consequently of surgical prognosis. Other investigators have found false negative and false positive results in a significant number of patients who subsequently came to surgery (Atkinson et al, 1980a). Agreement is

general that the fall in blood pressure with saralasin is proportional to the pre-infusion plasma renin and angiotensin II concentrations (Brunner et al, 1973; Brown et al, 1976). Enhancement of the fall in blood pressure by prior sodium depletion which produces rises in plasma renin and angiotensin II concentration is not uniformly thought to improve the diagnostic or prognostic accuracy of the test, since sodium depletion can produce a similar response in patients with essential hypertension. The use of short-term infusions of converting enzyme inhibitor (teprotide) has produced similar results to saralasin infusions (Genest et al, 1977).

Accurate prediction of the fall in blood pressure after surgery would be more likely after the long-term (6 weeks) administration of oral converting enzyme inhibitor (captopril), if the evidence supporting a slow pressor effect of angiotensin II is correct. Consistent with this contention, Atkinson, Brown, Fraser, Leckie, Lever, Morton, and Robertson (1979a) found an additional fall in blood pressure after 6 weeks compared with 2 hours of captopril administration in patients with renal artery stenosis, and found a good correlation between blood pressure after 6 weeks of captopril and blood pressure 6 months after surgery. Caution must be exercised in advocating this as a prognostic test, however, since

captopril has an intrinsic hypotensive action in addition to that resulting from the inhibition of the activity of angiotensin I converting enzyme (Atkinson and Robertson, 1979).

10. Renal biopsy.

Biopsy of the affected kidney may demonstrate hyperplasia of the juxtaglomerular apparatus (Brown et al, 1960), with increased cell counts (Turgeon and Sommers, 1969) and granularity (Crocker, Newton, Mahoney, and Harrison, 1962) as well as 'ischaemic atrophy' of the tubules (Barajes, Lupu, Kaufman, Latta, and Maxwell, 1967). Proponents of this test (Munck, Faarup, Gammelgaard, Ladefoged, Mathieson, and Pederson, 1968; Genest et al, 1977) claim a close correlation between the histological changes and the degree of ischaemia, but it is not performed routinely in many centres. Drawbacks include sampling difficulties since the histological abnormalities may be patchy, and the usual morbidity inherent in the biopsy technique.

Biopsy of the contralateral kidney in rats (Floyer, 1957) led to the recognition of ischaemic damage in those animals which subsequently failed to become normotensive after excision of the clipped kidney. Vertes, Geruth, Leb, and Galvin (1965) have likewise correlated ischaemic damage in the contralateral kidney with reduced PAH

clearance on that side and a poor response to surgery, though Palmer, Tesluk, and Sullivan (1975) were unable to confirm this relationship.

Summary.

The combination of tests used in the preoperative assessment of patients with renovascular hypertension varies markedly depending on the centre concerned. In this centre intravenous urography, arteriography, bilateral ureteric catheterisation studies and renal vein sampling are the usual order of investigation. Others lay greater stress on the place of renography and plasma renin concentration, while many find bilateral ureteric catheterisation studies too complex and time consuming, despite their yield of information.

2:8 MANAGEMENT.

I. Surgical.

Indications. The commonest indication for surgical management of renal artery stenosis is the cure of hypertension in patients whose preoperative assessment has indicated that a successful outcome is likely. However, as has been shown above, prognostic indices are numerous, none are completely reliable, and in consequence each patient has a variety of prognostic tests performed. Where these tests are in agreement, the decision about surgery may not

be difficult; but where, as commonly happens, there is a measure of disagreement between tests, recommending surgery becomes more hazardous (Brown et al, 1979b). A further difficulty is that even where prognostic tests are unanimous, the degree of abnormality which they demonstrate may not be sufficient to satisfy the arbitrary criteria for success in a particular centre. Nevertheless, many such patients come to surgery: for example in the review of renal vein renin ratio in 21 studies by Marks and Maxwell (1975) discussed above, 126 out of 412 patients did not satisfy the prescribed ratio for their particular centre, but did come to operation which was successful in 62 (49%). The question of management decisions is covered in greater detail in the discussion (Chapter 12).

Indications for renovascular surgery, other than lowering of blood pressure, may be more important (Bengtsson, Bergentz, and Norback, 1974). In hypertensive patients with chronic renal impairment secondary to bilateral renal artery disease (Morris, de Bakey, Cooley, and Crawford, 1963; Sheil, May, Stokes, Johnson, Tiller, and Stewart, 1973) or to stenosis or occlusion of the artery to a single kidney (Kaufman, 1973) attempts to recover renal function may be paramount. Rarely surgery is mandatory in view of the conditions causing the stenosis

which itself assumes secondary importance. Two such circumstances are constriction of the origin of a renal artery by a dissecting aortic aneurysm, and extrinsic compression of a renal artery by a phaeochromocytoma (Agabiti et al, 1976).

Choice of operation. The principal surgical choice is between excision of all or part of a kidney and revascularisation of the ischaemic kidney. Equivalent blood pressure reduction may be obtained after either procedure (Foster et al, 1975), though a policy of preservation of renal tissue where at all possible is common-place (Luke et al, 1968). Future surgical alternatives are severely limited by nephrectomy should contralateral disease develop postoperatively. However, the choice of procedure becomes crucial where there is impairment of renal function, since remarkable functional recovery has been recorded even in small and apparently atrophic kidneys, which have not excreted urine for up to 39 days (Perkins, Jacobson, Feder, Lipchik, and Fine, 1967; Morgan, Wilson, Johnston, Clunie, and Gordon, 1974) and since uraemia is a major cause of operative mortality (Franklin, Young, Maxwell, Foster, Palmer, Cerny, and Varady, 1975). Nevertheless, where overall renal function is normal or mildly impaired many workers feel that nephrectomy is indicated in patients with small

and non-functional kidneys (Genest et al, 1977). Technical reasons, such as aberrant renal arteries, small and friable vessels, multiple intrarenal branch lesions, and renal artery aneurysms may preclude revascularisation procedures. Nephrectomy may be the sole option when a graft has thrombosed.

Procedures. 1 Revascularisation.

i. Aorto-renal bypass graft - this is the commonest and most successful revascularisation procedure. Grafts may be of synthetic knitted dacron or of autogenous saphenous vein (Ernst, Stanley, Marshall, and Fry, 1972) or ovarian/testicular vein (Owen, 1964). The major problem associated with this technique is thrombosis of the graft: in the cooperative study of renovascular hypertension (Foster et al, 1975) 'anatomic failure rates' of 18-45% were recorded in patients with unilateral stenosis depending on the institution concerned; in smaller series lower failure rates have been found.

ii. Splenorenal anastomoses - commonly used in the 1950's this technique is rarely used now. Difficulty in mobilising a vascular pedicle because of numerous pancreatic branches, atheroma of the splenic artery and restenosis at the anastomosis site were the major problems with this method.

iii. Endarterectomy - this is a valid alternative procedure with or without a patch graft where an atherosclerotic plaque has caused the stenosis.

iv. Autotransplantation - excision of the affected kidney, possibly with extracorporeal tailoring of the stenosed artery and reimplantation into the right (usually) internal iliac artery has been used successfully in some centres (Clunie, Gordon, Hartley, Petrie, and Hardie, 1975).

v. Percutaneous transluminal dilatation - this recently introduced technique adds a new dimension to revascularisation. The dilatation procedure is performed without open operation, a Grüntzig balloon catheter being passed into the stenosed segment of renal artery following femoral artery catheterisation by the Seldinger technique under local anaesthesia. Inflation of the balloon to a pressure of 5-6 atmospheres ($\bar{c}$ 500-600 kPa) renders the arterial lumen patient (Grüntzig, Kuhlmann, Vetter, Lütoff, Meier, and Siegenthaler, 1978, Millan and Madias, 1979; Katzen, Chang, Lukowsky, and Abramson, 1979). Though the technique is in its infancy in renal artery stenosis, it has been used extensively and to good effect in the management of peripheral arterial disease (Grüntzig, 1977) and to a lesser extent in coronary artery stenosis (Grüntzig, 1978); 2 years after dilatation of the iliac and femoropopliteal stenoses, the

patency rate has exceeded 70%. Rupture of the vessel at the site of dilatation has not occurred commonly in the present limited experience, and where it has the retroperitoneal bleed has not proved troublesome. The place of this exciting and relatively non-invasive procedure has still to be fully assessed in renal artery stenosis, but it certainly offers an alternative to medical therapy in the older patient who is unfit for surgery.

2. Excision

Operative complications are necessarily less when nephrectomy, or heminephrectomy where a branch occlusion exists, is performed. An abdominal or loin approach may be used. Where a planned revascularisation has to be abandoned, nephrectomy may be performed at the same operation: nephrectomy is equally successful as a secondary procedure after thrombosis of a graft as it is as a primary procedure (Foster et al, 1975).

Results of Surgery.

Objectivity is of great importance in assessing the results of surgery, as illustrated by the wave of rather indiscriminate nephrectomies in the 1940's, arrested by Homer Smith's critical analyses in 1948 and 1956. He recommended postoperative assessment at least one year after the operation and a strict criterion of normality

(B.P. <140/90 mmHg). Floyer (1951) demonstrated the importance of prolonged follow-up in his work with two-kidney hypertension in rats; about half of the animals whose renal artery had been clipped for at least 8 weeks became normotensive for several weeks after unclipping or nephrectomy of the clipped kidney, before returning to hypertensive levels.

Smith's criterion of a normal blood pressure is only one of several. Most take into account a group of patients whose blood pressure control is easier after surgery, though levels are not normal. However, few studies take into account that normal blood pressure rises with age (Hamilton, Pickering, Roberts and Sowry, 1954) (see Chapter 4:12). Maxwell, Bleifer, Franklin, and Varady (1972) in the co-operative study of renovascular hypertension used the following criteria in patients surviving 12 months after surgery:-

"1. Cured: Patients with average diastolic blood pressures of 90 mmHg, or less, and with at least 10 mmHg decrease from the preoperative level.

2. Improved: Patients with a 15%, or greater, decrease in average diastolic blood pressure, and whose diastolic blood pressure is greater than 90 mmHg, but less than 110 mmHg.

3. Failure:
   a) Patients with less than a 15% decrease in average diastolic blood pressure and whose diastolic blood pressure is greater than 90 mmHg.
   b) Patients with a diastolic blood pressure greater than 110 mmHg. "

On the other hand, Hunt et al (1974) classify their results on the basis of a diastolic blood pressure <90 mmHg, without medication (success), or with mild medication - "diuretic or methyldopa" (improved), while failures, regardless of blood pressure, required sympatholytic drugs. In a further large series (Shapiro et al, 1969) five different categories of response are defined, while in another (Messerli, Genest, Nowaczynski, Kuchel, Cartier, Rojo-Ortega, Schürch, Honda, and Boucher, 1975) blood pressure reduction of over 20 mmHg, without complete normality, is classed as a "fair" response.

It is obvious that criteria for success are almost as numerous as the studies of surgical management themselves. In consequence, comparison of results from different centres is very difficult. Moreover, since the evaluation of prognostic tests is based on the criteria for success and failure, strict comparison of these tests between centres is invalid.

However, with these provisos borne in mind, it may be seen from pooled data for 1,827 patients (Table 2) that roughly one half of patients are cured, one third are improved and one fifth are failures. These data do not include patients who do not survive the first year after operation - 5% (Capelli et al, 1973), 5.9% (Franklin et al, 1975) of all operated patients.

TABLE 2

RESULTS OF SURGERY.

A review of 1,827 patients with renal artery stenosis.

Author	No. of patients	Blood pressure		
		Normal	Improved	Unchanged
Munck et al, 1968	23	12 (52%)	4 (17%)	7 (31%)
Luke et al, 1968	24	16 (67%)	7 (29%)	1 (4%)
Shapiro et al, 1969	28	5 (18%)	16 (57%)	7 (25%)
Capelli et al, 1973 - review of 12 studies.	1220	561 (46%)	427 (35%)	232 (19%)
Hunt et al, 1974	99	55 (56%)	29 (29%)	15 (15%)
Messerli et al, 1975	49	18 (37%)	17 (35%)	14 (28%)
Foster et al, 1975	384	196 (51%)	58 (15%)	130 (34%)
Overall	1827	863 (47%)	558 (31%)	406 (22%)

These definitions of success are based on blood pressure reduction. Paradoxically, surgical failure so defined does not necessarily imply that the operation was of no benefit to the patient. Many patients, while still hypertensive, are much more easily controlled and require less of medications whose side-effects may have been disabling. A further small group of patients in whom the principal indication for surgery was recovery of renal function (Bengtsson et al, 1974; Mackay,(in press)) had their lives saved, but are still failures from the point of view of their blood pressure.

It has been recognised that some subgroups of patients have a better surgical outcome than others. Patients with fibromuscular hyperplasia do better than those with atheroma, and the indications are that relative youth and freedom from contralateral renal disease may be responsible for this. Also, probably for the latter reason, patients with bilateral disease fair worse than those with unilateral disease (Foster et al, 1975).

Uraemia was the commonest cause of postoperative mortality in the co-operative study (Franklin et al, 1975), and it is of note that 13 out of 19 such patients had overall renal impairment pre-operatively, indicating significant damage to the contralateral kidney. Other common causes of operative mortality were haemorrhage

from the gastrointestinal tract, or operation site, myocardial infarction, infection and congestive cardiac failure. Not surprisingly, operative morbidity and mortality were associated with age, vascular disease at other sites, including previous myocardial infarctions (Hunt et al, 1974), and atheromatous stenosis rather than fibromuscular disease.

II. Medical.

Much less has been written on the medical management of renal artery stenosis, and to date no controlled trial has been published comparing medical and surgical management. It is therefore fallacious to interpret a long-term mortality of 40% with medical treatment and 16% with surgical treatment (Hunt et al, 1974) as a demonstration of the superiority of surgical management; patients treated medically were older and had more vascular disease at the time of presentation than those treated surgically. This trend is apparent in most studies.

The long-term mortality is high no matter which form management takes, and however well blood pressure is controlled (Morris et al, 1966; Shapiro et al, 1969; Franklin et al, 1975). As in patients with essential hypertension, the risk of myocardial infarction in particular persists (Shapiro et al, 1969) indicating perhaps

irreversible vascular damage ante-dating discovery of the renal arterial disease.

Logically, medical management with drugs which lower plasma angiotensin II concentration should be the first choice. For this reason Laragh et al, (1979) have advocated the use of beta-adrenergic neuron blocking drugs. Antagonists or inhibitors of the renin-angiotensin-system are a logical alternative. Until recently only parenteral preparations were available, but latterly the converting enzyme inhibitor, captopril (SQ 14225), has proved to be highly efficacious in the short and longer term management of patients with renovascular hypertension (Atkinson et al, 1980b). However, caution must be exercised in the long-term use of this agent because of side-effects particularly proteinuria and agranulocytosis (Lancet, 1980).

2:9 CONCLUSION.

Developments are far from static in the field of renovascular hypertension. Having passed the 'era of romance' (Stamey, 1963) in the 1960's, and an era of cost-effectiveness assessments in the 1970's, perhaps the 1980's will see the expansion of two new logical and relatively non-invasive treatments - converting enzyme inhibitors and percutaneous transluminal angioplasty. However, even at best, management of renal artery stenosis

by open operation will hold an important place for many years to come; and as this literature survey has shown many uncertainties and questions still remain in the pre-operative investigation, prognostic evaluation and long-term value of the various forms of treatment in renal artery stenosis.

CHAPTER 3

AIMS OF THESIS

Because surgical correction of renal artery stenosis may cure some hypertensive patients, recognition of unilateral ischaemia on initial screening, usually by intravenous urography, is thought to be important. However, the value of this test is partly undermined by false negative and false positive results. Once the diagnosis of renovascular hypertension has been established by definitive tests, surgery may be recommended on the basis of favourable prognostic tests such as a high renal vein renin ratio. Despite prognostication, however, one-third to one-half of patients in all large series continue to have elevated blood pressure postoperatively. Many difficulties and pitfalls thus surround the preoperative assessment of patients with renal artery stenosis.

Accordingly, the aims of this thesis are:-

i) to examine the management of 86 hypertensive patients with renal artery stenosis seen over an 11 year period, to determine what clinical features and tests led to further investigation or operation, and to determine whether reliable criteria can be established for predicting the outcome of surgery.

ii)/

ii) to evaluate intravenous urography as a diagnostic test, to determine whether urographic appearances in renal artery stenosis can be explained in terms of deranged biochemical function in the affected kidney, and to assess whether administration of prostaglandin synthetase inhibitors prior to urography improves the diagnostic yield.

iii) to assess whether ^{123}I-hippuran renography and a gamma camera technique can be used to quantify accurately total and divided effective renal plasma flow in patients with renal artery stenosis.

iv) to study serum sodium concentrations, total exchangeable sodium, and urinary sodium excretion in renal artery stenosis, and to evaluate sodium excretion of the affected kidney in relation to mean arterial pressure as a predictor of the outcome of surgery, and to determine changes in sodium excretion after surgery.

v) to compare changes in renal function after reconstructive surgery and after nephrectomy.

vi) to study smoking habits in patients with renal artery stenosis, since excessive cigarette smoking has been found in malignant phase hypertension and in atheromatous disease affecting other organs.

vii) to study changes in blood pressure across removal of the clipped kidney in Goldblatt two-kidney hypertensive rats.

The results of studies designed to fulfil these aims are discussed, and a rational approach to the management of renal artery stenosis proposed on the basis of the findings.

CHAPTER 4

METHODS

4:1 MEASUREMENT OF COMPONENTS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM.

Most measurements of angiotensin I (generated during plasma renin concentration measurements), angiotensin II and aldosterone in this thesis were made using the technique of radioimmunoassay, which was first described by Berson and Yalow in 1959 as a tool for measuring plasma insulin levels. The principle on which radioimmunoassay is based (Antoniades, 1976) is that a hormone acts in certain experimental circumstances as an antigen such that specific antibody to that hormone is raised. Where the hormone is itself non-antigenic the formation of an albumin-hormone complex may be necessary to create antigenicity. A standard preparation of purified hormone is then labelled with a radioisotope and a known amount added to a known quantity of specific antibody. If unlabelled test hormone is now added to this mixture, the concentration of the test hormone may be determined from the degree of binding of antibody by labelled hormone, using a series of standard curves which have been constructed from the results of binding of known concentrations of test hormone. Important features of the assay system are thus the acquisition of antibody of appropriate specificity and high avidity for the antigen, such that the system is sufficiently

sensitive within the range of interest; a suitably labelled substrate; and an appropriate incubation procedure for separation of bound and free radioactivity.

i) Plasma angiotensin II concentration. In the technique for measurement of plasma angiotensin II concentration, when approximately 80% of labelled angiotensin II is bound to antibody, the assay system becomes extremely sensitive to the addition of small amounts of unlabelled angiotensin. Making use of this fact were the technique originally described by Düsterdieck and McElwee (1971) and the slight modification described by Morton, Semple, Waite, Brown, Lever, and Robertson (1976). In both of these it is important that the blood sample is taken directly into inhibitor (EDTA/orthophenanthroline) so that generation of further angiotensin II from angiotensin I is immediately stopped. For this angiotensin II assay the coefficient of variation is 10%, and the limit of detectability is 5 pg of angiotensin II per 5 ml blood sample. Under normal circumstances there is a clinically unimportant degree of cross-reactivity between angiotensin II antibody and angiotensin I - less than 1%. However, where converting enzyme inhibitor has been administered to the patient, angiotensin I builds up in the circulation and correction for angiotensin I may be necessary (Atkinson, Morton, Brown, Davies, Fraser, Kelly, Leckie, Lever, and Robertson, 1980b). The normal range of peripheral venous plasma angiotensin II concentration

based on the results in 33 healthy laboratory workers aged 18-45 years on unrestricted diet ranged from 5-35 pg/ml.

ii) Plasma aldosterone concentration. This was assayed either by the double isotope derivative technique described by Fraser and James (1968) or by radioimmunoassay (Fraser, Guest,and Young,1973). No significant difference has been found between the results of the two techniques, though the latter is cheaper, quicker, and requires less plasma (Fraser et al, 1973). A normal plasma pool gave a mean concentration of 9.8 $\pm$ 0.53 (S.D.) ng/100 ml, and the normal range was less than 18 ng/100 ml.

iii) Plasma renin concentration. Between 1968 and 1974 estimations of plasma renin concentration were made according to the enzyme kinetic technique of Brown, Davies, Lever, Robertson, and Tree (1964). In this technique plasma renin concentration was measured by extracting the enzyme, incubating it with exogenous substrate and measuring the rate of angiotensin formation using a bioassay. Between 1974 and 1976 a modification of this earlier technique was employed using a radioimmunoassay to measure generation of angiotensin I, as described by Waite (1973).

From 1976 onwards measurements of plasma total and active renin concentrations have been based on the antibody-trapping method of Poulsen and Jorgensen (1974), using a radioimmunoassay for angiotensin I. This technique

has been described in detail elsewhere (Millar, Leckie, Morton, Jordan, and Tree, 1980). Also the international reference preparation of renin (National Institute for Biological Standards and Control, as described by Bangham et al (1975)) has been employed.

Characteristics of the assay were a coefficient of replicate variation for active renin of 5.5%±1.4 (S.E.M.) and for total renin of ±3.0%. Recovery of hormone was 97±12% (S.D.) and the limit of detectability was 1.5 μU/ml. The normal range for active renin was 15-50 μU/ml in normal volunteers on a normal free sodium intake, and for total renin was 60-200 μU/ml. Both of the earlier techniques measured combined active and inactive, or total, renin (Leckie, McConnell, Grant, Morton, Tree, and Brown, 1977), and the normal range was 4-20 U/l. Multiplication of these values by a factor of 5.27 allows plasma renin concentration obtained by the earlier methods to be expressed in terms of the international reference preparation of human renin in μU/ml (Bangham et al, 1975), thereby permitting comparison of plasma total renin concentration throughout the 12 years of this study.

4:2. SODIUM MEASUREMENTS.

1. Total exchangeable sodium (Na_E).

Na_E has been measured according to a modification of the technique described by Davies and Robertson (1973), based on the principle of isotope dilution. Following oral administration of a known amount of ^{24}Na (Radiochemical Centre, Amersham) equilibration with stable endogenous sodium (^{22}Na) is allowed to occur. This usually takes 12 hours, but may require 24 hours in oedematous subjects. The ratio of radioactive to endogenous element is then calculated and from this the amount of total exchangeable element can be derived. In the modification employed, total exchangeable sodium and total exchangeable potassium (K_E) were measured together after simultaneous administration of ^{24}Na and ^{43}K. Urine was collected during four periods (0-24 hours, 24-42 hours, 42-43 hours and 43-44 hours). The two 1 hour samples were used to calculate K_E. The 24 hour collection was used to correct for isotope excretion during the equilibration period. Blood samples for Na_E estimation were taken into lithium heparin tubes at 22 and 24 hours. Patients were fasted for 12 hours prior to the 22 and 24 hour blood samples and again for 12 hours prior to the 42-44 hour urine samples.

Radioactivity was measured using a sodium iodide well scintillation counter and a correction factor applied to

allow for interference of one isotope on estimation of the other. Radioactive counts and stable electrolyte concentrations were then used to calculate total Na_E and K_E. By this technique the coefficient of variation for duplicate plasma ^{24}Na activity was 1.51% and for successive Na_E estimations on the same patient at 22, 23 and 24 hours 1.77%. Results are quoted in absolute terms (mmol/kg) or as a percentage of Na_E in mmol/kg expected for a normal individual of the same leanness index. The use of this index, which is the ratio of $height^3$ to weight, in deriving expected Na_E has been validated by Davies, Schalekamp, Beevers, Brown, Briggs, Medina, Robertson, Lever, Morton, and Tree (1973).

2. Plasma and urine sodium and potassium concentrations.

These were measured by flame photometry. The coefficient of variation was less than 0.5% for the stable elements. Normal range for plasma sodium was 136-144 mmol/l and for plasma potassium 3.5-5.0 mmol/l.

4:3. BLOOD SAMPLING.

Blood samples for estimation of plasma renin, angiotensin II, aldosterone, and sodium concentrations and for Na_E were obtained between 08.30 and 10.30 a.m. after overnight fasting and recumbency in patients eating a diet with a fixed known and normal content of sodium and potassium or on a normal ward diet.

4:4. BLOOD PRESSURE MEASUREMENTS.

Unless otherwise stated blood pressure has been measured on sitting or lying patients using a standard clinical mercury sphygmomanometer with a 14 cm cuff. Phase V of the Korotkoff sounds has been taken as the diastolic blood pressure. Mean blood pressure has been calculated as the diastolic blood pressure plus one third of the pulse pressure.

4:5. INTRAVENOUS UROGRAPHY.

Standard intravenous urography was performed after 12 hours water restriction. Following control radiographs of the renal and bladder areas, 100 ml of sodium meglumine diatrizoate (Urografin 325) was injected rapidly into a peripheral vein. Coned radiographs of the renal areas were obtained at the end of the intravenous injection and at 2,3,4, and 10 minutes. A renal radiograph was taken at 20 minutes as well as a radiograph of the bladder. In most patients the examination was terminated at this point. However in some (see Chapter 8:3), one litre of water was then given to drink and a further radiograph of the renal areas taken at 40 minutes to show washout of contrast medium. If washout was unsatisfactory at this stage, a further 500 ml of water was given and a further radiograph taken at 80 minutes.

4:6. RENAL ARTERIOGRAPHY

Renal arteriography was performed using the technique first described by Seldinger (1953). In this technique the region overlying the femoral artery in the groin was infiltrated with 2% lignocaine. The femoral artery was then punctured by a metal needle, a metal guidewire introduced through the needle into the artery, and the needle removed over the wire. Thereafter a plastic catheter was threaded over the wire through the skin, the guide wire removed and the catheter introduced under fluoroscopic control into the desired position. For main stream arteriography the catheter tip was left in the suprarenal aorta and 50 ml of Conray 325 injected under pressure over 3-4 seconds, with 12-14 X-ray plates taken over this time using an automatic film changing device. For selective arteriography, the plastic catheter was manipulated into one of the renal arteries, or one of its branches, and 6-15 ml of Conray 280 injected over 3-4 seconds as for main stream arteriography. At the end of the procedure haemostasis was secured by constant manual pressure over the femoral artery puncture site for at least 10 minutes. Patients were nursed in the supine position for the subsequent 24 hours.

4:7. RENAL VEIN SAMPLING.

Patients who came to renal vein sampling were sodium replete, having received a standard ward diet of normal sodium and potassium content, and having been off all medications likely to influence secretion of renin, including diuretics for at least 3 weeks prior to the investigation. Where drug therapy was necessary over that period, bethanidine, whose action is short-lived in contrast to other hypotensive drugs, was employed but was withdrawn if at all possible for the 24 hours prior to sampling. All patients were required to give their written consent after the procedure was fully explained to them. After recumbency for at least one hour patients were transferred to the special investigation room of the Radiology Department, where under sterile conditions both femoral veins were catheterised under local anaesthesia by the Seldinger technique. Catheters were then sited in both renal veins under fluoroscopic control. Since 1977 patients have had an additional sampling catheter sited in their aorta at the level of the renal artery. Sampling catheters were kept patent by boluses of heparinised saline and before each blood sample was withdrawn 2 ml of dead space was also withdrawn from each catheter and discarded. Samples were drawn from the three sites -

right renal vein, left renal vein and aorta - simultaneously and quickly, but without application of excessive suction. Three sets of samples for plasma renin concentration (5 ml) and plasma angiotensin II concentration (20 ml) were obtained, total sampling time averaging 4-6 minutes. Total blood loss was 350 ml, insufficient to stimulate renin secretion in its own right. After sampling, a small bolus of contrast was injected into each renal vein to confirm correct siting of the catheter tip. Additional samples were drawn from the intrarenal inferior vena cava both before and after sampling from the renal veins.

4:8. BILATERAL URETERIC CATHETERISATION STUDIES.

The conditions of study with respect to sodium status, medications, and informed consent were the same as for renal vein sampling. On the morning of the investigation, patients were encouraged to drink 1 litre and if possible, 2 litres of water. In the ward a 500 ml intravenous infusion of normal saline was begun into a vein in the right forearm, and a 3-way tap inserted in a vein in the opposite arm. Following transfer to the Urology Theatre, a saddle block spinal anaesthetic was administered. Then with the patient in the lithotomy position ureteral catheters (No. 7 French gauge, if possible, to ensure a tight fit) were

passed via a cystoscope, and were left in situ. The cystoscope was withdrawn, and a Foley catheter passed to detect any urine leaking past ill-fitting ureteral catheters.

Before ureteral catheters were passed, a loading intravenous dose of 0.0365 ml/kg of 20% paraamino-hippurate (PAH) ("amino-hippurate", Merck, Sharp & Dohme) was administered followed by an intravenous infusion of 2.65 ml 20% PAH in 500 ml 10% mannitol at 19 ml/min. Specimens of urine from each kidney were sent for bacteriological culture, including that for alcohol- and acid-fast bacilli. Following a run-in period of 45 minutes, four timed urine collections were obtained from each kidney; each collection period was usually of 5 minutes duration, with blood samples for plasma creatinine and PAH concentration being obtained in the middle of each collection period. Blood pressure was measured at regular intervals throughout the procedure, including one measurement in the middle of each collection period.

Ureteral catheters were then removed, but the Foley catheter was left in situ for 6 hours after return of the patient to the ward, or longer if haematuria was persistent. The patient was then nursed in the supine position for 24 hours. Intravenous fluids were discontinued as soon as a good oral intake was re-established:

a high fluid intake was encouraged. A mid-stream specimen of urine was taken for bacteriological culture on the 3 days following the test, but no prophylactic antibiotics were given.

The volume of each urine collection was measured. Sodium content of each collection was estimated by flame photometry. Creatinine concentration was measured by a standard autoanalyser technique. PAH was measured according to the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (1945) from 1968 to 1974, but thereafter by the method of Waugh and Beall (1974). Creatinine and PAH clearances were calculated by the standard formula UV/P where U was the urinary concentration of the test substance, V was the urine volume in unit time, and P the plasma concentration. Clearances were expressed in ml/min. Creatinine clearance was taken as an estimate of glomerular filtration rate, and PAH clearance as an estimate of effective renal plasma flow.

4:9. PAH CLEARANCE.

In studies to be described comparing total PAH clearance with ^{123}I-hippuran clearance, the former test was performed on the day of ^{123}I-hippuran renography. The method of the former test was similar to that employed in bilateral ureteric catheterisation studies, except that

no anaesthesia or instrumentation of the urinary tract was necessary; urine specimens were voided spontaneously and three 30 minute urine collection periods were used.

4:10 ^{123}I-HIPPURAN RENOGRAPHY.

Sodium ^{123}I-hippuran was prepared by the copper sulphate method first described by Wanek, Hupf, and O'Brien (1977), and later modified by Herman, Shields, Elliott, Hawkins, Horton, Little, and Umbers (1979), using sodium ^{123}I-iodide obtained from the Atomic Energy Research Establishment, Harwell. Renal images were recorded and analysed using a Nuclear Enterprises large field of view gamma camera connected to a Varian V-76 computer with colour television display. Each patient was positioned prone beneath the gamma camera with the kidneys central in the field of view. Following an intravenous bolus of 1 mCi ^{123}I-hippuran 40 thirty second images were recorded. Water loading of patients was avoided during the study. No patients were taking drugs such as antibiotics or probenecid (Waugh and Ozdemir, 1970; Brodkey, Schlegel and Derouen, 1979) which might have competed with iodo-hippuran at the transport sites in the proximal renal tubules.

In the subsequent analysis, all the images were first summed to provide a well-defined image for selection of regions of interest for quantification. Five

regions were selected as shown in Figure 2. An activity/time curve was then calculated for each region using the sequential data for this series of images.

Variations in gross kidney activity were provided by the curves obtained from regions 1 and 2. The net variations in kidney activity were obtained by subtracting the background variation observed in regions 1A and 2A surrounding each kidney from the gross activity variation after normalisation for the different areas in each case,

i.e. $k(t) = K(t) - cb(t)$ where

$k(t)$ - the net kidney count,

$K(t)$ - the gross kidney count,

$b(t)$ - the count in the background area, and

c is the normalising factor = $\frac{\text{kidney area}}{\text{background area}}$

e.g. $\frac{(\text{area of region 1})}{(\text{area of region 1A})}$.

The selection of the area surrounding the kidney as representing the background to kidney activity has been validated by Short, Glass, Chisholm, Vernon, and Silvester (1973) using nephrectomy sites. The technique has also been used by Piepz, Dobbeleir, and Erbsmann (1977) in the study of the clearance of Tc^{m} ^{99}-DTPA (diethylene triamine pentacetate).

Region 3 superior to the kidneys was taken solely as an area of vascular activity to assess the variation of blood activity with time. The activity at this stage

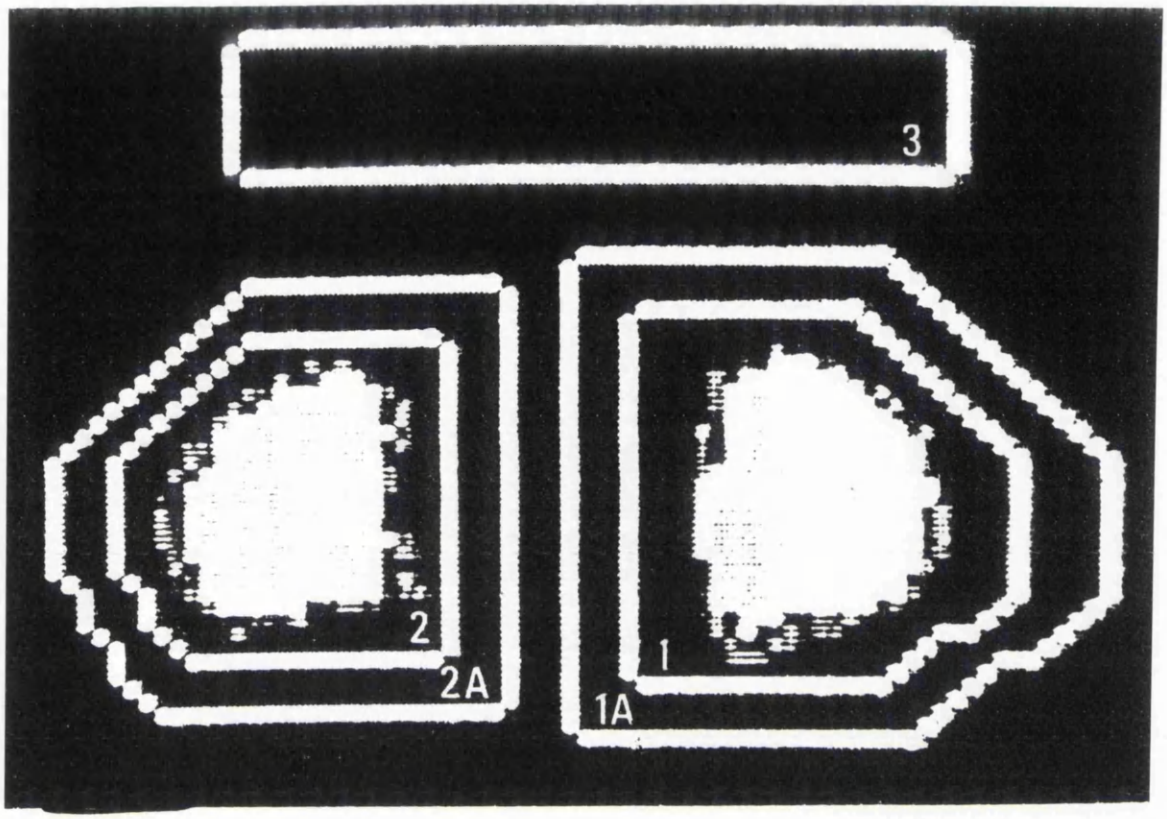


Figure 2: ^{123}I-hippuran renogram showing the regions of interest for quantitative analysis. Regions 1 and 2 are kidney regions: regions 1A and 2A are perirenal background areas: region 3 is the area of vascular activity.

The model describes the renogram curve during the stage of increasing renal activity before excretion of hippuran to the renal pelvis takes place. The total net kidney activity, k(t), is given by:-

$$k(t) = E.R.P.F. \cdot B(t)$$

where B(t) is the integrated kidney background activity which is assumed to follow the concentration of hippuran presented to the kidneys.

The original expression has been slightly simplified by assuming that the hippuran arrives simultaneously at the kidney and the kidney background regions on each side. This model has been used previously by Brodkey et al (1979) to calculate total E.R.P.F. In the present study it has been assumed that for the two kidneys:

$$k_L(t) = E.R.P.F._L \cdot B_L(t)$$

and $$k_R(t) = E.R.P.F._R \cdot B_R(t)$$

where the subscripts L and R refer to the left and right kidneys respectively. In each kidney the individual E.R.P.F. can therefore be derived from the slope of a linear relationship between k(t) and B(t). The ratio of the plasma clearance is then given by:

$$\frac{E.R.P.F._L}{E.R.P.F._R} = \frac{k_L(t)/B_L(t)}{k_R(t)/B_R(t)}$$

To determine the slopes experimentally, the values of net kidney activity were graphed against the integrated kidney background activity for each image in the period 0.5 to 2.5 min after administration of hippuran. The first

0.5 minutes was excluded to ensure that the kidney background was proportional to the blood concentration of hippuran, as described by Holroyd, Chisholm, and Glass (1970). In all studies, the peak of the kidney activity curve was reached after 2.5 minutes and the applicability of the analysis to the phase before hippuran excretion would appear to be valid. Regression lines were fitted to the data for each kidney using the method of least squares and the slopes noted. The ratio of the individual effective renal plasma flows was taken as the ratio of the two slopes.

