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HYPERTENSION AND THE KIDNEY*

II. EXPERIMENTAL BASIS OF RENAL HYPERTENSION

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In turning from the observations largely on human hypertension which I covered in my first lecture, the experimental work which has emerged in part because of this sort of observation in man must now be considered. The first important point to make is that part of the confusion in considering experimental hypertension is that so many species of animal have been used, and it is often forgotten that it is not always possible to transfer an argument based on data obtained in one species to a different one. A great deal of lip-service has been paid to knowledge of this sort in this as in other fields.

Roles of the Kidney

Table I shows some of the possible roles of the kidney in hypertension. In attempting to cover this field adequately, I will show great bias in the selection and interpretation of the most significant contributions.

TABLE I.—Possible Roles of Kidney in Hypertension

1. Failure to excrete or destroy an extrarenal pressor substance
2. Failure to produce a vasodilator
3. Increased responsiveness of normal pressor mechanisms
4. Decreased response of baroreceptors
5. Stimulation of some extrarenal pressor system—e.g., the adrenal
6. Redistribution of electrolytes and water
7. Production of a vasoconstrictor

Failure of Excretion or Destruction

I previously considered the concept of uraemia as having a causal role in hypertension, and discussed the differences in man between anuria with acute glomerulonephritis and anuria with tubular necrosis in their different effects on the blood-pressure. It was natural for early workers in this field to wonder whether it was possible to reproduce this sort of situation experimentally; for example, Grollman *et al.* (1943) showed that in the rat subjected to complete nephrectomy the blood-pressure would rise and would stay up so long as the animal lived. This did not clarify the situation, however, with respect to the failure of excretion, and Grollman *et al.* (1949) went further with the nephrectomized dog and showed that when the animal was maintained in good condition by dialysis, so that its blood urea was kept down, hypertension still supervened. This showed very clearly that a failure to excrete could not alone be invoked. These experiments have been confirmed by Floyer (1951) in the rat and by Kolff and Page (1955) in the dog.

It was pointed out that with the kidney transplant in the identical twins mentioned in the first lecture (Murray *et al.*, 1958) the blood-pressure subsided

after the introduction of the healthy kidney while the diseased ones were still present. This is in direct line with the observations of Muirhead *et al.* (1956), who showed in the dog that a homograft would reduce the blood-pressure of the nephrectomized animal to normal. In our own experience (Robertson and Peart, 1958, unpublished), using the rabbit with a clipped kidney to produce hypertension, a rise in blood urea is the usual concomitant of a rise in blood-pressure. This is shown in Fig. 1, where it can be seen that a high blood-pressure is never present with a blood urea which is within the limits of normal. It can be further seen that there is no direct relation in this preparation between the level of blood urea and the rise of blood-

FIG. 1.—Relationship of blood-pressure to blood urea. The graph is constructed from 90 observations on 58 rabbits. ○ = normal rabbits which all have a blood urea less than 50 mg./100 ml., represented by the vertical line, and a blood-pressure less than 90 mm. Hg. represented by the horizontal line. No rabbit has a blood-pressure higher than 90 mm. Hg. without a rise of blood urea. ● = One kidney removed, the other renal artery constricted.

pressure. In some experimental situations this rise of blood urea, and other things consequent upon it, perhaps may play some part, nevertheless, in the rise of blood-pressure. Surprisingly few complete studies have been made on this aspect of hypertension associated with interference with the kidney, and some impairment of renal function is often produced.

From the sort of observation considered above, there arose the concept that all renal hypertension might be explained by the bringing into play of extrarenal factors, since it was clear that hypertension would develop in the absence of the kidneys. This concept is known as renoprival hypertension. In addition to covering the possibility of failure of excretion, it also includes the

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possible metabolic effects of the presence of the normal kidney. That extrarenal factors are brought into play in any form of renal hypertension is suggested by the observations of Pickering (1945) in the rabbit, when he showed that removal of the clipped kidney within the first eight weeks was followed by a fall of blood-pressure to normal, but that after eight weeks the blood-pressure would stay up.

