Section of Experimental Medicine & Therapeutics

President J M Ledingham FRCP

Meeting May 12 1970

President's Address

Mechanisms in Renal Hypertension

by Professor J M Ledingham MD FRCP
(*Medical Unit, The London Hospital, London E1 1BB*)

Over a century and a quarter ago, the alert observations of Richard Bright (1836) drew attention to the association of proteinuria and dropsy in life with cardiac hypertrophy in death. Although the concept of blood pressure in clinical medicine was ill defined, Bright speculated that the cardiac hypertrophy might be due to some 'altered quality' of the blood which led either to direct stimulation of the heart or to some alteration in the peripheral vessels resulting in greater action necessary to force the blood through them.

The sophisticated tools of the twentieth century have placed the responsibility for chronic renal hypertension on the second of Richard Bright's two suggestions, an increase of peripheral resistance; but the nature of the 'altered quality' of the blood which brings about this increase in peripheral resistance is still a subject of controversy. The renin-angiotensin system, which at first seemed so obviously implicated in bringing about the increase in peripheral resistance through a direct vasoconstrictor action on the arterioles, has not stood up to critical assessment in this respect. For the nonspecialist in this field the present situation must be most confusing, for we know that the severer forms of hypertension, including malignant hypertension, are associated with increased plasma renin and we use the differential renal venous renin concentration as a guide to the likelihood of renovascular hypertension. Nonetheless, in chronic renal as in chronic essential hypertension, the plasma renin is usually normal or depressed below the normal range. I hope that in this Address I may be able to resolve these seemingly contradictory observations.

Human Renal Hypertension

In man, practically all forms of renal disease may be complicated by hypertension. Nevertheless, some patients may advance to terminal renal failure without ever manifesting hypertension; others develop hypertension relatively early in the course of their illness. There are no clear guidelines to predicting which patients suffering from renal disease will and which will not develop hypertension. However, in the terminal stages it is noteworthy that a tendency to sodium loss is an accompaniment of normotension and that those with hypertension usually have a greatly increased exchangeable sodium in comparison with those having a normal blood pressure. Such observations point strongly to a disturbance of sodium homeostasis as being an important factor in the pathogenesis of hypertension.

Unilateral renal artery stenosis is an important, albeit rare, form of renal hypertension. Its importance, from the point of view of this Address, lies in its potential reversibility. The observations which have been made in human renovascular hypertension so closely resemble those in experimental renal hypertension in animals that I am going to devote the next part of this paper to the experimental model. My chief reason for choosing to discuss at length the experimental model is that hypertension is a disturbance in blood pressure regulation which takes place over a finite time and to understand its pathogenesis I believe that it must be studied not only in the established state, but also during its development and, if possible, during its reversal as well. Now this is not possible in human hypertension which is studied usually at one point only in its natural history and always when hypertension has already been established. On the other hand, studies in experimental hypertension can cover all these phases and are more likely to reveal underlying mechanisms.

Hæmodynamic Changes in Experimental Renal Hypertension

The experimental models which I shall discuss are shown in Fig 1. The one-kidney preparation has certain advantages over the two-kidney preparation. Hypertension is more consistently produced and, however long the high blood pressure has been present, it can be completely relieved by removing the renal artery constriction (Byrom & Dodson 1949). The latter does not apply to the two-kidney preparation, for hypertensive vascular damage may occur in the contralateral kidney resulting in residual hypertension after removing the constriction (Floyer 1951). Our own work in this field has been exclusively in rats. They have the great advantage, being of inbred stock, of providing a uniform population for experiment but the disadvantage of small size for circulatory studies. I shall therefore briefly describe our technical methods, which we have considered should be made applicable to the unanæsthetized resting animal, conditioned to the experimental procedures.

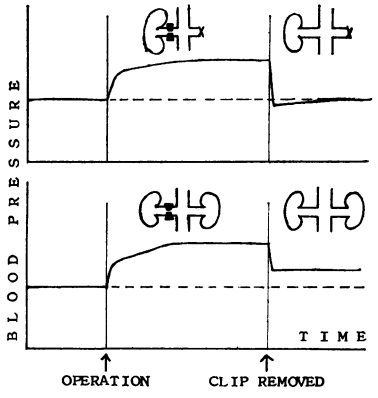

Fig 1 *Schematic representation of blood pressure changes in the rat following application and subsequent removal of constriction on right renal artery, with and without contralateral nephrectomy*

The measurement of mean arterial blood pressure is made via a cannula, implanted into the abdominal aorta below the renal arteries. In long-term experiments involving the circulation, it is of the utmost importance that indwelling cannulæ should be placed distal to the renal arteries because of the danger, however remote, of renal embolization. The measurement of cardiac output is by electromagnetic flowmetry: for this purpose a miniaturized flowmeter is implanted on the ascending aorta. Recordings from the flowmeter cannot be transformed into absolute values of cardiac output, but since it is a change in output which is being followed, it is only necessary to show that the recordings are linearly related to true output. That this is so is shown in Fig 2 where a comparison has been

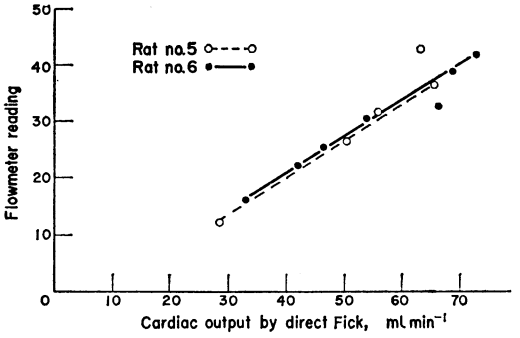

Fig 2 *Calibration* in vivo *of electromagnetic flowmeter: simultaneous measurements of cardiac output by direct Fick method and by electromagnetic flowmetry (arbitrary units). (Reproduced from Browning* et al. *1969, by kind permission)*

made between measurements of cardiac output by the Fick method and by electromagnetic flowmetry. It will be seen that there is a linear relationship. During hæmodynamic measurements, the animal is kept in a restraining cage at a temperature of 30–34°C, in which range its basal metabolic rate is constant and at a minimum.