4:11 SARALASIN INFUSIONS.

Infusions of Sar-1-Ala-8-angiotensin II (saralasin) were performed on sodium replete subjects who remained supine throughout the procedure as well as for at least the preceding hour. The infusion was administered at a constant rate by an electrically driven pump (Dascon, Unden, Holland) via a plastic cannula in a forearm vein. Blood samples for measurement of plasma renin, angiotensin II and aldosterone concentrations were obtained via an indwelling plastic cannula in the opposite forearm. Blood pressure was measured by an Elag-Köln semi-automatic blood pressure recorder at 3-5 minute intervals, checked at intervals by a traditional clinical mercury sphygmomanometer. The patient's diet was controlled so that it contained known and normal amounts of sodium and potassium for at least three days before the infusion. Hypotensive agents

other than bethanidine had been avoided for at least 3 weeks.

During an hour run-in period when the patient received 5% dextrose, plasma samples for baseline hormone concentrations were obtained at 30 and 60 minutes. Thereafter, saralasin was infused at 0.625 µg/kg/min for 15 minutes, at 1.25 µg/kg/min for 15 minutes, at 2.5 µg/kg/min for 30 minutes, at 5 µg/kg/min for 60 minutes and at 10 µg/kg/min for 60 minutes, followed by a further 5% dextrose infusion for 1 hour. Repeat hormone estimations were made at the end of the period of maximum infusion rate and at the end of the follow-up period. The procedure was terminated at the sub-maximal infusion rates where marked falls of blood pressure occurred.

4:12 DEFINITION OF SURGICAL AND MEDICAL SUCCESS.

Surgical success was defined as reduction of systolic and diastolic blood pressures to within one standard deviation of the age and sex-related mean pressures as described by Hamilton, Pickering, Roberts, and Sowry (1954) who derived their data from outpatients being assessed for minor surgical procedures. These values have been plotted in Figure 3 and illustrate the normal rise in blood pressure with age. Increments of approximately 25% between the ages of 20 and 60 were normal in both sexes. Success was determined in this study on lying or sitting outpatient blood pressure measurements obtained 1 year after surgery.

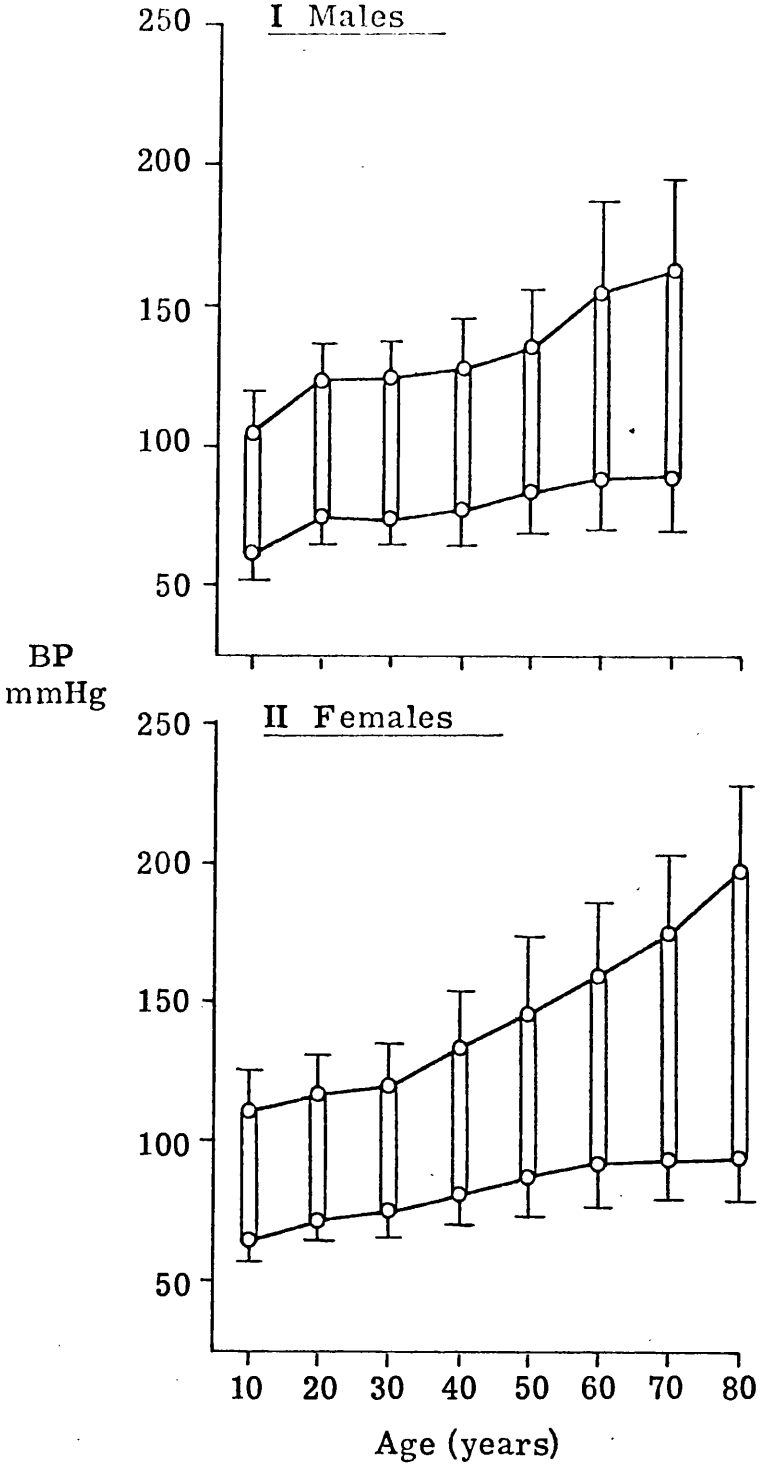


Figure 3: Arterial pressure in the general population by age
I. Males II. Females. Data derived from Hamilton, Pickering, Roberts, and Sowry (1954). Open circles represent systolic and diastolic blood pressures and the bars represent one standard deviation from the mean.

Patients were classed as surgical failures where anti-hypertensive drugs were required to attain the same levels as in patients having successful surgery, or where arterial pressure exceeded these levels with, or without, the use of drugs, one year after surgery. This arbitrary definition classifies as failures many patients in whom blood pressure control was improved and patients in whom surgery may have been life-saving, though pressures were not returned to normal levels.

In a similar manner medical success was defined as the reduction of blood pressure on outpatient recordings after one year's follow up to within one standard deviation of the criteria of Hamilton et al (1954) with the use of hypotensive drugs, while in medical failures blood pressure could not be controlled within these limits despite medication.

4:13 RAT EXPERIMENTS.

In all experiments, male Sprague-Dawley rats weighing 175-250 g at the outset were used. Rats were kept in two's or three's per cage, fed standard Oxoid 41b diet, and were given unrestricted supplies of tap water in which there were no additives.

i) Blood pressure was measured by the technique of tail plethysmography using a BP recorder 8005 (W & W Electronics, Basel:Munchenstein, Switzerland). Animals were first warmed at 37^{o}C for 20 minutes to ensure vasodilatation. No anaesthetics were used.

ii) Renal artery clipping was performed as in the experiments of Floyer (1951) using a silver ribbon clip of 0.2 mm (8 thousandths of an inch) internal diameter. Animals were anaesthetised with ether for this procedure, and the midline abdominal approach employed. After application of the clip to the left renal artery, the peritoneum was closed with 4/0 catgut and the skin closed with Michelle clips. These clips were removed one week after the operation.

iii) The procedure for sham clipping involved ether anaesthesia, an abdominal incision, reflection of the viscera, and a similar closure of the wound without interference with the renal artery.

iv) Nephrectomy of the clipped kidney was performed through a small left loin incision, through which the kidney was delivered. A single silk suture was placed round the vascular pedicle and ureter after dissection free of the adrenal gland. The kidney was then excised. The wound was closed with catgut sutures to the muscle wall and Michelle clips to the skin. Ether anaesthesia was used.

4:14 STATISICAL METHODS

These are described at the relevant points in each study.

CHAPTER 5

HYPERTENSION SECONDARY TO RENAL ARTERY DISEASE - THREE KEY ILLUSTRATIVE CASES.

By way of introduction to the series of 86 patients with renal artery stenosis or occlusion, 3 unusual cases are presented below. The first is unusual in that "classical" radiographic, biochemical and humoral abnormalities were identified in the same patient: results of these tests are described in detail so that a basis for comparison may be established for the data in subsequent chapters. The second is unusual in that the primary indication for reconstructive surgery was relief of renal failure and not of hypertension. The third is unique in that a detailed assessment of the renin-angiotensin system is available before and after development of an acute renal artery stenosis with severe hypertension, and after cure by unilateral nephrectomy: the pattern of changes in this patient previously has been established only in experimental animals.

I. CLASSICAL CASE OF UNILATERAL RENAL ARTERY STENOSIS AND HYPERTENSION CURED BY RECONSTRUCTIVE RENAL ARTERY SURGERY.

Case Report

A 46 year old industrial nurse began taking the combined oestrogen-progesterone oral contraceptive pill in 1964 after the completion of her fourth successful pregnancy. Ten years later she presented to her general

practitioner with a short history of occipital headaches and was found to have a blood pressure of 170/106 mmHg. The oral contraceptive was discontinued and the patient referred to a gynaecology clinic for further advice. Eight months later, the patient's blood pressure had risen to 180/112 mmHg and she was referred to the Blood Pressure Unit for assessment.

The patient gave an interesting history of recurrent dragging abdominal pain and dysuria in her late teens. Following hospital investigation in the South of England a diagnosis of nephroptosis had been reached and a nephropexy performed in 1949 with subsequent relief of symptoms. No elevation of her blood pressure was recorded at that time, or during her pregnancies. She had no family history of hypertension, cardiovascular or renal disease. She smoked 20 cigarettes a day, but was taking no medications.

On examination the patient was tall (172 cm) and she weighed 68 kg. Her blood pressure was 202/134 mmHg lying, 204/128 mmHg standing and her pulse regular at 72 beats per minute. Her apex beat was in the 5th intercostal space in the anterior axillary line. Fundal examination revealed no retinal haemorrhages, exudates or papilloedema. An abdominal bruit was audible above her umbilicus, on the right side of her abdomen, and in the right lumbar region. The clinical diagnosis was of right renal artery stenosis.

Initial investigations revealed a normal full blood count (haemoglobin 14.2 g/dl), normal serum electrolytes (sodium 141 mmol/l, potassium 4.7 mmol/l, chloride 99 mmol/l, bicarbonate 28 mmol/l), serum urea 5.7 mmol/l and serum creatinine 105 μmol/l. Her creatinine clearance was 106 ml/min and her exchangeable sodium 110.4% of the predicted value. There was no haematuria or proteinuria. Hormonal estimations from a peripheral venous blood sample obtained under standard conditions (see Methods) were: total plasma renin concentration 157 μU/ml (N.R.60-200 μU/ml), plasma angiotensin II concentration 20 pg/ml (N.R. 5-35 pg/ml) and plasma aldosterone concentration 6 ng/100 ml (N.R. <18 ng/100 ml). Peripheral plasma renin concentration within the normal range was typical in the series of patients to be described in Chapter 6-11.

Classical results were found in the following investigations:-

1. Intravenous urogram (Fig. 4). The right kidney measured 12.5 cm in bipolar diameter while the left measured 14.6 cm. There was delay in the appearance of contrast on the right side and in later films the concentration of contrast was increased on the right. The difference in density between the sides was emphasised after an oral water load.

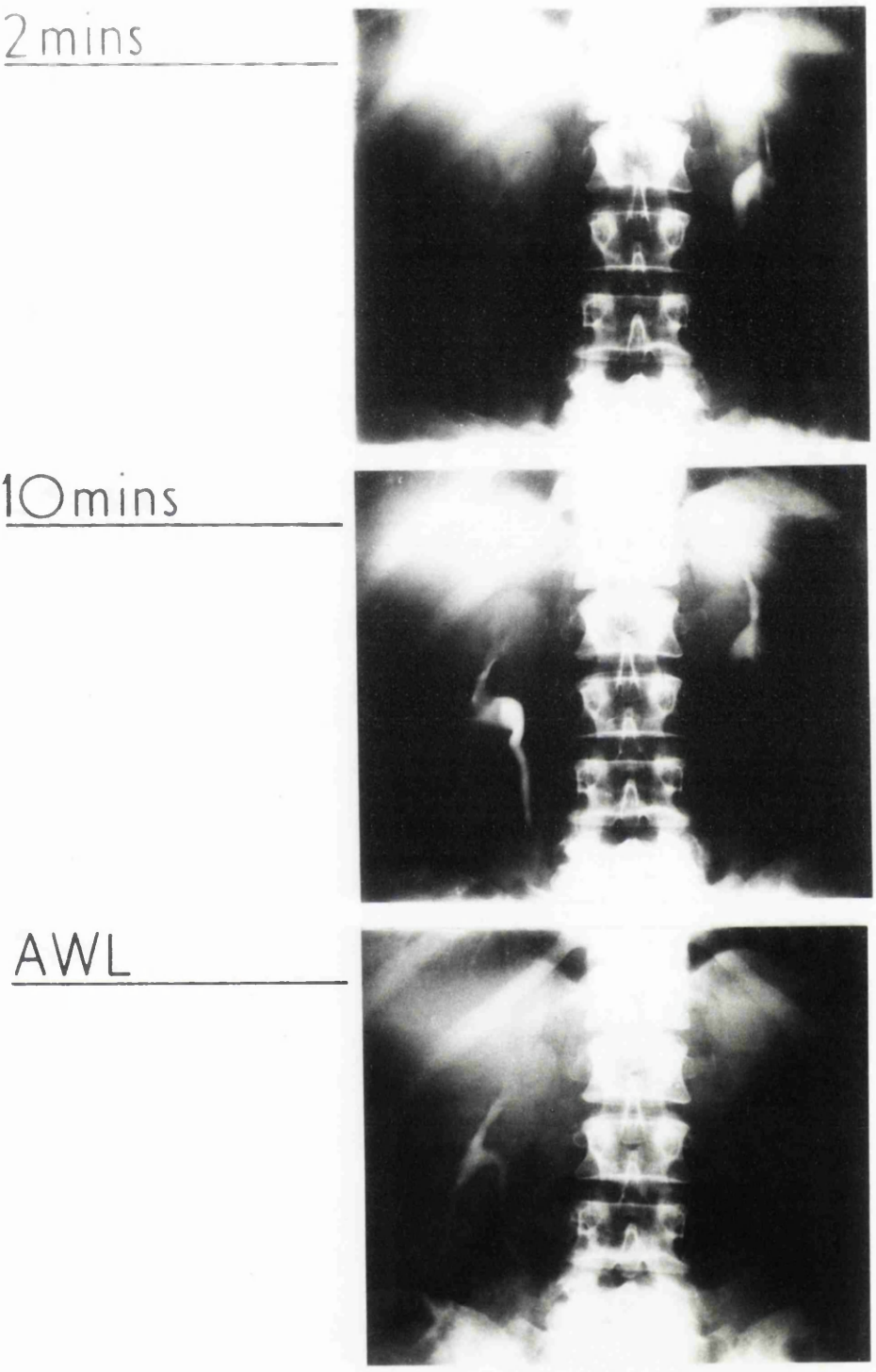


Figure 4: Intravenous urogram series of a 46 year old woman with right renal artery stenosis. Note the delay in the appearance of contrast on the right at 2 minutes, the increased density of contrast on the right at 10 minutes, and the delay in the washout of contrast on the affected side after an oral water load.

2. Arteriography (Fig. 5). An area of narrowing with the typical beaded appearance of fibro-muscular hyperplasia (Youngberg et al 1977) was demonstrated in the middle third of the right renal artery 2.5 cm distal to its origin from the aorta. There was post-stenotic dilatation and a collateral circulation via inferior adrenal and ureteric vessels.

3. Bilateral ureteric catheterisation studies (Fig. 6). The classical changes of right-sided ischaemia were noted. Urine flow and urinary sodium concentrations were reduced on the affected side. Concentrations of non-reabsorbable solute (creatinine and PAH) were increased on the affected side while the clearances of creatinine and PAH were reduced. The blood flow to the normal kidney was well maintained.

4. Renal vein sampling (Fig. 7). Total plasma renin concentrations in blood drawn from both renal veins and the aorta revealed a positive venoarterial difference on the right, a negative venoarterial difference on the left and a renal vein renin ratio (right to left) of 1.61. Total plasma renin concentrations from peripheral venous blood accorded with values from arterial blood at 157 and 146 μU/ml respectively.

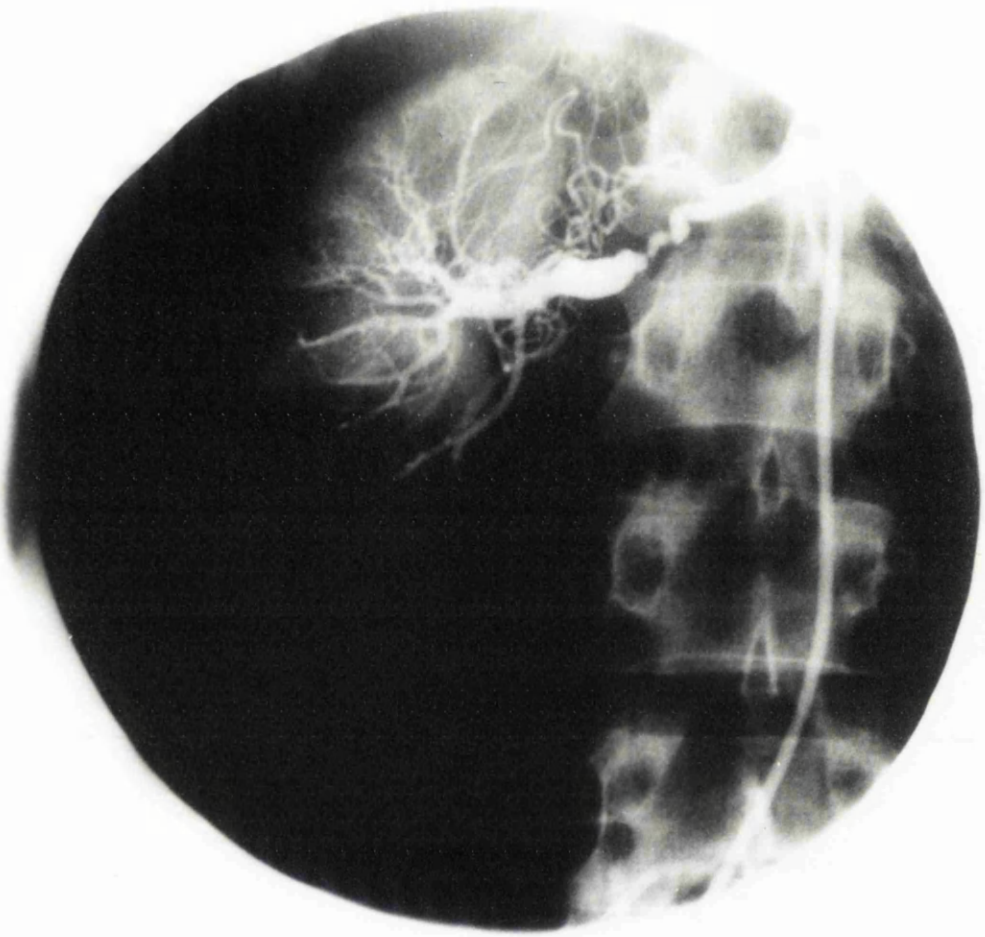
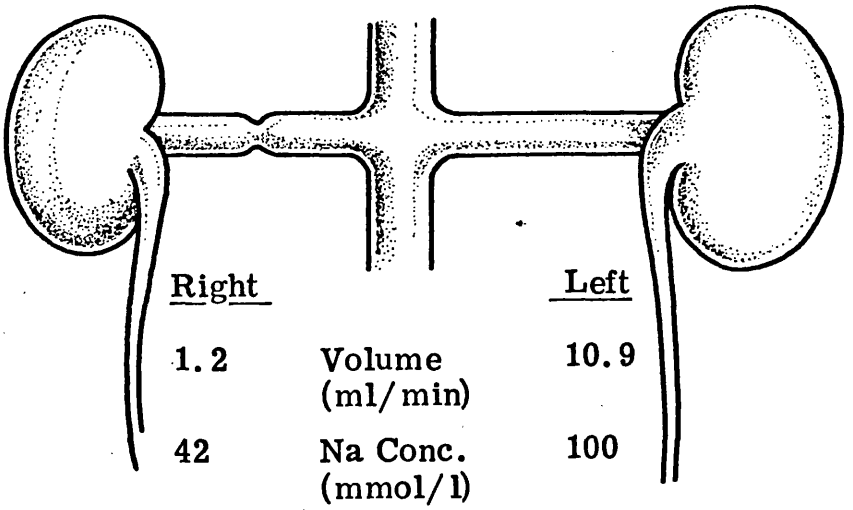


Figure 5: Right selective arteriogram of a 46 year old woman with renal artery stenosis, showing the characteristic 'string of beads' appearances of the affected artery with post-stenotic dilatation, and a collateral circulation via the inferior adrenal, and to a lesser extent, periureteric vessels.

Bilateral Ureteric Catheterisation Studies



Right		Left
1.2	Volume (ml/min)	10.9
42	Na Conc. (mmol/l)	100
1.90	Creat. Conc. (mmol/l)	0.52
8.37	PAH Conc (mmol/l)	2.18
38	C_{Cr} (ml/min)	93
120	C_{PAH} (ml/min)	283

Figure 6: Bilateral ureteric catheterisation studies in a 46 year old woman with right renal artery stenosis. Characteristic features of ischaemia are present on the right, with reduced urine volume and sodium concentration, increased concentration of non-reabsorbable solutes (creatinine and PAH), and reduced clearance of creatinine and PAH.

Renal Vein Sampling

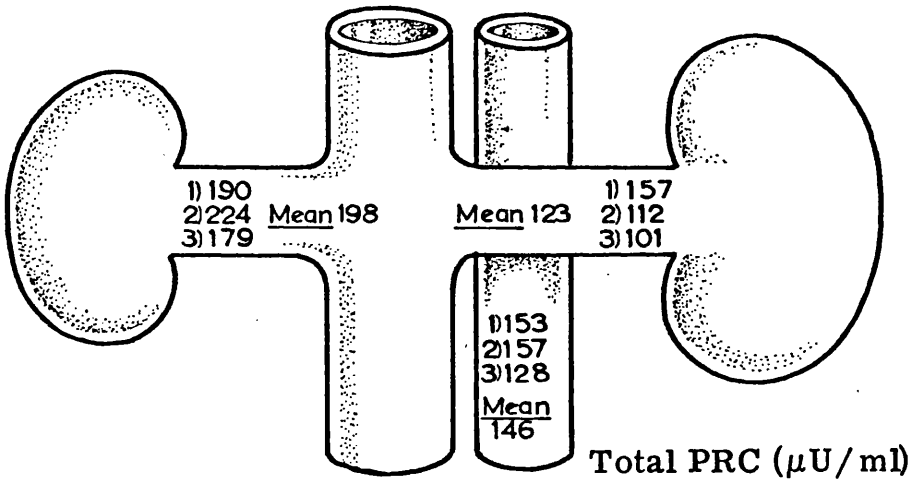


Figure 7: Renal vein sampling in a 46 year old woman with right renal artery stenosis. Total plasma renin concentration is expressed in μU/ml (normal range 60-200 μU/ml). Mean values of triplicate sampling are given. Compared with aortic concentrations (146 μU/ml) there is an increased plasma renin concentration in right renal vein blood and a reduced plasma renin concentration in left renal vein blood.

All the available evidence pointed to the likelihood of surgery effecting a cure for this patient's hypertension. At operation in January, 1976, a 55 mmHg pressure gradient was detected across the stenosis, but this cleared after the insertion of a 6 mm knitted double velour dacron graft between the side of the renal artery distal to the stenosis and the side of the aorta. The patient's postoperative course was uneventful, and her blood pressure had fallen to 150/90 mmHg by the first postoperative day, and to 122/70 mmHg on no treatment one year later. Four years later she remains well and requires no drugs; her blood pressure is 128/78 mmHg and the effective renal plasma flow to her right and left kidneys as determined by ^{123}I-hippuran renography and a gamma camera technique (see Methods) is 178 and 122 mls/min respectively.

2. RELIEF OF URAEMIA BY RECONSTRUCTIVE SURGERY IN A HYPERTENSIVE PATIENT WITH RENAL ARTERY OCCLUSION AND PREVIOUS CONTRALATERAL NEPHRECTOMY.

Case Report

A 48 year old housewife was admitted in May, 1978, with a 3 week history of increasing exertional dyspnoea, worsening angina pectoris, occipital headaches and a supine blood pressure of 260/160 mmHg. In 1970 her general practitioner first found her blood pressure elevated at 160/100 mmHg, but easily controlled this with a thiazide diuretic. Late in 1975 her blood pressure increased to diastolic values ranging from 104 to

126 mmHg, despite the addition of sotalol and clonidine and she developed symptoms of angina pectoris and intermittent claudication. Her subsequent clinical course, blood pressure and serum creatinine are charted in Fig. 8 Other risk factors relating to her atheromatous disease were cigarette smoking (10/day), and Frederickson Type-IV hyperlipidaemia,(serum cholesterol 6.0 mmol/l,(N.R. 4.1-7.4 mmol/l) and serum triglycerides 3.5 mmol/l (N.R. <1.8 mmol/l)). In July, 1976 she suffered a left-sided stroke, but made a full recovery. An intravenous urogram then showed poor excretion of dye by the right kidney, but total renal function was not severely impaired, since her serum urea was 5.9 mmol/l and serum creatinine was 114 μmol/l. Serum electrolytes were normal.

Following referral to the Blood Pressure Unit renal arteriography was performed and demonstrated two small right renal arteries, both occluded at their origins with some collateral circulation from lumbar vessels (Fig.9), and a single left renal artery with a minor stenosis at its origin. The right kidney was 11 cm and the left 15 cm in bipolar length; bilateral cortical irregularity was noted. The appearances of the aorta suggested diffuse atheroma.

Total renin concentration in plasma samples drawn simultaneously from the left renal vein, right renal vein and aorta yielded mean values of 286, 493 and 319 μU/ml

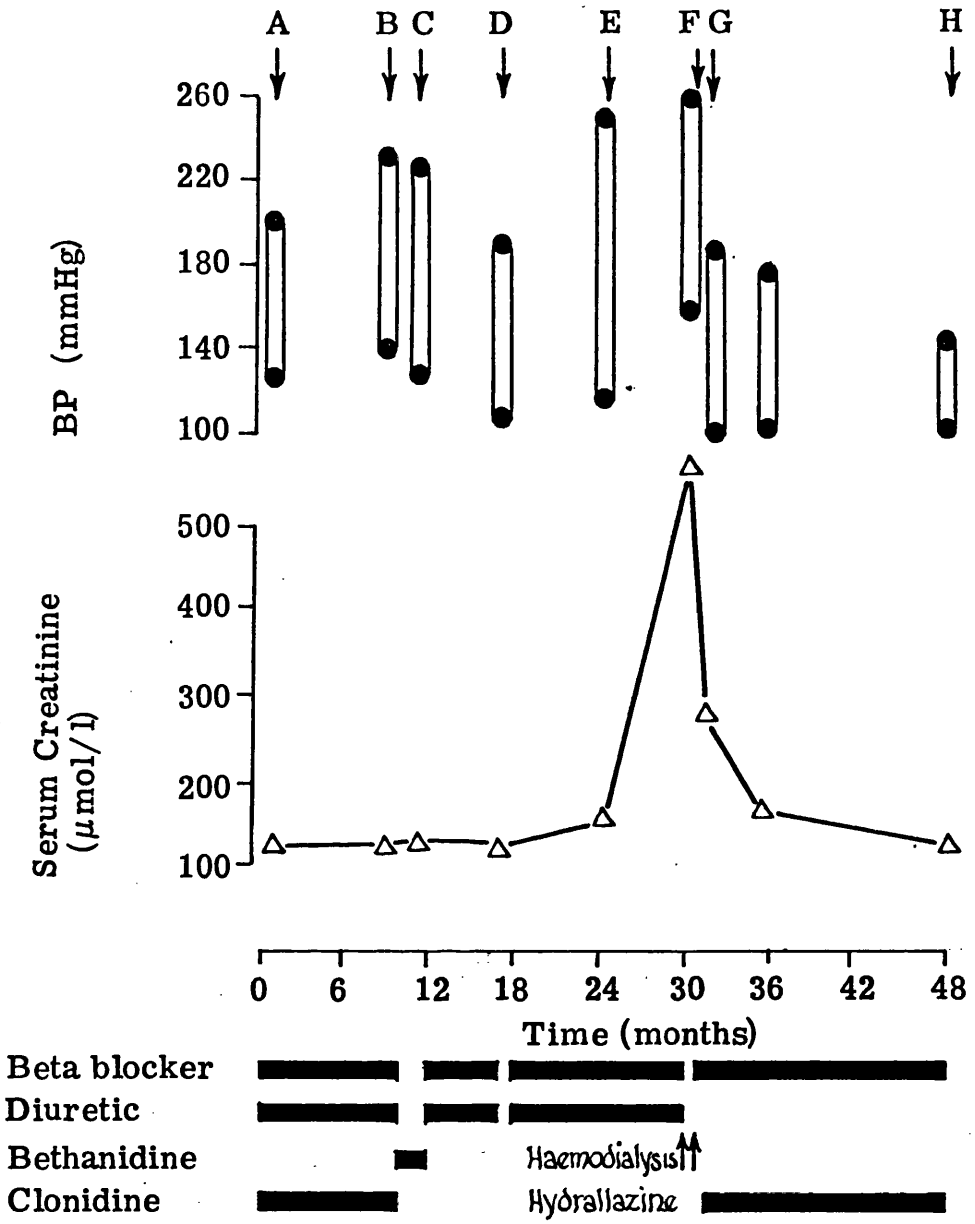


Figure 8: Flow diagram of clinical events, blood pressure, renal function and drug therapy in a 48 year old woman. Solid circles denote systolic and diastolic blood pressures.
A = development of angina pectoris and intermittent claudication.
B = left-sided stroke.
C = referral for investigation.
D = right nephrectomy.
E = left brachial artery occlusion.
F = left renal artery occlusion and arterial reconstruction.
G = discharge from hospital.
H = 17 months after operation.

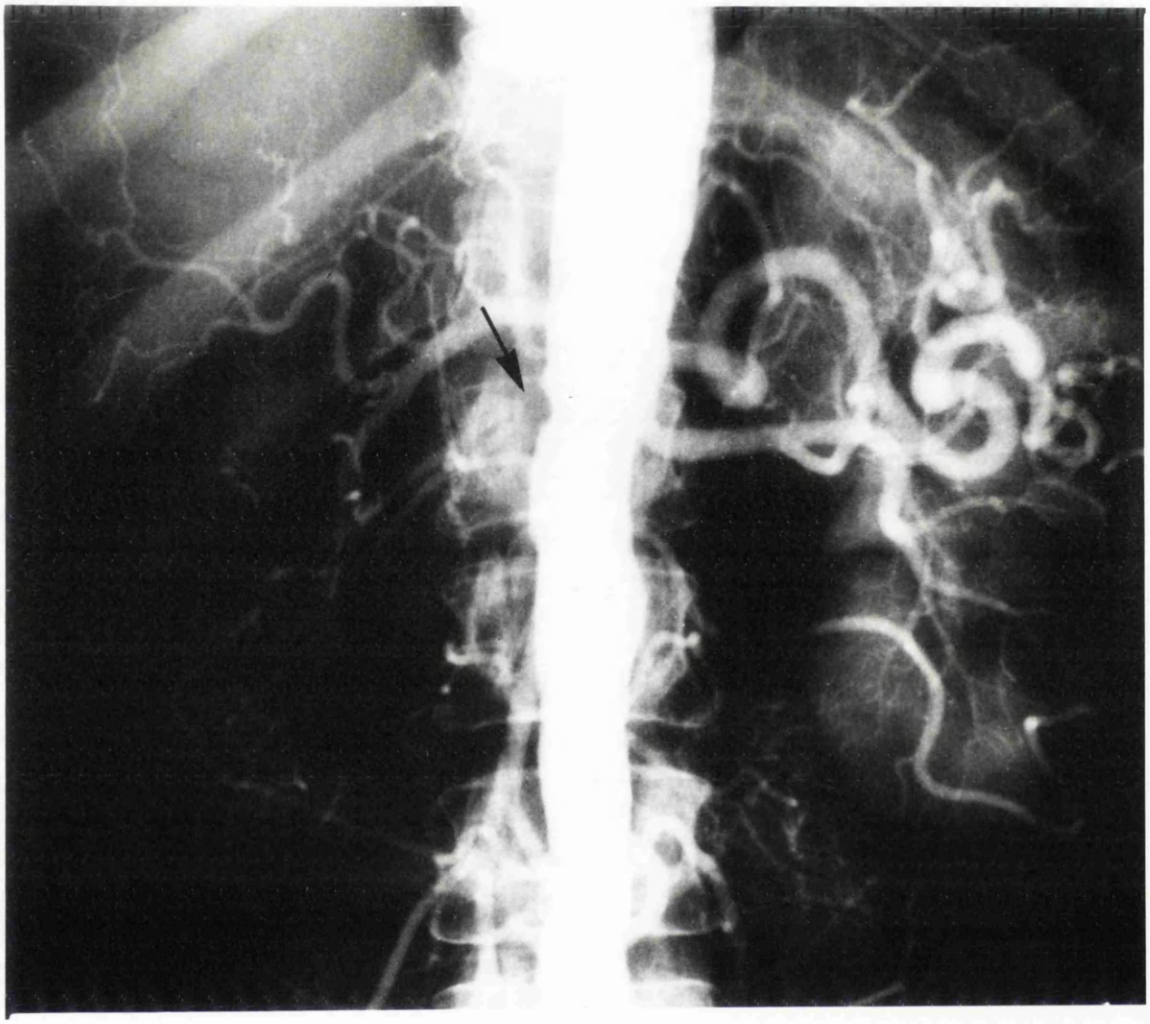


Figure 9: Main stream arteriogram of a 48 year old woman, showing retrograde filling of two right renal arteries which are blocked (arrowed) at their origin from the aorta.

respectively. Thus, there was evidence of excess renin production by the right kidney, a negative venoarterial difference on the left (suggesting a net consumption of renin by that kidney), and a renal vein renin ratio of 1.72 to 1. At bilateral ureteric catheterisation studies no urine was obtained from the right catheter while the left kidney had a creatinine clearance of 68 ml/min and a PAH clearance of 293 ml/min. Thus, while function of the left kidney was good there was strong evidence that occlusion of the right renal arteries was contributing to the patient's hypertension, and that reconstructive surgery or right nephrectomy might alleviate this.

At operation in March, 1977, two small friable occluded right renal arteries were identified and the 76g right kidney excised. The cortical irregularities seen on arteriography were shown by histology to be areas of ischaemic scarring. Generalised focal hyperplasia of the juxtaglomerular cells was noted, as was widespread tubular atrophy and loss with fibrous replacement. Postoperatively, renal function was well preserved, but blood pressure remained high despite treatment (see Fig. 8).

A further admission with a brachial artery occlusion occurred before the patient was re-admitted to the Blood Pressure Unit in May, 1978 with a blood pressure of 260/160 mmHg. On examination she had bilateral

basal crepitations but examination of the optic fundi did not show any haemorrhages, exudates or papilloedema. The day after admission the patient became nauseated and vomited once. During the next 24 hours she passed no urine, despite a fluid intake of 1650 ml and she developed left-sided abdominal tenderness. Serum urea and creatinine were found to be high (20.5 mmol/l, 583 μmol/l respectively). The clinical impression that her remaining renal artery had occluded was quickly confirmed by arteriography and at emergency operation the same evening the kidney, initially dark and mottled, became distinctly redder following the insertion of a 6 mm diameter dacron graft between the side of the renal artery distal to the occlusion and the side of the aorta. Renal biopsy performed during the operation showed changes of acute tubular necrosis superimposed on chronic ischaemic changes. Urine volume remained <600 ml/day during the first 6 days after operation, but increased to 1,040 ml on the 7th day, indicating the onset of the diuretic recovery phase. Haemodialysis was performed on the 6th and 9th postoperative days, before spontaneous improvement of renal function occurred. By the time of her discharge from hospital 3 weeks after admission, her creatinine clearance had risen from 2 ml/min to 16 ml/min. In the immediate postoperative period, the patient's blood pressure was 120/70 mmHg but this rose to 190/104 mmHg

during convalescence and was treated with propranolol.

Seventeen months postoperatively the patient's supine blood pressure was 150/106 mmHg, her drug therapy propranolol (480 mg daily) and hydrallazine (100 mg daily) and her renal function further recovered with a serum urea of 8.3 mmol/l, serum creatinine of 138 μmol/l, creatinine clearance 23 ml/min and PAH clearance of 330 ml/min. She continues to be troubled with angina pectoris and while her hyperlipidaemia is controlled by diet, she still smokes 10 cigarettes per day despite strong advice to the contrary.