Further, in the rabbit, Daniel *et al.* (1954) showed that removing the clip from the renal artery did not relieve the hypertension when this had been present for 12 weeks. This was in contrast to the observations of Blacket and Sellers (1951), who stated that the blood-pressure would fall if this were done. This conflict may depend upon the state of the renal artery after clipping in the two sets of experiments. In the rat, Byrom and Dodson (1949) showed that the blood-pressure would fall when the clip was removed up to the twelfth week, and this could be related to the observations of Wilson and Byrom (1941), who showed that whether the blood-pressure remained up or came down when a clipped kidney was removed depended on whether arterial change had occurred in the opposite kidney. From this arose the concept of the vicious circle in renal hypertension due to unilateral disease. This work was extended by Floyer (1955), and certainly in the rat the perpetuation of hypertension by vascular damage to the opposite kidney seems well established.

The conclusion, then, seems to be that in most forms of renal hypertension a change undoubtedly occurs in the body which leads to maintenance of the hypertension when the damaged kidney is removed. Whatever the mechanism is, it seems to take a certain minimum time to come into operation. In man, however, unilateral renal disease can be in existence for many years and a successful result can still occur with unilateral nephrectomy (Pickering and Heptinstall, 1953), so that the situation must be examined for each particular species and type of hypertension.

The protective action of healthy renal tissue in some situations and, paradoxically, its failure to protect with certain forms of renal hypertension, have been further clarified by the experiment first performed by Rodbard and Katz (1941). In the dog they clamped one renal artery and led the ureter from the opposite normal kidney into the inferior vena cava. Removal of the "ischaemic kidney" then led to a fall in blood-pressure to normal within a few hours, just as if a normal kidney had been present. This suggests that it is some metabolic function of the kidney rather than an excretory function. This type of experiment has been repeated by Grollman *et al.* (1949) in the dog and by Floyer (1955) in the rat with exactly the same result. These observations are clearly the starting-point for further work on this aspect of kidney function in hypertension.

Failure of Vasodilator Production

The hypothesis that the kidney has its main effect on the blood-pressure by providing a vasodilator to keep the blood-pressure down and that hypertension may be due to renal damage, with a failure of production of such a substance or effect was first propounded by Grollman *et al.* (1940). There is no direct evidence showing the production of such a vasodilator. However, Hamilton and Grollman (1958) have shown that a purified extract of kidneys when fed to rats with renal hypertension has the property of lowering the blood-pressure. The exact significance of this observation requires much further work before it can be defined.

Increased Response of a Normal Pressor Mechanism

It would, of course, be possible for a diseased kidney to produce a substance which increased the effects of the normal known pressor systems in the body. For example, the sympathetic nervous system could have an increased effect due to some sort of facilitation, either in the hypothalamus, at the ganglia, or on the effect of noradrenaline liberated at the nerve endings. There is no good evidence which indicates that this is so, whereas there is excellent evidence that the sympathetic nervous system is not playing a causal part in any form of sustained hypertension (Pickering, 1936a). Much has been made of the fact that in animals made hypertensive by renal interference the blood-pressure cannot be lowered readily in the first few weeks by drugs such as yohimbine or pentolinium (Reed *et al.*, 1944; Goldblatt, 1958c), but that when the hypertension has been in existence for many weeks these drugs become capable of lowering the blood-pressure, suggesting that a nervous mechanism may be important. This is a very indirect method of assaying nervous activity.

From the point of view of an increased sensitivity to substances like noradrenaline, it must always be remembered that in hypertension the peripheral resistance arterioles must be narrower than normal, and that observations of increased rises of blood-pressure to intravenous injections of pressor substances do not constitute proof of increased sensitivity of blood-vessels, merely that the drug is acting on narrower vessels (Ogden *et al.*, 1940; Conway, 1955, 1958; Duff, 1957).

Decreased Response of the Baroreceptors

Heymans (1956) has proposed the view that the fault in hypertension may lie in the baroreceptors, such as the carotid sinus, and that they, by altering their response, allow the blood-pressure to rise to a higher level. It has always seemed to me unlikely as a primary cause, and certainly the mechanisms for adjusting the blood-pressure over long periods in the body seem poor, particularly so far as rises of blood-pressure are concerned. It appears that if a minimum blood-flow is maintained to particular tissues, then the level of blood-pressure is of less importance. The most significant observation in this field is that of McCubbin, Green, and Page (1956), who showed in the dog with renal hypertension that the depressor mechanism rapidly became reset at the higher level of blood-pressure obtaining, and only came into play temporarily when the blood-pressure was even further elevated.