The blood pressure changes after constricting the artery to one remaining kidney are shown in Fig 3. In this and subsequent experiments, two groups of animals are always compared, one bearing a tight clip on the renal artery and developing hypertension and one a loose clip and remaining normotensive. In long-term experiments of this kind it is of the utmost importance to have a very similarly handled control group.

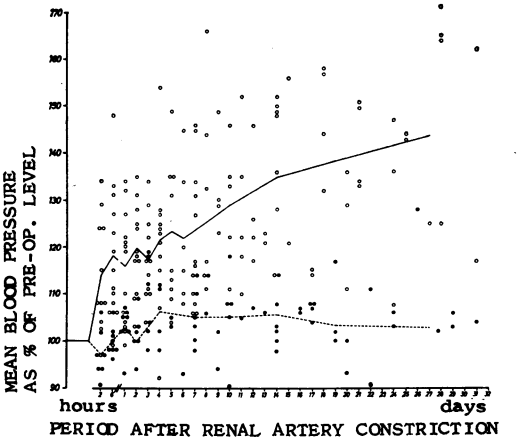

Fig 3 *Mean arterial blood pressure in unanæsthetized rats after left nephrectomy and application of clip to left renal artery, expressed as percentage of mean pre-operative level. White and black circles refer to use of narrow (0·009 in.) and wide (0·018 in.) clips respectively. Continuous and dotted lines indicate means for the two groups. (Reproduced from Ledingham 1966, by kind permission)*

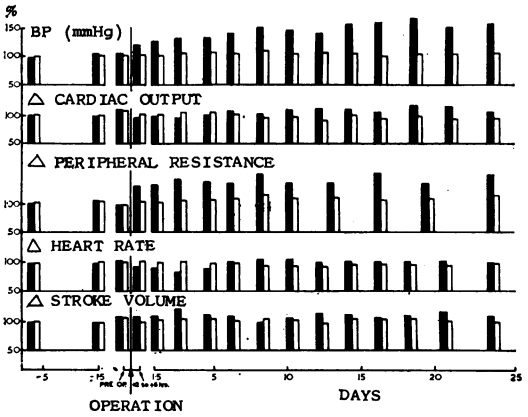

Fig 4 *Hæmodynamic changes in two groups of unanæsthetized rats after left nephrectomy and application of a tight clip (hypertensive group; black columns, 10 rats) or a loose clip (normotensive control group; white columns, 6 rats) to right renal artery. Results expressed as percentage of mean pre-operative levels. (Modified from Ledingham & Pelling 1967, by kind permission)*

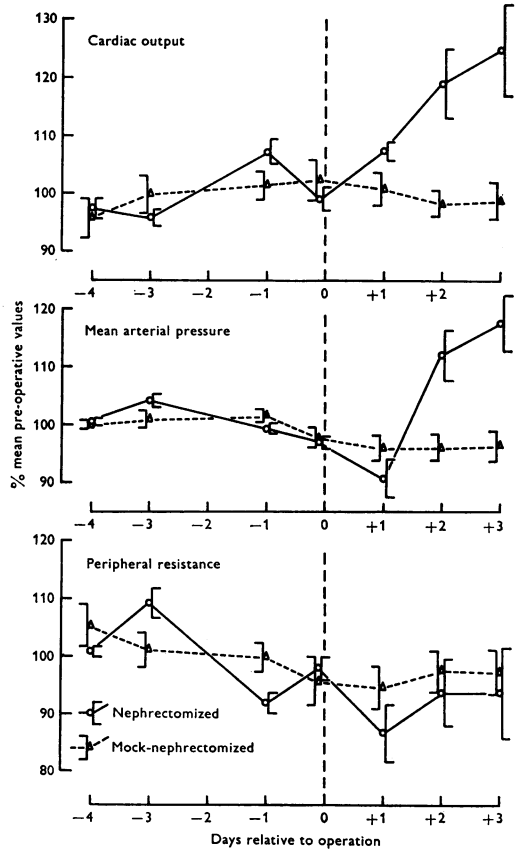

Fig 5 *Mean hæmodynamic changes (± S.E.M.) in rats before and after nephrectomy (circles, continuous line) or mock nephrectomy (triangles, dotted line). Values expressed as percentage of mean value before nephrectomy. (Reproduced from Ledingham & Pelling 1970, by kind permission)*

It will be seen that within two hours the mean pressure of the experimental group has risen sharply. After this, the rate of development of hypertension is very much more gradual and, in fact, several animals may show a transient fall in blood pressure lasting for some days.

The mean hæmodynamic changes are shown in Fig 4. The cardiac output falls below the level of the control group for the first five days and then consistently exceeds that of the control group. The heart rate changes in an interesting fashion, showing an immediate, followed by a delayed, fall lasting five days, presumably related to resetting of baroreceptor mechanisms (McCubbin *et al.* 1956, Krieger 1970). Stroke volume rises at once and, apart from one short period, consistently exceeds that in the control group.

The calculated peripheral resistance reveals the immediate increase at two hours and then the gradual subsequent rise. At all stages the increased blood pressure is mainly attributable to increased resistance.

Other workers in this field have studied the hæmodynamic changes in dogs developing this type of renal hypertension. The results of Bianchi *et al.* (1970) are very similar to our own, in that an early fall in cardiac output, followed by a statistically significant rise above the control level, was observed. Others (Olmsted & Page 1965) have failed to find a delayed elevation in cardiac output and the matter is still under investigation.

I shall now attempt an interpretation of what is happening in the early and late phases of the development of renal hypertension.