3. UNIQUE CASE OF RENAL ARTERY STENOSIS WITH SEVERE HYPERTENSION INCLUDING A DETAILED ASSESSMENT OF THE RENIN-ANGIOTENSIN SYSTEM BEFORE AND AFTER DEVELOPMENT OF A LESION.

Case Report

The patient, a 33 year old labourer, first presented in February 1976 with a subarachnoid haemorrhage caused by a ruptured berry aneurysm of the posterior communicating artery. At craniotomy clipping of the aneurysm was technically impossible. After the operation his blood pressure was 150/106 mmHg. Propranolol (80 mg daily) was introduced as an outpatient and blood pressure control was good, averaging 120/78 mmHg on four visits to his general practitioner.

In February, 1977 the patient was referred to the Blood Pressure Unit for assessment and after one month without treatment was admitted for investigation. Arterial pressure was then 140/102 mmHg (mean of six readings) and his optic fundi were normal. Physical examination did not demonstrate any cause for the increase in blood pressure. He smoked 20 cigarettes a day. There was no family history of hypertension, though his father had died, aged 51, after a myocardial infarction. Investigation (March 1977) in the metabolic ward revealed normal serum electrolytes and peripheral plasma concentration of active renin - 18 μU/ml (N.R. 9-50 μU/ml), angiotensin II - 19 pg/ml (N.R. 5-35 pg/ml) and aldosterone - 11 ng/100 ml (N.R. <18 ng/100 ml). Other normal results were serum urea (4.2 mmol/l) and creatinine (86 μmol/l), creatinine clearance (85 ml/min), fasting lipids, urinary normetadrenaline, electrocardiogram and chest X-ray. Exchangeable sodium and potassium were 91.7% and 99.2% of expected values respectively. An intravenous pyelogram was normal, apart from a suspicion of a small calyceal cyst on the right side. Because of this finding and the patient's age, plasma concentrations of renin and angiotensin II were estimated in blood samples taken from the renal veins and these were normal with no suggestion of a unilateral lesion (Table 3).

TABLE 3.

RENAL VEIN SAMPLING BEFORE AND AFTER DEVELOPMENT OF ACUTE RENAL ARTERY STENOSIS.

ACTIVE RENIN (μU/ml)

	MARCH 1977 Samples				MAY 1978 Samples			
	1	2	3	Mean	1	2	3	Mean
Left renal vein	14	16	16	15.3	344	308	372	341.3
Right renal vein	15	15	17	15.6	535	902	999	812.0
Aorta	15	14	16	15.0	360	347	467	391.3

ANGIOTENSIN II (pg/ml)

	MARCH 1977 Samples				MAY 1978 Samples			
	1	2	3	Mean	1	2	3	Mean
Left renal vein	13	13	14	13.3	39	40	48	42.3
Right renal vein	15	13	18	15.3	52	80	68	66.7
Aorta	14	17	15	15.3	71	88	90	83.3

Active renin levels (normal range 9 to 50 μU/ml) and angiotensin II levels (normal range 5 to 35 pmol/l) on simultaneous sampling from the left renal vein, right renal vein, and aorta. In March 1977 the patient was on no drugs, in May 1978 he was on frusemide, prazosin and hydrallazine.

After discharge from hospital, blood pressure was well controlled by propranolol (80 mg daily): April 1977, 136/84 mmHg; August 1977, 134/86 mmHg; October 1977, 140/88 mmHg; and February 1978, 136/86 mmHg. However, at his next outpatient visit in May 1978, after severe frontal headaches for 3 weeks, he was re-admitted with a blood pressure of 210/144 mmHg and bilateral retinal haemorrhages and exudates, though no papilloedema, were present. Blood pressure was reduced, but not to normal (176/108 mmHg, mean of ten readings) with atenolol (200 mg daily), minoxidil (20 mg daily), and frusemide (80 mg daily).

His intravenous urogram now showed features suggestive of right-sided renal artery stenosis with increased concentration of contrast both before and after a water load. Arteriography confirmed that he had developed a tight 1 cm long stenosis beginning 4 mm from the origin of his right renal artery (Fig. 10). Repeat renal vein samples (Table 3) then showed a distinct excess of renin in plasma from the right renal vein contrasted with the negative venoarterial difference across the left kidney, indicating net extraction of renin by the unaffected contralateral kidney. Angiotensin II levels in renal vein plasma were also consistently higher on the right than on the left. These

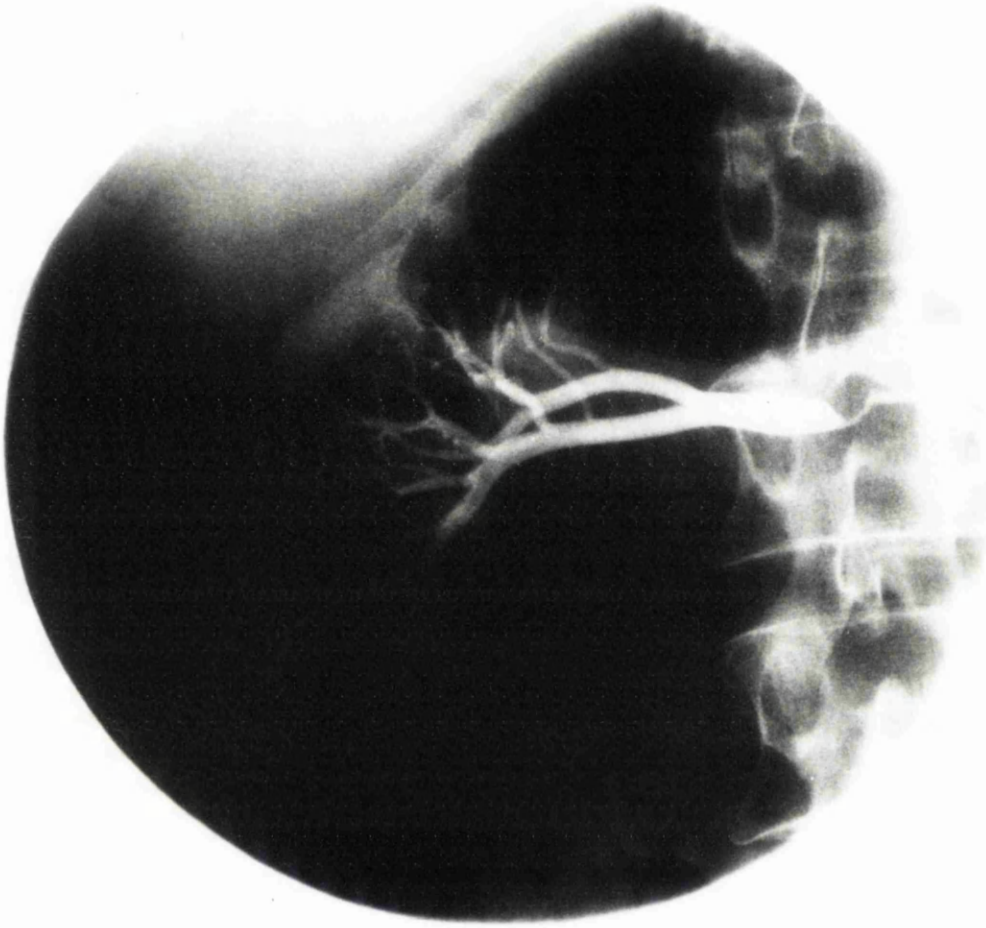


Figure 10: Right selective renal arteriogram of a 33 year old man showing a tight 1 cm long stenosis beginning 4 mm from the origin of the right renal artery.

were, therefore, classical findings of unilateral renal artery stenosis. Bilateral ureteric catheterisation studies also showed changes characteristic of right renal artery stenosis with on the affected side a reduced urine flow rate (2.6 compared with 8.5 ml/min) and an increased urinary creatinine concentration (1.51 compared with 0.85 mmol/l) and PAH concentration (8.42 compared with 4.24 mmol/l) (Brown, Owen, Peart, Robertson, and Sutton, 1960).

In an effort to correct the hypertension, a right aortorenal bypass graft was inserted in June 1978 but the graft thrombosed within 5 days and his blood pressure remained high. The infarcted right kidney was removed one week later. The blood pressure fell by 10 days after nephrectomy to 164/104 mmHg and was controlled easily with atenolol (100 mg daily). Three months after operation, beta-adrenergic blockade was withdrawn and blood pressure therafter remained consistently below 140 mmHg systolic, 90 mmHg diastolic. Six months after the operation, repeat estimations of peripheral plasma concentrations of active renin, (24 μU/ml), angiotensin II (20 pg/ml), and aldosterone (8 ng/100 ml) were all normal in samples obtained in recumbency. Two years later his blood pressure was 130/84 mmHg off treatment.

CHAPTER 6

CLINICAL PRESENTATION

Eighty-six patients with arteriographic evidence of stenosis or occlusion of one or more renal arteries were investigated in the Blood Pressure Unit between 1969 and 1979. All presented as outpatients with diastolic blood pressures (Vth phase) consistently in excess of 100 mmHg. A causal relationship between the stenosis and the hypertension was not a prerequisite for inclusion in this study, since one of its objects was to analyse the processes by which the presence of such a relationship was or was not established. In Figure 11 the management of the 86 patients has been outlined.

Clinical features and test results for individual patients are detailed in Tables 1-4 of the Appendix, and are summarised for groups having no detailed investigation, investigations but no surgery, successful surgery and unsuccessful surgery in Table 4. Aspects of the clinical presentation are described in 6:1 to 6:5 below, and the prognostic relevance of clinical features assessed in 9:1.

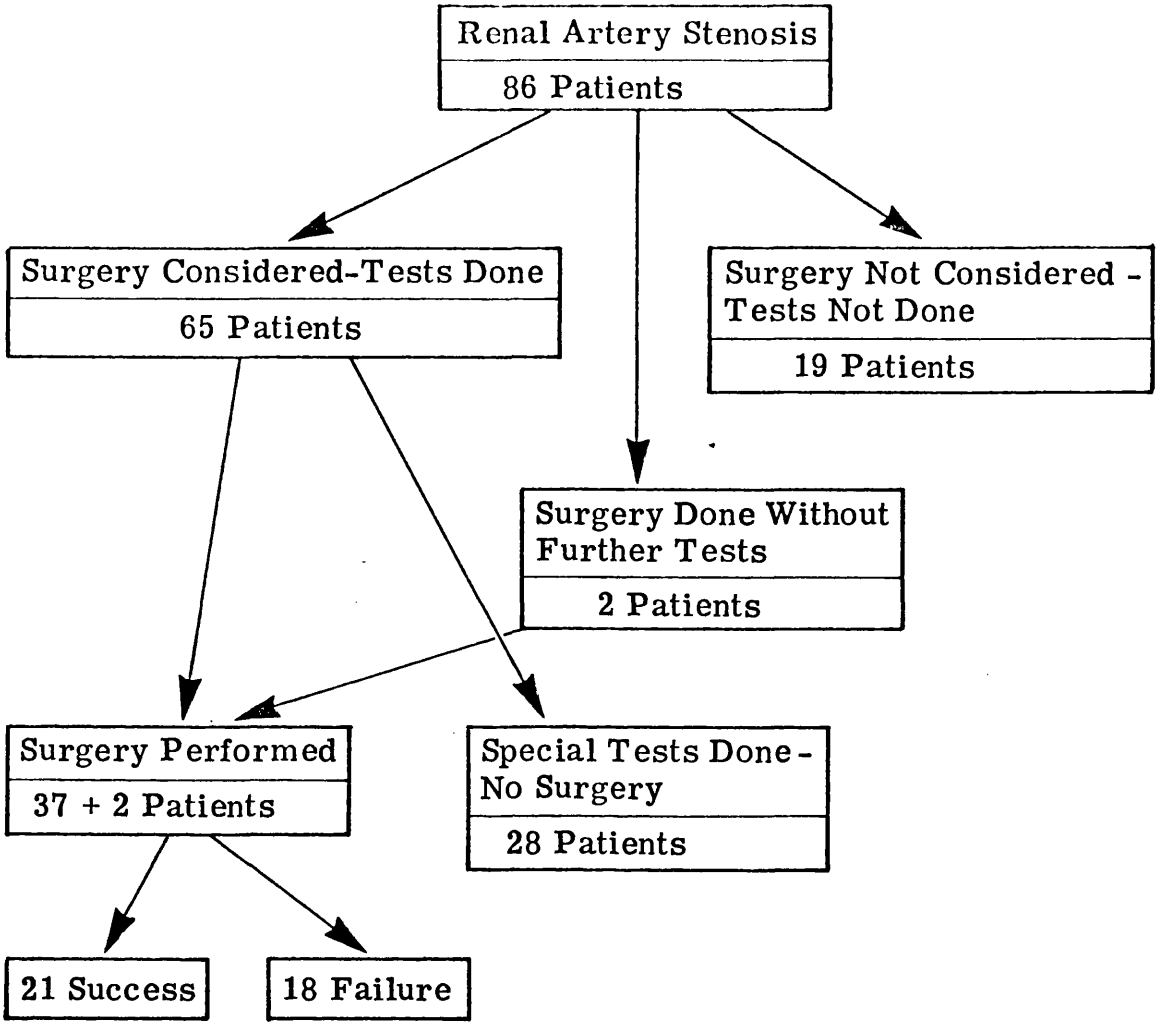


Figure 11: Scheme of the investigation and management of 86 hypertensive patients with arteriographic evidence of renal artery stenosis or occlusion.

TABLE 4. CLINICAL FEATURES AND RESULTS OF TESTS IN 86 PATIENTS WITH RENAL ARTERY STENOSIS

Group of patients	n	Age (years)	Sex M/F	BP at presentation Syst.	Diast.	Benign/ Malig.	Result of medical treatment	Other vasc. disease	Arteriography S/O/B	U/Bil.	Ath/FMH
Surgery not considered Tests not done	19	52±9	7M 12F	216 ±32	119 ±13	13B 6M	10Succ. 9Fail.	12 PVD 6 IHD 5 stroke 5	11S 3O 5B	14U 5B	15 Ath 4 FMH
Surgery performed Tests not done	2	37±16	1M 1F	223 ±52	150 ±14	2B	2Fail	1 PVD 1 IHD 1 stroke 1	1S 1B	1U 1B	1 Ath 1 Phaeo
Tests done. Decision against surgery	18	43±12	7M 11F	209 ±36	129 ±20	14B 4M	12Succ. 6Fail	2 stroke 2	18S	11U 7B	11 Ath 7 FMH
Tests done, decision to operate, but subsequent events precluded surgery	10	42±11	8M 2F	190 ±32	116 ±16	8B 2M	5Succ. 5Succ.	6 PVD 4 IHD 2 stroke 3	8S 2O	10U	9 Ath 1 FMH
Successful surgery	21	37±13	10M 11F	204 ±22	125 ±13	13B 8M	6Succ. 15Fail	4 PVD 2 IHD 2 stroke 2	16S 5O	21U	14 Ath 6 FMH 1 Phaeo
Failed surgery	18	42±12	6M 12F	215 ±37	133 ±23	14B 4M	5S 13F	6 PVD 4 IHD 5 stroke 2	9S 5O 4B	12U 6B	13 Ath 5 FMH

See page 1 of Appendix for key to abbreviations. Values are expressed as mean ± one standard deviation. Arteriography revealed stenosis (S), occlusion (O), or both (B); unilaterally (U) or bilaterally (B).

TABLE 4. Cont'd

Group of patients	Serum urea mmol/l	Renal vein renin ratio	Ureteric catheterisation	Saralasin Δ BP mmHg	Operation	BP 1 year postoperative Syst.	BP 1 year postoperative Diast.	Follow-up (months)	Outcome
Surgery not considered Tests not done	7.0 ± 2.9							42 ±20	13 alive 6 dead MI - 2 Stroke - 2 CCF - 1 Resp.F - 1
Surgery performed Tests not done	13.2 ±10.3							36 ±24	2 alive
Tests done. Decision against surgery	6.5 ± 3.4	1.40 ±0.61	Isch. 13 No isch. 4 Uninterp. 1					44 ±26	17 alive 1 dead ? cause
Tests done, decision to operate, but subsequent events precluded surgery	6.4 ± 2.9	1.68 ±0.48	Isch. 8 No isch. 1 Uninterp. 1					35 ±27	6 alive 4 dead MI - 2 Stroke - 2
Successful surgery	5.1 ± 1.8	1.99 ±1.08	Isch. 20 Not done 1	(n = 5) - 4 + 8 -16 -28 -21	9 Recon. 12 Neph.	132 ± 15	81 ± 9	51 ±36	21 alive
Failed surgery	7.7 ± 5.2	1.41 ±0.33	Isch. 17 Not done 1	(n = 4) - 5 -34 -56 +11	6 Recon. 12 Neph.	172 ± 29	107 ±12	40 ±36	12 alive 6 dead MI - 4 Stroke - 1 Uraemia - 1

6:1 PRESENTING SYMPTOMS.

Presenting symptoms are detailed in Figure 12, but few of these were suggestive in themselves of renal artery disease; indeed, 21% of patients were asymptomatic. Those patients presenting with visual upset, however, were of particular interest; three-quarters had bilateral optic fundal haemorrhages and exudates and half had bilateral papilloedema, consistent with a diagnosis of malignant phase hypertension. One of these patients also had epileptic seizures associated with hypertensive encephalopathy. Three patients presented with loin pain and haematuria: each subsequently proved to have occluded a renal artery, with infarction of the kidney. A further 7 patients presented with loin pain alone, and of these 3 were shown to have occluded renal arteries. Those 3 patients who presented with polyuria and polydipsia and proved to be suffering from the hyponatraemic hypertensive syndrome are considered in detail in 7:2.

Eight patients (4 men, 4 women) complained of recurrent central chest pain at the time of presentation, consistent with a diagnosis of angina pectoris. These 4 women formed part of a larger study of ischaemic heart disease in young hypertensive women, a brief description of which follows in 6:2.

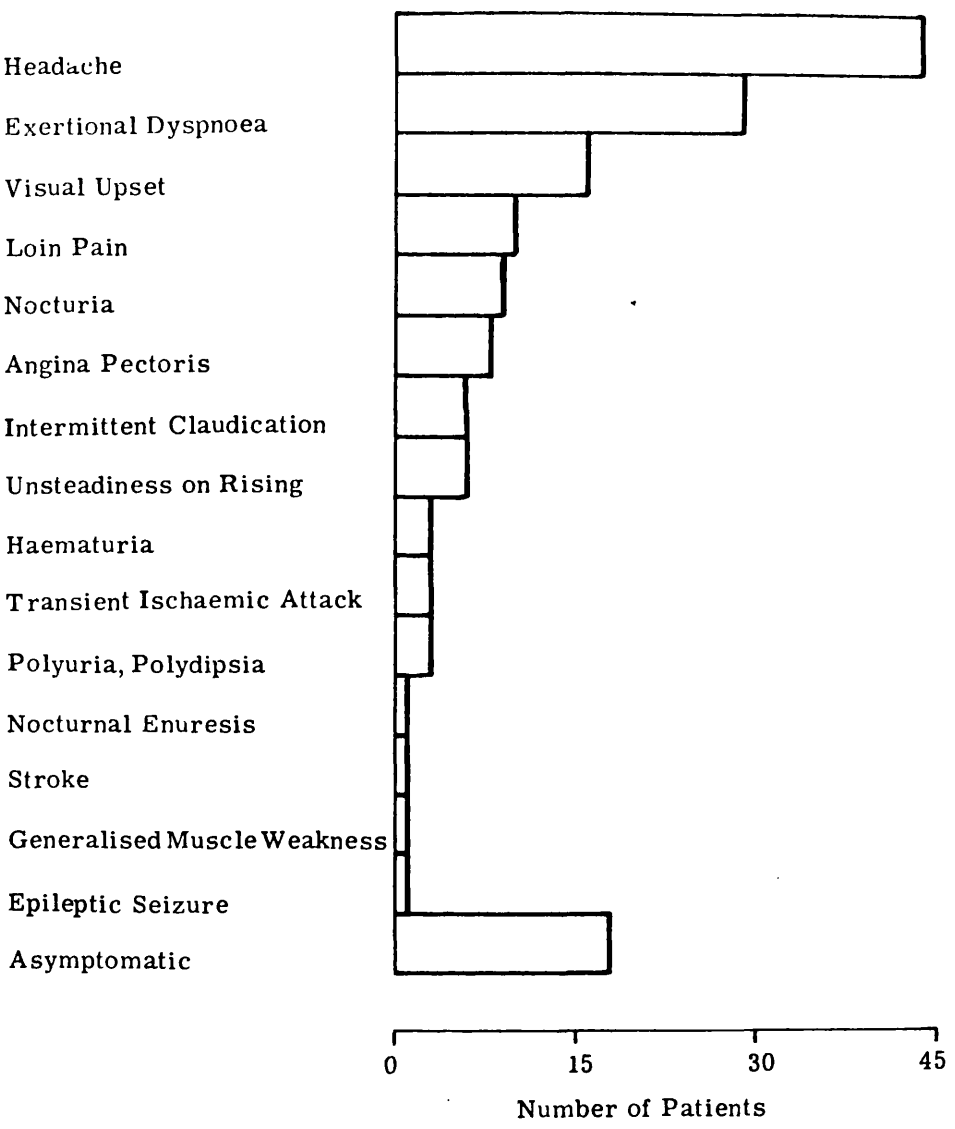


Figure 12: Presenting symptoms of 86 patients with renal artery stenosis.

6:2 ISCHAEMIC HEART DISEASE IN YOUNG HYPERTENSIVE WOMEN.

In a study of 50 premenopausal women under 45 years of age who presented to the Blood Pressure Unit over a 7 year period with outpatient diastolic pressure recordings of 120 mmHg or more (Mackay, Cumming, Brown, Lever, and Robertson, 1980), 23 (46%) had renal artery stenosis. Of these 11 had the arteriographic appearances of fibromuscular hyperplasia while atheroma was the apparent cause of the stenosis in 12. Four of these women with renal artery stenosis had a history of angina pectoris as defined by Rose (1962) while 11 of the whole group had angina pectoris. The 4 women with renal artery stenosis and angina pectoris had electrocardiographic changes consistent with ischaemia (ST depression $\geq$ 1 mm, Minnesota Code 4,1 (Blackburn, Keys, Simonson, Rautahargju, and Punsar, 1960)), as did a further 5 without angina pectoris. Additional risk factors were common in these women, particularly a history of cigarette smoking.

6:3 REASON(S) FOR REFERRAL.

Patients in this study were referred for further investigation and management from as far afield as Inverness and Swansea. The commonest reason for referral (Fig.13) was evidence of unilateral ischaemia on intravenous urography (48%). The eventual diagnosis was

REASON FOR REFERRAL

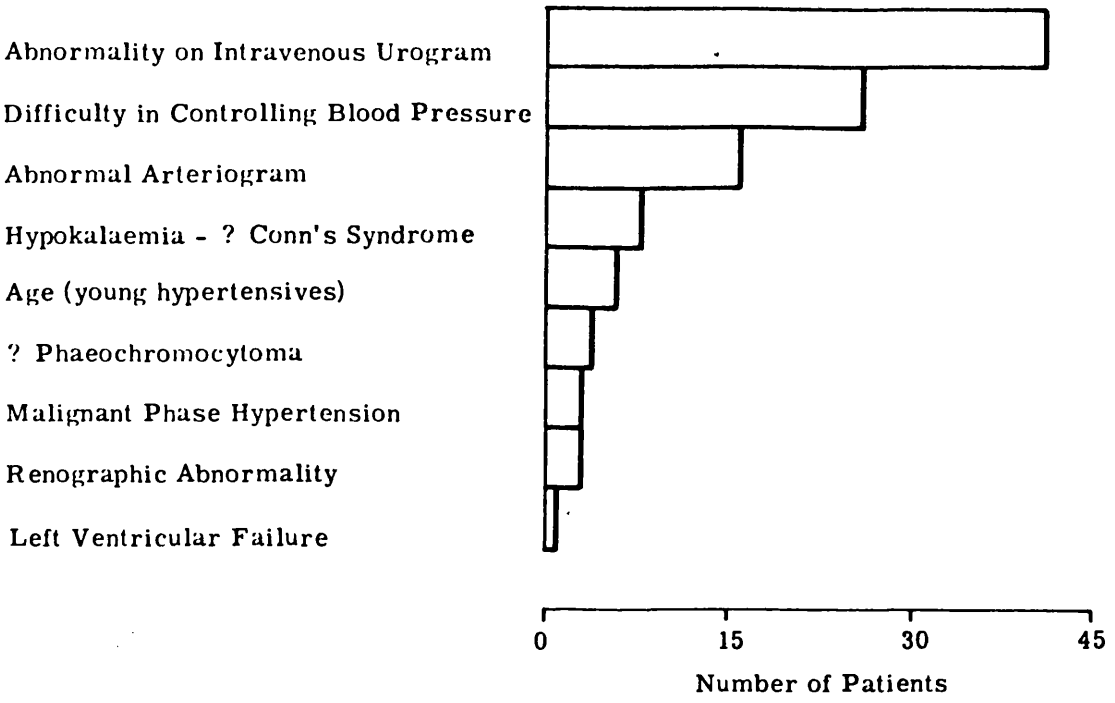


Figure 13: Reason(s) for referral for inpatient investigation in 86 patients in whom arteriography showed renal artery stenosis or occlusion.

not suspected at the time of referral in 41% of patients while a wrong diagnosis was suspected in 13%, the majority of whom had hypokalaemia resulting from secondary hyperaldosteronism, though primary hyperaldosteronism was suspected initially.

6:4 PAST MEDICAL HISTORY.

A history of previous and/or continuing vascular disease was obtained in 35% of patients overall. As can be seen in Table 4, this comprised strokes in 16% of patients, ischaemic heart disease in 16% and peripheral vascular disease in 19%. Eleven patients had more than one form of vascular disease. Most vascular disease occurred in the older patients, as is evident in group 1 of Table 4, but younger patients were not free from serious vascular ailments (e.g. patient 48, Appendix, Table 2B).

6:5 PHYSICAL EXAMINATION.

As detailed in Table 4 the mean blood pressure of the whole group at presentation was 208 mmHg systolic, 125 mmHg diastolic. Overall 22 patients (26%) had the optic fundal changes of malignant phase hypertension, while in the remainder no haemorrhages, exudates or papilloedema were visualised.

An abdominal or loin bruit was heard in 21 patients overall (24%): this comprised 8 patients with fibromuscular hyperplasia (35%) and 13 who appeared to have

an atheromatous stenosis (29%). An abdominal bruit with no lateralisation was heard in one patient with an occluded artery in whom the source of the bruit was assumed to be an atheromatous aorta.

CHAPTER 7

PATHOGENESIS

7:1 RELATIONSHIP BETWEEN SODIUM AND ARTERIAL PRESSURE IN RENAL ARTERY STENOSIS

In this section the relationships between total exchangeable sodium (Na_E), plasma sodium concentration and urinary sodium excretion, and arterial pressure in patients with renal artery stenosis are examined. Seven patients with the hyponatraemic hypertensive syndrome are presented in detail.

Patients and Methods.

Thirty-five patients with renal artery stenosis had measurements of plasma sodium concentration and Na_E carried out in the manner described above (4:2). All medication had been withdrawn one month previously, or patients had been maintained on bethanidine alone, this being withdrawn 24 hours before the tests. No diuretic had been administered within one month of the measurements. Twenty-five patients had unilateral stenosis with normal overall renal function, while 10 who have been analysed separately (Table 5) had either bilateral stenoses or impaired renal function (serum urea $\geq$ 7.1 mmol/l) or both.

For the purposes of comparison equivalent data from 21 untreated patients with an adrenal adenoma (subsequently confirmed by surgery), 32 patients with chronic

TABLE 5. EXCHANGEABLE SODIUM AND BLOOD PRESSURE

Diagnosis	Sex M	Sex F	Age (yrs)	Blood Pressure Syst.	Blood Pressure Diast.	Blood Pressure Mean	NaE (%)	Correlation (r) NaE : BP Syst.	Correlation (r) NaE : BP Mean
Renal artery stenosis.									
Unilateral (urea <7.1 mmol/l)	11	14	41.7	192.2	117.5	142.1	96.3	-0.54**	-0.62***
Bilateral and/or urea ≥7.1 mmol/l	5	5	50.0	221.7	126.4	158.5	101.4	-0.17	-0.15
All	16	19	44.2	200.6	120.1	146.8	97.7	-0.26	-0.34**
Conn's syndrome untreated	7	14	42.6	182.4	112.3	135.6	115.6	+0.62***	+0.56**
Chronic renal failure	16	16	35.2	151.0	89.0	111.0	103.0	+0.57***	+0.45**
Essential hypertension	33	20	45.0	169.7	106.1	127.4	99.9	+0.37**	+0.28*
Normals	12	4	43.8	123.6	74.9	90.9	98.6	+0.148	+0.11

Relationship between total exchangeable sodium (NaE) and blood pressure in renal artery stenosis and other forms of hypertension. M = male. F = female.
Significance of correlation coefficients: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

renal failure (serum urea consistently >7.1 mmol/l) and 53 patients with essential hypertension have been detailed in Table 5. Results from a control group comprising 6 strictly normal individuals and 10 patients with uncomplicated peptic ulcer have also been included.

Plasma angiotensin II concentrations measured on the day of Na_E measurements have been studied in the group with unilateral renal artery stenosis; in patients with the hyponatraemic hypertensive syndrome, plasma renin and aldosterone concentrations measured at the same time have also been examined.

Urinary sodium excretion measurements from the abnormal and untouched kidneys were available in 37 patients with unilateral renal artery stenosis in whom bilateral ureteric catheterisation studies had been performed more than 4 weeks after withdrawal of diuretic therapy. Twenty-one of these patients were taking no drugs, 12 were receiving bethanidine only and 4 were receiving hypotensive agents (propranolol, labetalol, clonidine or debrisoquine).

Results.

1. Exchangeable sodium(Na_E). The relationship between Na_E and mean arterial pressure in patients with unilateral renal artery stenosis and normal overall renal function was negative and significant ($r = -0.62$, $p < 0.001$), as depicted in Figure 14. From Table 5 it may be seen that in patients with bilateral stenoses or unilateral

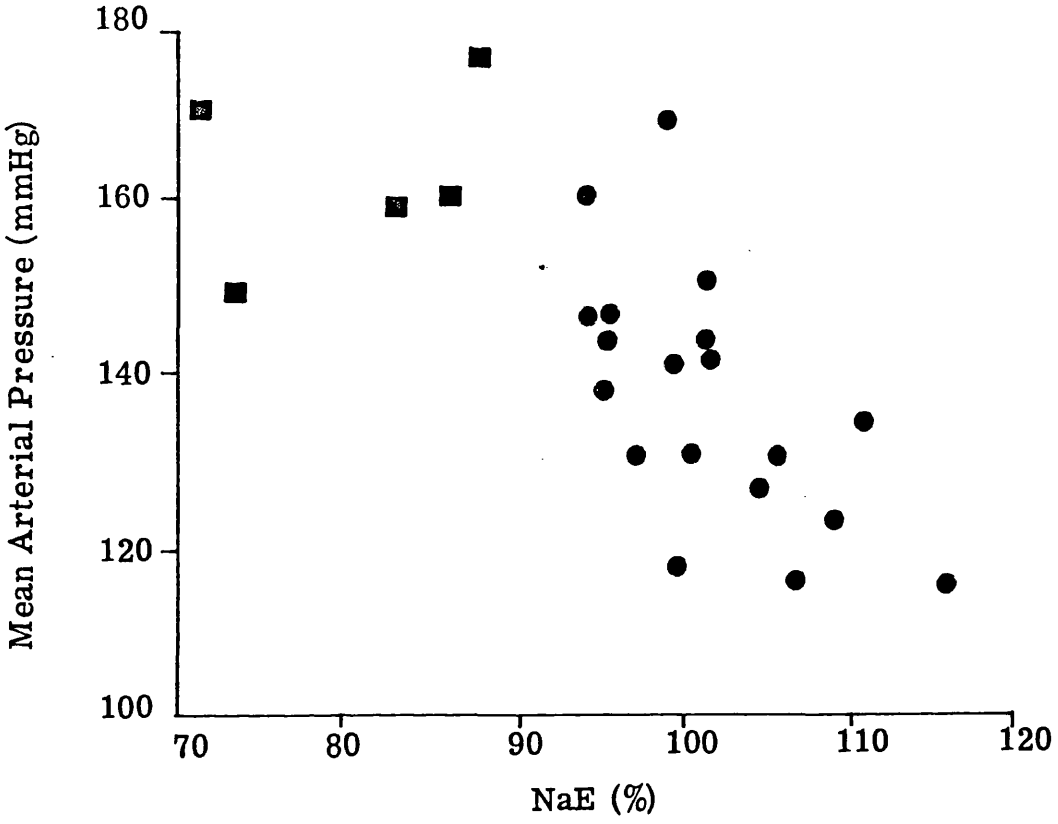


Figure 14: Relation of exchangeable sodium (Na_E(%)) and mean arterial pressure in patients with unilateral renal artery stenosis, all having a serum urea concentration less than 7.1 mmol/l. The 5 patients indicated by the solid squares have evidence of the hyponatraemic hypertensive syndrome (7:1,4).

stenosis with overall impairment of renal function. There was no significant correlation of Na_E and blood pressure. However, a significant though weaker relationship still held between Na_E and mean arterial pressure for all patients irrespective of their level of renal function.

The negative relation between Na_E and blood pressure in unilateral renal artery stenosis may be contrasted (Table 5) with the significant positive relations in untreated Conn's syndrome, chronic renal failure, and essential hypertension, and the lack of a significant relationship in normal controls.

In the 25 patients with unilateral renal artery stenosis a significant negative relationship was also established between log plasma angiotensin II concentration and Na_E measured on the same day ($r = -0.57$, $p < 0.01$). Log plasma angiotensin II concentration in turn correlated positively and significantly with mean arterial pressure ($r = +0.46$, $p = 0.05$).

2. Plasma sodium concentration and mean arterial pressure in patients with unilateral renal artery stenosis and normal overall renal function were related ($r = -0.48$, $p < 0.02$) - Figure 15. Plasma sodium concentration and Na_E measured on the same day correlated closely ($r = 0.77$, $p < 0.001$). A significant negative relation was observed between log plasma angiotensin II concentration and plasma sodium concentration on the same day ($r = -0.72$, $p < 0.001$).

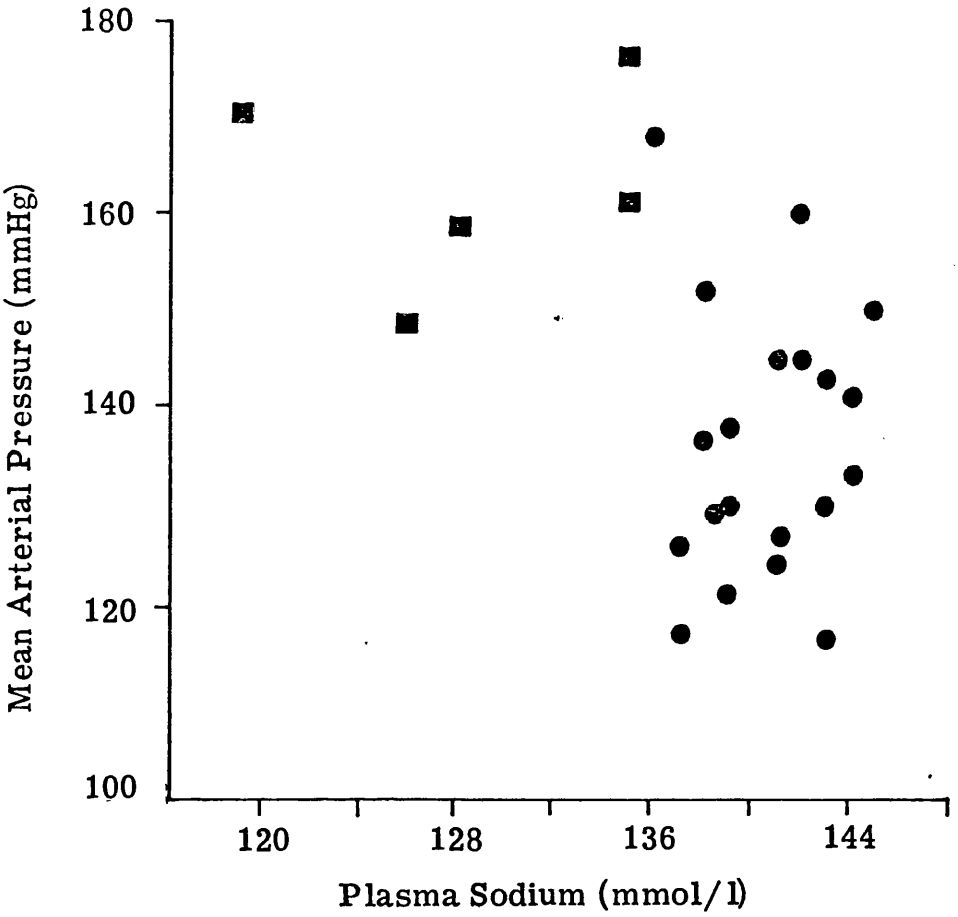


Figure 15: Relation of plasma sodium concentration (mmol/l) and mean arterial pressure in patients with unilateral renal artery stenosis and normal renal function. The 5 patients indicated by solid squares have a plasma sodium of 135 mmol/l or less, and have other evidence of the hyponatraemic hypertensive syndrome (7:1,4).