Stimulation of Extrarenal Pressor System

Since, as has been seen previously, extrarenal pressor systems must come into play in renal hypertension, the idea that the kidney might stimulate such a system must be considered. The main end-organ in this respect is, of course, the adrenal. This hypothesis received a great fillip when Goldblatt (1937) showed in the dog with renal clamp hypertension that adrenalectomy would return the blood-pressure to normal, and that prior adrenalectomy would prevent the development of such hypertension. These experiments led directly to the performance of adrenalectomy in man for the relief of hypertension. It must be said that this operation has not proved to be very successful in most patients, though there are some in whom a good result has been achieved, and it may be that the operation has too often been performed in the very severe cases (Thorn *et al.*, 1952; Jeffers *et al.*, 1953). Experimentally, the most

significant observation, however, is that of Fregly (1957), who showed that in the rat after adrenalectomy it was still possible to cause hypertension by clamping the renal artery. Overall, I believe there is no direct evidence of overactivity of the adrenals in any form of renal hypertension, and that the adrenals merely play a permissive part, maintaining the normal background on which hypertension develops.

Redistribution of Water and Electrolytes

As the kidneys play such an important part in the maintenance of the water and electrolyte balance in the body, it is natural to wonder whether a disturbance in this function could in itself lead to hypertension. It is clear that a mere retention of sodium and of water, as in cardiac failure and cirrhosis of the liver, does not in itself lead to a raised blood-pressure, and the aspect which has received most study is that of an altered distribution between extracellular and intracellular tissues. Eichelberger (1943) was the first to suggest that there might be an increase in intracellular sodium in voluntary muscle in hypertension, and Tobian and Binion (1954) have claimed that in the aorta of man and other animals with renal hypertension there is a definite increase in intracellular sodium. Ledingham (1953) claimed that in the rat with renal hypertension the intracellular sodium in heart muscle was lower than normal. The difficulties that stand in the way of measuring the true intracellular composition of any tissue should be pointed out.

In between the cells lies an undetermined amount of extracellular fluid; it is extremely difficult to make an accurate allowance for changes in this quantity, and this may throw out the determinations and lead to false conclusions. In acute experiments, Friedman *et al.* (1957) have claimed that the normal response of blood-vessels in animals to an acute rise of blood-pressure induced by such substances as noradrenaline and pitressin is for sodium and water to enter and potassium to leave the cell within seconds. Studies in man of the total body sodium, which might, of course, be related to elevation within cells, since extracellular sodium is not raised in most forms of hypertension, do not show any consistent relation to the level of blood-pressure. Ross (1956) found an elevated total exchangeable sodium in some patients, but lowering this by treatment was not related necessarily to lowering the blood-pressure. Moore *et al.* (1954) and Hollander *et al.* (1956-7) have not found an increase in total exchangeable sodium. It is, of course, tempting to wonder whether the entry of sodium and water into intimal or smooth-muscle cells and arterioles could lead to swelling and therefore to an increase in the peripheral resistance, but there is no real evidence bearing on this aspect.

Effect on Kidney Excretion

From the experiments on animals, it has been known for many years that renal hypertension in particular is associated with an increased excretion of both chloride and water (Farnsworth and Barker, 1943). Brodsky and Graubarth (1953) were the first to show that the patient with high blood-pressure behaves differently in response to sodium-loading compared with the normal in that the kidney then excretes much more sodium. Cottier *et al.* (1958) have shown that the patient with hypertension is excreting water and sodium at an increased rate compared with the normal. These observations would lead one to suppose that sodium depletion would be inevitable. However, Sapirstein

(1958) has pointed out that, despite the increased total excretion of sodium, there is relatively more water excreted than in the normal kidney, so that the effect would be to increase the body sodium relative to water. It may be asked whether this is a cause of the hypertension or whether the hypertension is the cause of the change in renal function.

White (1950) and Selkurt (1951) showed in the dog that the excretion of sodium and water was directly proportional to the pressure in the renal artery, so that it would be expected that a rise in the pressure would lead to an increase of sodium and water excretion. There is very strong evidence to support the view that these changes in the kidney are secondary to the rise in blood-pressure, since Thompson *et al.* (1954) showed that lowering the blood-pressure by sympathectomy lowered the excretion of sodium and water towards normal, and, similarly, Hollander *et al.* (1956-7) have shown the same effect with hypotensive drugs. The overall view, then, is that, while there is this abnormality in handling sodium and water in hypertension, it is a secondary and not a primary happening.