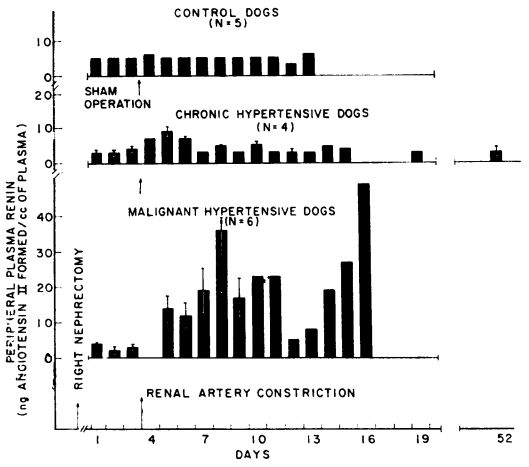

Fig 6 *Peripheral plasma level of renin in 5 control, sham-operated dogs, in 4 chronic hypertensive dogs and in 6 malignant hypertensive dogs. Measurements made every one to two days; values presented are averages for the groups. (Reproduced from Brown, Davis, Olichney & Johnston 1966, by kind permission)*

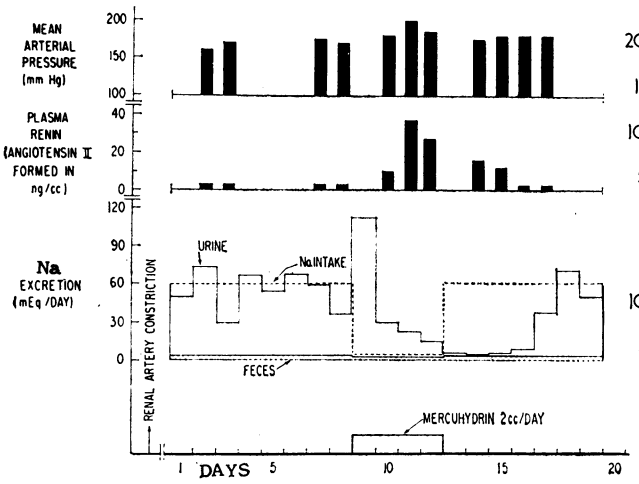

Fig 7 *Response of a chronic renal hypertensive dog to sodium depletion. Plasma renin increased but arterial pressure was unchanged. (Reproduced from Brown, Davis, Olichney & Johnston 1966, by kind permission)*

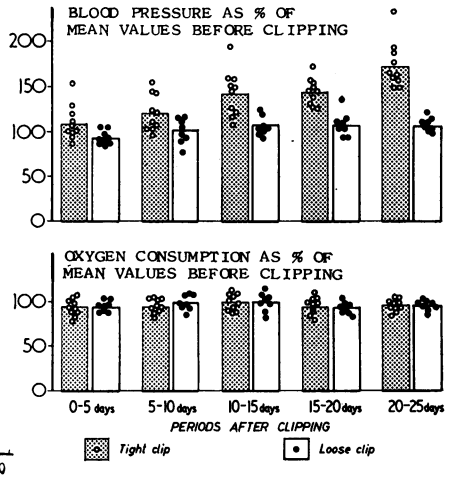

Fig 9 *Changes in blood pressure and in oxygen consumption in rats subjected to left nephrectomy and application of a tight clip (hypertensive group; shaded columns, white circles) or a loose clip (control normotensive group; white columns, black circles) on right renal artery. (Reproduced from Meinders 1965, by kind permission)*

(1) *The Early Phase*

It seems highly probable that the kidney is actively responsible for the immediate changes and that these are not due to some extrarenal pressor mechanism operating unrestrained by the normal kidney. Simple total nephrectomy is certainly followed by an elevation of blood pressure (renoprival hypertension), but this does not occur until the second day (Fig 5). It is therefore very reasonable to consider whether renin release and the direct action of angiotensin on the peripheral arterioles could account for this phase.

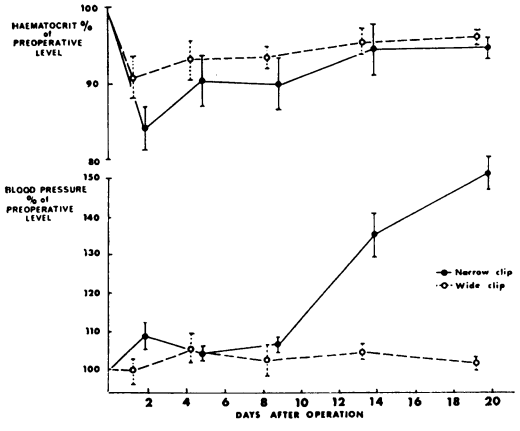

Fig 8 *Group mean changes (± 1 S.E.M.) in mean arterial blood pressure and in arterial hæmatocrit in two groups of rats subjected to left nephrectomy and application of a wide clip (white circles) or a narrow clip (black circles) on right renal artery. (Reproduced from Ledingham & Pelling 1967, by kind permission)*

There have been many observations on plasma renin levels in this type of preparation and the observations of Davis and his colleagues are shown in Fig 6 (Brown T C *et al.* 1966). There is general agreement that a transient increase in plasma renin occurs in animals which proceed to chronic benign type hypertension. Only in animals developing a malignant type of hypertension does the plasma renin remain elevated.

Bianchi and his colleagues (1970) have shown that the plasma levels of renin reached during this phase are such that if they were produced by an infusion of renin into a normal animal, a similar rise in blood pressure would take place. Therefore it seems reasonable to attribute the early acute rise of blood pressure to renin released from the kidney in the acute phase after renal artery constriction.

(2) *The Late Phase*

Vasoconstrictor substances: As I mentioned earlier, the level of plasma renin is usually within the normal range in the chronic benign type of experimental renal hypertension. This has been observed in rats, rabbits and dogs (Gross *et al.* 1964, Brown *et al.* 1964, Fasciolo *et al.* 1964) and similar observations have been made for the plasma level of angiotensin (Scornik & Paladini 1964). During this phase, the divergence between the levels of plasma renin and blood pressure has been most clearly demonstrated (Fig 7, Brown T C *et al.* 1966). Attempts to demonstrate other vasoconstrictor substances in the blood in

chronic hypertension have failed. We must conclude that no humoral factor has yet emerged which could be held responsible for the increased peripheral resistance in chronic experimental hypertension. We cannot, however, exclude this possibility, particularly if such a factor had some delayed effect which would render it undetectable by commonly used assay procedures.