3. Urinary sodium excretion ($U_{Na}V$). In 36 of the 37 patients with unilateral renal artery stenosis in whom data were available, urinary sodium excretion ($U_{Na}V$ μmol/min) was lower in the abnormal than in the opposite "untouched" kidney and in one the values were the same on both sides. Mean arterial pressure during ureteric catheterisation correlated positively and significantly with sodium excretion from the untouched kidney but not from the abnormal kidney (Table 6 - Fig. 16). Treatment with hypotensive drugs did not appear to influence these findings (Table 6).

This relationship between sodium excretion and arterial pressure is examined further in patients with unilateral renal artery stenosis coming to surgery in a further section on prognostic tests (9:6).

Urinary sodium excretion from the untouched kidney in all patients with unilateral renal artery stenosis irrespective of therapy at the time of ureteric catheterisation correlated weakly but positively with plasma angiotensin II concentration measured on a separate occasion (within 4 weeks) off treatment ($r = +0.38$, $p < 0.05$).

4. The hyponatraemic hypertensive syndrome. Among the patients with unilateral renal artery stenosis and normal renal function were 5 with a plasma sodium concentration of 135 mmol/l or less at the time of measurement of Na_E (represented by solid squares in Figs. 14 and 15). To

TABLE 6. URINARY SODIUM IN RENAL ARTERY STENOSIS

Patients	n	$U_{Na}V$ (μmol/min)		Mean blood pressure/log $U_{Na}V$	
		Abnormal kidney	Untouched kidney	Abnormal kidney	Untouched kidney
Untreated	21	212	600	-0.13	+0.49*
Untreated and bethanidine-treated	33	191	665	-0.06	+0.48**
Untreated and treated with various hypotensive drugs.	37	186	673	+0.01	+0.51**

Sodium excretion from abnormal and untouched kidneys in patients with unilateral renal artery stenosis. Measurements were made during bilateral ureteric catheterisation. Drugs taken by patients in the third group were bethanidine, clonidine, labetalol, propranolol or debrisoquine. Significance of correlation coefficient: * $p < 0.05$; ** $p < 0.01$

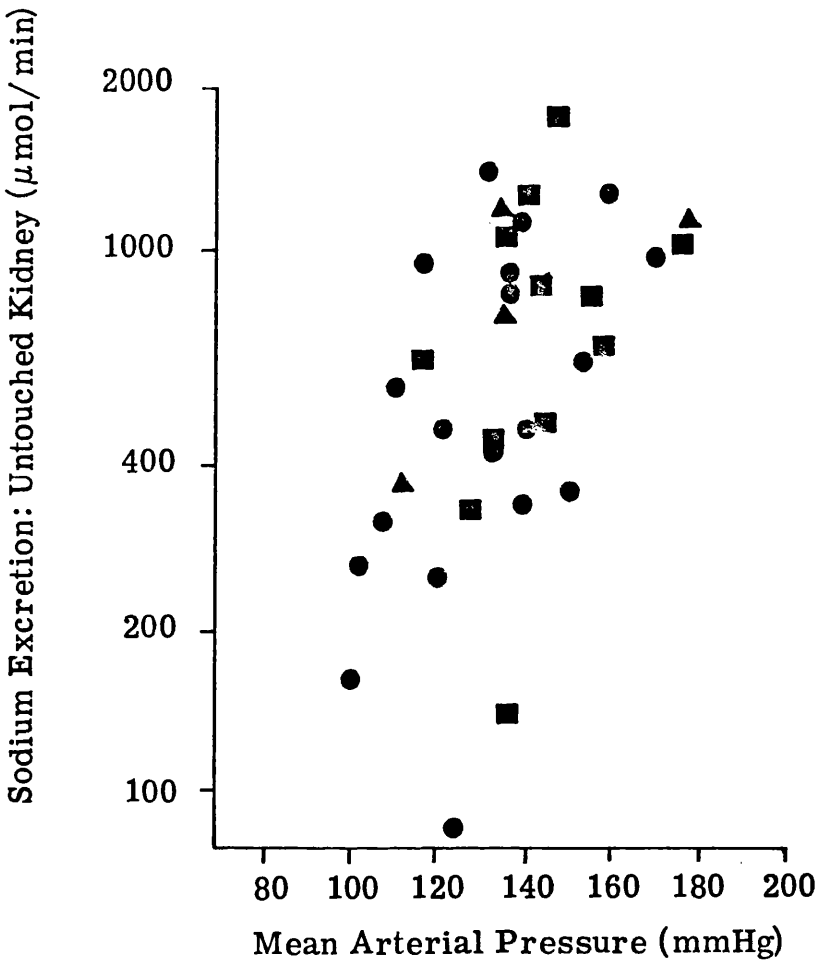


Figure 16: Relation of urinary sodium excretion from the untouched kidney and mean arterial pressure in patients with unilateral renal artery stenosis. Solid circles - untreated patients. Solid squares - patients receiving bethanidine. Solid triangles - patients receiving other hypotensive drugs.

TABLE 7. HYPONATRAEMIC HYPERTENSIVE SYNDROME

ient o.	Age	Sex	R_X	Diagnosis	Malignant Phase	Mean Arterial Pressure (mm Hg)	Plasma Sodium (mmol/l)	Plasma Potassium (mmol/l)	Na_E(%)	Total P.R.C. (μU/ml)	$P_{AII}C$ (pg/ml)	$P_{Aldo}C$ (ng/100 ml)	Symptoms
1	20	M	Nil	Occlusion	Yes	170	113	2.1	71	>1,000	-	-	Polyuria,polydips weight loss.
2	52	F	Nil	Occlusion	Yes	148	126	2.8	73	303	86	21	Polyuria,polydips weight loss.
3	68	F	Nil	Occlusion	No	159	128	2.4	83	294	461	-	Polyuria.
4	23	F	Beth.	Stenosis	No	176	135	3.6	89	84	31	12	Asymptomatic.
5	44	F	Nil	Occlusion	No	161	135	4.0	86	342	122	20	Loin pain,dysuria
6	46	F	Nil	Occlusion	Yes	198	129	2.9	85	585	171	18	Polyuria,polydips weight loss.
7	40	F	Nil	Stenosis	Yes	152	134	2.8	88	660	-	79	Polyuria,polydips salt craving.
n SD	42±17	6F 1M		5 Occl. 2 Sten.	4 MPH	166±17	128.6±7.7	2.9±0.7	82.1±7.2	467 ±304	174±168 (n=5)	30±28 (n=5)	

Clinical features and test results of 7 patients with renal artery stenosis or occlusion presenting with a plasma sodium concentration of 135 mmol/l or less

M=male; F=female; Beth.=bethanidine; PRC, P_{AII}, and $P_{Aldo}C$ = plasma renin, angiotensin II and aldosterone concentration respectively. Normal ranges are 200<μU/ml, 5.35 pg/ml. <18 ng/100 ml.

these two other similar patients outwith the major study of 86 patients, who also were investigated in the Blood Pressure Unit have been added. Clinical details and biochemical test results are presented in Table 7. The patients had either an occluded or tightly stenosed renal artery on one side with a normal contralateral kidney and normal overall renal function. Presenting blood pressures were very high, and 4 patients had malignant phase hypertension, one with hypertensive encephalopathy. Accompanying low exchangeable and plasma sodium levels was hormonal evidence of secondary hyperaldosteronism and consequent hypokalaemia. The most clamant cases were characterised by polyuria, polydipsia, weight loss and in one instance, by salt craving.

7:2 SMOKING IN RENAL ARTERY STENOSIS.

The smoking habits of 85 of the patients in Table 4 were analysed. The remaining patient, a 68 year old woman, was a cigarette smoker who presented after completion of this analysis and before closure of the series. Her initial blood pressure was 230/120 mmHg: she was found to have a left renal artery occlusion but did not have malignant phase hypertension.

Since excessive cigarette smoking is known to be associated with malignant-phase hypertension (Isles, Brown, Cumming, Lever, McAreavey, Robertson, Hawthorne, Stewart, Robertson, and Wapshaw, 1979; Bloxham, Beevers, and Walker, 1979), those 22 patients who presented with bilateral optic fundal haemorrhages and exudates with (18 patients) or without (4 patients) papilloedema, and whose mean (± 1 S.D.) diastolic blood pressure at presentation was 142 ± 14 mmHg have been analysed separately. The mean blood pressure at presentation of 63 patients without malignant phase hypertension was 119 ± 14 mmHg.

Data on smoking habits were extracted from case records retrospectively. A smoker was defined as a person who habitually smoked cigarettes or cigars within two months of presentation, which was taken as the date of first admission to the wards. Ex-smokers were classified as non-smokers. There were no pipe smokers in this study.

Control Group A. The 63 patients with non-malignant hypertension and renal artery stenosis were matched for age (± 1 year) and sex with 63 patients with non-malignant hypertension randomly drawn from a group of 893 patients attending the Glasgow Blood Pressure Clinic (The Glasgow Blood Pressure Clinic, 1972). The mean diastolic blood pressure of the controls was 122 ± 16 mmHg. The smoking habits of these controls have been examined.

Control Group B. Comparison of smoking habits was also made in a control group of hypertensive inpatients. Each of the 63 patients with non-malignant hypertension and renal artery stenosis was matched for age (± 3 years) and sex with a patient with non-malignant hypertension and no urographic evidence of a renal lesion. The mean diastolic blood pressure of these controls was 120 ± 14 mmHg.

Results

Smoking was nearly twice as common in patients with renal artery stenosis and non-malignant hypertension as in each control group. The differences were apparent and significant for males and females separately and together (Table 8). In both control groups the prevalence of smoking was similar to that found in a population sample in the Glasgow area (52% for men and women, all forms of smoking, 56% for male cigarette smokers, 64% for males smoking all forms of tobacco, 42% for females smoking all forms of tobacco (Isles et al, 1979) - data were derived from a local epidemiological study described by Hawthorne (1977)). Compared with the controls smoking was also more common in patients with renal artery occlusion, with fibromuscular hyperplasia and with renal artery stenosis due to atheroma when each of the latter groups was considered separately. The association with smoking was most marked in patients with occlusion of a renal artery who all were smokers, and least strong in patients with fibromuscular hyperplasia of whom 72% were smokers.

TABLE 8. SMOKING HABITS IN PATIENTS WITH NON-MALIGNANT HYPERTENSION AND RENAL ARTERY STENOSIS AND IN TWO CONTROL GROUPS.

	Renal artery stenosis		Control Group A			Control Group B		
	No.	%	No.	%	X^2	No.	%	X^2
All patients (n = 63)					***			***
Smokers	53	84	28	44	21.60	29	46	20.11
Non-smokers	10	16	33	56		34	54	
Males (n = 27)					**			**
Smokers	24	89	14	52	8.88	13	48	10.39
Non-smokers	3	11	13	48		14	52	
Females (n = 36)					***			**
Smokers	29	81	14	39	12.99	16	44	10.01
Non-smokers	7	10	22	61		20	56	
Fibromuscular hyperplasia (n = 18)					*			NS
Smokers	13	72	7	39	4.05	8	44	2.86
Non-smokers	5	28	11	61		10	56	
Renal artery occlusion (n = 13)					**			***
Smokers	13	100	6	46	9.58	5	38	11.56
Non-smokers	0	0	7	54		8	62	
Atheromatous stenoses (n = 32)					**			**
Smokers	27	84	15	47	9.97	16	50	8.58
Non-smokers	5	16	17	53		16	50	

Asterisks indicate the significance of the differences comparing renal artery stenosis with the appropriate control groups. Both control groups comprised patients with non-malignant hypertension not associated with renal artery disease.

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ NS $p > 0.05$

The 22 patients with renal artery stenosis who presented in malignant phase hypertension were considered separately. Twenty (91%) of these smoked, a mean of 21.2 cigarettes per day, compared with 15.4 cigarettes per day for the 52 patients who did not have malignant hypertension but smoked ($t = 2.16$, $p < 0.05$).

7:3 PATHOGENETIC FACTORS IN FIBROMUSCULAR HYPERPLASIA.

Twenty-three patients in this study had a diagnosis of fibromuscular hyperplasia, based on the arteriographic appearances with histological confirmation in six instances. The following features may be of pathogenetic significance.

1. Sex. Twenty-one of the affected patients (91%) were women and only two (9%) were men.

2. Age. The mean age of women with fibromuscular hyperplasia was 38 years (range 10-62 years) while the mean age of women with atheromatous lesions was 45 years (range 19 to 68 years). This difference was statistically significant ($t = 2.24$, $p < 0.05$).

3. Smoking. See Chapter 7:2.

4. Hypertension during pregnancy. Two women with a past history of pre-eclamptic toxaemia subsequently were diagnosed as having fibromuscular hyperplasia, while 4 women with previous toxaemia subsequently developed atheromatous lesions. Similarly, 3 women who subsequently

developed fibromuscular hyperplasia and 4 who subsequently developed atheromatous lesions suffered from hypertension during pregnancy short of toxaemia.

5. Relation to pregnancy. Eighteen (86%) of the women with fibromuscular hyperplasia had been pregnant a mean of 8.9 years previously (range 6 months to 21 years); of the other 3, one was infertile, one was aged 10 years at presentation, and one had a pregnancy after successful surgical management of her condition. Of the women with atheromatous disease 23 (88%) had been pregnant a mean of 12.7 years previously (range 1 year to 34 years).

6. Height. The mean height of the women with fibromuscular hyperplasia was 157 $\pm$ 10 cm, while that of women with other forms of renal artery disease was 160 $\pm$ 6 cm. This difference was small and not statistically different.

7. Lateralisation. Twelve women had fibromuscular hyperplasia of the right renal artery only (52%) while 5 (22%) had the left renal artery only affected and 6 women (26%) had bilateral changes, worse on the right in three instances.

The possible significance of these features is discussed in Chapter 12:1, 4.

CHAPTER 8

DIAGNOSTIC TESTS

8:1 RENAL ARTERIOGRAPHY

On the basis of the arteriographic appearances described in Chapter 2:7,3, 27% of patients were diagnosed as having probable fibromuscular hyperplasia; this diagnosis was confirmed in 6 patients in whom a portion of arterial wall was subsequently examined histologically. The remaining patients (Table 9-I) had either an occluded vessel or the appearances of atheromatous narrowing of the renal artery except for one patient in whom a phaeochromocytoma was found to be pressing on the renal artery. A detailed breakdown of the main-stem and segmental vessel involvement, of collateral circulation and post-stenotic dilatation is presented in Table 9-II. In 17 of 19 patients with occluded arteries a collateral circulation was present, suggesting a gradual progression from stenosis to complete obstruction. In Figure 17 the left selective arteriogram of a patient who had almost occluded his main renal artery demonstrates the contribution which collateral vessels may make.

In general renal arteriography was a very safe procedure. In 14 patients a groin haematoma was recorded in the case records, but all resolved spontaneously. No other morbidity or mortality was recorded.

TABLE 9. RESULTS OF ARTERIOGRAPHY

I. a) Diagnoses based on arteriographic appearances	No. of patients	
Fibromuscular hyperplasia	23	(27%)
Occlusion	19	(22%)
Atheromatous stenosis	43	(50%)
Phaeochromocytoma	1	(1%)
Total:	86	

II. b) Arteriographic abnormalities	Stenosis		Occlusion	
	ATH	FMH	ATH	FMH
Single artery involved	33	16	14	1
More than one artery involved	11	6	5	0
Main stem artery	42	21	18	1
Segmental vessel	5	5	1	0
Collaterals	5	6	16	1
Post-stenotic dilatation	25	6	3*	0
Bilateral disease	6	6	5**	0

* Retrograde flow

** Stenosis opposite side.

ATH Atheromatous stenosis

FMH Stenosis caused by fibromuscular hyperplasia

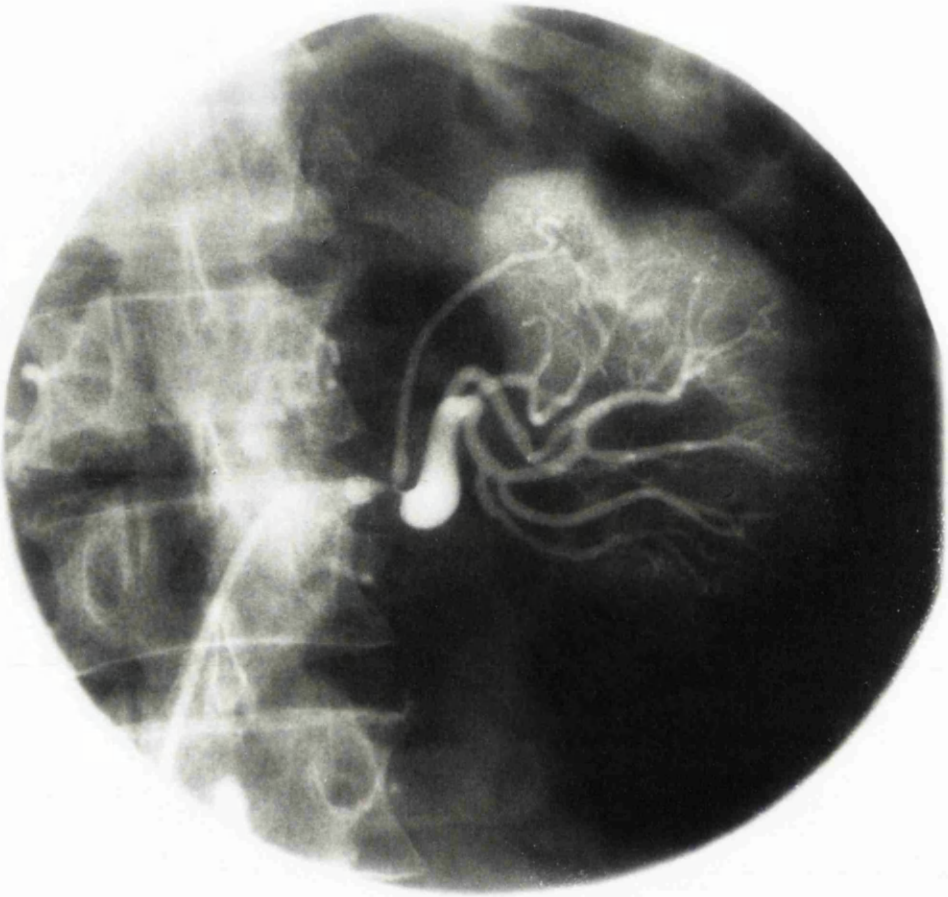


Figure 17: Left selective renal arteriogram showing tight stenosis at the junction of the proximal and middle thirds of the renal artery with post-stenotic dilatation and a large collateral vessel to the upper pole of the kidney.

8:2 BILATERAL URETERIC CATHETERISATION STUDIES

Sixty-three successful studies were performed including 10 in whom a small leak of urine past the ureteric catheters occurred, but could be localised to one side. In two further studies, because of bilateral by-passing of the ureteral catheters, interpretation of the data was not possible. In 56 patients the pattern of ischaemia described above (2:7,4) with decreased urine volume and increased urinary creatinine and PAH concentration on the affected side was found. In 7 patients no such pattern was found. The value of this pattern of abnormality in diagnosing ischaemia is apparent in Figure 18 - see Chapter 8:3 - where the changes in urine volume and solute concentration are compared in patients with unilateral renal artery stenosis or occlusion and in patients with unilateral kidney disease of non-ischaemic aetiology. In the latter group, urinary creatinine and PAH concentration was uniformly less on the affected side than on the unaffected.

The data obtained from ureteric catheter studies are examined in greater detail in studies of intravenous urography (8:3) and isotope renography (8:5).

Morbidity associated with ureteric catheter studies is described in Table 10. No single instance of urinary tract infection was recorded after the studies. All events in Table 10 were transient and required symptomatic treatment only.

TABLE 10. MORBIDITY OF BILATERAL URETERIC CATHETERISATION STUDIES

65 studies in patients with renal artery stenosis

No urinary tract infection

Transient abdominal/loin pain	10 patients
Meningism	5 patients
Vasovagal attack at lumbar puncture	2 patients
Hysterical paraplegia	1 patient

8:3 INTRAVENOUS UROGRAPHY: CORRELATION OF RADIOGRAPHIC FINDINGS WITH THE RESULTS OF BILATERAL URETERIC CATHETERISATION WITH A TEST OF OBSERVER VARIATION.

In this section answers are proposed to two main questions. First, how readily and reliably can the urographic abnormalities of renal artery stenosis be observed? Second, how well do the observations on the intravenous urogram relate to changes in function of the affected kidney?

Patients and Methods.

Thirty-seven hypertensive patients were studied: 17 were men with ages ranging from 16 to 58 years and 20 were women with ages ranging from 18 to 62 years. All had intravenous urography with initial minute sequence films in 29 and further films after an oral water load of 1,000 ml in 18. All had renal arteriography, bilateral ureteric catheterisation studies and renal vein sampling with measurement of plasma active renin concentration in samples obtained simultaneously from both renal veins.

Arteriography showed unilateral renal artery stenosis in 18 patients, unilateral renal artery occlusion in 7, and bilateral renal artery stenoses in 5. In every case of renal artery stenosis ureteric catheterisation showed reduced urine flow rate and increased urinary concentration of creatinine and para-aminohippurate (PAH) on the affected side in unilateral disease (Figure 18a), and on the more seriously affected side in bilateral

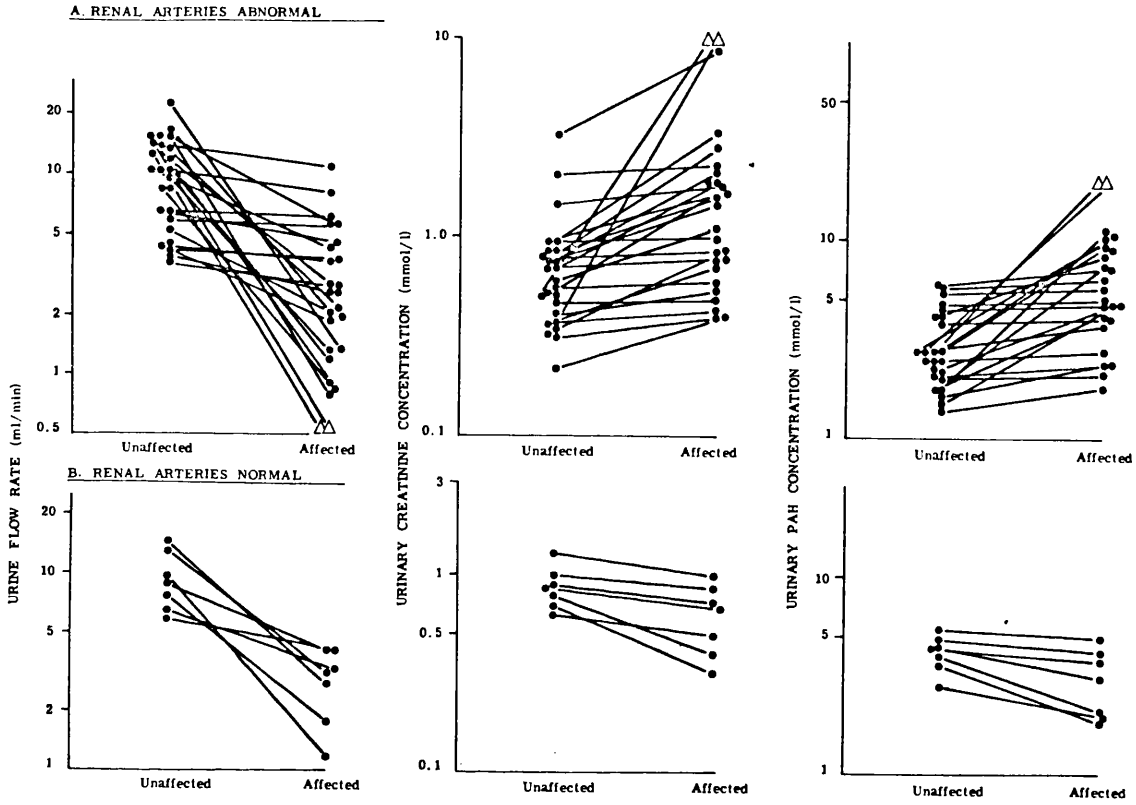


Figure 18: Results of bilateral ureteric catheterisation studies in patients

A) with unilateral renal artery stenosis or occlusion and

B) with normal renal vessels. Open triangles represent assigned values for patients with no urine flow on the affected side.

disease. The remaining 7 patients were included for comparison and had unilateral small kidneys: arteriography showed no evidence of renal artery stenosis, and ureteric catheter studies revealed decreased urine solute concentration as well as lower urine flow rate on the affected side (Figure 18b). Final diagnoses in these patients were chronic pyelonephritis (3 patients), renal tuberculosis (1 patient) and irradiation damage (1 patient). In 2 the aetiology was not established.

Five physicians and one radiologist, all of whom had a special interest in hypertension, were asked to re-report all 37 intravenous urograms, without knowing the patients' names, or any clinical details; the only information given was that some of the films came from patients with renal artery disease and some did not. Each observer completed a questionnaire on each set of radiographs, measuring kidney size and assessing the presence, or absence, of delay in the appearance of contrast, density differences both before and after an oral water load (where available), and finally the likelihood of ischaemia or other diagnoses. Observations were scored as follows: delay - none (0), slight (1), marked (2), no pyelogram (3); density differences - none (0), slight (1), marked (2); diagnostic score - no ischaemia (0), probable stenosis (1), stenosis or occlusion (2). A composite score for the three diagnostic features was reached empirically by summing:

$$\text{Delay score} + \text{density score} + \left[\frac{\text{size of unaffected kidney}}{\text{size of affected kidney}} - 1\right] \times 30.$$

Results

Consistency of reporting. The 6 observers agreed more often than they disagreed in their reporting of delay and density differences on the urogram (Figs. 19A and B). However, the measure of disagreement becomes clearer when account is taken of those patients on whom observers unanimously agreed about urographic features (denoted by the cross-hatched areas in Figs. 19A and B) presumably because the urographic findings were clear. Measurements of kidney length (Fig. 19C) were more consistent than subjective assessments of density differences or delay. In all instances where one standard deviation of the mean kidney length was greater than 1.0 cm at least one, and usually more than one, observer had felt unable to measure kidney size because the renal outline had been obscured, mainly by bowel gas. There was more disagreement in interpreting the findings of delay, density difference and kidney size as to whether or not ischaemia was present (Fig. 20).

The consistency of reporting was similar for patients with unilateral stenosis, unilateral occlusion, bilateral stenosis and unilateral disease with normal vasculature.

Accuracy of reporting. Comparison of the true diagnoses (as defined by both arteriography and ureteric catheterisation) with opinions on the urograms of patients with unilateral disease is presented in Table 11. The correct diagnosis, whether firm or tentative, was reached

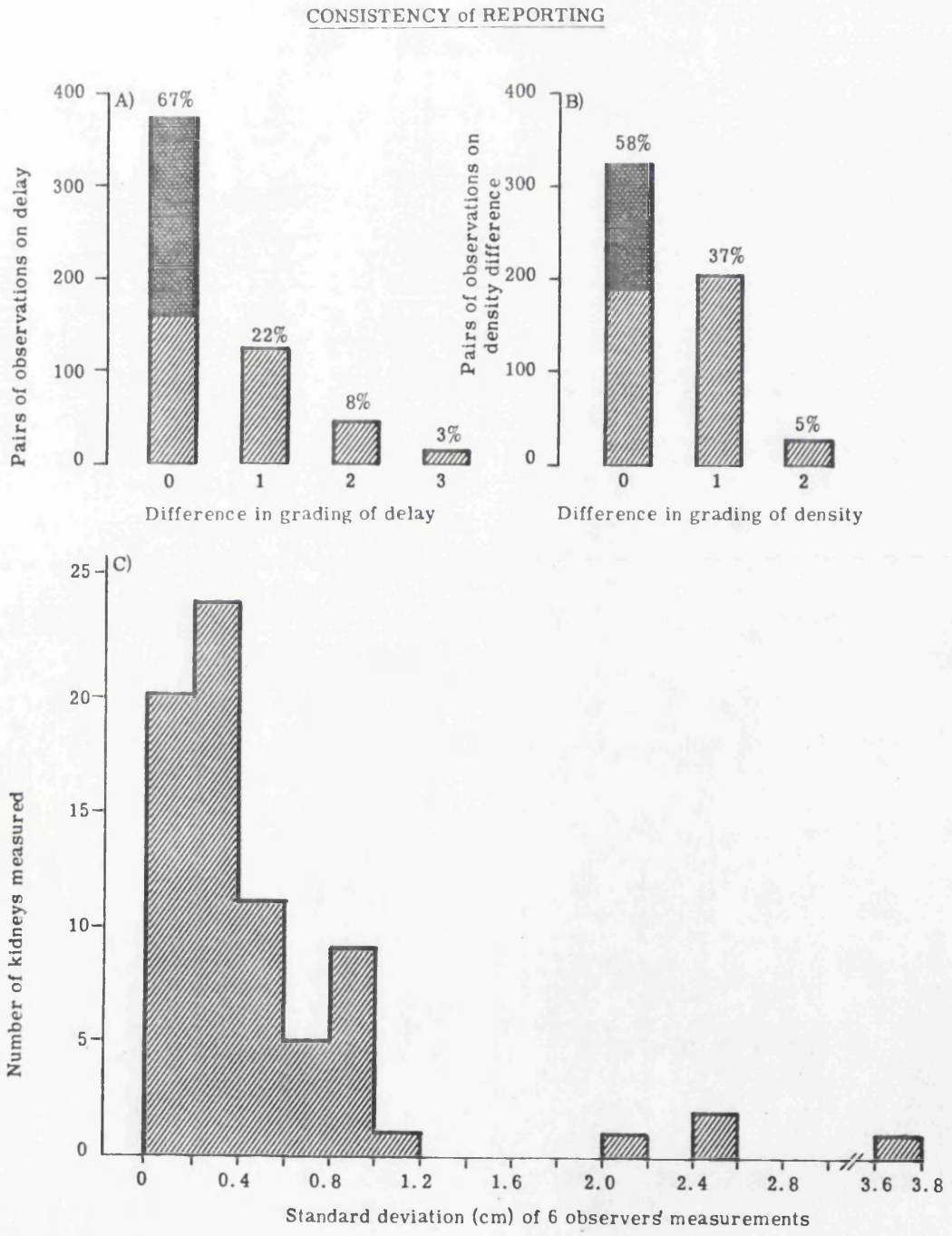


Figure 19: Consistency of reporting. Number of agreements and disagreements between pairs of observers in reporting A) delay and B) density difference. Cross hatched areas in the columns for zero score difference are agreements arising from unanimous reports for each urogram. The frequency distribution of the standard deviations of measurements of bipolar diameter of individual kidneys is presented in Figure C).

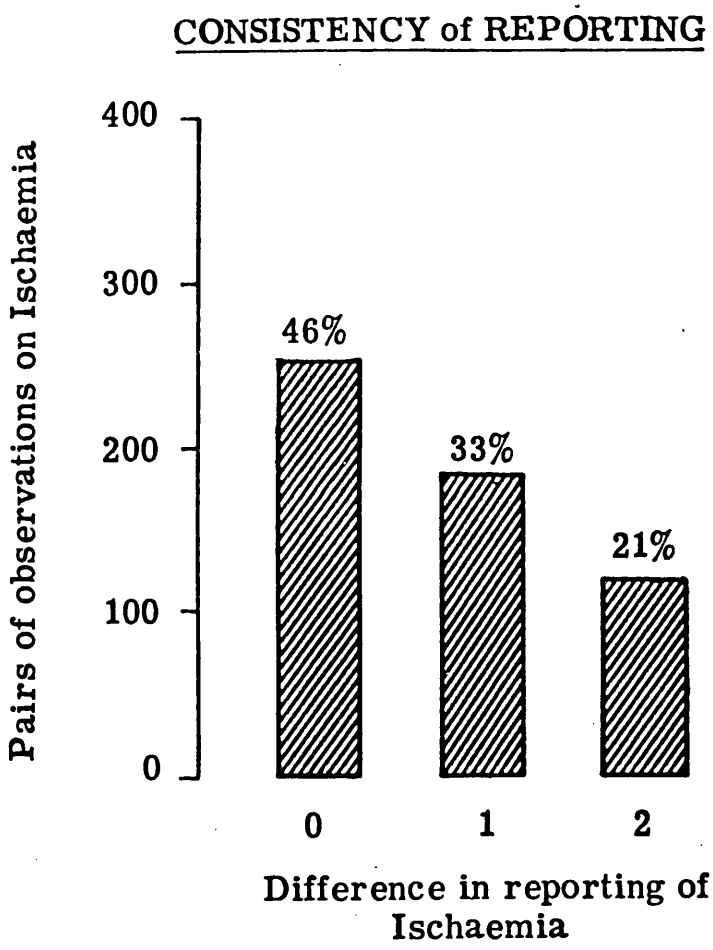


Figure 20: Consistency of reporting. Number of agreements and disagreements between pairs of observers regarding the diagnosis of renal ischaemia.

TABLE 11. DIAGNOSTIC ACCURACY.

			UROGRAPHY REPORTS								
			Renal artery stenosis				Unilateral disease not stenosis				Normal
			Side correct		Side incorrect		Side correct		Side incorrect		
Diagnostic group	No of patients	No of reports	C	P	C	P	C	P	C	P	
unilateral renal artery stenosis/ occlusion	25	150	63(42%)	26(17%)	4(3%)	7(5%)	6(4%)	0	0	0	44(29%)
U.K.D.	7	42	18(43%)	8(19%)	2(5%)	1(2%)	13(31%)	0	0	0	0

Comparison of the urographic diagnoses reached by six observers with the true diagnoses as defined by renal arteriography and bilateral ureteric catheterisation studies. U.K.D. = unilateral kidney disease of non-ischaemic aetiology. C = certain. P = probable diagnosis.

on the urogram in 53% of the 222 reports. The percentage of correct diagnoses was 59% for patients with unilateral stenosis and 31% for patients with unilateral kidney disease with normal vessels. In patients with unilateral stenosis ischaemia was diagnosed on the normal side in 7% and no ischaemia reported in 34%. Unilateral ischaemia was suspected on the side of the small kidney in 62% of instances where no renovascular abnormalities were present, while disease was suspected on the normal side in 7%. Overall 23% of films were reported as normal.

The density difference score correlated well with the final diagnostic score in patients with unilateral ischaemia ($r = 0.75$, $p < 0.001$), with the regression equation not significantly different from the 45° line ($y = 0.93x - 0.07$). Delay score both including ($r = 0.44$, NS) and excluding ($r = 0.45$, NS) patients who did not have early minute sequence films did not correlate with the diagnostic score, though the ratio of bipolar diameters did ($r = 0.49$, $p < 0.05$). The composite score derived from the three main features correlated more closely with the diagnostic score ($r = 0.58$, $p < 0.01$). Thus, density differences appear to have been the most influential abnormality in arriving at the final urographic diagnosis.

Additional films after an oral water load were available in 18 patients. Of a possible 108 observations of density diffference before water load films, 74 instances of density difference were recorded. The water load films

led to an alteration in the time of maximum density difference in 19 (26%) of these. Of the 34 observations of absent density difference before a water load, 11 (32%) were changed to a density difference after the water load. However, on only seven occasions was a diagnosis changed because of these findings; two were in patients with unilateral stenosis, while five were in 3 patients with bilateral stenosis.

The mean diagnostic score for unilateral stenosis was 6.3 from a possible maximum of 12. For unilateral occlusion it was 7.9 and for unilateral ischaemia overall 6.8; but for unilateral small kidney of non-ischaemic aetiology, it was 7.0. The only patient with the maximum possible score of 12 had slight delay, marked density difference, and a size ratio of 1.36, but had pyelonephritis with normal vasculature not renal artery stenosis. Thus the diagnosis on the urogram was often inaccurate.

Comparison of diagnostic features and diagnostic score with ureteric catheterisation data (Table 12).

The next problem was to determine whether the accuracy of diagnosis and special features on the urogram could be explained by changes in renal function. The ratios of urine flow rate, urinary sodium, creatinine and PAH concentration and creatinine and PAH clearance from the two kidneys were compared with the three main diagnostic features as well as the overall diagnostic score. The results are set down in Table 12. For patients with unilateral ischaemia scores for delay and density

TABLE 12. CORRELATION OF BILATERAL URETERIC CATHETERISATION DATA WITH IVU FEATURES.

		Linear correlation coefficients				
		Delay score	Density difference score	Size ratio	Diagnostic score	Renal vein renin ratio
Unilateral renal ischaemia (n = 25).	log ratio urine flow rate (U:A)	0.47*	0.41*	0.73***	0.59*	0.39
	log ratio urine Na concentration (U:A)	0.40	0.29	0.62**	0.25	0.19
	log ratio urine creatinine concentration (A:U)	0.62**	0.45*	0.65***	0.28	0.31
	log ratio urine PAH concentration (A:U)	0.54**	0.44*	0.66***	0.34	0.35
	log ratio creatinine clearance (U:A)	0.66***	0.50*	0.76***	0.38	0.39
	log ratio PAH clearance (U:A)	0.70***	0.54**	0.76***	0.32	0.42*

A affected side U unaffected side

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

difference and the ratio of kidney size correlated significantly with each of biochemical ratios obtained from catheterisation studies, except for the sodium concentration ratio. Size ratio correlated more closely with the biochemical ratios than did delay score, which in turn correlated more closely than did the density difference score. The closest correlations of each diagnostic feature were with creatinine clearance, and PAH clearance ratios. The overall diagnostic score correlated less well with the catheterisation data, only urine flow rate being significantly correlated.