Vasoconstrictors

The production or occurrence of vasoconstrictors in relation to renal hypertension has a very long history. In 1898 Tigerstedt and Bergman discovered that saline extracts of kidney contained a pressor substance which they named renin. They subsequently showed most of its properties as a protein, but this work then lay fallow, despite interest in the relation between the kidney and high blood-pressure, for thirty-six years until Goldblatt *et al.* (1934) performed their memorable experiment of clamping the renal artery, and showed that this sort of interference with the kidney circulation led to hypertension. Interest was then reawakened in kidney extracts, and among others Pickering and Prinzmetal (1938a) confirmed the existence of renin.

Braun-Menéndez *et al.* (1939) and Page and Helmer (1940) independently arrived at the conclusion that renin

must be an enzyme acting on a substrate in the plasma to produce the end-product which received the names of hypertensin and angiotonin. Braun-Menéndez and Page (1958) have suggested the name angiotensin for this final product. Both renin and hypertensin are extremely active in raising the blood-pressure, and

FIG. 2.—Comparison of the pressor action of renin and hypertensin. Rat blood-pressure. R and H= injection of renin and hypertensin respectively. Note the difference in the shape of the pressor responses.

enzymeproducing hypertensin, during its circulation is to be compared with the short-acting hypertensin effect. It is known that, in the rabbit kidney, renin is situated very close to the glomeruli (Cook *et al.*, 1957; Cook and Pickering, 1958); certainly not in the tubules, but in which precise structure has yet to be determined.

Hypertensin

Hypertensin, or angiotonin, has been isolated and its amino-acid sequence determined (Peart, 1955, 1956; Elliott and Peart, 1956, 1957; Skeggs *et al.*, 1955, 1956b).

1	2	3	4	5	6	7	8	9	10
Asp	Arg	Val	Tyr	Val	His	Pro	Phe	His	Leu
Elliott & Peart Ox substrate									
Asp	Arg	"	"	Ileu	"	"	"	"	"
Skeggs <i>et al.</i> Horse substrate									
Asp	Arg	"	"	Ileu	"	"	"	"	"
Schwyzer <i>et al.</i> Synthetic									
Asp	Arg	"	"	Val	"	"	"	"	"

FIG. 3.—Structural relationship of natural and synthetic hypertensin peptides. Amino-acid sequences.

Synthesis of this and similar peptides has been achieved by Schwyzer and Sieber (1956), Rittel *et al.* (1957), Bumpus *et al.* (1957), and Schwyzer *et al.* (1958). Fig. 3 shows the relation between these peptides. Skeggs *et al.* (1956a) showed that there was present in normal plasma a "converting enzyme" which was capable of removing the two C terminal amino-acids, his-leu, from the decapeptide and converting it to the octapeptide, which was equally active in raising the blood-pressure. It is therefore believed that it is the octapeptide which normally is the substance active in the circulation. It is also known that these peptides act by directly contracting the smooth muscle of the arterial wall.

With the advance in knowledge of the biochemistry of renin and hypertensin, it has been possible to re-examine the proposition that these substances have a role in human and experimental hypertension. In the past twenty years there have been numerous claims that renin is responsible for a raised blood-pressure in one or other of these situations, and before discussing them I would like to report some of our own unpublished observations.

The first essential in man is to be able to measure renin in the circulation accurately. Robertson and I decided that it was best to allow human renin to make hypertensin and then to assay the latter substance in the rat, since this preparation is extremely sensitive to hypertensin. It should here be pointed out that hypertensin is up to twenty times as active, molecule for molecule, in raising the blood-pressure as is noradrenaline. Fig. 4 shows a typical bracket assay

FIG. 4.—Human hypertensin assay. Rat blood-pressure. P = unknown plasma. St.H = standard human hypertensin. Doses in ml. Result: 0.05 P $\equiv$ 0.15-0.18 St.H.

of human hypertensin in the rat. We decided that it was necessary to be able to collect blood from both kidneys in man almost simultaneously, so that, especially in unilateral renal disease, we would then be able to compare the blood from both kidneys. A guided

tip catheter was therefore devised (Peart and Sutton, 1958), and samples were collected readily by this means. Fig. 5 shows the catheter. In addition, samples were collected direct from the renal vein at operation in many patients. Table II shows that a wide range of patients with severe hypertension were studied, including those with renal-artery stenosis. The blood collected from the renal veins in this way was incubated, and, as control, renin was added to it to show that in all cases

FIG. 5.—Guided tip catheter. Traction on the nylon thread bends the tip as needed.