The observed increase in cardiac output appearing five days after renal artery constriction: This increase is of very great significance in the consideration of the pathogenesis of hypertension. Were the primary hæmodynamic disturbance in hypertension an increase in peripheral resistance, it would be expected that cardiac output would be depressed or, at the most, lie within the normal range. We have indeed seen that in the early phase the cardiac output is depressed, probably in consequence of baroreceptor reflexes. The baroreceptor reflexes have been shown to reset to the higher level in hypertension and during this process the cardiac output would be expected to return to normal. The observation that it exceeds the level in the controls demands an explanation. The precise factors governing the level of resting cardiac output have not been fully defined. It is well recognized that cardiac output increases when there is central anoxia or when there is reduced oxygen-carrying capacity of the blood. There is no evidence of the former in chronic hypertension; however, there is a moderate fall in hæmatocrit during the development of experimental hypertension (Fig 8), but this is little greater than in the controls and disappears while cardiac output remains elevated. Another possible explanation is an increase in basal metabolic rate. To investigate this possibility, the metabolic rate of rats developing renal hypertension was compared with that of control operated animals (Fig 9). Again, no difference emerged which might explain the enhanced cardiac output. Thus, the explanation for this increase remains a mystery and it is indeed possible that it represents an inappropriate response to tissue requirements and is determined by some other homeostatic requirement in the body. I will return to this problem later. In the meantime we should examine the possible immediate mechanisms which bring it about. Many years ago the observation was made that the extracellular fluid volume (ECFV) (inulin space) was increased early in experimental renal hypertension but returned towards normal later (Ledingham 1953). This has been confirmed more recently using the thiocyanate space (Fig 10). In these experiments, ECFV was studied from the time of renal artery constriction and the results compared with a group of operated controls in order to allow for the nonspecific effects of surgical trauma. The expansion of ECFV was significantly greater in the hypertensive group. The plasma volume increased in parallel. This increase could well be a factor in increasing cardiac output through raising cardiac filling pressure: unfortunately, reliable measurements of true cardiac filling pressure have not proved possible in the rat. It is, of course, quite possible that other factors may be partly or wholly responsible, such as an increase in tone in the capacitance vessels or an increase in myocardial contractility.

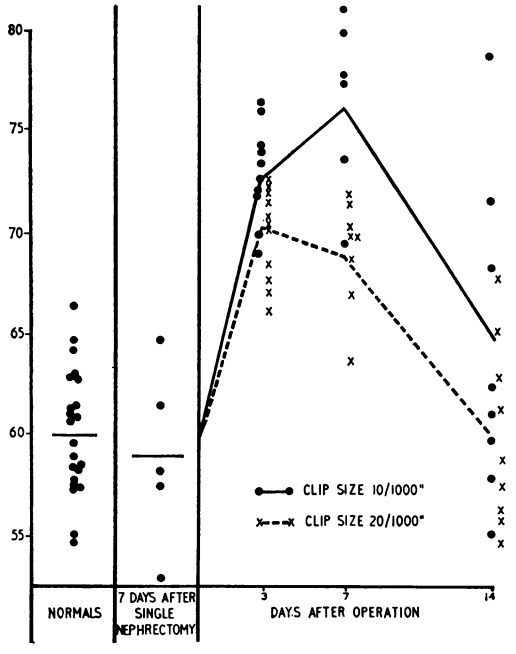

Fig 10 *Thiocyanate spaces (in ml/200 g body weight) in a group of normal rats, in a group subjected to unilateral nephrectomy and in two groups at varying intervals after right renal artery constriction with either a tight clip (hypertensive group) or a loose clip (normotensive control group) and contralateral nephrectomy. (Reproduced from Ledingham & Cohen 1964, by kind permission)*

I shall now return to the significance of the increase in cardiac output in chronic experimental renal hypertension. As I indicated before, it seems inappropriate to tissue requirements. Tissues appear to regulate the blood flow through them and to resist, by vasoconstriction, an increased flow as the perfusion pressure is raised. This is one form of autoregulation which I shall refer to as pressure autoregulation and it has been demonstrated in nearly all vascular territories (in skeletal muscle, Folkow 1949, 1952, Folkow & Oberg 1961, Greenfield & Patterson 1954, Stainsby & Renkin 1961; in heart muscle, Mosher *et al.* 1964; in intestine, Johnson 1960, Texter *et al.* 1962), and also in the body as a

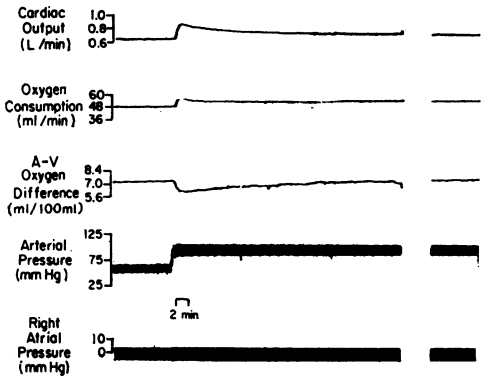

Fig 11 *Effects in a dog of a single-step increase in arterial pressure, produced by blood volume expansion, on cardiac output, oxygen consumption, A-V oxygen difference and right atrial pressure. (Reproduced from Granger & Guyton 1969, by kind permission)*

whole (Folkow 1952, Conway 1966, Granger & Guyton 1969). Fig 11, taken from recent work in Professor Guyton's laboratory, shows the effects of a sudden expansion of blood volume in a dog after complete destruction of its nervous system. The expansion was done in such a way as to maintain a steady elevation of blood pressure. It will be seen that there is an initial rise in cardiac output, but over the next 30 minutes the cardiac output falls towards its original level and the raised blood pressure becomes attributable to increased peripheral resistance. Oxygen consumption shows a small transient rise, but soon returns to normal.