The possibility that differences in urographic appearance were dependent on the function of the affected kidney was examined by making an arbitrary division of patients with unilateral ischaemia into a group of 12 whose glomerular filtration rate on the affected side was greater than 70% of that on the normal side and a group of 13 whose glomerular filtration rate was 70% or less of that on the normal side. As can be seen from Table 13, although the observed urographic abnormalities were less in patients with the less severe impairment of function in the affected kidney, the eventual diagnostic score was similar in the two groups. Furthermore in the group whose glomerular filtration rate was well maintained, the density difference score (Table 14) correlated more closely with urinary creatinine and PAH

TABLE 13. COMPARISON OF DIAGNOSTIC FEATURES AND DIAGNOSTIC SCORE IN GROUPS WITH DIFFERING GLOMERULAR FILTRATION RATE TO THE AFFECTED KIDNEY.

	Delay score	Density difference score	Size ratio	Diagnostic score
Glomerular filtration rate on affected side >70% unaffected side (n = 12)	0.7	4.8	1.06	5.9
Glomerular filtration rate on affected side <70% unaffected side (n = 13)	7.0	8.2	1.19	6.1

TABLE 14. CORRELATION OF SELECTED BILATERAL URETERIC CATHETERISATION DATA WITH DELAY AND DENSITY DIFFERENCE SCORES IN GROUPS WITH DIFFERING GLOMERULAR FILTRATION RATE TO THE AFFECTED KIDNEY.

		Correlation Coefficients		
		GFR on affected side in comparison with unaffected side		
Ordinate	Abscissa	(A) >70% n=12	(B) <70% n=13	All unilateral ischaemia
Log urine flow rate ratio (U:A)	Delay score	+0.95***	-0.45	+0.47*
Log creatinine concentration ratio (A:U)	Density difference score	+0.44	+0.31	+0.45*
Log PAH concentration ratio (A:U)	Density difference score	+0.47	+0.24	+0.44*

A = affected side U = unaffected side *p <0.05 ***p <0.001

concentrations and delay score correlated more closely with urine flow rate, than in the group whose renal function was more severely impaired. However, the correlation between delay score and urine flow rate for patients with good function was spuriously high since for half of these patients the delay score was unamimously reported as zero; nevertheless, excepting those patients, a positive correlation ($r = +0.48$) was still found in contrast to the negative correlation for patients with poor renal function.

Comparison of diagnostic features and diagnostic score with renal vein renin ratios.

The ratio of plasma active renin concentration from renal venous blood of the affected : unaffected kidney was available in 23 patients with unilateral ischaemia. It did not correlate significantly with the delay score ($r = 0.31$), size ratio ($r = 0.27$), or diagnostic score ($r = 0.35$), but a weak positive correlation was established with the density difference score ($r = 0.42$, $p < 0.05$). With the exception of the PAH clearance ratio, which correlated weakly with the renal vein renin ratio ($r = 0.42$, $p < 0.05$), no significant relationships between the results of bilateral ureteric catheterisation and renal vein sampling studies were observed (Table 12).

8:4 DOES INHIBITION OF PROSTAGLANDIN SYNTHESIS INCREASE THE DIAGNOSTIC ACCURACY OF THE INTRAVENOUS UROGRAM IN RENAL ARTERY STENOSIS?

Over the past decade evidence has accumulated that the release of renal prostaglandins is increased by renal ischaemia (McGiff, Crowshaw, Terragno, Longro, Strand, Williamson, Lee, and Ng, 1970) and that the activity of the main components of this series of hormones, prostaglandins E and $F_{2\alpha}$ is vasodilator in most species including man (Hollenberg, 1979). Indeed the vasoconstrictor response to intravenous injection of angiotensin II has been potentiated by prior administration of the prostaglandin synthetase inhibitors, indomethacin and meclofenamate, in two-kidney hypertensive dogs (Satoh and Zimmerman, 1975), whilein two-kidney hypertensive rats, prolonged administration of indomethacin resulted in an augmented pressor response to renal artery clipping (Pugsley, Beilin, and Peto, 1975).

This increase in prostaglandin synthesis may be a compensatory physiological mechanism. If it is suppressed, the unilateral renal ischaemia might increase and the urographic changes subsequently become more obvious. This hypothesis was examined in 9 hypertensive patients aged 16-52 years, in each of whom arteriography had demonstrated unilateral renal artery stenosis, but the urographic appearances at the time of referral were thought to be equivocal (n = 4), or normal (n = 5) by

the referring physicians and radiologists. Bilateral ureteric catheterisation studies showed a pattern of ischaemia on the stenosed side in each case, while renal vein renin studies performed in 7 of the 9 patients, showed lateralisation to the side of ischaemia in each. None of the patients had contraindications to indomethacin therapy.

Intravenous urography was perfomed as described above (4:6). 48 hours after the initial rapid series intravenous urogram, the patients received indomethacin 25 mg orally, four times daily for 48 hours, followed by a final dose of 50 mg on the third day. One hour later, a second directly comparable intravenous urogram was performed.

The radiographs were then prepared so that no clinical details, apart from the timing of the films were available, and they were then assessed in pairs by two observers working independently. A standard protocol was used which required assessment of delay in the appearance of contrast, pyelographic density differences before the water load, and pyelographic density differences after the water load.

Results.

Table 15 shows the findings in the patients. Delay in the appearance of the pyelogram in the control intravenous urogram series was identified in only one patient by both observers and in one other patient by a single observer. After indomethacin, no enhancement of this diagnostic feature was noted.

TABLE 15. UROGRAPHIC ABNORMALITIES BEFORE AND AFTER INDOMETHACIN IN NINE HYPERTENSIVE PATIENTS WITH RENAL ARTERY STENOSIS

	Control series						Series after indomethacin					
Patient	Delay		Density		AWL		Delay		Density		AWL	
	A	B	A	B	A	B	A	B	A	B	A	B
1	0	0	0	0	0	+	0	0	++	++	++	+
2	0	0	+	+	+	0	0	0	+	+	+	0
3	0	0	0	+	NA		0	0	+	0	+	+
4	0	0	+	+	+	+	0	0	+	+	+	0
5	0	+	0	+	NA		0	0	0	+	0	0
6	+	+	+	+	+	+	+	+	+	+	+	0
7	0	0	+	+	+	+	0	0	+	+	+	+
8	0	0	+	++	+	++	0	0	+	+	+	+
9	0	0	+	+	+	+	0	0	+	+	+	+

Reports of two independent observers (A and B) on the intravenous urogram of 9 patients with renal artery stenosis before and after indomethacin - see text for details.

AWL = after water load

0 = no abnormality

\+ = slight difference

++ = marked difference

NA = not available

Increased density of the pyelogram on the affected side was noted by both observers in 6 patients in the control series, with an increase noted by a single observer in another two patients. In only one patient (patient 1) was a major difference noted after indomethacin. Radiographs after a water load were of no additional diagnostic value over the standard intravenous urogram films either in the control series or in the series after indomethacin.

One patient developed a neutropenia (white cell count 0.8 x 10^9/l) while receiving indomethacin but this resolved within 72 hours. No other side-effects were recorded.

8:5 COMPARISON OF ^{123}I-HIPPURAN RENOGRAPHY AND BILATERAL URETERIC CATHETERISATION STUDIES IN THE MEASUREMENT OF TOTAL AND DIVIDED RENAL PLASMA FLOW.

While measurements of the renal clearance of radioactively labelled hippuran have been used as a accurate means of measuring total effective renal plasma flow (2:7,2) accurate comparison of divided renal function assessed by renography and by bilateral ureteric catheterisation studies are lacking in man. In this section such a comparison has been made using ^{123}I-hippuran renography and a gamma camera technique described in Chapter 4:10.

Patients and Methods.

Nine men and 7 women with a mean age of 44 years (range 15-56 years) were studied. Renal arteriography demonstrated unilateral renal artery stenosis in 13 patients and occlusion in 3 patients; the appearances were those of atheroma in 14 and fibromuscular hyperplasia in 2. Subsequent bilateral ureteric catheterisation studies demonstrated a pattern of abnormality suggestive of unilateral ischaemia with reduced urine flow rate and increased urinary concentration of creatinine and PAH on the affected side in each case.

Total and divided PAH clearance (C_{PAH}) was measured at ureteric catheterisation: total and divided ^{123}I-hippuran clearance was measured at the time of renography a mean of 3.1 months later (range 1 day - 17 months); total C_{PAH} and creatinine clearance were reassessed on the day of renography to detect any deterioration in renal function between the time of ureteric catheterisation and renography. Renography was performed 2-3 hours after total C_{PAH}, and not simultaneously, so that competition at the proximal renal tubules between large quantities of PAH and minute quantities of radionuclide would not be a problem (Britton and Brown, 1970).

Results.

Total effective renal plasma flow. Hippuran clearance was little different from C_{PAH} performed on the same day, over a wide range of clearance values

(75-800 ml/min) as shown in Figure 21. The line of best fit corresponded almost exactly to the line of identity. No significant difference on paired t-testing was found between C_{PAH} (mean 321 $\pm$ 199 ml/min) and hippuran clearance (mean 318 $\pm$ 206 ml/min) (t = 0.23, N.S.), the latter being 99% of the former.

A wider scatter of results, but nevertheless a significant correlation, was found between C_{PAH} at ureteric catheterisation and C_{PAH} on the day of renography (Figure 22). This greater scatter may largely be explained in terms of deterioration in renal function between the two tests. Three patients shown as solid circles in Figure 22 had the greatest time interval between tests (mean 11.2 months) over which creatinine clearance had fallen by a mean 24 ml/min. Mean C_{PAH} at ureteric catheterisation (361 $\pm$ 174 ml/min) was not however significantly greater than the later C_{PAH} measurement.

In view of these results the correlation between hippuran clearance and C_{PAH} at ureteric catheterisation presented in Figure 23 was not unexpected, but the correlation was felt to be sufficiently close (r = 0.74) and the mean clearances sufficiently similar (t = 1.17, NS) to permit a valid comparison of divided function.

A further evidence of the correlation between the three techniques was derived from the multiple correlation coefficient ($R_{YY}{}^{1}$), (Edwards, 1976). By this method $R^2{}_{YY}{}^{1}$ = 0.55, F = 7.33, p <0.05.

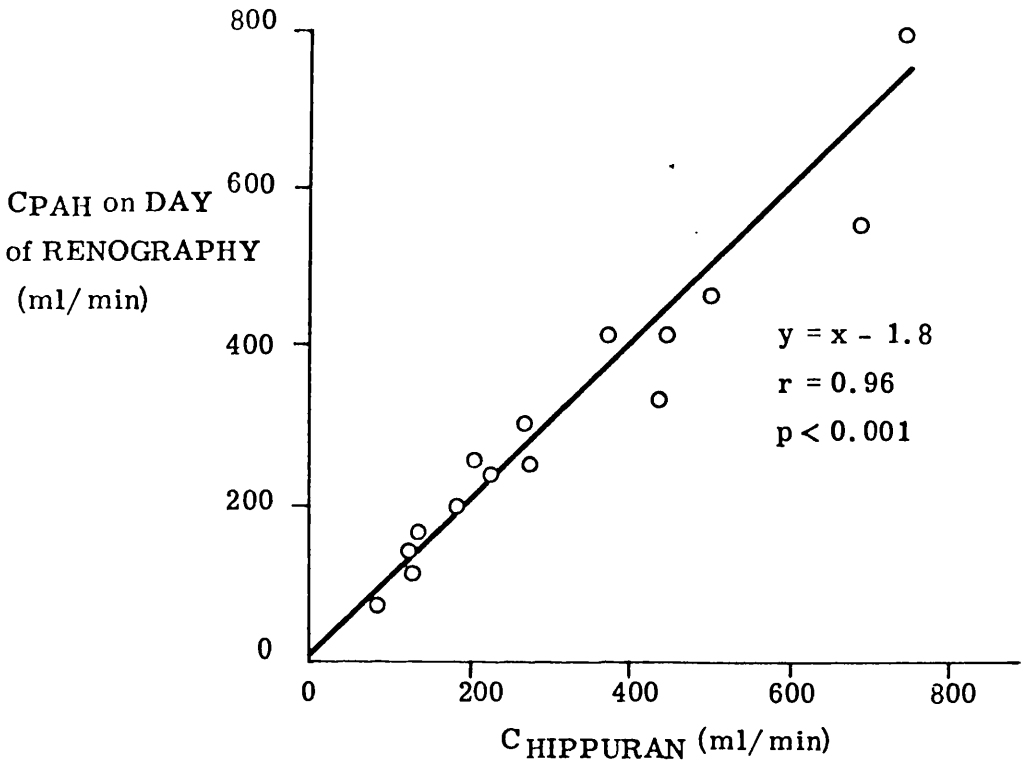


Figure 21: Total effective renal plasma flow in patients with renal artery stenosis. Comparison of PAH and hippuran clearances measured on the same day.

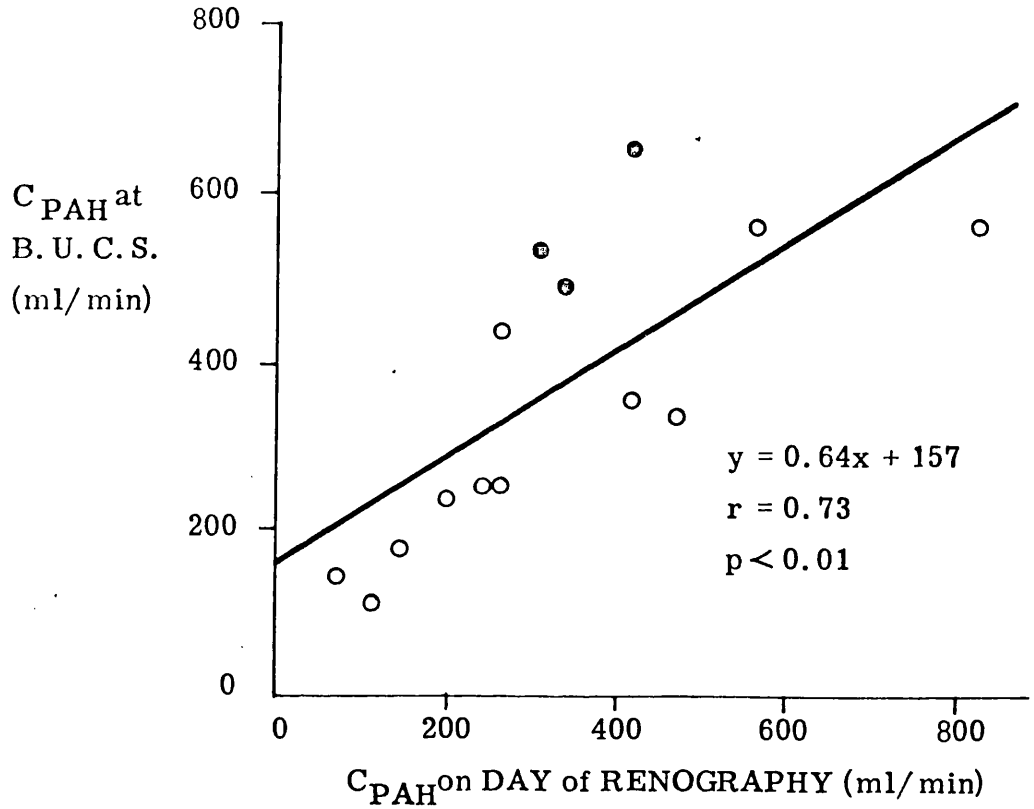


Figure 22: Total effective renal plasma flow in patients with renal artery stenosis. Comparison of C_{PAH} at bilateral ureteric catheterisation studies with C_{PAH} on the day of renography. Solid circles represent those patients with the greatest time interval between the two measurements.

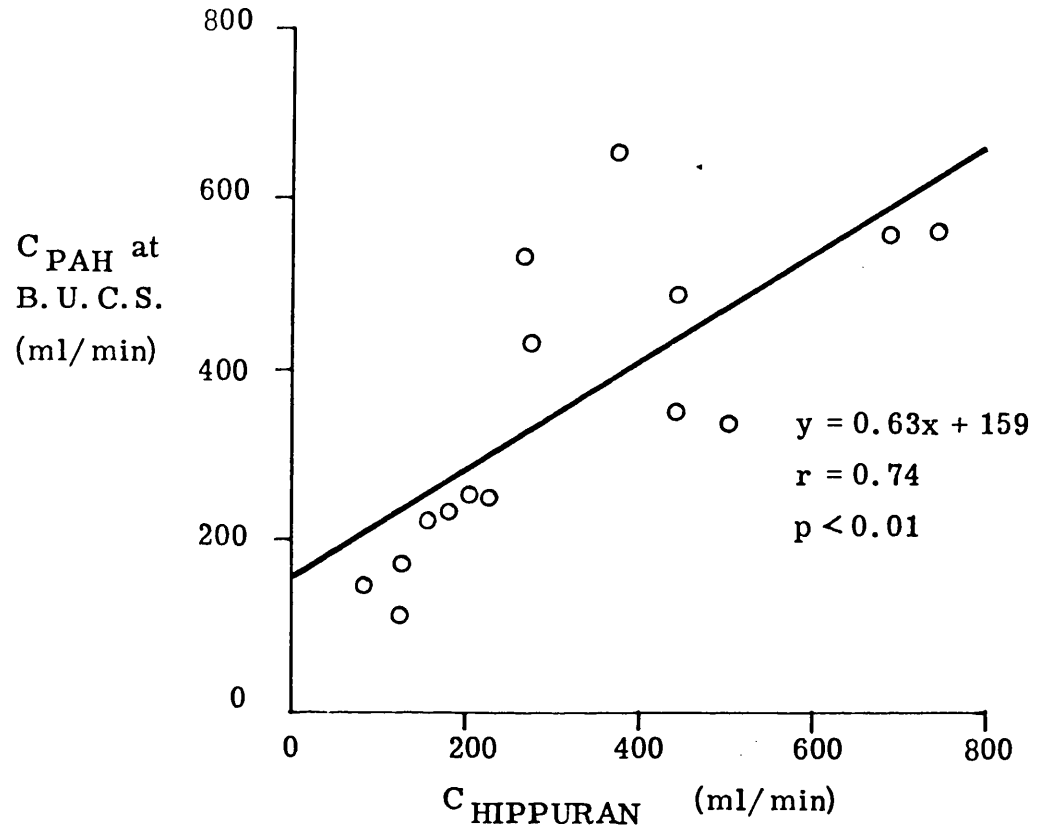


Figure 23: Total effective renal plasma flow in patients with renal artery stenosis. Comparison of C_{PAH} at bilateral ureteric catheterisation studies with hippuran clearance.

Divided effective renal plasma flow. The ratio of C_{PAH} affected side : unaffected side at bilateral ureteric catheterisation studies correlated closely with the ratio of hippuran clearance affected : unaffected at renography, the coefficient of correlation being 0.94 ($p < 0.001$). The derived values of hippuran clearance to individual kidneys also correlated well with C_{PAH}, despite the time interval between the tests, on both stenosed and unaffected sides (Figure 24). Mean clearances did not differ significantly either on the affected side (C_{PAH} 119 $\pm$ 99 ml/min; hippuran clearance 98 $\pm$ 70 ml/min; $t = 1.23$, N.S.) or the unaffected side (C_{PAH} 236 $\pm$ 108 ml/min; hippuran clearance 232 $\pm$ 152 ml/min; $t = 0.19$, N.S.).

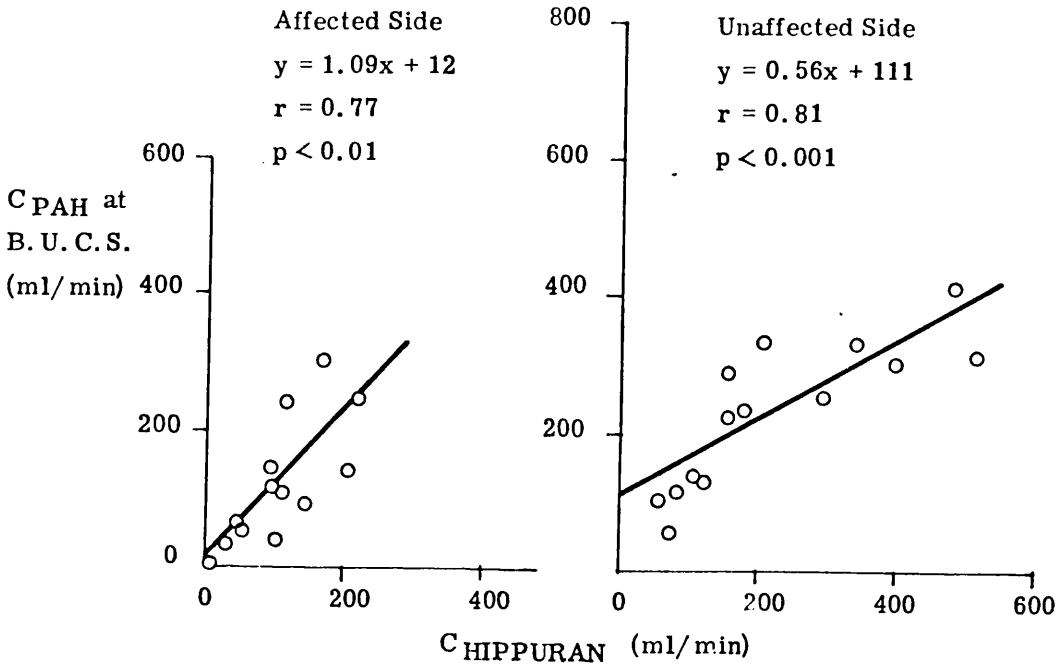


Figure 24: Effective renal plasma flow to individual kidneys in patients with renal artery stenosis. Comparison of C_{PAH} at bilateral ureteric catheterisation studies with hippuran clearance on stenosed and unaffected sides.

CHAPTER 9

PROGNOSTIC TESTS

In this chapter the accuracy of prognostic tests, singly and in combination, has been analysed retrospectively in those 39 patients who underwent surgery. According to the arbitrary but strict definition of surgical success detailed in Chapter 4:12, 21 patients had a successful outcome while 18 did not.

9:1 CLINICAL FEATURES AND SIMPLE TESTS.

Surgical success and failure occurred in patients with similar ranges of age, sex and initial blood pressure. The response to medical treatment and the presence or absence of other vascular disease (Table 16) did not separate the two groups. Mean serum urea and creatinine concentrations were higher amongst those in whom surgery failed, with the difference reaching significance at $p < 0.05$ for serum urea, but the overlap for both urea and creatinine within the groups was very large. Two features were clearly more common in surgical failures, bilateral disease ($\chi^2 = 8.27$, $p < 0.01$), and left ventricular hypertrophy ($\chi^2 = 6.21$, $p < 0.02$), but as can be seen in Table 16 no single test or clinical feature gave useful separation of the two groups.

TABLE 16. PROGNOSIS - CLINICAL FEATURES

	Surgical success n = 21	Surgical failure n = 18	t	p
Age (years)	37 ± 13	42 ± 12	1.20	NS
Serum urea (mmol/l)	5.2 ± 1.8	8.4 ± 6.7	2.14	<0.05
Serum creatinine (μmol/l)	100 ± 35	154 ± 142	1.68	NS

	Surgical success n = 21	Surgical failure n = 18	X^2	p
Malignant phase	8	4	1.15	NS
Abdominal bruit	8	3	2.20	NS
Intercurrent vascular disease	4	7	1.88	NS
Bilateral disease	0	6	8.27	<0.01
Fibromuscular hyperplasia	5	5	0.08	NS
Unilateral FMH	5	4	0.01	NS
Occlusion	5	9	2.89	NS
Cardiothoracic ratio >50%	3	8	4.35	<0.05
$RV_6 + 5V_1 > 35$ mm	8	14	6.21	<0.02
Minnesota code 3,1 change	10	15	5.37	<0.05
Successful medical treatment	6	5	0.003	NS

9:2 PERIPHERAL PLASMA RENIN CONCENTRATION.

Peripheral total plasma renin concentration (Figure 25) had little discriminative power with regard to surgical prognosis. Using results from plasma samples obtained under standard conditions (n = 35), the mean plasma total renin concentration in surgical successes was 197 ± 211 μU/ml (range 36-1020 μU/ml; omitting one result of 1020 μU/ml, the range was 36-362 μU/ml). Surgical failures in whom the mean plasma renin concentration was 159 ± 132 μU/ml (range 40-438 μU/ml) did not have significantly lower values than successes (t = 0.60, N.S.). Likewise, plasma active renin concentrations (n = 32) were similar in successes and failures (72 ± 75 μU/ml and 58 ± 51 μU/ml respectively, t = 0.58, N.S.).

9:3 RENAL VEIN RENIN RATIO.

The results of this test, the most popular prognostic index in the recent literature, are presented in Figure 26. It may be seen that all patients with a ratio of 2.0 or more had a successful response to surgery. Unfortunately, the use of such a ratio as an absolute criterion for operation, while avoiding failures, would also have excluded 11 of those patients who did have a favourable outcome. Likewise, while a ratio of 1.5 or more would have included four more successes, it would

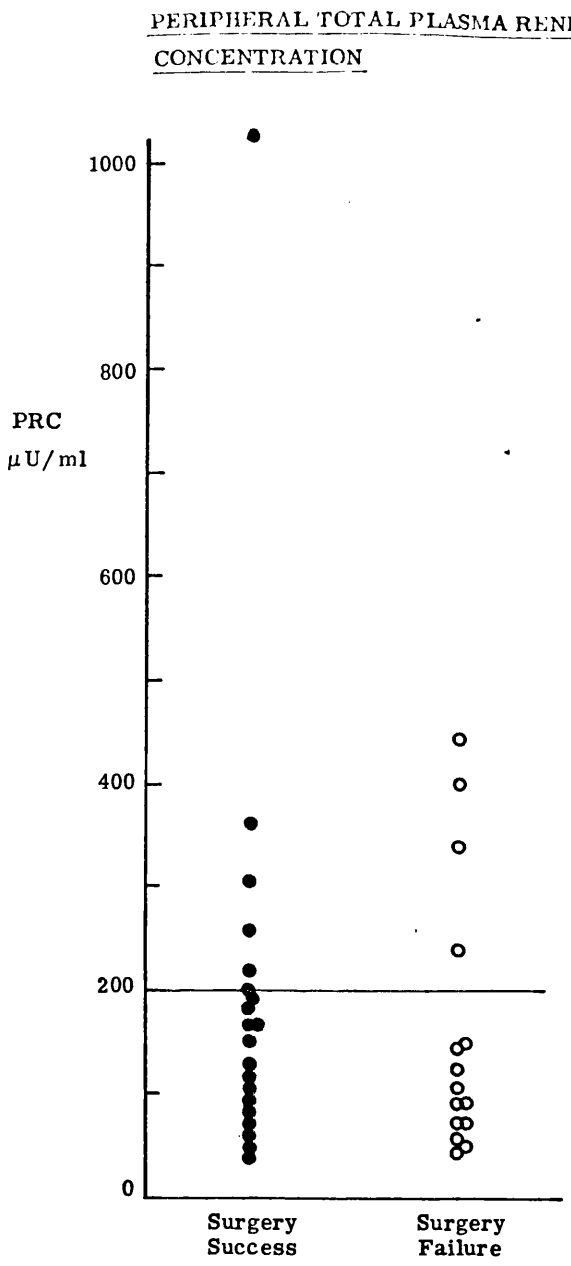


Figure 25: Preoperative peripheral total plasma renin concentration in μU/ml (normal range 60-200 μU/ml, the latter figure denoted by the solid horizontal line) in patients who subsequently underwent successful (closed circles) or unsuccessful (open circles) surgery.

RENAL VEIN RENIN RATIO-

PLASMA ACTIVE RENIN CONCENTRATION

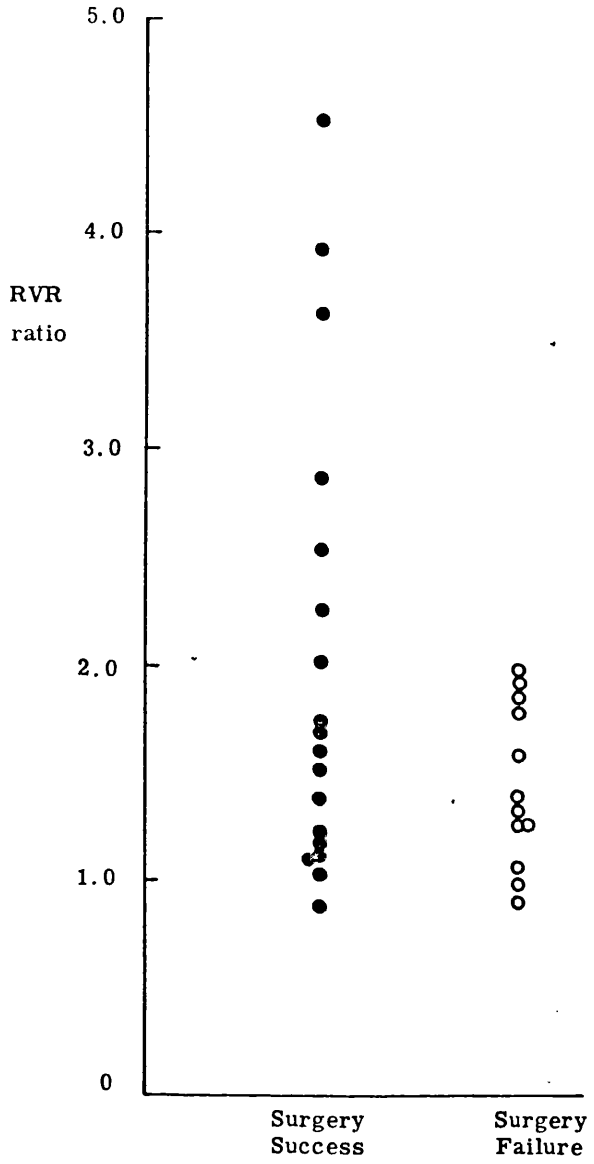


Figure 26: Preoperative renal vein renin ratio (affected : unaffected) in patients with renal artery stenosis who subsequently underwent successful (closed circles) or unsuccessful (open circles) surgery.

still have excluded 7 successes and would, moreover, have included 7 failures. Thus, in this series there is no absolutely satisfactory renal vein renin ratio which reliably predicted success and failure.

9:4 SARALASIN INFUSION.

The change in mean arterial pressure following an infusion of saralasin at the maximal rate of 10 μg/kg/min (see 4:11 for method) was assessed in 9 sodium replete patients coming to surgery. As shown in Table 17 a substantial fall of arterial pressure occurred in 3 of 5 patients subsequently having successful surgery, but in all underestimated the fall of blood pressure which occurred postoperatively; in 2 successes no fall occurred with saralasin. Likewise amongst 4 surgical failures, failure was correctly predicted in 2 and success falsely predicted in 2. Of interest is the increase in mean arterial pressure during infusion in 2 patients, possibly demonstrating the partial agonist properties of the competitive inhibitor.

9:5 BILATERAL URETERIC CATHETERISATION STUDIES.

Unilateral renal artery stenosis produced a consistent pattern of ischaemia in both surgical successes and failures (Figure 27, see also Figure 18, Chapter 8:3): urine flow was reduced and the urinary concentrations of

TABLE 17. PROGNOSTIC TESTS - SARALASIN INFUSIONS

BP mmHg before saralasin infusion	Lowest BP during saralasin infusion	(ΔMAP mmHg)	Operation	Result of surgery	BP 3 months after operation, if on no treatment then	(ΔMAP mmHg)	BP before start of treatment postoperatively and time at which started	(ΔMAP mmHg)
170/120	168/116	(- 4)	R	Success	130/85	(-37)		
181/133	161/119	(-16)	R	Success	120/75	(-59)		
182/100	200/102	(+ 8)	R	Success	122/74	(-37)		
198/128	169/111	(-21)	N	Success	126/78	(-57)		
242/112	194/93	(-28)	N	Success	134/84	(-54)		
222/123	212/120	(- 5)	R	Failure			218/122 - 1 month	(- 2)
220/128	130/90	(-56)	N	Failure			210/120 - 4 days	(- 9)
204/136	222/144	(+11)	N	Failure			178/116 - 7 days	(-22)
228/133	175/109	(-33)	N	Failure	170/120	(-27)		

Maximal blood pressure changes (mmHg) during saralasin infusion in 9 sodium-replete patients with renal artery stenosis subsequently having surgery. Figures in parenthesis indicate the change in mean arterial pressure (MAP)

R = arterial reconstruction. N = unilateral nephrectomy

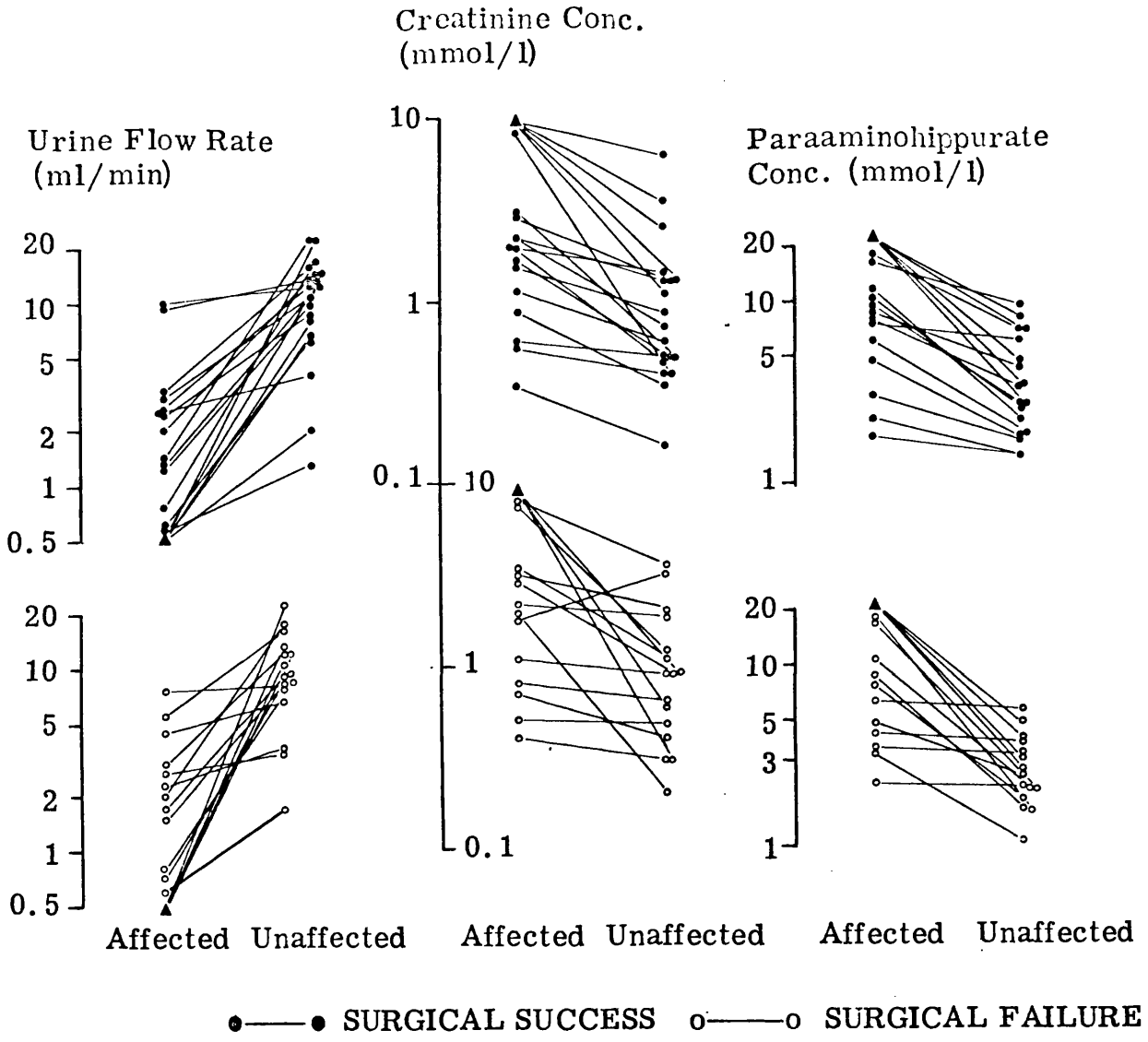


Figure 27: Results of ureteric catheterisation studies in patients having A) successful surgery (closed circles) and B) unsuccessful surgery (open circles), comparing data from affected and untouched kidneys. Closed triangles represent assigned values for patients with no urine flow on the affected side. The pattern of ischaemia is indistinguishable in successes and failures.

creatinine and para-aminohippurate were increased in the affected kidney of all patients except one, in whom values were equal.

Using these and other data from the ureteric catheterisation studies a number of published formulae used to predict surgical success were examined (Table 18). None absolutely separated the successes in this series from failures, as typified by the criterion of Capelli et al (1973) (Figure 28). Even the best (Figure 29 - derived from Fournier et al (1973)) while predicting success in 95% of successes also predicted success in 59% of failures.