In experimental hypertension, if cardiac output were to rise inappropriately to tissue requirements, it might be expected that vasoconstriction would take place in the resistance vessels and raise blood pressure further. Such a hypothesis to explain the increased peripheral resistance in hypertension was advanced by Ledingham (1956). Over the years the evidence for this hypothesis has slowly accumulated, but it is far from being established. It will be appreciated that it can only be established by the exclusion of other vasoconstrictor mechanisms, and by the demonstration that conditions are such that autoregulation is likely to occur.

We consider that chronic benign renal hypertension is a response to some imposed disturbance of one or more specific aspects of renal function. The most likely one of these in relation to hypertension is that of sodium homeostasis, but it is possible that some other aspect of function closely associated with sodium homeostasis may be primarily involved. In the experimental situation, when a clip is placed on the artery to a sole remaining kidney, the central blood pressure

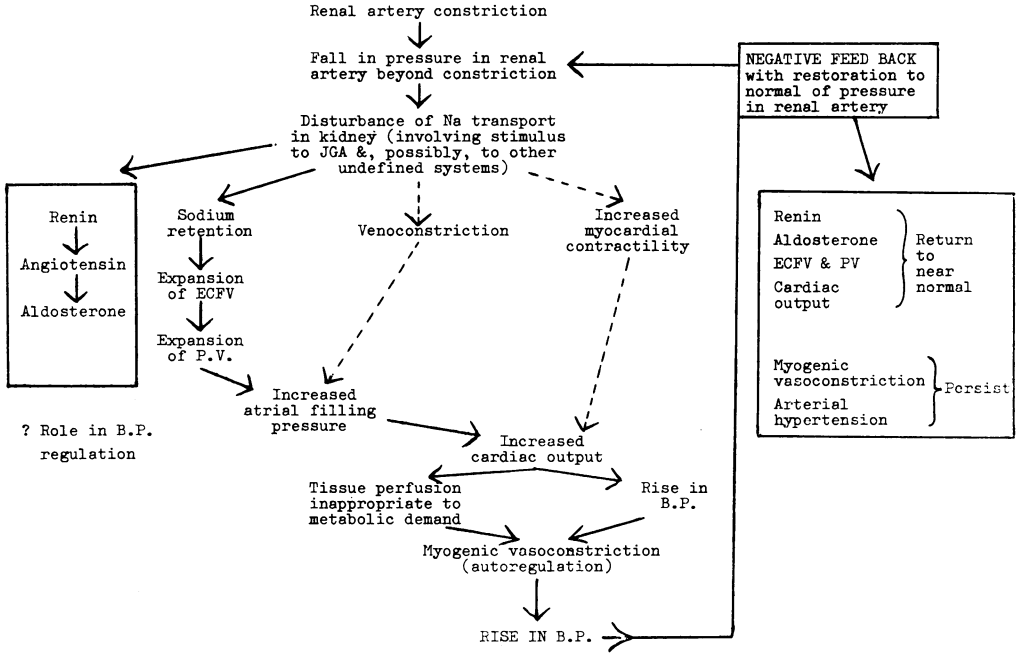

Fig 12 *Hypothetical scheme for pathogenesis of chronic benign phase of renal hypertension. Actually observed steps in the pathways are indicated by continuous lines, unobserved but postulated or possible steps by interrupted lines*

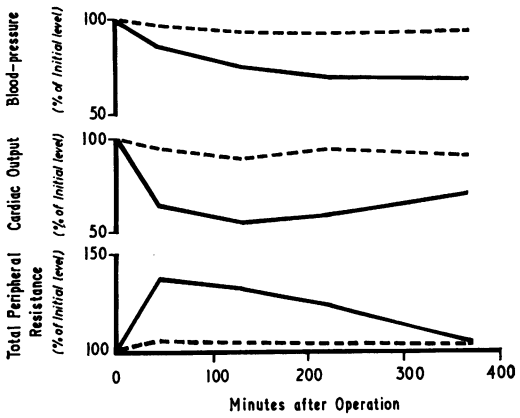

Fig 13 *Continuous lines show average changes in mean arterial pressure, cardiac output and total peripheral resistance in renal hypertensive rats (right renal artery constriction and left nephrectomy) following release of renal artery constriction. Interrupted lines indicate changes in a group of hypertensive rats subjected to sham operation. (Composite, from Ledingham & Cohen 1962)*

rises until the pressure beyond the clip has been restored to normal (Mason *et al.* 1940). It would therefore appear that hypertension is a form of negative feedback to maintain normal renal perfusion pressure. Since renal perfusion pressure and sodium excretion are so closely linked, it is indeed possible that the negative feedback is primarily applied to sodium homeostasis. Our concept of this chronic phase in renal hypertension is shown in Fig 12. Sodium is retained after renal artery constriction. This expands ECFV and plasma volume (PV) thereby increasing cardiac filling pressure and cardiac output. The precise mechanism of myogenic vasoconstriction (autoregulation) following an increase of cardiac output is unknown, but whether it is brought about through tissue perfusion inappropriate to metabolic demand or through a stretch response from raised intravascular pressure, the consequence of widespread autoregulation must be to raise blood pressure further. The process continues until renal perfusion pressure is restored and sodium homeostasis re-established. At this new position of equilibrium ECFV, PV and cardiac output would be expected to be only marginally above the original level. This is precisely what has been found for cardiac output. Such a mechanism may, in fact, be the chief determinant of many, if not all, forms of chronic hypertension, including renal hypertension, salt hypertension and steroid hypertension. Similar concepts have been advanced by Borst & Borst-de-Geus (1963) and, more recently, by Guyton & Coleman (1969) who have applied the technique of system analysis to show that the concept is theoretically sound. This concept of long-term blood pressure regulation has not so far met with wide acceptance. Perhaps this is because the renin-angiotensin system seems so obviously designed to provide a peripheral vasoconstrictor hormone that any other complicating mechanism seems redundant. Furthermore, as we have seen, there is an increased peripheral plasma renin level in the early stages of the hypertension and, in the malignant form, throughout the cause of the hypertension. In these circumstances, the circulatory changes induced by renin obscure the processes which I have outlined and may dominate the picture in malignant hypertension. Nonetheless, in the chronic benign phase of hypertension, the renin-angiotensin system cannot be responsible solely through its action as a peripheral vasoconstrictor.

Reversal of Experimental Renal Hypertension

If this postulated sequence of events takes place during the development of renal hypertension, it might be expected that the relief of the hypertension brought about by removing the constriction on the renal artery would be accompanied by the reversed findings, that is, by a primary fall in cardiac output and a secondary fall in peripheral resistance. This was precisely what happened when a clip was removed from a group of hypertensive rats and a mock operation was performed on a control group of similarly hypertensive rats (Fig 13). There was an early fall in cardiac output with the blood pressure falling more slowly due to a transient phase of arterial vasoconstriction, probably secondary to baroreceptor reflexes. The fall in cardiac output was associated with a fall in plasma volume and

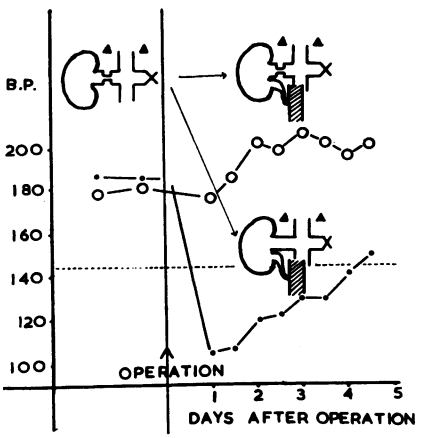

Fig 14 *Mean changes in blood pressure in renal hypertensive rats following ureterocaval anastomosis (white circles) and ureterocaval anastomosis with simultaneous release of renal artery constriction (black circles). (Modified from Floyer 1955)*

this may have been responsible for the cardiac output changes. In these experiments, removal of the renal artery constriction led to a profuse diuresis and this could have contributed to the fall in plasma volume, although in a few experiments returning the urine to the circulation seemed to make no difference to the fall in cardiac output. This observation suggests that other factors may have been at least partly responsible for the fall in cardiac output, and hence in blood pressure. In this context, it is of great interest to recall the observations of Floyer (1955) who demonstrated that if the clip is removed from the renal artery of a hypertensive rat and, at the same time, the ureter is implanted into the inferior vena cava, the blood pressure falls to normal as usual without any external loss of salt and water (Fig 14). This would suggest that the release of the constriction had led to some internal redistribution of sodium and water or possibly to an alteration in capacity vessel tone, although other interpretations of this interesting observation are possible. It is such observations which require us to keep a very open mind on the possible ways in which the clipped kidney could influence the hæmodynamic situation. Some of these hypothetical pathways are set out in Fig 15. Although I suspect that the primary disturbance leading to hypertension is concerned with sodium homeostasis, it is quite possible that many other factors could play a part in modifying the rate at which sodium homeostasis is regained after renal artery constriction.

The Human Situation

I have been dealing up to now with experimental hypertension. I will now turn briefly to the human situation. Here we are in difficulties for in the clinical field we are rarely completely sure that we are dealing with renal rather than essential hypertension, Even in patients with advanced bilateral renal disease, the possibility of pre-existing essential hypertension is difficult to exclude. For the purpose of this discussion, I must therefore restrict the field to cases of unilateral renal artery stenosis which are cured by relief of the stenosis or by nephrectomy. It will be recognized at once that this is not an exact parallel of the experimental model with one clipped kidney and contralateral nephrectomy with which we have been mainly concerned up to now. Such a clinical situation certainly occurs but it is rarely reported and few or no data are available. In the more commonly occurring unilateral artery stenosis many observations have now been made on the activity of the renin-angiotensin system. Although the plasma renin level in peripheral blood is frequently raised, it may lie within the normal range in one-third of cases in reported series (Brown *et al.* 1965, Brown J J *et al.* 1966). In this it closely resembles essential hypertension. In both conditions, the peripheral plasma renin level rises in the presence of vascular damage, as indicated by severe retinopathy, but otherwise is normal. This frequent normality of peripheral plasma renin level in renal artery stenosis is none the less associated with a differential renal venous

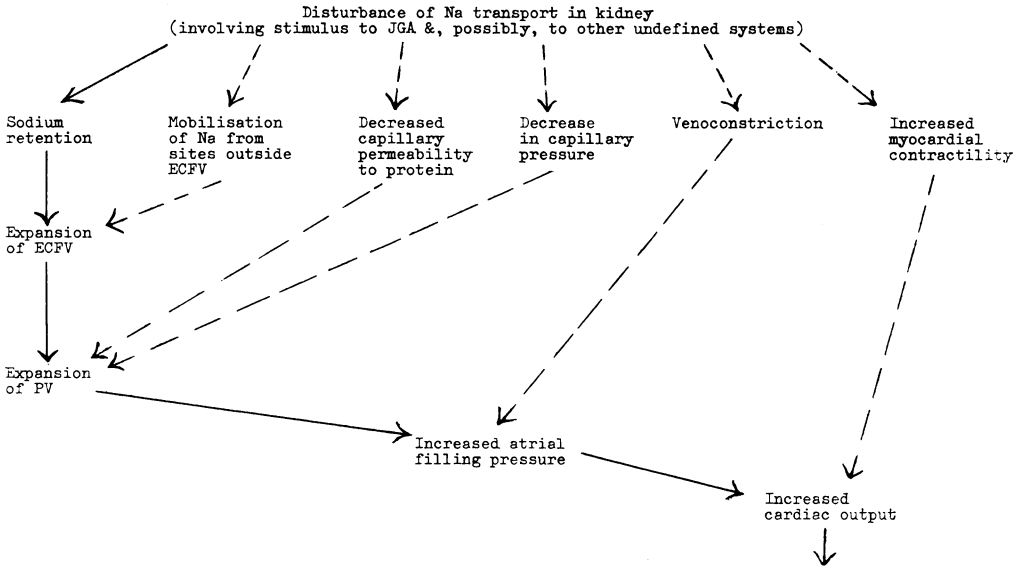

Fig 15 *Hypothetical pathways concerned with elevation of cardiac output in development of renal hypertension. (To be considered together with Fig 12)*