Measurement of PAH clearance in the contralateral kidney of those patients coming to nephrectomy has been said to have prognostic value (Stamey et al, 1961), but this was not apparent in this study as shown in Figure 30. The mean PAH clearance of the unaffected kidney before nephrectomy in surgical successes was 218 ml/min, while in operations with a disappointing response it was 209 ml/min ($t = 0.22$, N.S.).

Thus, though bilateral ureteric catheterisation studies were of considerable value in diagnosis (8:2) they were of less value in surgical prognosis.

TABLE 18. RESULTS OF PROGNOSTIC CRITERIA DERIVED FROM URETERIC CATHETERISATION STUDIES

Author	Criterion	No of successes fulfilling criterion	No of failures fulfilling criterion	χ^2	p
Stamey et al, 1961	Affected kidney ≥50% volume ↓ ≥200% PAH conc. ↑	13/19	9/15	0.26	NS
Howard & Connor, 1964	Affected kidney ≥50% volume ↓ ≥15% Na conc. ↑ ≥200% creat. conc. ↑	12/19	8/13	0.01	NS
Rapoport et al, 1960	Tubular rejection fraction ratio for sodium >1.6 (R. stenosis) <0.6 (L. stenosis)	16/19	9/14	1.74	NS
Capelli et al, 1973	PAH clearance ischaemic non-ischaemic kidney <0.65	11/17	10/16	0.02	NS
Fournier et al, 1973	$\Delta U_{creat}\%$ $\left(\frac{\text{affected - unaffected}}{\text{affected}}\right)$ ≥20%	18/19	10/17	6.70	<0.01

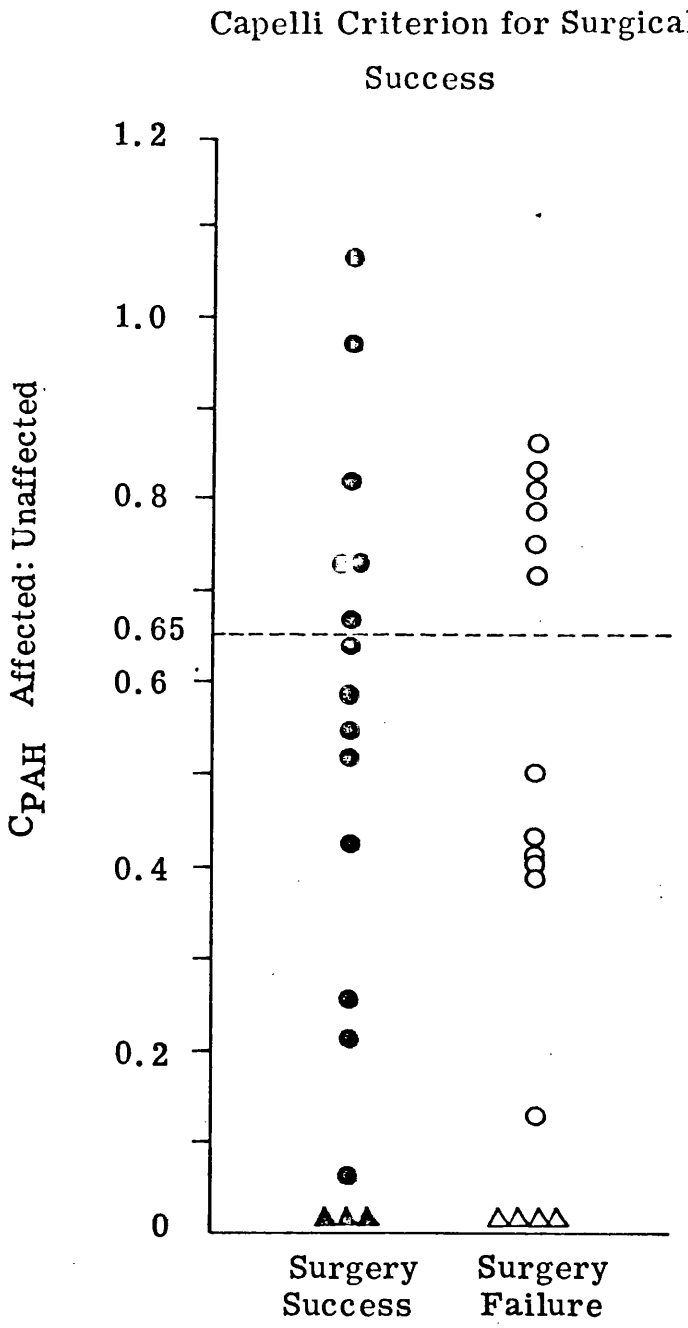


Figure 28: Application of the criterion of Capelli et al (1973) to patients coming to successful (closed circles) and unsuccessful (open circles) surgery. Triangles represent assigned values for patients with no urine flow on the affected side (success - closed triangles: failure - open triangles). A positive criterion is a PAH clearance ischaemic : non-ischaemic kidney of less than 0.65 (interrupted line).

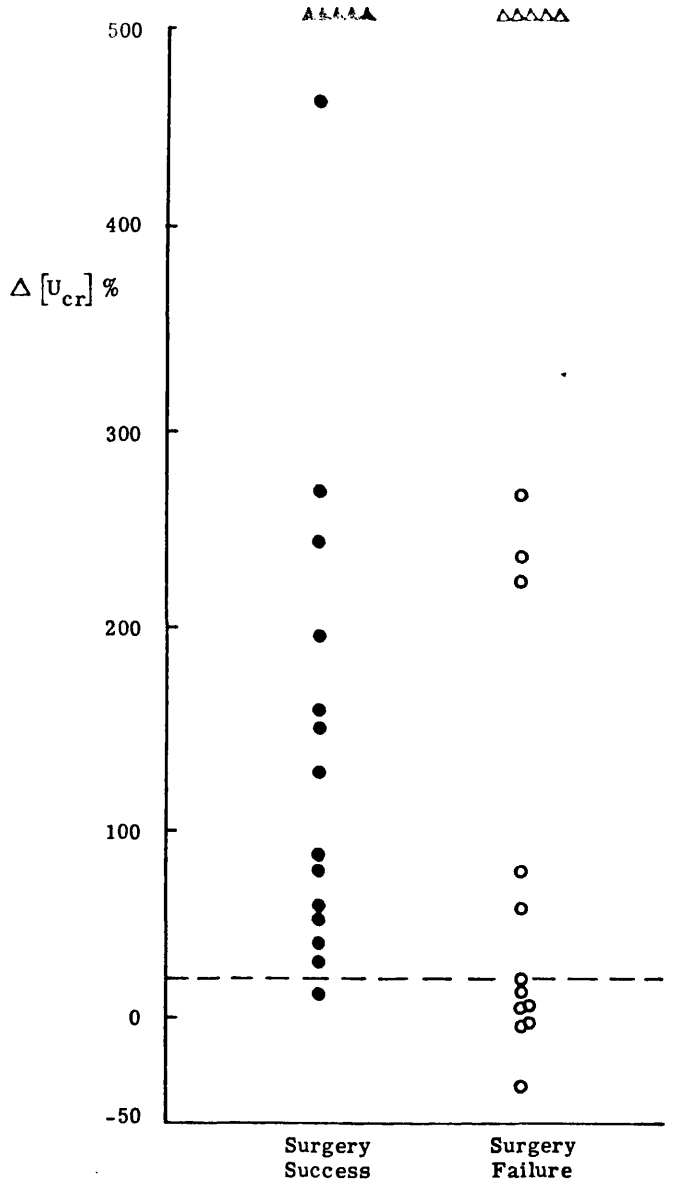


Figure 29: Application of Fournier criterion ($\Delta U_{creat}\% \frac{\text{affected - unaffected}}{\text{affected}} \geq 20\%$) to patients having successful (closed circles) and unsuccessful (open circles) surgery. Triangles represent assigned values for patients with no urine flow on the affected side.

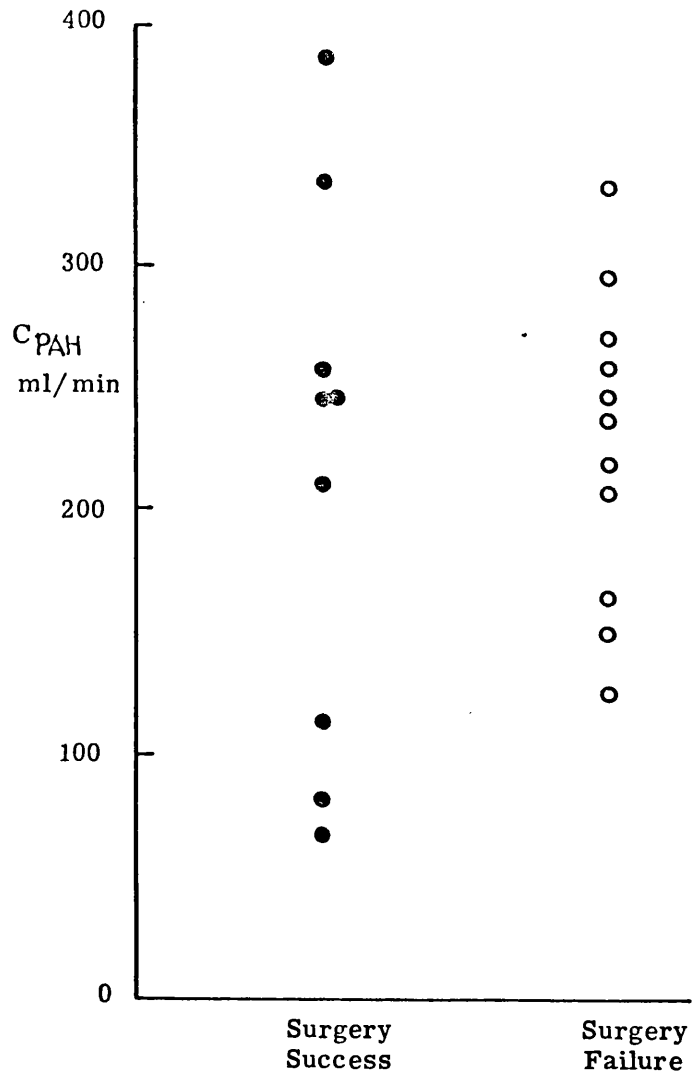


Figure 30: Clearance of para-aminohippurate in the "untouched" kidneys of patients with renal artery stenosis or occlusion subsequently having a nephrectomy with a a successful (closed circles) or unsuccessful (open circles) outcome.

9:6 RELATION OF URINARY SODIUM EXCRETION FROM THE UNTOUCHED KIDNEY AND ARTERIAL PRESSURE.

The relation between urinary sodium excretion from the untouched kidney and mean arterial pressure has been discussed in 37 patients with unilateral renal artery stenosis in 7:2. Of these patients 22 subsequently underwent surgery: 14 were successes and 8 were failures. Figure 31 depicts the same relation in the 22 patients. Although the number of observations is small, the results suggest that surgery lowers blood pressure least in patients in whom the relation of arterial pressure and sodium excretion is shifted downwards and to the right in the untouched kidney. The relationship is interesting, but its potential value as a prognostic test is again vitiated by overlap between successes and failures.

9:7 TESTS IN COMBINATION.

Since no single test successfully separates successes from failures, two further approaches have been followed in an effort to identify tests or combinations of tests which would prevent surgical failures coming to surgery, while not excluding potential successes from having an operation. As described above, a renal vein renin ratio of 2.0 or more predicted success, and bilateral renal artery stenosis predicted failure. Application of both criteria in a retrospective fashion to the 39 patients having surgery (Figure 32A) shows that while surgical

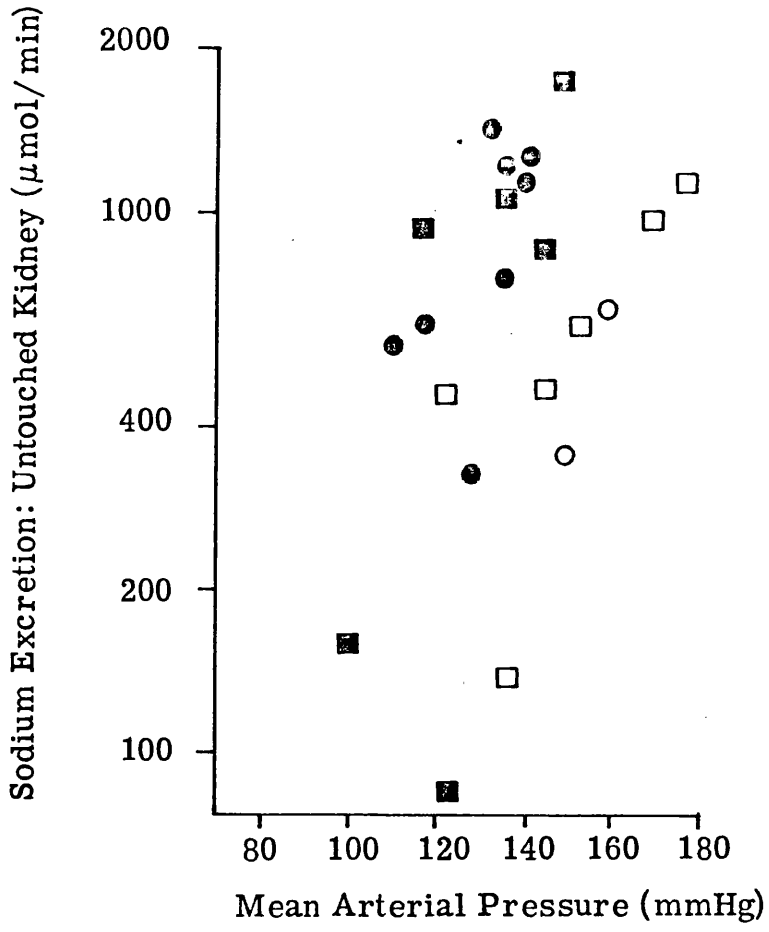


Figure 31: Relation of urinary sodium excretion from the untouched kidney and mean arterial pressure in patients with unilateral renal artery stenosis who subsequently underwent surgery. Solid symbols represent surgical cures; open symbols represent surgical failures. Squares represent patients who underwent unilateral nephrectomy; circles represent patients who underwent reconstructive surgery.

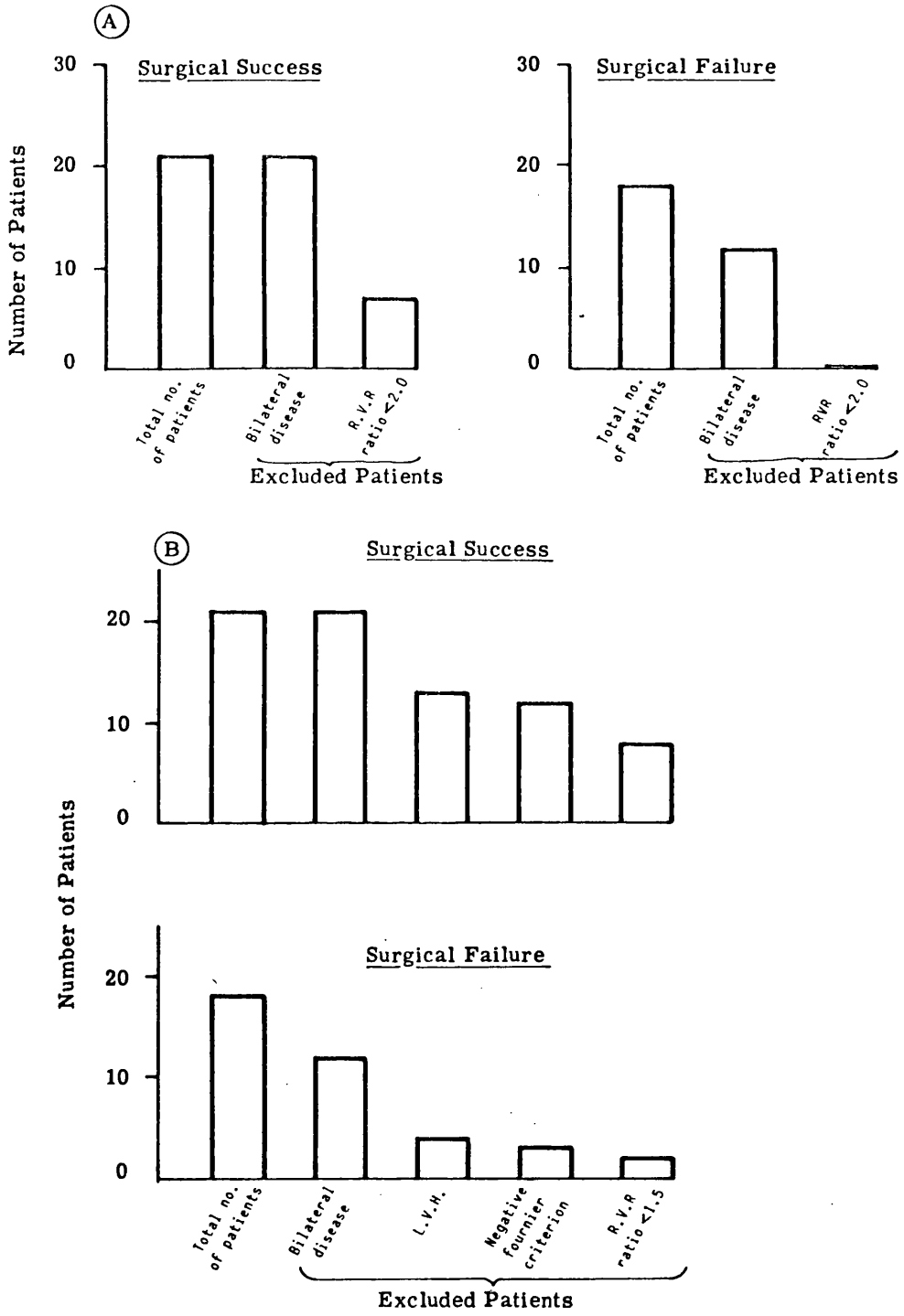


Figure 32: Application of prognostic indices. A) use of absolute criteria, B) use of less stringent criteria. Each left-hand column represents the total number of patients in each group. It can be seen that surgical failures can be limited by the use of these criteria, but only at the expense of preventing potentially successful surgery taking place.

failures could have been prevented, most of those having successful surgery would have been disqualified pre-operatively also. The same was true of other combinations tested, such as that illustrated in Figure 32B: surgical failure was prevented at the expense of limiting surgical success.

The second approach takes into account all data (Appendix Tables 3 and 4), but neither a simple linear discriminant function nor a logistic discriminant function (Armitage, 1971) could be found which separated surgical success from surgical failure. Again all failures could be predicted correctly but only at the expense of wrongly classifying a large proportion of successes.

CHAPTER 10

DECISIONS ON MANAGEMENT

10:1 DECISION TO DO SPECIAL TESTS.

The 19 patients in whom surgery was not considered and in whom tests other than arteriography were not performed (Appendix, Table 1) do not form a homogeneous group and no single reason emerged why investigations were curtailed at this stage. However, three relevant factors were present, at least one in each patient; age at presentation of 60 years or over (5 patients), the presence of severe intercurrent illness, usually vascular in nature (13 patients) and good control of blood pressure by medical means (10 patients). None of these was an absolute contraindication to further investigation but during the follow-up period (51 patient years) loss of blood pressure control was not observed in these patients. It is also apparent from Table 1 (Appendix), as might be expected, that the oldest patients were those with most intercurrent disease. However, if the presence of one or more of these criteria were always a reason not to investigate further, fewer tests and fewer operations would have been done but the proportion of successful operations would not have improved (Figure 33).

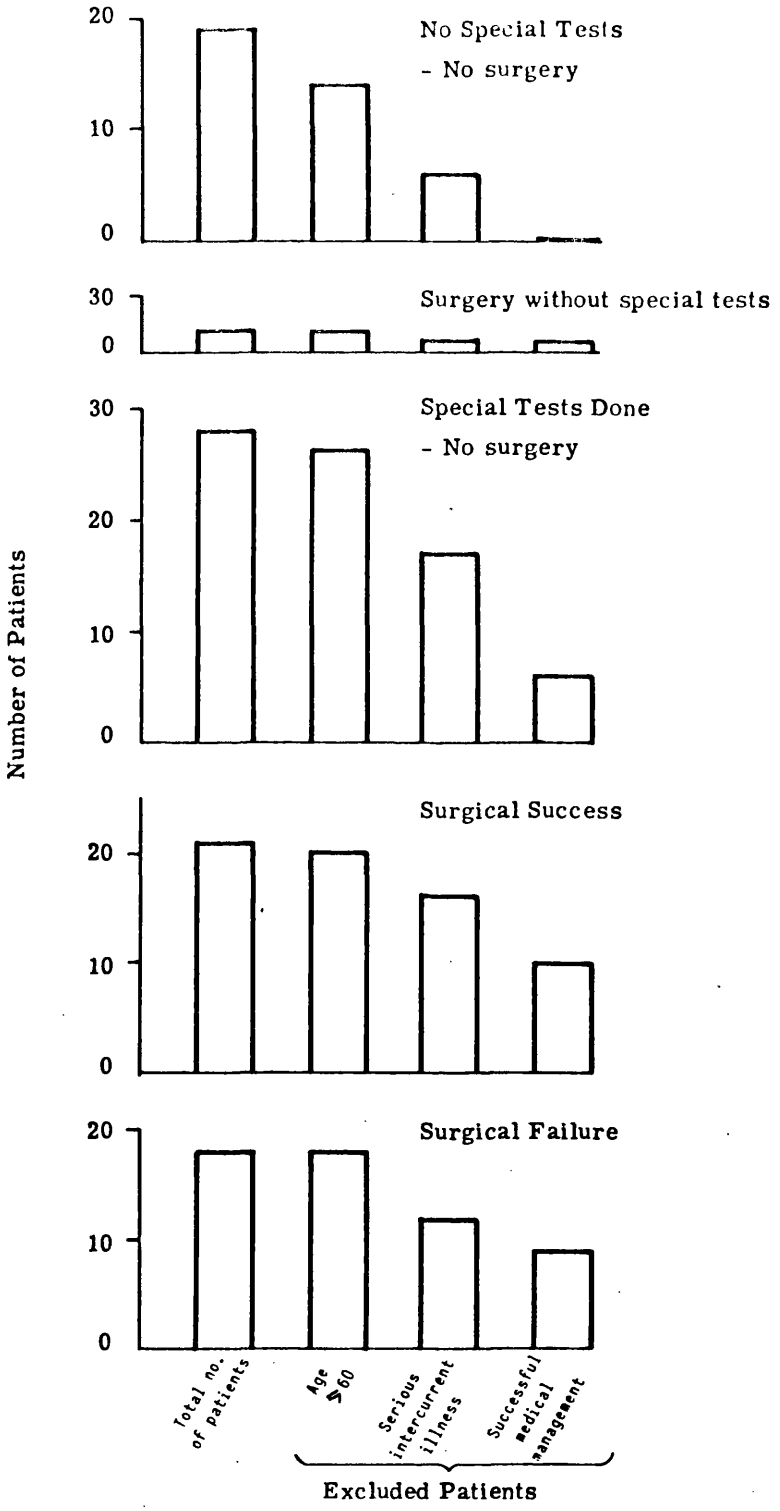


Figure 33: Decision against special tests. Application of factors influencing the decision against special tests to all patients including those eventually undergoing surgery. The left-hand column in each group represents the total number of patients.

In two patients who were not investigated but did come to surgery considerations other than cure of hypertension secondary to renal artery stenosis were paramount. One of these who 14 months previously had a nephrectomy for a renal artery occlusion, required emergency reconstructive surgery after occluding the artery to her remaining kidney and developing acute renal failure: this patient has been fully described in Chapter 5:2. In the other patient extrinsic pressure from a phaeochromocytoma was the cause of the renal artery stenosis, and excision of the neoplasm with the adherent kidney the necessary consequence without further provocative tests (Agabiti-Rosei et al, 1976).

10:2 DECISION TO OPERATE.

A further 65 patients were fully assessed with a view to surgery, and had both divided renal function studies and renal vein catheterisation studies carried out. They were slightly younger on average than those who did not have these tests performed, and had less concurrent vascular disease, but were very similar to that group in terms of sex distribution, severity of hypertension, ease of medical management and renal function.

In 28 patients who were fully investigated surgery was not performed. In 10 this arose either because severe illness developed or existing disease worsened before surgery was due; or because patients failed to attend clinics or to take medication. One patient came to elective nephrectomy after this series was closed and is normotensive without hypotensive drugs 9 months postoperatively.

The remaining 18 patients (Nos. 22-39, Table 2A) were not operated on probably for four principal reasons which often occurred in combination: absence of clear evidence of ischaemia on bilateral ureteric catheterisation studies despite the arteriographic appearance (7 patients), abnormalities in both kidneys (7 patients), severe intercurrent disease (3 patients) and easy control of blood pressure by drugs (12 patients). However, as Figure 34 illustrates application of these criteria to patients undergoing surgery would have led to exclusion of half of these including those who benefited from operation.

A decision was thus reached to operate in 39 patients. Apart from the two who had surgery without investigation as described above, all had features or tests which suggested that surgery would be beneficial. But with surgery done and with the advantage of hindsight no single criterion or group of criteria consistently predicted success. One important feature which emerged from

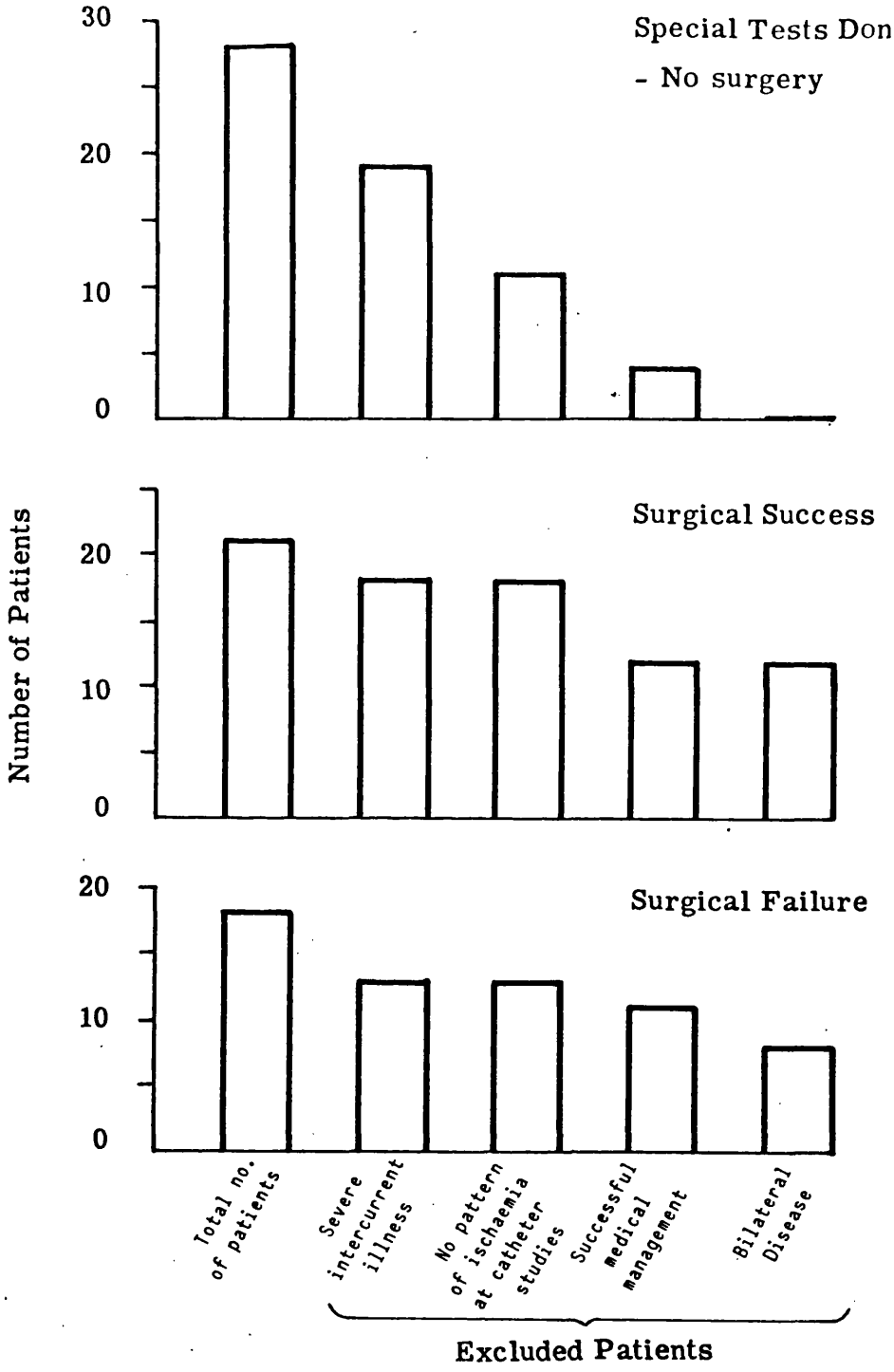


Figure 34: Decision against surgery. Application of factors apparently influencing the decision not to operate in some patients to those who eventually underwent surgery. Left-hand columns represent the total number of patients in each group.

the follow-up period was the much higher mortality and morbidity in the failures (Table 4 Appendix). In combination with the greater incidence of bilateral disease, left ventricular hypertrophy, and slightly poorer overall renal function, this may reflect a greater duration of hypertension with ensuing vascular disease prior to presentation.

CHAPTER 11

RESULTS OF SURGERY

Surgery was performed in 37 patients who were fully investigated and in 2 patients (Table 1B, Appendix) who were not. In 15 patients reconstructive surgery was the only procedure performed (dacron graft in 13, autogenous saphenous vein graft in 2). In 5 patients reconstructive surgery was attempted, but ipsilateral nephrectomy proved necessary at the same operation in 3, and at a second operation in 2. A further 19 patients had a nephrectomy as the primary procedure.

11:1 CHANGES IN BLOOD PRESSURE.

In 21 patients (Table 3, Appendix) blood pressure was consistently within one standard deviation of the age and sex-related mean (Hamilton et al, 1954) at least one year after surgery, without hypotensive drugs. Mean systolic blood pressure fell from 204 $\pm$ 22 mmHg to 132 $\pm$ 15 mmHg ($p < 0.001$) and diastolic blood pressure fell from 125 $\pm$ 13 mmHg to 81 $\pm$ 9 mmHg ($p < 0.001$).

In 18 patients (Table 4, Appendix) blood pressure was not restored to these normal limits. Drugs were required in 16 patients, and the mean systolic values of the whole group one year after surgery was 172 $\pm$ 29/ 107 $\pm$ 12 mmHg compared with recordings of 215 $\pm$ 37/ 133 $\pm$ 23 mmHg at presentation ($p < 0.001$ for systolic

and diastolic values). Neither mean systolic nor diastolic pressures were significantly different in groups having successful and unsuccessful surgery at the time of presentation. From Table 4 (Appendix) it can be seen that despite improvement as a group no beneficial effect of surgery could be detected in 6 of the 18 failures in whom the mean arterial pressure fell by less than 15 mmHg or even rose after surgery; the remaining 12 patients experienced a mean fall in mean arterial pressure of 49 mmHg ($p < 0.001$). The separation of success and failure is, however, arbitrary and it does not follow that failure was total. Five of the 6 failures who had reconstructive surgery had no evidence of unilateral ischaemia on postoperative intravenous urograms while the sixth paitnet who died on the second postoperative day with multiple myocardial necroses (Agabiti-Rosei et al, 1976) had a patent graft at post mortem examination.

11:2 BLOOD PRESSURE CHANGES AFTER EXCISION OF THE CLIPPED KIDNEY IN RATS WITH TWO KIDNEY HYPERTENSION.

In this study changes in blood pressure after excision of the clipped kidney have been examined in rats after short-term (5 weeks) and long-term (12 weeks) clipping.

Materials and methods have been described in detail in Chapter 4:13. Male Sprague-Dawley rats weighing

175-250g and maintained on Oxoid 41b diet and tap water ad libitum were studied. Systolic blood pressure was measured by tail plethysmography: each value was the mean of four readings. Animals were rendered hypertensive by application of a silver clip (0.2 mm internal diameter) to the left renal artery via an abdominal incision. Sham operations involved opening of the peritoneum and reflection of the viscera. Subsequent left nephrectomies were performed via a loin incision. All operations were performed under ether anaesthesia.

Baseline blood pressure readings on two days were recorded in 24 animals. Twelve animals were then clipped and 12 had sham operations. Blood pressure was recorded regularly in 6 clipped and 6 sham-operated animals for 5 weeks before excision of the clipped kidney and for 12 weeks thereafter. The remaining animals were followed for 12 weeks before and 12 weeks after left nephrectomy.

Results

A. Animals clipped for 5 weeks (Figure 35, upper panel)

Blood pressure rose significantly after clipping ($p < 0.001$) compared with recordings before clipping and in sham-operated animals. Following nephrectomy blood pressure fell over 24 hours to a mean of 9 mmHg below controls (N.S.) before rising gradually to values significantly greater than controls 12 weeks later ($p < 0.05$).

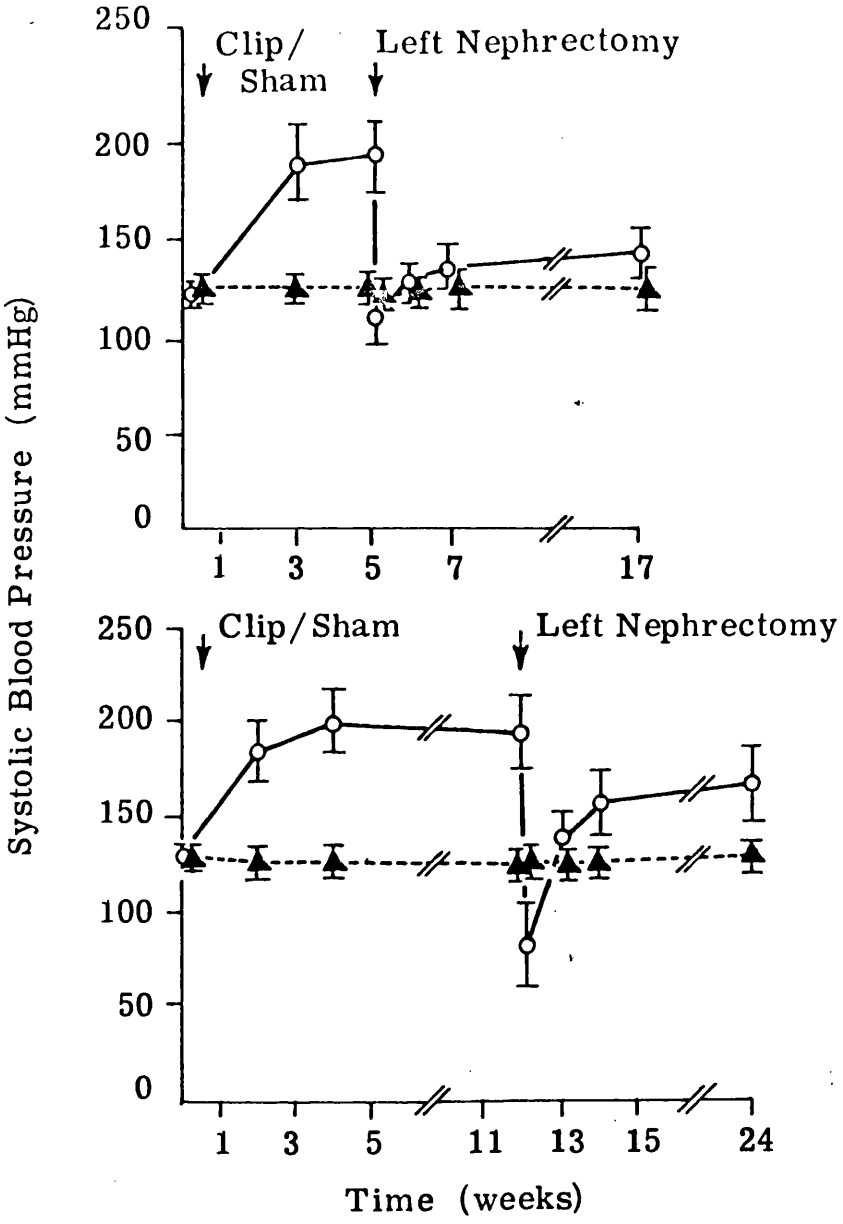


Figure 35: Blood pressure changes in clipped (open circles) and sham-operated (closed triangles) rats after clipping for 5 weeks (upper panel) or 12 weeks (lower panel), and after subsequent excision of the clipped kidney. Each symbol represents mean systolic blood pressure readings for 6 animals ± one standard deviation. Note interruptions in time axis.

B. Animals clipped for 12 weeks (Figure 35, lower panel)

These animals followed a similar pattern after clipping. One day after nephrectomy, however, blood pressure fell steeply by a mean of 113 mmHg. The mean nadir was 81 mmHg, which was significantly lower than in control animals ($p < 0.01$), than pre-clip values in the same animals ($p < 0.01$), and lower than comparable measurements in animals clipped for 5 weeks ($p < 0.05$). Blood pressure 12 weeks after nephrectomy was again greater than pre-clip values ($p < 0.001$), greater than in controls ($p < 0.01$) and greater than comparable values in animals clipped for 5 weeks, though the difference was not statistically significant.

C. Sham-operated animals.

Blood pressure did not change significantly in either group of control animals throughout the study.

11:3 CHANGES IN RENAL FUNCTION: A COMPARISON OF THE EFFECTS OF RECONSTRUCTIVE SURGERY AND NEPHRECTOMY.

Twenty-six patients with unilateral renal artery disease were studied. Fourteen were men with a mean age of 46 years (range 16-62 years), while 12 were women, with a mean age of 44 years (range 19-55 years). The arteriographic appearances were of occlusion in 9, atheromatous stenosis in 15, and fibromuscular hyperplasia in 2. Bilateral ureteric catheterisation studies confirmed unilateral ischaemia and permitted

separate measurement of clearances of PAH and endogenous creatinine from each kidney. In addition total creatinine clearance was estimated on two occasions in each patient in 24 hour urine collections. These pre-operative assessments were performed while subjects were receiving no treatment (18 patients) or bethanidine only (8 patients); in all instances any diuretics had been withdrawn at least 4 weeks previously.

Eleven patients (9 with stenosis and 2 with occlusion) then underwent renal artery reconstruction and 15 (8 with stenosis, 7 with occlusion) underwent unilateral nephrectomy. After a minimum follow-up of one year (mean 19 months) blood pressure, serum urea, serum creatinine, and 24 hour creatinine clearance were reassessed. At this point 23 patients were off all treatment: two post-nephrectomy and one post-reconstruction patient were on beta-blockers: no patient was receiving diuretics. Bilateral ureteric catheterisation studies, with measurements of PAH clearance were repeated in 2 patients. In 15 cases after operation plasma flow to each kidney was measured using ^{123}I-hippuran and a gamma-camera technique (4:10, 8:5) and compared with pre-operative divided PAH clearances. Pre-operative and postoperative data were compared using the Wilcoxon matched-pairs signed-rank one-tailed test (Siegel, 1956).

Results

Both reconstructive surgery and nephrectomy led to significant reductions in mean values for systolic, diastolic and mean blood pressure at one year ($p < 0.001$ for each - see Figure 36). The response was slightly, but insignificantly, greater following arterial reconstruction (Δ mean BP 45.3 mmHg) than after nephrectomy (Δ mean BP 35.8 mmHg).

Pre-operative serum urea (mean 5.4 mmol/l, range 3.4 - 10.1 mmol/l) and creatinine (mean 102 µmol/l, range 55 - 146 µmol/l) levels were within, or just above, the respective normal ranges, and the mean pre-operative values were not different in the groups having nephrectomy or arterial reconstruction. Clearances of creatinine and PAH were slightly (15% and 11% respectively), but not significantly, lower in the patients coming to nephrectomy (see Figure 36).

Postoperatively, patients who underwent nephrectomy experienced a 35% increase in serum urea ($p < 0.005$), a 23% increase in serum creatinine ($p < 0.005$), a 24% decrease in creatinine clearance ($p < 0.005$) and a 21% decrease in total PAH clearance ($p < 0.005$). The lowest creatinine clearance postoperatively was 24 ml/min and no patient subsequently required dialysis. By contrast, after reconstructive surgery, there was a 13% increase in creatinine clearance ($p = 0.025$), a 9% increase in

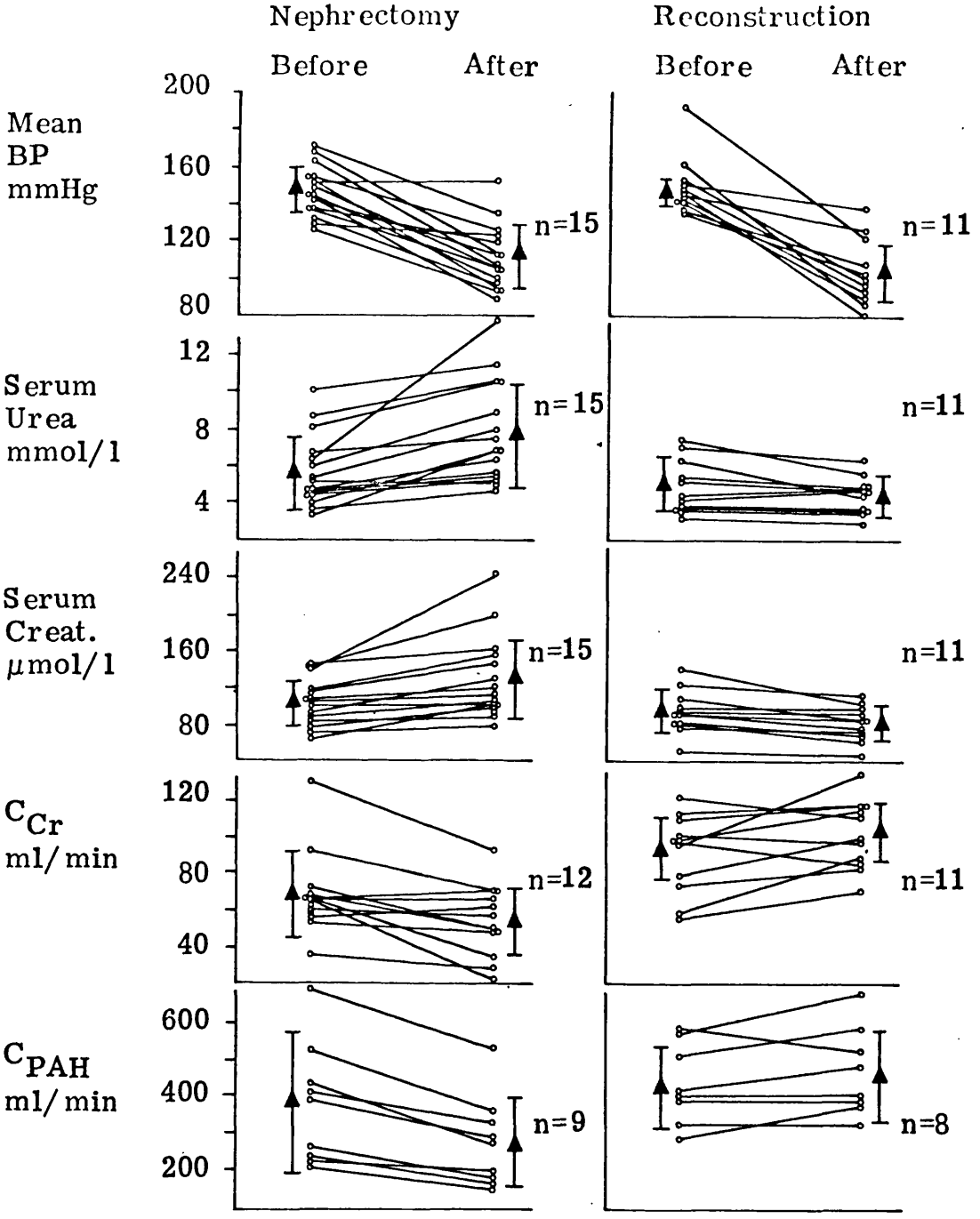


Figure 36: Consequences of surgery in renal artery stenosis - changes in A) mean arterial pressure (mmHg)
B) serum urea concentration (mmol/l)
C) serum creatinine concentration (µmol/l)
D) creatinine clearance (ml/min)
E) para-aminohippurate clearance (ml/min).

Closed triangles with bars represent mean ± one standard deviation.

total PAH clearance (N.S.), an 8% decrease in serum urea (N.S.) and a 14% decrease in serum creatinine ($p < 0.005$).

After renal artery reconstruction, effective renal plasma flow rose on the operated side by 25% from a mean of 156 ml/min to 195 ml/min ($p = 0.025$). However, on the unoperated side there was a postoperative fall of 13%, from 316 ml/min to 275 ml/min (N.S.); thus, net PAH clearance rose by only 9%. Similarly in patients who had unilateral nephrectomy renal plasma flow fell by 5% (N.S.) from 285 ml/min to 270 ml/min in the contralateral kidney.

11:4 CHANGES IN THE RELATIONSHIP BETWEEN MEAN ARTERIAL PRESSURE AND PLASMA ANGIOTENSIN II CONCENTRATIONS.

Previous work (Cuesta et al, 1976) has demonstrated an upward shift of the relation between mean arterial pressure and plasma angiotensin II concentration in patients with renal artery stenosis compared with normal subjects infused with angiotensin II. In Chapter 7:1 a significant positive correlation between mean arterial pressure and log plasma angiotensin II concentration was established in 25 patients who had measurements of total exchangeable sodium. In a larger group of patients ($n = 36$) who had plasma angiotensin II concentration measurements made free from drug therapy a similar relationship was observed (Figure 37A) but the correlation did not reach statistical significance ($r = 0.19$).

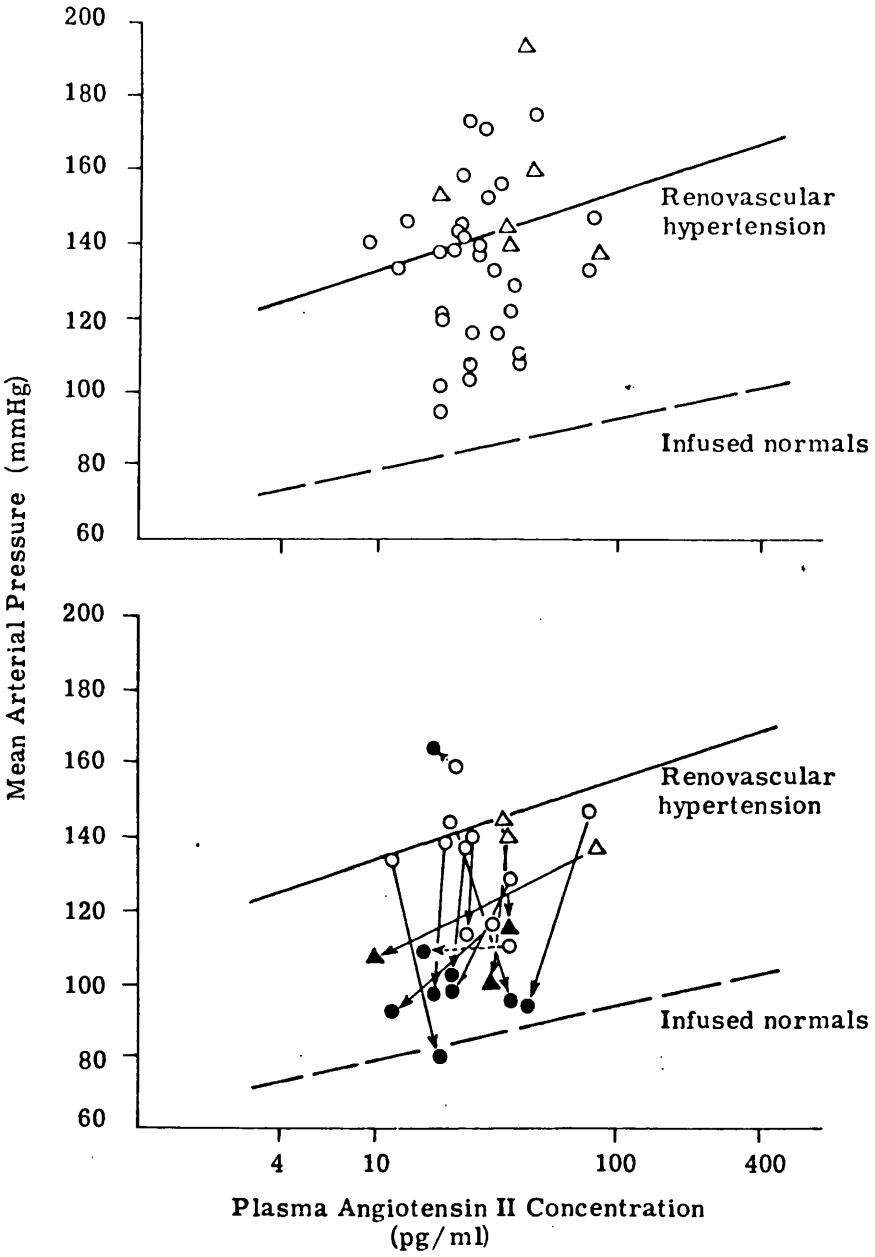


Figure 37A (upper panel). Venous plasma angiotensin II concentrations (pg/ml) compared with mean arterial pressure in patients with untreated renal artery stenosis. The solid line represents the regression equation for these patients. Open circles represent patients not in the malignant phase, and open triangles those in malignant phase hypertension. The lower interrupted line represents the regression equation for data from Cuesta et al (1977) for normal subjects infused with angiotensin II.

Figure 37B (lower panel). Results of operative treatment of 13 patients from Figure 37A. Solid symbols represent plasma angiotensin II concentrations off treatment at least one year after surgery. Dotted lines show changes after unsuccessful surgery in 2 patients while solid lines indicate the changes after successful surgery.

However, the regression equation was parallel to that from infused normals but was displaced upwards.

Measurements of plasma angiotensin II concentration were also available in 13 patients who were reassessed at least one year after operation having been free from drug therapy for at least one month (Figure 37B). Eleven had a successful outcome from surgery, 2 (indicated by the interrupted lines, Figure 37B) did not. It can be seen that after successful surgery there was a shift in the relation between mean arterial pressure and plasma angiotensin II concentration back towards that of infused normals.

11:5 CHANGES IN URINARY SODIUM EXCRETION.

Five of those patients in whom the relationship between urinary sodium excretion by the untouched kidney and mean arterial pressure was established pre-operatively (Figure 31: Chapter 9:6) subsequently underwent arterial reconstruction and had bilateral ureteric catheterisation studies repeated at least one year after surgery, off treatment. Three patients had a successful outcome from surgery, while 2 had a disappointing response. Changes in the relation between urinary sodium excretion and mean arterial pressure have been plotted in Figure 38. The number of patients is too small to draw firm conclusions but it appears from the available

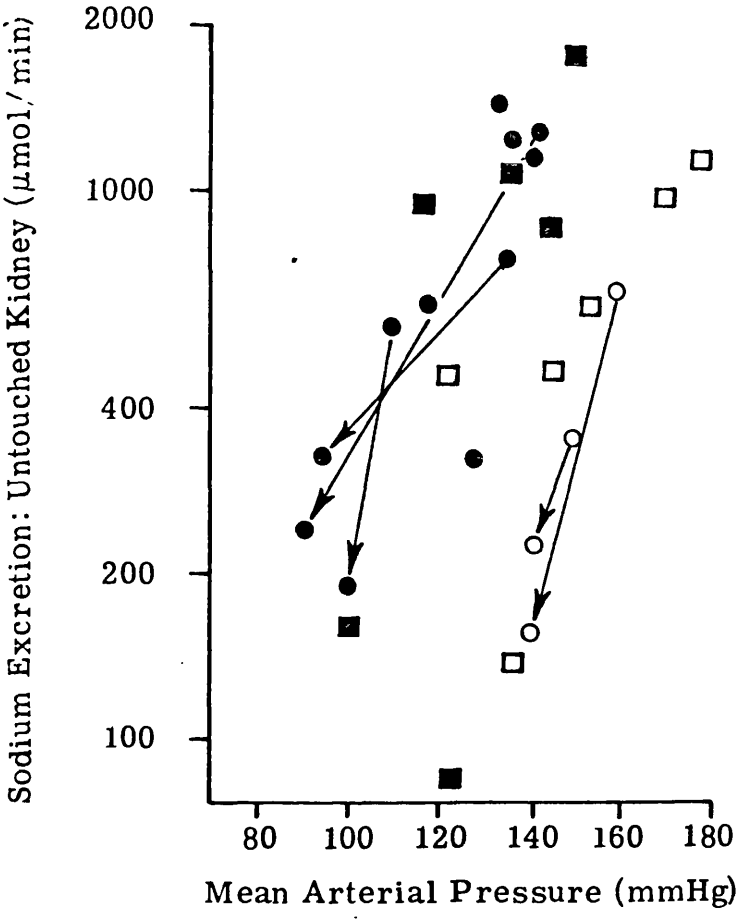


Figure 38: Relation of urinary sodium excretion from the untouched kidney and mean arterial pressure in patients with unilateral renal artery stenosis who subsequently underwent surgery. The changes in sodium excretion one year postoperatively are arrowed in 3 patients having successful reconstructive surgery (solid circles) and 2 patients having unsuccessful surgery (open circles). Squares represent nephrectomy patients - see Figure 31.

data that the relation between urinary sodium excretion and mean arterial pressure is still shifted downwards and to the right after surgery in patients who were surgical failures.

11:6 MORTALITY AFTER SURGERY.

Two patients died within 2 weeks of surgery. The first was a 23 year old woman with unilateral fibromuscular hyperplasia who died 2 days after reconstructive surgery with multiple myocardial necroses, despite patency of her graft, as shown at autopsy. The possible relationship between myocardial necroses and high circulating plasma angiotensin II levels has been discussed elsewhere (Agabiti-Rosei et al, 1976). The second, a 58 year old man without previous history of ischaemic heart disease, suffered an acute anterior myocardial infarction 2 weeks postoperatively.

Four other deaths occurred in patients whose blood pressure did not return to normal levels after surgery. Causes of death and duration of survival after surgery were stroke (6 months), uraemia (7 months) and myocardial infarction in 2 patients (13,42 months).

These 6 deaths after surgery during 60 patient years follow-up in surgical failures contrasts with no mortality during 89 patient years follow-up in surgical successes and is in accord with the latter group being

on average 5 years younger and having less vascular disease before surgery than the former.

Because this study was not a controlled trial of the efficacy of medical and surgical treatment of renal artery stenosis, and because medically treated patients (Tables 1 and 2, Appendix) were older than those treated surgically, comparisons of the mortality after each form of management cannot usefully be made.

CHAPTER 12

DISCUSSION

Many aspects of renovascular hypertension have been discussed in Chapter 2 of this thesis. In discussing the results which have been presented in Chapters 5 to 11 I wish to major on those observations on pathogenesis, diagnosis, prognosis and management which are original and which may influence the future investigation and management of hypertensive patients with renal artery stenosis.

12:1 PATHOGENESIS

1. Relationship between sodium and blood pressure in renal artery stenosis.

In Chapter 7:1 significant negative relationships between mean arterial pressure and both total exchangeable sodium ($r = -0.62$, $p < 0.001$) and plasma sodium concentration ($r = -0.48$, $p < 0.02$) were found in hypertensive patients with unilateral renal artery stenosis and normal renal function. These findings were in contradistinction to the significant positive relationships between exchangeable sodium and blood pressure in other forms of hypertension - Conn's syndrome, chronic renal failure, and essential hypertension (Table 5). It was also found that urinary sodium excretion from the untouched kidney in unilateral renal artery stenosis

correlated significantly and positively with mean arterial pressure, in contrast to sodium excretion from the abnormal kidney (Table 6), and that the relation in the untouched kidney was shifted downwards and to the right in patients who had a poor response to reconstructive surgery or nephrectomy compared to those who had successful surgery (Figure 31).

Since the role which sodium retention and volume expansion may play in the pathogenesis of many forms of hypertension is still a matter of controversy these findings are interesting. The potential importance of the phenomenon of pressure-natriuresis (Selkurt, 1951) whereby a small increment in arterial pressure is accompanied by a large increment in urinary sodium excretion has been discussed in Chapter 2:3. If an imbalance between sodium status and arterial pressure is the primary abnormality leading to hypertension, pressure-natriuresis would tend to restore sodium balance to normal, a mechanism which Guyton et al (1972) described as being theoretically 100% efficient, having "infinite gain". However, to maintain normal sodium status in the long-term the pressure-natriuresis curve would require to be reset, or shifted to the right. Ledingham (1971), Guyton et al (1972) and Brown, Lever, Robertson, and Schalekamp (1974) favour such a disturbance as a fundamental fault in hypertension.

Several pieces of evidence from the present study are consistent with the concept of pressure-natriuresis in the untouched kidney in unilateral renal artery stenosis. First, there is the negative relation between blood pressure and exchangeable sodium, and the positive relation between blood pressure and urinary sodium excretion from the untouched kidney. In the most extreme cases with the lowest exchangeable and plasma sodium a distinct syndrome - the hyponatraemic hypertensive syndrome - occurs, with the most clamant cases complaining of polyuria, polydipsia, weight loss, and in one instance a craving for salt - see Figures 14, 15 and Table 7. These severely hypertensive patients, most with malignant phase hypertension and occluded renal arteries, had the arterial lesion as the primary stimulus to renin secretion and the formation of high circulating levels of angiotensin II. Well preserved contralateral kidney function without resetting of the pressure-natriuresis curve is necessary to produce the disproportionate sodium loss from the untouched kidney, which acts as a further powerful stimulus to renin, angiotensin II and aldosterone formation. Also contributing to the sodium loss are direct intrarenal actions of high angiotensin II levels (Brown and Peart, 1962; Brown, Matthew, and Robertson, 1964). A further stimulus to renin secretion is hypokalaemia, resulting

from the secondary hyperaldosteronism in this syndrome (Brunner, Baer, Sealey, Ledingham, and Laragh, 1970). There are thus many interlinking factors in the pathogenesis of this condition, which have been reviewed in detail by Atkinson et al (1979a).

Second, the data in Figure 16 may represent a pressure-natriuresis curve. However, interpretation of urinary sodium excretion results is compromised to some extent by the unphysiological conditions under which ureteric catheterisation studies are performed, where saline - mannitol diuresis and spinal anaesthesia both contribute to natriuresis, the absolute values for sodium excretion being many times higher than would normally occur in these patients. Similar problems surround the interpretation of experimental data on pressure-natriuresis (Thomson and Dickinson, 1973).

Third, the relation between urinary sodium excretion from the untouched kidney and mean arterial pressure is different in patients having successful surgery from those in whom surgery failed to lower blood pressure to normal (Figure 31). While the number of patients is small the findings are, nevertheless, consistent with resetting of the pressure-natriuresis curve in the untouched kidney of patients having unsuccessful surgery. It is interesting then that in the 5 patients who had further measurements of urinary sodium excretion after reconstructive surgery (successful in 3, unsuccessful in 2 - Figure 38), the data seem to differentiate between

postoperative changes along one pressure-natriuresis curve in successes and along another in failures.

2. Angiotensin II in renal artery stenosis.

Evidence concerning the role of angiotensin II in raising blood pressure in man and animals with renal artery stenosis was reviewed in Chapter 2:3. The possibility of a slow as well as a rapid component to the pressor action of angiotensin II was discussed, and the work of Cuesta et al (1976) demonstrating that mean arterial pressure in patients with renal artery stenosis was disproportionately high in relation to concurrent plasma angiotensin II concentrations when compared with normal controls infused with angiotensin II was relevant to this. The present study has confirmed that this relationship is abnormal in patients with unilateral renal artery stenosis, and that after successful surgery (Figure 37) there is a tendency for the relationship to be restored towards normal.

The concept of pressure-natriuresis from the untouched kidney in patients with unilateral renal artery stenosis leading to hyponatraemia and secondary hyperaldosteronism has already been discussed (12:1,1). In keeping with this concept were the significant and negative relationship between plasma angiotensin II concentration and both total exchangeable sodium ($r = -0.57$,

$p < 0.01$) and plasma sodium concentration ($r = -0.72$, $p < 0.001$) and the positive relationship which was weaker but still significant between urinary sodium excretion from the untouched kidney and mean arterial pressure ($r = +0.38$, $p < 0.05$). Furthermore, plasma angiotensin II concentration correlated with concurrent mean arterial pressure in patients with unilateral renal artery stenosis ($r = +0.46$, $p = 0.05$). This weak correlation was consistent with the direct and rapid pressor action of angiotensin II; Atkinson et al (1979b) also found that the initial fall in blood pressure after administration of captopril was related to the pretreatment plasma angiotensin II concentration, but that a slower secondary fall in blood pressure occurred over 6 weeks and that this was not related to the pretreatment plasma angiotensin II concentration.

3. Smoking in renal artery stenosis.

Among patients with non-malignant hypertension and renal artery stenosis (Chapter 7:2) there was a highly significant excess of smokers in comparison with control groups who had non-malignant hypertension of comparable severity. Recent studies have found excess smoking in malignant-phase hypertension (Bloxham et al, 1979; Isles et al, 1979) and this association was also apparent in the present analysis of patients with malignant-phase hypertension and renal artery stenosis. Thus, excess

smoking was a feature of malignant-phase hypertension and of renal artery stenosis whether considered separately or together. Within the group with renal artery stenosis and non-malignant hypertension, excess smoking was apparent in patients with renal artery occlusion, with fibromuscular hyperplasia and with other forms of renal artery stenosis.

In a retrospective analysis of this sort several possible sources of error or bias exist. An individual's smoking habits may vary from year to year, and smoking also varies with sex, age and social class (Royal College of Physicians Report,1977). Also the smoking habits of renal artery stenosis patients were not recorded in a standardised way, but the clinicians recording the data in this and control group B were not aware that statistical analysis would be performed. In control group A smoking habits were recorded in a standardised way.

It is unlikely, however, that bias affected the differences seen in renal artery stenosis; the two control groups gave similar results, which in turn were similar to those in a control group derived from the same population and that seen in a general population survey conducted in the Glasgow area (Hawthorne, 1977; Isles et al, 1979). Moreover the difference in smoking habits between renal artery stenosis and controls was large, was present in men and women separately and together

and was apparent in three different groups. It is likely, therefore, that there is a genuine excess of smoking in renal artery stenosis.

Cigarette smoking has now been linked with vascular disease, usually atheromatous, in the heart,brain, peripheral circulation (Doll and Peto, 1976), eye (Ellis, Hamer, Hunt, Lever, Lever, Peart, and Walker, 1964; Paetkau, Boyd, Winship, and Grace, 1977) and kidneys. However, the present study has also identified excess smoking in a non-atheromatous form of vascular disease, namely fibromuscular hyperplasia, whose aetiology is as yet undetermined (Stanley, Gewertz, Bove, Sottiurai, and Fry, 1975; Youngberg et al, 1977). While the excess smoking was not as marked in this as in the other subgroups of renal artery stenosis and the diagnoses were made on arteriographic rather than histological appearances, nearly three-quarters of the patients with fibromuscular hyperplasia smoked. Smoking has not previously been noted as a risk factor for this condition.

There are three possible interpretations of the association between smoking and renal artery stenosis. First, the smoking may have predisposed to the development of the stenosis; second, the stenosis may have encouraged patients to smoke; last, a third agent may have encouraged both smoking and renal artery stenosis. There is no evidence to support the second or third

contentions, and it is likely that smoking was a factor leading to the development of renal artery stenosis. Hypertensive subjects who smoke thus incur two separate and cumulative risks of vascular disease. Moreover, because renal arterial lesions can per se lead to further elevation of blood pressure, their development will be likely to have particularly adverse consequences. These finding are, therefore, a further indictment of cigarette smoking.

4. Factors in the pathogenesis of fibromuscular hyperplasia.

The aetiology of this interesting condition, or series of conditions (Chapter 2:4), is incompletely understood. Previous suggestions have invoked stretching of the renal vessels during pregnancy, abnormalities of pressure-wave conduction (Twigg and Palmisano, 1965) or undue mobility of the kidneys as possible pathogenetic mechanisms, which are not mutually exclusive.

Several observations in this thesis are of interest. First, as discussed above (12:1,3) a significant relationship exists between smoking and fibromuscular hyperplasia. Second, while 91% of cases were women, who were significantly younger than women with atheromatous stenosis, no relationship between fibromuscular hyperplasia and the number of pregnancies, hypertension during pregnancy, or height could be established. Third, 52% of cases involved the right renal artery alone and

only 22% the left alone, while in 26% there was bilateral involvement. Similar lateralisation was observed in the cooperative study of renovascular hypertension (Simon et al, 1972) where 57% of cases were solely on the right, 19% on the left and 24% bilateral. Why this should occur is not completely clear, but it is of interest that nephroptosis, as in the patient described in Chapter 5:1, is a condition principally affecting the right kidney of young women (Bianchi, Bonadio, and Andriole, 1976). Furthermore, in patients who develop renal artery stenosis or thrombosis after blunt abdominal trauma, and in particular deceleration injuries, subintimal damage has been demonstrated in the middle or distal third of renal artery (Ross, Ackerman, and Pierce, 1970) which is mobile in comparison with the relatively fixed proximal third of the artery (Evan and Mogg, 1971). In view of this the fact that fibromuscular hyperplasia affects principally the middle and the distal third of the renal artery is all the more interesting, and suggests that undue movement of the more mobile parts of the renal artery may have a role in the pathogenesis of fibromuscular hyperplasia.

12:2 DIAGNOSIS

1. Clinical features.

As renal artery stenosis is potentially remediable it is unfortunate that symptoms and signs specific for the diagnosis are rarely found. The presenting complaints

analysed in Chapter 6:1, however, highlight a few individuals in whom a high index of suspicion is justified. Where loin pain, haematuria and hypertension co-exist, the possibility of renal infarction should be considered and a history of trauma, especially deceleration injury sought (Stables, Fouche, Niekerk, Cremin, Holt, and Peterson, 1976); however, even with this history, alternative diagnoses such as renal stones or pyelitis may prove correct. In patients with malignant phase hypertension a lesion of rapid onset such as renal artery stenosis or occlusion should be considered, though the rapidity of onset can rarely be established with certainty as in the unique patient described in Chapter 5:3. 26% of the patients in this series presented in the malignant phase, and over half of these (14%) had presented complaining of impaired vision. In the cooperative study of renovascular hypertension (Simon et al, 1972) a similar proportion of patients with renal artery stenosis (15%) had optic fundal changes of malignant hypertension, while Genest et al (1977) found 20% of patients so affected. The unusual hyponatraemic hypertensive syndrome characterised by polyuria, polydipsia, and weight loss has already been discussed (Chapter 12:1,1). The great majority of patients, however, had non-specific complaints or were asymptomatic at presentation (Figure 12).

The limitations of an abdominal or loin bruit as a diagnostic sign were discussed in Chapter 2:6, as bruits also arise from the atheromatous aortas of patients with essential hypertension, and are absent when renal blood flow is slightly or markedly reduced in patients with renal artery stenosis. In this series a bruit was not often detected (24% of patients) in comparison with other studies (Chapter 2:6) where an incidence of 48-58% was noted, but in keeping with the work of Hunt et al (1974) bruits were heard more often in patients with fibromuscular hyperplasia than in those with atheromatous stenosis.

2. Intravenous urography.

Since clinical features generally are non-specific in patients with renal artery stenosis, a simple non-invasive but accurate screening test is desirable. Intravenous urography is the most widely available test, but it has been criticised (Chapter 2:7,1) for its lack of sensitivity and specificity. Delay in the appearance of contrast and differences in contrast density are rarely seen with such clarity as is depicted in Figure 4. The failure of referring clinicians to have reached the correct diagnosis on the basis of urographic appearances in half of the cases (Figure 13) also attests to a high incidence of apparently false negative results.

In Chapter 8:3 the results of intravenous urography, arteriography, renal vein sampling, and bilateral ureteric catheterisation studies in a series of hypertensive patients were analysed so that a re-evaluation of the diagnostic merits of intravenous urography could be made. Of the other tests renal arteriography is a measure of anatomy alone and says little or nothing of function (Brown et al, 1979a). Renal vein sampling permits measurement of plasma renin concentration in blood coming from the affected kidney and a comparison with that in blood coming from the contralateral kidney (Millar et al, 1978). Bilateral ureteric catheterisation studies allow measurement of function in the two kidneys in absolute terms as well as comparison of a number of biochemical function tests from each kidney (Stamey, 1966; Capelli et al, 1973): their value in diagnosis is clear from Figure 18 where unilateral renal artery stenosis or occlusion is seen to have caused a spectrum of biochemical differences between the two kidneys which is quite distinct from that seen in unilateral parenchymal disease with normal renal vasculature. The functional abnormality in ischaemia has been confirmed in animal studies (Zweig et al, 1972; DeForrest et al, 1978) and has two components: first, there is increased water reabsorption which is reflected in reduced urine flow rate and increased urinary

concentration of endogenous (creatinine) and exogenous (PAH) non-reabsorbable solute on the affected side; second, there is a reduction in glomerular filtration rate. Increased sodium reabsorption may result in low urinary sodium concentration on the affected side. The extent of encroachment on the renal artery lumen by stenotic lesions varies in different patients with a continuous distribution: the extent of the differences in findings at ureteric catheterisation is similarly distributed continuously. Therefore, instead of selecting one of a number of possible arbitrary cut-off points (Capelli et al, 1973) above which the difference between the sides in patients with ischaemia is deemed 'significant' the spectrum of biochemical and humoral abnormalities in patients with ischaemia was compared quantitatively with the spectrum of diagnostic abnormalities in the intravenous urogram. Quantitative comparison of the results of intravenous urography with those of other tests was made possible in this study by scoring the qualitative reports of 6 observers on each intravenous urogram.

Changes on the intravenous urogram. Observer error is common in the reporting of intravenous urograms as Figures 19 and 20 show. Bookstein et al (1972a) likewise found considerable variation between reporters in the cooperative study of renovascular hypertension. The

present data on consistency of reporting emphasise that conclusions about the normality or otherwise of the intravenous urogram of a hypertensive patient should not depend on the comments of one observer, since even experienced observers may vary. Indeed a single observer may well vary in his interpretation of the same films, although this was not tested. It could also be recommended on the basis of the data that where one observer detects even slight delay or density difference renal arteriography is usually worthwhile. Since the intravenous urogram is only an initial screening test, not a definitive investigation, false positives which might result from this plan of action will be relatively common, but will be more desirable than false negative tests. From 7% (Maxwell et al, 1964) to 28% (Wilson et al, 1963) of false negative urograms have been reported in renal artery stenosis and in the present study 29% of reports on patients with unilateral ischaemia were falsely normal, despite a high index of suspicion on the part of the observers. While many of these false negatives occurred in patients with mild ischaemia, it nevertheless underlies a real lack of sensitivity of the test. Furthermore, 7% of reports suggested ischaemia on the wrong side, though the observers were never unanimously wrong in any patient.

A number of modifications of the standard intravenous urogram technique have been suggested to improve the diagnostic accuracy. A further radiograph after an oral water load has been suggested (Sutton et al, 1961) but such films were of limited benefit in this study. An intravenous solute load during urography (Amplatz, 1962; Schreiber et al, 1964) was in vogue in the mid-1960's, but did not prove to be consistently useful. One of the more useful modifications has been rapid sequence radiographs in the 5 minutes immediately following injection of contrast, thereby increasing recognition of delay in the appearance of contrast on the affected side (Maxwell et al, 1964; Bookstein et al, 1972b). A pilot study (Chapter 8:4) failed to demonstrate a useful increase in diagnostic accuracy of a further possible modification - administration of indomethacin to patients with unilateral renal artery stenosis for 2 days before urography. Such differences as did occur (Table 15) could equally be attributed to variations in gas and faeces overlying the kidneys or to the position of the patient (Saxton, 1969) as to a true pharmacological effect of indomethacin. Larger studies both in animals and man may yet demonstrate minor alterations in the urographic appearances by prostaglandin synthetase inhibitors, as there is abundant evidence reviewed by Hollenberg (1979) and Dunn (1979) that prostaglandins do modulate renal perfusion and function in man

and animals. However, any widespread clinical application seems to be ruled out by this pilot study.

False positive urogram reports were also analysed in the comparative study of urography and ureteric catheterisation studies (Chapter 8:3). There were too few patients for proper assessment of false positives but the results suggest that here too the rate of error may be high. Selected for comparison because of the presence of unilateral small kidneys, these patients provided a difficult test for the specificity of the intravenous urogram and 62% of reports were of ischaemia. In another study where a control group of unselected patients with essential hypertension was used (Bookstein et al, 1972b) 11.4% of normal intravenous urograms were falsely reported as being positive. However, the lack of specificity in the present study is not of great significance in practical terms so long as abnormalities are not missed, and all patients would have been referred for further investigation.

Correspondence of intravenous urography with renal function tests.

Since the contrast media used in intravenous urography are non-reabsorbable solutes (Fry and Cattell, 1979) which are filtered by the renal glomeruli a possible explanation of the urographic changes in renal artery stenosis has been proposed on the basis of ureteric catheterisation data. By this theory

(Brown et al, 1960, 1979a) delay in the appearance of contrast would result from reduced urine volume in the ischaemic kidney, and increased contrast density would reflect water reabsorption producing hyperconcentration of non-reabsorbable solute. Both contentions receive support from this study. Thus delay in the appearance of contrast significantly correlates with urine volume reduction. This urine volume reduction is likely in turn to comprise a reduction in glomerular filtration rate (another significant correlation) and an increase in water reabsorption (suggested by another significant correlation with creatinine clearance ratio). Likewise, density differences are significantly correlated with the ratio of concentrations of non-reabsorbable solutes, creatinine and PAH. In turn these concentrations depend on urine flow rate and glomerular filtration rate (two further significant correlations).

Further weight is lent to this explanation by the findings presented in Table 14. In the course of bilateral ureteric catheterisation studies, a run-in period takes place to allow a steady state to be established before urine and plasma collections are made. Where glomerular filtration rate is well maintained in the ischaemic kidney, non-reabsorbable solutes such as urographic contrast medium which is injected by bolus would be expected to reach that steady state quickly. Thus urographic and ureteric catheter data would be

expected to agree. This is indeed the case (Table 15). On the other hand, where glomerular filtration rate is poorly maintained on the affected side a bolus of solute would not be expected to reach steady state conditions so promptly if at all; urographic and ureteric catheter data would be expected to correlate less well than in the group with well maintained glomerular filtration rate. Our findings are consistent with this contention.