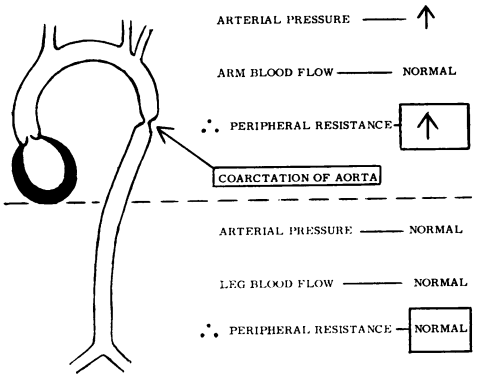

Fig 16 *Schematic representation of findings in coarctation of aorta*

renin concentration on the two sides (Winer *et al.* 1967, Fitz 1967). The affected kidney appears to be responsible for releasing the renin and the other kidney adds no renin to the blood passing through it. Such interesting observations have proved useful in predicting the likelihood of surgical cure. However, to return to our problem of pathogenesis of the hypertension, there is little to support the claims for renin as the mediator of the hypertension through a direct vasoconstrictor action on the peripheral vessels.

Circulatory studies in human renal hypertension have been few. One group of workers (Frohlich *et al.* 1967) reported a significantly raised cardiac output in renovascular hypertension compared with matched controls, whereas another group (Brod 1968) could not confirm this finding. In renal parenchymal disease the cardiac output has been found raised in comparison with controls (Brod *et al.* 1961). Human studies of this kind are open to errors arising from the large number of uncontrolled variables usually present, including anæmia, coronary disease and sodium status.

Perhaps the most important observations of all in relation to the pathogenesis of hypertension in man are those in coarctation of the aorta. The mean arterial blood pressure in the lower half of the body is normal, yet the tissue blood flow in upper and lower limbs remains normal despite marked disparity in perfusion pressure (Patterson *et al.* 1957). This signifies that the peripheral resistance is much higher above than below the aortic constriction (Fig 16). It is difficult to conceive either a neurogenic or a humoral basis for this difference, whereas autoregulation would readily account for it. The plasma renin activity in coarctation of the aorta, as in the chronic phase of renal hypertension, is normal (Yagi *et al.* 1968).

Conclusions

I believe we have reached a stage in the exploration of mechanisms of renal hypertension at which we can draw some tentative conclusions. The experimental evidence would seem to support the existence of two mechanisms as follows:

(1) Renin-angiotensin system, producing a *direct vasoconstrictor* action on peripheral resistance vessels: This first mechanism is seen most obviously in action in the developmental phase of experimental renal hypertension from renal artery constriction. The amounts of renin circulating in this phase are such that they would satisfactorily account for the increased peripheral resistance and the other hæmodynamic features. In the benign form of hypertension, the renin plasma level falls into or below the normal range, but with severe renal ischæmia, unrelieved by the pressure rise, the malignant form of hypertension develops and here we see high levels of renin persisting and probably playing the dominant role in the hypertension.

(2) Sodium homeostatic system: This second mechanism operates through changes in sodium and water balance which bring about alterations in cardiac output and so stimulate *autoregulatory responses* from resistance vessels. Changes in blood pressure, so mediated, restore the state of sodium balance through their effects on renal perfusion pressure. This mechanism now seems likely to be responsible for the chronic benign phase of renal hypertension. Here renin levels are normal or even suppressed. Incidentally, this mechanism is very likely responsible for the hypertension in primary aldosteronism and experimental desoxycorticosterone hypertension.

An outstanding problem is the precise role of the renin-angiotensin system in chronic benign renal hypertension. The first possibility to be considered is whether the response to normal levels of angiotensin could be enhanced by a slightly positive sodium balance. It should be noted in passing that such a positive sodium balance could not be attributed to an increase in aldosterone secretion rate since this is usually normal in both chronic benign experimental renal hypertension and in hypertension in man resulting from unilateral renal artery stenosis (Laragh *et al.* 1960, Carpenter *et al.* 1961, Cope *et al.* 1962, Mulrow 1964). It has been shown by Laragh and his colleagues (Ames *et al.* 1965) that the rate of infusion of angiotensin required to produce a constant moderate rise in blood pressure becomes progressively lower if a positive sodium balance is permitted to occur. This has been confirmed by the MRC Blood Pressure Research Unit (Bianchi *et al.* 1968). However,

two recent observations render this mechanism most improbable. In the first place, anti-angiotensin serum only produces transient lowering of blood pressure in chronic experimental hypertension (Meyer, personal communication); secondly, Professor Peart and his colleagues have shown that active immunization of rabbits against angiotensin does not interfere with the development or maintenance of renal hypertension induced by renal artery constriction with contralateral nephrectomy (Louis *et al.* 1970). Both these observations would, I believe, rule out a role for angiotensin as a direct pressor agent in chronic hypertension.

The second possibility is that angiotensin might have an intrarenal role as suggested by Thurau (1969), and promote sodium conservation by redistributing filtrate from superficial to deep glomeruli. It is possible that this effect could be operative without any rise in the peripheral renin level in the chronic phase. In this sense, renin would here be playing a strictly local intrarenal role and would be responsible for sodium homeostasis through a mechanism not involving its extrarenal action on aldosterone secretion. This is an attractive hypothesis, but it receives no support from the finding of lower than normal plasma renin levels in some cases of chronic hypertension, nor from the observations referred to above concerning the effects of anti-angiotensin serum and the active immunization of animals against angiotensin. However, neither of these two findings rules out the hypothesis of an intrarenal role for angiotensin, since inhibition of its peripheral action does not necessarily imply efficient inhibition at its site of production in the kidney.

Thus, in our final analysis we must realize that blood pressure regulation is highly complex: but basically it must depend on the interplay of circulating renin and the state of sodium and water balance in the body and the influence of the latter on cardiac output and hence on autoregulatory responses. There seems good evidence that the kidney plays a dominant role in long-term blood pressure regulation, mainly through its function in relation to sodium homeostasis.

Acknowledgments: I am grateful to all those colleagues at The London Hospital who have shared in the work on experimental hypertension, particularly to Dr M A Floyer, Dr R D Cohen, Mr D Pelling and Mr C Browning; also to Professor C Wilson for his continual support through both encouraging and discouraging phases of this work over the years and to him and to Dr F Goodwin for most valuable discussions.

REFERENCES

Ames R P, Borkowski A J, Sicinski A M & Laragh J H
(1965) *J. clin. Invest.* **44**, 1171
Bianchi G, Brown J J, Lever A F, Robertson J I S & Roth N
(1968) *Clin. Sci.* **34**, 303
Bianchi G, Tilde Tenconi L & Lucca R (1970) *Clin. Sci.* **38**, 741
Borst J G G & Borst-de-Geus A (1963) *Lancet* i, 677
Bright R (1836) *Guy's Hosp. Rep.* **1**, 338
Brod J (1968) In: Renal Hypertension. Ed. I H Page & J W McCubbin. Chicago; p 362
Brod J, Hejl Z, Ulrych M, Fencl V & Jirka J
(1961) *Cs. Fysiol.* **10**, 228
Brown J J, Davies D L, Lever A F & Robertson J I S
(1964) *Canad. med. Ass. J.* **90**, 201
(1965) *Brit. med. J.* ii, 1215
(1966) *Brit. med. J.* ii, 268
Brown T C, Davis J O, Olichney M J & Johnston C I
(1966) *Circulat. Res.* **18**, 475
Browning C, Pelling D & Ledingham J M
(1969) *Med. biol. Engng* **7**, 549
Byrom F B & Dodson L F (1949) *Clin. Sci.* **8**, 1
Carpenter C C J, Davis J O & Ayers C R
(1961) *J. clin. Invest.* **40**, 2026
Conway J (1966) *Circulat. Res.* **18**, 190
Cope C L, Harwood M & Pearson J
(1962) *Brit. med. J.* i, 659
Fasciolo J C, De Vito E, Romero J L & Cucchiani J N
(1964) *Canad. med. Ass. J.* **90**, 206
Fitz A (1967) *Circulation* **36**, 942
Floyer M A
(1951) *Clin. Sci.* **10**, 405
(1955) *Clin. Sci.* **14**, 163
Folkow B
(1949) *Acta physiol. scand.* **17**, 289
(1952) *Acta physiol. scand.* **27**, 99
Folkow B & Oberg B (1961) *Acta physiol. scand.* **53**, 105
Frohlich E D, Ulrych M, Tarazi R C, Dustan H P & Page I H
(1967) *Circulation* **35**, 289
Granger H J & Guyton A C (1969) *Circulat. Res.* **25**, 379
Greenfield A D M & Patterson G C
(1954) *J. Physiol. (Lond.)* **125**, 508
Gross F, Schaechtelin G, Brunner H & Peters G
(1964) *Canad. med. Ass. J.* **90**, 258
Guyton A C & Coleman T G
(1969) *Circulat. Res.* **24**, Suppl. 1, p 1
Johnson P C (1960) *Amer. J. Physiol.* **199**, 311
Krieger E M (1970) *Amer. J. Physiol.* **218**, 486
Laragh J H, Ulick S, Januszewicz V, Deming Q B, Kelly W G & Lieberman S (1960) *J. clin. Invest.* **39**, 1091
Ledingham J M
(1953) *Clin. Sci.* **12**, 337
(1956) In: Symposium on Hypotensive Drugs. Ed. M Harington. London; p 183
(1966) In: International Club on Arteria Hypertension, First Meeting. Paris; p 393
Ledingham J M & Cohen R D
(1962) *Clin. Sci.* **22**, 69
(1964) *Canad. med. Ass. J.* **90**, 292
Ledingham J M & Pelling D
(1967) *Circulat. Res.* **21**, Suppl. 2, p 187
(1970) *J. Physiol. (Lond.)* **210**, 233
Louis W J, MacDonald G J, Renzini V, Boyd G W & Peart W S
(1970) *Lancet* i, 333
McCubbin J W, Green M B & Page I H
(1956) *Circulat. Res.* **4**, 205
Mason M F, Robinson C S & Blalock A
(1940) *J. exp. Med.* **72**, 289
Meinders A E (1965) *Nature (Lond.)* **207**, 196
Mosher P, Ross J, McFate A & Shaw R F
(1964) *Circulat. Res.* **14**, 250
Mulrow P J (1964) *Canad. med. Ass. J.* **90**, 277
Olmsted F & Page I H (1965) *Circulat. Res.* **16**, 134
Patterson G C, Shepherd J T & Whelan R F
(1957) *Clin. Sci.* **16**, 627
Scornik O A & Paladini A C (1964) *Canad. med. Ass. J.* **90**, 201
Stainsby W N & Renkin E M (1961) *Amer. J. Physiol.* **201**, 117
Texter E C, Merrill S, Schwartz M, Derstappen G van & Haddy F J
(1962) *Amer. J. Physiol.* **202**, 253
Thurau K (1969) *Proc. roy. Soc. Med.* **62**, 1118
Winer B M, Lubbe W F, Simon M & Williams J A
(1967) *J. Amer. med. Ass.* **202**, 121
Yagi S, Kramsch D M, Madoff I M & Hollander W
(1968) *Amer. J. Physiol.* **215**, 605