In contrast to the results of ureteric catheterisation, the renal vein renin ratios correlated poorly with diagnostic features on intravenous urography. This is not surprising since the aspects of disordered function which they reflect are different. However, it is interesting to note that the only ureteric catheterisation result with which renal vein renin ratios correlated significantly in this study was the PAH clearance ratio. The implications of such a relationship and its influence on the renin secretion rate has been discussed in detail elsewhere (Brown et al, 1979b).

Quantitative analysis of the intravenous urogram such as has been described here has not been described previously. Evidence in support of an explanation of the urographic findings based on altered water reabsorption and solute concentrations in the face of well maintained glomerular filtration in the ischaemic kidney has been provided. The lack of sensitivity and specificity of the

intravenous urogram in renal artery stenosis has been emphasised, as has the importance of more than one observer viewing the intravenous urogram of a hypertensive patient before declaring it normal. Also the classical features of renal artery stenosis should not be expected or required before proceeding to arteriography and any minor abnormality in the intravenous urogram should be followed up in this manner. Arteriography should also be performed if good blood pressure control rapidly deteriorates and if blood pressure is uncontrollable by conventional means or if a hypertensive patient develops unexplained renal dysfunction (Chapter 5:2).

3. ^{123}I-hippuran renography and a gamma camera technique in the measurement of total and divided renal function.

A new non-invasive technique for the assessment of total and divided effective plasma flow, using ^{123}I-hippuran and a gamma camera, was compared with an established technique using bilateral ureteric catheterisation in Chapter 8:5. Such a comparison is lacking in the literature. The correlation between the two techniques was close on both stenosed ($r = 0.77$) and unaffected ($r = 0.81$) sides, despite the time interval between the performance of these tests. Furthermore, the close correlations between the ratio of plasma flows (affected : unaffected) at renography and ureteric

catheterisation (r = 0.94) and between total hippuran clearance and PAH clearance performed on the same day (r = 0.96) suggest that if ureteric catheterisation and renography had been performed on the same day a still closer relationship between the two points would have been established.

Several previous studies have shown the validity of using total clearance of hippuran, labelled with a variety of iodine isotopes (Ram et al, 1968; Tauxe et al, 1971; Short et al, 1973), as a means of estimating total effective renal plasma flow and this has been confirmed here using ^{123}I-hippuran. However, it must be remembered in appraising the results of such studies that while hippuran (ortho-iodohippurate) and PAH (p-aminohippurate) are analogues, there are systematic differences in their protein binding capacity and red cell uptake which lead to an apparent underestimate of plasma flow by the radionuclide technique. This underestimate has resulted in hippuran clearance values varying from 84% (Maher & Tauxe, 1969) to 96% (Cutler and Glatte, 1965; Brodkey et al, 1979) of true PAH clearance values in previous reports, though in the present study mean hippuran clearance was 99% of mean para-aminohippurate clearance performed on the same day. Contributing to the closeness of this relationship was the minimum interval of 2 hours which elapsed between the two tests, ensuring no competition at tubular transport sites

between large quantities of infused PAH and small amounts of hippuran tracer. Britton (1979) has written that "there is no non-invasive method, based on the use of radionuclides for obtaining from each kidney a precise estimate of the absolute measure in man of any function". While agreeing with this sentiment, in this study the use of hippuran labelled with ^{123}I permitted sufficient accuracy of quantitation for valid and clinically applicable (Norman, 1974) measurements of effective renal plasma flow to be made.

PAH or hippuran clearance is only one aspect of renal function, however. The merit of bilateral ureteric catheterisation studies is the number of different quantitative measurements which are obtained for each kidney (Figures 6 and 18). Its major disadvantage is its invasiveness (Munck et al, 1968; Genest et al, 1977), resulting in morbidity, especially urinary tract infections. However, with experienced staff such morbidity may be minimised. The incidence of complications arising from 65 consecutive bilateral ureteric catheterisation studies over a period of 10 years in patients with renal artery stenosis was small (Table 10). No single instance of urinary tract infection occurred after these studies. The most worrying complications related to the lumber puncture rather than the catheterisation itself, since abdominal or loin pain

experienced by 10 patients was transient and responded readily to analgesics. Despite their invasiveness ureteric catheterisation studies still have much to offer in diagnosis particularly where the results of other tests are equivocal. On the other hand, ^{123}I-hippuran renography is an accurate quick and non-invasive means of assessing total and divided effective renal plasma flow under physiological conditions. Because of its patient acceptability repeated estimations of renal function may be made: this may prove to be of value in longitudinal studies of renovascular hypertension.

12:3 PROGNOSIS.

Prediction of those patients with renal artery stenosis in whom surgery will fail to cure the hypertension is clearly desirable, and tests aimed at accurate prognosis important. However, from reviewing the literature on renal artery stenosis over the past 20 years and despite the introduction of newer prognostic tests based on renal vein sampling, bilateral ureteric catheterisation studies, and the use of antagonists and inhibitors of the renin-angiotensin system, it is apparent that the rate of surgical success has not altered much over that time. This implies that while newer tests permit greater diagnostic accuracy they add little to prognostic accuracy.

In the present retrospective analysis no single test - clinical features (Chapter 9:1) serum urea or creatinine concentration (Chapter 9:1), peripheral plasma renin concentration (Chapter 9:2), renal vein renin ratio (Chapter 9:3), incremental saralasin infusion (Chapter 9:4), many criteria based on bilateral ureteric catheterisation studies (Chapter 9:5, Table 18, Figures 27-30), or the relation of urinary sodium excretion and mean arterial pressure (Chapter 9:6) - uniformly separated succes from failure in all patients. Furthermore, no group of tests (Figure 32) nor any discriminant function (Chapter 9:7) could be found with greater prognostic merit.

In a small number of patients, however, the outcome could have been predicted: a renal vein renin ratio of 2.0 or more reliably predicted success in 18% of patients and the presence of bilateral disease reliably predicted failure in 15%. But in 67% of patients extensive investigations were not reliable in predicting the outcome. At the time of deciding on surgery in these patients no single prognostic test was considered as being of overriding importance. Indeed if the results of special tests had been ignored and the decision on surgery made solely on the basis of age, the presence of other vascular disease and renal function, the rate of surgical success would have been little different, though the actual numbers coming to surgery would have been less (Figure 33).

Claims have been made that many tests have much greater prognostic accuracy than has been found in this study, but there is no unanimity between centres on how a particular test should be performed, on what constitutes a positive test pointing to a successful outcome from surgery, or even in strict terms what constitutes a normal blood pressure postoperatively. Tests which identify the presence of a functional stenosis (i.e. diagnostic tests) must be clearly distinguished from tests which predict the extent of blood pressure reduction, if any, after surgery (i.e. prognostic tests); sometimes different aspects of the same test such as bilateral ureteric catheterisation studies may be relevant to both diagnosis and prognosis. However, unequivocal identification of a functional stenosis does not necessarily imply a good prognosis.

Variations in the conditions under which a test is performed, such as the sodium status, posture and drug treatment of the patient, are a source of confusion in evaluating prognostic tests from different centres, and may influence the degree of abnormality which is accepted as a positive test (Chapter 2:7,7). Mannick et al (1969) advocate renal vein blood sampling after a bolus of hydrallazine, while Genest et al (1977) advocate the same test under conditions of stimulation of the

renin-angiotensin-aldosterone axis by sodium depletion and upright posture. Many workers, however, assess their patients under conditions of sodium repletion but not loading, supine posture, and absence of medication: these baseline conditions have been adhered to in this study. A further source of variation is in the measurement of plasma renin concentration. Early studies in the 1960's (see Marks and Maxwell, 1975) used a bioassay for the measurement of angiotensin I generated during the test while later studies have used a radioimmunoassay technique, but even with this, the results were not standardised: the recent introduction of the international standard for renin (Bangham et al, 1975) may help to minimize this source of variation. However, even under similar conditions of sampling and measurement, there is a wide variation in the recommended prognostic criteria for a single test - Michelakis et al (1967) and many others recommend a renal vein renin ratio of 1.5 or more, while Gunnells et al (1969) recommend a ratio of 2.0 or more and Amsterdam et al (1969) a ratio of 2.5 or more. Recommended criteria differ depending on the degree of certainty which the proponent wishes to demand. As Marks and Maxwell (1975) point out 81% confidence limits exist where a renal vein renin ratio of 1.5 or more is used, while there are 95% confidence limits with a ratio of 1.96 or more. However, while the use of a strict

criterion in a prospective fashion will certainly enhance its credibility as a prognostic test, it will do so at the expense of preventing potentially curable patients from coming to surgery.

It must also be recognised that criteria predicting success may differ depending on the type of surgery to be performed. The results of nephrectomy will depend on the state of the contralateral kidney, while the results of arterial reconstruction will depend on both the ischaemic and the contralateral kidney. Criteria based on the results of bilateral ureteric catheterisation studies would be particularly affected (Brown et al, 1979b).

From examination of the present data, certain helpful trends in assessing the eventual outcome were observed. Successful surgery occurred on average in slightly younger patients with less renal impairment, less vascular disease at other sites, less radiological evidence of cardiomegaly and less electrocardiographic evidence of left ventricular hypertrophy, but with a greater incidence of malignant phase hypertension at presentation, slightly higher peripheral plasma renin concentration, higher renal vein renin ratio, and more marked evidence of ischaemia of the affected kidney and better preservation of the contralateral function. The majority of such trends as are detectable point to a greater duration of hypertension in failures prior to presentation.

The greater incidence of morbid events of a vascular nature in surgical failures in the follow-up period also attests to this, although because of continuing poor control in some, even with drugs, firm conclusions can be drawn.

Why some patients continue to have elevated blood pressure after technically successful surgery following apparently favourable prognostic tests is not completely clear. The prognostic tests themselves may be too inaccurate (Chapter 9). Animal studies (Byrom and Dodson, 1949; Floyer, 1951) suggest that persistent hypertension after removal of a renal artery stenosis by unclipping or nephrectomy reflects hypertensive damage to the contralateral kidney, which in turn reflects the severity and duration of the hypertension; it is possible that resetting of the pressure-natriuresis curve in the contralateral kidney is the underlying abnormality (Chapter 12:1,1); but even where in man contralateral function is excellent, surgery may be unsuccessful. Moreover, as was emphasised in the introduction to this thesis in man there is often no means of determining accurately the duration of hypertension before presentation - the case presented in Chapter 5:3 is exceptional in this respect - but it is true that those patients with widespread vascular disease or bilateral atheromatous

stenoses, consistent with longstanding hypertension, fare worse after operation. Also, patients with essential hypertension who have a consequent increase in atherogenesis may subsequently develop a renal artery stenosis which elevates the blood pressure further: technically excellent surgery will then at best only lower blood pressure to the elevated pre-stenosis level. Whatever the reason or reasons for the failure of surgery and despite 20 years' experience with prognostic tests, it must be concluded that accurate prediction of surgical outcome is possible at present only in a small proportion of hypertensive patients with renal artery stenosis.

12:4 MANAGEMENT

1. Results of surgery

In this study 54% of patients with renovascular hypertension who underwent surgery had, at least one year postoperatively, blood pressure recordings consistently within one standard deviation of the age- and sex-related mean pressure as described by Hamilton et al (1954). By contrast, 46% of patients were not cured, but these comprised 31% who were improved though they still required antihypertensive drugs and 15% in whom there was no improvement. These results of surgery are similar to those in most published series: data from 18 series and a total of 1827 patients were reviewed in Table 2. Bearing in mind the

minor variations in each study in the definition of success, it can be seen that overall 47% of patients were cured, 31% were improved and 22% were failures.

These surgical cure rates are similar to those in other surgically correctable forms of hypertension. Of 48 hypertensive patients in whom an adrenal adenoma was excised, and in whom biochemical evidence of "cure" was obtained postoperatively, only 27 (56%) had a return of blood pressure to normal (Ferriss, Beevers, Boddy, Brown, Davies, Fraser, Kremer, Lever, and Robertson, 1978). Similarly up to half of persistently hypertensive patients in whom a phaeochromocytoma was excised and in whom postoperative urine concentrations of catecholamine derivatives were persistently normal did not experience a return of blood pressure to normal after the operation (Gifford, Kvale, Maher, Roth, and Priestley, 1964; Pickering, 1968).

Great care must be taken in defining surgical "cure", as the experiments in two-kidney hypertensive rats (Chapter 11:2) illustrate, with hypotension in the week following removal of the clipped kidney being succeeded by a return to significantly elevated systolic pressures in the following weeks and months. Since this experimental model provides the closest parallel to renovascular hypertension in man (Davis, 1977), this study echoes the warnings of Homer Smith (1948, 1956) about the

inadvisability of pronouncing on blood pressure "cure" after nephrectomy without adequate longterm follow-up.

Hypotension in the days after removal of the clipped kidney in two-kidney hypertension is not a well recognised finding despite extensive use of this experimental model, only Liard and Peters (1973) having commented on similar findings. In the present study hypotension was mild (Δmean systolic blood pressure -9 mmHg, N.S.) after nephrectomy in animals clipped for 5 weeks, but was a marked and consistent finding (Δmean systolic blood pressure -43 mmHg, $p < 0.01$) in animals clipped for 12 weeks. The exact mechanism is at present under study, and preliminary results suggest that plasma renin concentration falls precipitously from high levels to low and often undetectable levels following nephrectomy. It is likely then that the severe hypertension in these tightly clipped animals was dependent on high circulating angiotensin II concentrations, and that the rats were relatively sodium deplete (Swales et al, 1972). Möhring et al (1975) have shown significant elevations of plasma renin concentrations 5 weeks after clipping in rats with similar blood pressure elevation after application of 0.2 mm internal diameter clips to one renal artery. Furthermore, administration of angiotensin II antagonists and converting enzyme inhibitor to two-kidney hypertensive rats results in lowering of blood pressure below baseline recordings

and this may be analogous to the present study (Thurston et al, 1980). The use of captopril in the hyponatraemic hypertensive syndrome in man has similarly produced rapid and profound hypotension (Atkinson et al, 1979a).

2. The effects of surgery on renal function.

An unusual case of reversal of acute renal failure by reconstructive surgery to the occluded renal artery of a woman whose contralateral kidney had been removed previously has been described in Chapter 5:2. However, the majority of patients with renovascular hypertension referred for surgery have normal or only mildly impaired renal function. In these, renal arterial reconstruction has been reported to result either in no change (Simon and Del Greco, 1964) or occasionally even mild deterioration (Kaufman, 1973) in renal function. Such findings are surprising because the kidney distal to renal artery stenosis should have potentially excellent function, being protected from the adverse effects of hypertension, whereas the contralateral kidney may have suffered vascular damage (Brown et al, 1960). This question was explored in Chapter 11:3.

In this series of patients the primary object of surgery was to lower elevated blood pressure, and this was achieved to a comparable extent in both surgically treated groups (Figure 36). However, while nephrectomy

produced a deterioration in renal function, arterial reconstruction resulted in improvement, albeit with values which were within the overall normal range for most patients both before and one year after surgery.

Kaufman (1973) described similar results after unilateral nephrectomy in patients having normal pre-operative function with a 19% reduction in creatinine clearance postoperatively. However, in contrast to the present study he found a small (5%) deterioration in mean creatinine clearance after reconstructive surgery also, though this was not statistically significant. Simon and Del Greco (1964) similarly failed to find any overall increase in function after arterial reconstruction in patients in whom pre-operative renal function was normal.

This issue becomes crucial when considering operation in patients with initial renal impairment. Several reports describe considerable improvement following reconstructive surgery in such patients (Simon and Del Greco, 1964; Smith, Shapiro, and Messner, 1968; Sheil, May, Stokes, Johnson, Tiller, and Stewart, 1973; Bengtsson, Bergentz, and Norbuck, 1974; Morgan, Wilson, Johnston, Clunie and Gordon, 1974) including the woman described in Chapter 5:2. Other evidence suggests that function may be recovered after restoring the blood supply to a chronically anuric kidney with an occluded

renal artery (Perkins, Jacobsen, Feder, Lipchik, and Fine, 1967); in such cases a collateral circulation has provided sufficient blood only to maintain viability of the renal parenchyma (Morris, Heider, and Moyer, 1955).

In the present study the 25% increase in effective renal plasma flow through the reconstructed renal artery was accompanied by a 13% fall in plasma flow to the contralateral kidney; thus overall only a 9% increase was recorded. Simon and Del Greco (1964) have previously noted this differential effect, and O'Conor (1973) also has described a contralateral decrease in both creatinine clearance and filtration fraction in patients whose stenosed renal artery was successfully reconstructed. By contrast, it has also been shown (Simon and Del Greco, 1964) that where reconstruction failed to lower blood pressure, considerable disparity between the function of the two kidneys remained. This may have been due to continuing ischaemia on the affected side, or to irreversible hypertensive damage in the contralateral kidney. The present study has also shown that a small decrease in plasma flow to the contralateral kidney occurred after unilateral nephrectomy. The reduction in mean blood pressure was similar in both operated groups, and the findings therefore suggest that the contralateral kidney, suffering variable intrarenal

hypertensive vascular changes, is partly dependent on a high perfusion pressure to sustain its function. This, together with the loss of the excised kidney, could account for the reduction in overall function after nephrectomy.

The present study has demonstrated the superiority of reconstructive surgery over unilateral nephrectomy in the surgical management of hypertensive patients with renal artery stenosis, particularly in the preservation of renal function. Furthermore, nephrectomy limits future surgical options should contralateral disease develop. The recent introduction of percutaneous transluminal angioplasty (Gruntzig, Kuhlmann, Vetter, Liitolf, Meier, and Siegenthaler, 1978; Katzen, Chang, Lukowsky, and Abramson, 1979) offers a further means of arterial reconstuction: although a controlled trial comparing this relatively non-invasive technique with conventional reconstructive surgery has not been published, current evidence suggests that angioplasty may be as effective in lowering blood pressure as conventional surgery, but free from the hazards of major abdominal surgery. Renal artery reconstruction (or perhaps dilatation) should therefore be preferred to nephrectomy in all patients with renal artery stenosis coming to operation.

3. Management decisions.

How then should the management of a hypertensive patient with renal artery stenosis be approached? As illustrated in Chapter 10 (Figures 33 and 34) the difficulties in formulating guidelines about investigation and surgery are formidable. One basic uncertainty is whether surgical management of renal artery stenosis has any advantage to offer over medical management in terms of morbidity and mortality. No current answer is available to this question since no controlled trial of medical and surgical treatment has been published. However, there is a prima facie case for the performance of a curative procedure in a young severely hypertensive patient with greatly reduced blood flow on the side of the stenosis and a renal vein renin ratio greater than 2.0 who is poorly controlled with many side-effects on available medication; likewise there is a prima facie case for medical treatment of a 60 year old moderately hypertensive smoker with a 10 year history of ischaemic heart disease and bilateral stenoses on arteriography who responds well to medical treatment. It must be remembered that contrary to the state of hypotensive therapy even 10 years ago there are few patients now who, with good compliance, cannot be controlled by drugs, particularly the vasodilator, minoxidil, in combination with beta-blockers and diuretics (Mackay, Isles, Henderson, Fife, and Kennedy, in press), or the oral

converting enzyme inhibitor, captopril, with or without diuretics (Atkinson et al, 1979b and 1980c). Unfortunately, most patients lie somewhere along the spectrum between the extreme cases described above in whom management decisions are relatively easy.

The major drawback of surgery is that, with a few exceptions, only a 50% chance of cure can be offered after major abdominal surgery with a 5.9% mortality rate (Franklin et al, 1975) in the first year, many of the fatalities being in the immediate postoperative period. Even in the data in the present series 2 patients, one 23 years old, died within 2 weeks of surgery (5.1% mortality at 2 weeks, 10.2% at one year). However, the possibility that transluminal angioplasty may prove to be an effective procedure with a low morbidity and mortality without the hazards of general anaesthesia is exciting. Again, to view the results of surgery only in terms of cure may be unduly pessimistic. Patients whose blood pressure control is improved, though not cured, entertain the likelihood of a longer and, with fewer drug side-effects, more agreeable survival than those in whom surgery is a complete failure. In assessing the results of surgery it must also be remembered that two indications for operation may co-exist - hypertension and renal impairment - as in the patient described in Chapter 5:2 where surgery was life-saving

and a remarkable success from the point of view of renal function, though blood pressure, while moderated by surgery, still required drug treatment. A further point to be consideredis that surgical success rates in renal artery stenosis are no worse than in other forms of surgically treated hypertension, such as Conn's syndrome.

Surgery, however, would be an extremely attractive form of management even accepting the operative morbidity and mortality if reliable pre-operative prediction could be made of its effectiveness in lowering blood pressure. In this thesis considerable effort has been directed at demonstrating the unreliability of prognostic tests, despite claims in the literature to the contrary. Since these prognostic tests do not work particularly well, it must be considered seriously whether they should be performed at all, especially if they have a significant morbidity or even mortality of their own. One major management decision is whether or not to investigate a patient with a view to surgery: that this is a decision at all reflects the hazards of the investigative procedures.

In practice then a possible investigative protocol with low morbidity in a patient suitable for elective surgery could be:- 1. intravenous urography, with films to be viewed by several observers, independently;

2. any abnormality, despite a possible high percentage of false positive urograms, to be followed up by renal arteriography; 3. if a stenosis or stenoses are visualised, estimation of divided renal plasma flow by ^{123}I-hippuran renography and a gamma camera technique is to be performed; 4. a decision on surgery could be made at this point or, 5. the results of serial renography over a period of months or years could be assessed in parallel with the quality of antihypertensive control and if the former shows the blood flow to be falling and the latter shows blood pressure to be increasingly difficult to control, then a decision to operate could then be reached.

Such a scheme, however, does not denigrate the more complex and invasive investigations such as ureteric catheterisation studies and renal vein sampling. Without these investigative tools invaluable insight into the pathogenesis of one of Nature's most fascinating medical "experiments" could never have been gained, and their contribution is still far from complete.

APPENDIX

TABLES 1-4

FACTORS INFLUENCING THE DECISIONS TO INVESTIGATE AND TO OPERATE IN 86 PATIENTS WITH HYPERTENSION AND RENAL ARTERY STENOSIS

Key to Tables:

Outcome	A	-	alive † - dead
	MI	-	myocardial infarction
	CCF	-	congestive cardiac failure
	COAD	-	chronic obstructive airways disease
	M.Nec	-	multiple myocardial necroses
	IHD	-	ischaemic heart disease
	PVD	-	peripheral vascular disease
	ND	-	not done
Drugs	Ben	-	bendrofluazide
	C	-	cyclopenthiazide
	Fr	-	frusemide
	Mod	-	moduretic
	Prop	-	propranolol
	Metop	-	metoprolol
	MD	-	methyldopa
	Hy	-	hydrallazine
	B	-	bethanidine
	G	-	guanethidine
	Cl	-	clonidine.

TABLE 1 .

A) SURGERY NOT CONSIDERED - TESTS NOT DONE.

Patient No.	Age	Sex	Blood Pressure (mmHg)		Benign/ Malig.	Medical Treatment	Other Vasc. Disease	Arteriography	Serum Urea (mmol/l)	Follow-up (months)	Outcome
1	68	F	230	120	B	F	I.H.D	(R) Occlusion	8.6	18	† M.I
2	64	M	260	130	B	F	Stroke	(L) RAS	9.8	20	† Stroke
3	64	M	258	106	B	F	PVD,Stroke,IH.D	(R) RAS	7.2	48	† C.C.F.
4	61	F	240	110	B	F	PVD	(R) RAS	4.9	33	A
5	60	F	200	110	B	S	PVD	(L) RAS	6.4	31	A
6	58	F	230	130	M	F	(COAD †)	(R) Occlusion:(L) RAS	6.7	16	† COAD
7	57	F	240	140	M	F	PVD,Stroke	Bilateral RAS (R) > (L)	8.3	76	† Stroke
8	57	M	206	108	B	S	-	Bilateral RAS (R) > (L)	4.4	36	A
9	56	F	210	140	M	F	M.I.	(R) Occlusion	7.1	11	† M.I.
10	52	F	240	120	B	S	-	(R) Occlusion	12.1	46	A
11	49	F	200	105	B	S	PVD	(L) RAS	7.5	39	A
12	47	F	202	108	B	S	-	(R) FMH	5.0	47	A
13	46	M	160	118	B	S	-	(R) RAS	6.7	18	A
14	46	F	230	130	B	S	-	Bilateral FMH (R) > (L)	2.8	77	A
15	46	M	200	120	B	F	PVD	(R) RAS	4.8	56	A
16	45	M	230	140	B	S	Stroke	(R) RAS	5.5	47	A
17	45	M	250	100	B	F	I.H.D,Stroke	(L) RAS	5.6	60	A
18	36	F	150	102	B	S	I.H.D.	(L) FMH	14.7	39	A
19	36	F	170	130	M	S	-	Bilateral FMH	4.2	73	A

B) SURGERY PERFORMED - TESTS NOT DONE.

20	48	F	260	160	B	F	PVD,IHD,Stroke	(R) Occlusion:(L) RAS	20.5	19	A
21	26	M	186	140	B	F	-	(L) RAS - PHAEO.	5.9	53	A

TABLE 2.

SPECIAL TESTS DONE - NO SURGERY

A. DECISION TAKEN AGAINST SURGERY

Patient No	Age	Sex	Blood Pressure (mmHg)		Benign/ Malig.	Medical Treatment	Other Vasc. Disease	Arteriography	Serum Urea (mmol/l)	Renal Vein Renin Ratio
22	62	F	210	130	B	S	-	Bilateral RAS: (R) > (L)	9.9	2.90
23	62	F	235	140	M	F	-	Bilateral FMH: (L) > (R)	5.0	0.89
24	56	M	230	140	B	F	Guillain-Barre	(L) RAS	16.2	2.90
25	54	M	202	112	B	S	-	(R) RAS	6.6	1.05
26	52	M	240	160	M	F	Dem.	Bilateral RAS: (R) > (L)	11.0	1.27
27	47	F	238	118	B	S	-	(R) FMH	3.7	1.31
28	47	F	240	120	B	F	-	(R) RAS	6.0	1.10
29	46	F	160	105	B	S	-	Bilateral FMH: (R) > (L)	5.7	1.22
30	43	F	210	120	B	S	-	(R) FMH	4.5	1.50
31	42	M	190	130	B	S	-	(L) RAS	4.6	0.93
32	40	M	190	150	M	S	Stroke	Bilateral RAS: (R) = (L)	11.4	1.25
33	37	M	300	180	M	F	-	Bilateral RAS: (L) > (R)	4.4	1.79
34	35	F	194	110	B	S	-	(L) FMH	5.2	1.13
35	34	F	200	130	B	F	-	(L) RAS	4.5	Not done
36	30	F	194	120	B	S	-	(R) FMH	3.4	0.94
37	30	F	200	120	B	S	-	Bilateral FMH: (L) > (R)	4.3	1.48
38	29	M	130	100	B	S	-	(R) RAS	5.4	1.07
39	19	F	200	130	B	S	-	(R) RAS	5.3	1.07

TABLE 2. Continued

A. DECISION TAKEN AGAINST SURGERY

Patient No.	Ureteric Catheterisation	ΔBP with Saralasin	Follow-up (months)	Outcome
22	Ischaemia on (R)	ND	54	A
23	Ischaemia on (L)	ND	66	A
24	Ischaemia on (L)	ND	15	A
25	Ischaemia on (R)	ND	27	A
26	Ischaemia on (R)	ND	7	† ? cause
27	No evidence of ischaemia	ND	24	A
28	Uninterpretable	+ 7 mmHg	56	A
29	Ischaemia on (R)	ND	21	A
30	Ischaemia on (R)	- 4 mmHg	52	A
31	Ischaemia on (L)	ND	23	A
32	No evidence of ischaemia	ND	20	A
33	Ischaemia on (L)	ND	67	A
34	Ischaemia on (L)	ND	70	A
35	No evidence of ischaemia	ND	36	A
36	Ischaemia on (R)	ND	113	A
37	Ischaemia on (L)	ND	62	A
38	No evidence of ischaemia	ND	43	A
39	Ischaemia on (R)	ND	37	A

TABLE 2.

SPECIAL TESTS DONE - NO SURGERY

B. DECISION TO OPERATE, BUT SUBSEQUENT EVENTS PRECLUDED SURGERY.

Patient No.	Age	Sex	Blood Pressure (mmHg)	Benign/ Malig.	Medical Treatment	Other Vasc. Disease	Arteriography	Serum Urea (mmol/l)	Renal Vein Renin Ratio
40	57	M	200 100	B	S	PVD, Dem.	(R) Occlusion	12.1	2.14
41	56	M	185 115	B	S	Stroke, PVD	(L) RAS	7.0	1.61
42	51	M	180 120	B	S	Stroke	(L) RAS	6.3	1.07
43	45	M	245 145	M	F	-	(R) RAS	10.6	1.74
44	41	M	154 104	B	S	IHD	(R) RAS	4.2	1.44
45	40	M	240 140	M	F	-	(R) RAS	6.5	2.53
46	38	M	195 110	B	F	PVD	(L) RAS	4.5	1.19
47	28	M	160 110	B	F	-	(L) Occlusion	4.0	2.13
48	27	F	180 120	B	F	IHD, PVD	(L) RAS	3.8	1.15
49	33	F	160 100	B	S	-	(R) FMH	4.8	1.78

TABLE 2. Continued

B. DECISION TO OPERATE, BUT SUBSEQUENT EVENTS PRECLUDED SURGERY

Patient No.	Ureteric Catheterisation	ΔBP with Saralasin	Follow-up (months)	Outcome
40	Ischaemia on (R)	ND	26	† MI
41	Ischaemia on (L)	+ 9 mmHg	36	A
42	Ischaemia on (L)	ND	73	A
43	Uninterpretable	- 5 mmHg	6	† MI
44	Ischaemia on (R)	ND	68	A
45	No evidence of ischaemia	ND	5	† Stroke
46	Ischaemia on (L)	- 9 mmHg	75	A
47	Ischaemia on (L)	ND	24	† Stroke
48	Ischaemia on (L)	ND	28	A
49	Ischaemia on (R)	ND	13	A

TABLE 3.

SURGERY PERFORMED - SUCCESS

Patient No.	Age	Sex	Blood Pressure (mmHg)		Benign/ Malig.	Medical Treatment	Other Vasc. Disease	Arteriography	Serum Urea mmol/l	Renal Vein Renin Ratio
50	47	M	230	130	M	F	-	(R) RAS	7.2	1.10
51	47	F	190	105	B	F	-	(R) FMH	5.3	1.35
52	41	M	200	128	M	F	-	(L) RAS	4.0	4.51
53	37	F	190	110	B	F	-	(L) RAS	4.7	1.52
54	36	F	230	140	B	F	-	(R) FMH	4.1	1.65
55	34	F	220	120	B	F	-	(R) FMH	4.4	1.09
56	26	M	230	150	M	F	-	(R) RAS	3.4	1.35
57	23	F	200	126	B	S	-	(R) RAS	3.8	1.15
58	15	M	190	120	B	S	-	(R) Occlusion	5.0	1.04
59	62	M	230	126	B	F	I.H.D.	(L) RAS	8.7	Not available
60	52	F	210	140	M	S	-	(R) Occlusion	4.4	1.98
61	49	M	210	130	B	F	I.H.D.,P.V.D.	(L) Occlusion	3.5	3.63
62	45	M	230	120	M	S	-	(R) RAS	6.7	1.70
63	45	F	180	105	B	F	Stroke,P.V.D.	(L) RAS	3.0	1.01
64	44	F	200	120	B	S	-	(R) Occlusion	4.7	3.89
65	41	M	216	132	M	F	-	(L) Occlusion	10.4	2.25
66	40	F	216	120	M	F	-	(R) FMH	3.6	Not available
67	33	M	210	144	M	F	S.A.H.	(R) RAS	4.1	2.51
68	16	M	170	120	B	S	-	(L) FMH	4.6	1.20
69	10	F	150	108	B	F	-	(R) FMH	4.6	2.83
21	26	M	186	140	B	F	-	(L) RAS - PHAEO	5.9	N.D.

TABLE 3. continued.

Patient No.	Ureteric Catheterisation	ΔBP with Saralasin	Operation	BP 1 Yr Post Op.		Follow-up (months)	Outcome
50	Ischaemia on (R)	- 4 mmHg	Recon.	130	85	30	A
51	Ischaemia on (R)	+ 8 mmHg	Recon.	122	74	49	A
52	Ischaemia on (L)	N.D.	Recon.	150	90	118	A
53	Ischaemia on (L)	N.D.	Recon.	100	70	72	A
54	Ischaemia on (R)	N.D.	Recon.	130	90	44	A
55	Ischaemia on (R)	N.D.	Recon.	120	70	18	A
56	Ischaemia on (R)	-16 mmHg	Recon.	134	80	59	A
57	Ischaemia on (R)	N.D.	Recon.	124	76	14	A
58	Ischaemia on (R)	N.D.	Recon.	138	66	12	A
59	Ischaemia on (L)	N.D.	Neph.	150	90	15	A
60	Ischaemia on (R)	N.D.	Neph.	152	88	15	A
61	Ischaemia on (L)	N.D.	Neph.	150	90	89	A
62	Ischaemia on (R)	-28 mmHg	Neph.	134	84	50	A
63	Ischaemia on (L)	N.D.	Neph.	125	80	87	A
64	Ischaemia on (R)	-21 mmHg	Neph.	126	78	54	A
65	Ischaemia on (L)	N.D.	Neph.	130	92	19	A
66	Ischaemia on (R)	N.D.	Neph.	142	88	143	A
67	Ischaemia on (R)	N.D.	Neph.	142	86	19	A
68	Ischaemia on (L)	N.D.	Neph.	136	78	42	A
69	Ischaemia on (R)	N.D.	Neph.	100	60	77	A
21	N.D.	N.D.	Neph.	128	86	53	A

TABLE 4.

SURGERY PERFORMED - FAILURE

Patient No.	Age	Sex	Blood Pressure (mmHg)	Benign/ Malig.	Medical Treatment	Other Vasc. Disease	Arteriography	Serum Urea (mmol/l)	Renal Vein Renin Ratio
70	55	F	150 100	B	S	IHD, PVD	(L) Occlusion:(R) RAS	8.2	Not available
71	53	M	190 120	B	F	-	(R) RAS	7.1	1.24
72	35	F	280 170	B	F	-	Bilateral FMH (R) >(L)	6.8	1.29
73	23	F	204 134	M	F	-	(R) FMH	5.0	1.75
74	21	M	216 152	B	F	-	(R) FMH	3.2	1.23
75	58	M	210 100	B	S	-	(L) Occlusion	7.1	1.85
76	54	M	225 120	B	F	PVD	(R) Occlusion:(L) RAS	6.0	Not available
77	49	F	160 100	B	F	-	(L) RAS	5.1	Not available
78	49	M	220 140	M	F	-	Bilateral RAS:(L) >(R)	21.0	Not available
79	47	F	230 160	B	S	-	(R) RAS	12.5	1.36
80	46	F	230 140	B	F	Stroke,PVD,IHD	(R) Occlusion:(L) RAS	6.2	1.72
81	42	M	180 130	B	S	IHD	(R) RAS	4.5	1.05
82	40	F	235 160	M	F	-	(R) Occlusion	6.1	1.56
83	40	F	180 120	B	F	IHD	(L) FMH	5.9	1.00
84	37	F	220 160	M	F	-	(R) Occlusion:(L) RAS	4.6	Not available
85	31	F	280 150	B	F	-	(L) Occlusion (FMH)	5.0	1.89
86	19	F	190 115	B	S	-	(R) Occlusion	4.0	1.01
20	48	F	262 164	B	F	Stroke,PVD,IHD	(L) Occlusion	20.5	N.D.

TABLE 4. Continued.

Patient No.	Ureteric Catheterisation	ΔBP with Saralasin	Operation	BP 1 Yr. Post-op.		Post-op. Drugs	Follow-up (months)	Outcome
70	Ischaemia on (L)	ND	Recon	140	110	Nil	13	† MI
71	Ischaemia on (R)	- 5 mmHg	Recon	190	114	B MD C	51	A
72	Ischaemia on (R)	ND	Recon	180	110	B	69	A
73	Ischaemia on (R)	ND	Recon	230	130	B	2 days	† M.Nec.
74	Ischaemia on (R)	ND	Recon	170	105	MD,Hy	128	A
75	Ischaemia on (L)	ND	Neph	152	102	MD, Ben	2/52	† MI
76	Ischaemia on (R)	ND	Neph	210	124	C1	7	† Uraemic
77	Ischaemia on (L)	-34 mmHg	Neph	170	100	Nil	37	A
78	Ischaemia on (L)	ND	Neph	170	110	MD, Fr.	6	† Stroke
79	Ischaemia on (R)	-56 mmHg	Neph	152	94	B,Ben,Prop	49	A
80	Ischaemia on (R)	ND	Neph	236	120	Metop, Ben	14	A
81	Ischaemia on (R)	ND	Neph	154	106	Ben, Prop	77	A
82	Ischaemia on (R)	ND	Neph	180	114	MD,Prop,Ben	29	A
83	Ischaemia on (L)	ND	Neph	162	106	Metop,Hy,Mod	29	A
84	Ischaemia on (R)	ND	Neph	152	102	B, MD, Mod	42	† MI
85	Ischaemia on (L)	ND	Neph	130	75	G	104	A
86	Ischaemia on (R)	+11 mmHg	Neph	146	96	MD, Prop	44	A
20	ND	ND	Recon	180	100	Prop	19	A

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