TABLE II.—Samples of Renal-vein Blood in Hypertension

No. of Patients	Diagnosis
14	"Essential" hypertension (8 malignant)
3	Pyelonephritis (1 malignant)
2	Glomerulonephritis (1 malignant)
1	Polycystic kidney
2	Unilateral hydronephrosis
3	Stenosed renal artery
1	Coarctation of aorta

the possibility of making hypertensin with the blood collected was present. Fig. 6 shows a typical assay in a patient with severe renal hypertension.

In all these investigations it was not possible to demonstrate any renin in the renal-vein blood. The amount of hypertensin which it was possible to make from the blood of normal and hypertensive patients was considerable — over 1 μ g. per ml. of plasma. Fig. 7 compares the amounts of hypertensin made by adding renin to plasma from a normal and a hypertensive patient to emphasize this point further. Both these subjects fell within the same range of production of hypertensin, and the lower limits of the assay at which we were usually working are shown in the bottom left-hand rectangle in Fig. 7. Now this evidence is in direct conflict with reports that renin is sometimes found in renal-vein blood in man (Dexter and Haynes, 1944; Haynes *et al.*, 1947; Margolin *et al.*, 1957). I believe that before any worker claims that renin or hypertensin is present in blood the criteria in Table III should be adhered to. There have been so many claims that have only added to confusion because of lack of rigid proof, and at this stage these criteria are essential to clarify the situation. It is so easy to produce artifacts in blood, and these vary according to the type of assay used.

FIG. 6.—Assay of human plasma in the rat. St. = standard human hypertensin. R = right kidney. L = left kidney. IVC = inferior vena cava. Doses in ml. No detectable hypertensin in any sample.

One objection to the experiments described above is that the assay might be too insensitive for the amounts of renin and hypertensin responsible for the hypertension in the patients studied. From the experiments we have performed, using synthetic hypertensin (Pickering, Sanderson, and Peart, 1958, unpublished), we know that it requires about 5-10 μ g. per minute intravenously to produce distinct hypertension in man. If we assume

FIG. 7.—Renin assay in human plasma. Abscissa: amount of standard renin added to same volume of plasma. Ordinate: hypertensin concentration (Asp-NH₂ Val 5). Small rectangle at bottom left is usual working range. Area of curve represents bracket limits of assay. Curve constructed by assay on normal peripheral plasma and on renal-vein plasma from patient with severe renal hypertension.

from renal plasma flow, as derived from para-aminohippurate (P.A.H.) clearance techniques, that this amount would be added to 250 ml. of plasma per minute, then we obtain a concentration of 0.02–0.04 µg. per ml. of plasma, which is within our assay range on the rat. Further, most of our patients studied had severe hypertension and the renal plasma flow was much lower than this, so that we think we should have been able to demonstrate hypertensin if it had been produced there by renin.

It might be argued that in patients with hypertension there could be a greater response to smaller quantities of hypertensin than those required in the normal, or that some other mechanism is responsible for maintaining the blood-pressure in the presence of smaller quantities of hypertensin which could be regarded as the initiating cause. This secondary mechanism has

TABLE III.—Suggested Criteria for Identification of Renin and Hypertensin

Renin	
1.	The form of the pressor effect should be identical with standard renin
2.	Activity should be lost by heating
3.	The ability to make hypertensin should be demonstrated
Hypertensin	
1.	The form of the pressor effect should be identical with pure substance
2a.	Action on other test objects should be the same as the pure substance
2b.	Identity of behaviour with the pure substance using different methods of physical separation

been discussed previously. It has further been claimed that if the renal artery in man and animals is clamped to produce total ischaemia for minutes, the venous blood contains renin on releasing the clamp (Quinby *et al.*, 1945). We have repeated these experiments in patients whose renal arteries had to be clamped during the course of an operation, and we have been unable to show the presence of renin, though it was easy to demonstrate renin added to the blood.

Renin in Renal-artery Clipping

Following the renal-artery-clamp procedure of Goldblatt *et al.* (1934), it became a natural assumption that the hypertension thereby caused was due to the release of renin into the circulation, but direct evidence

is striking by its absence. Robertson and I (1958, unpublished) have re-examined this problem in the rabbit. Rabbit renin can be assayed directly and readily in the rat. Rabbits were made hypertensive by putting a clip on the renal artery and removing the other kidney (Pickering and Prinzmetal, 1938b). Samples were collected from the renal vein of rabbits at all stages of hypertension, both early (up to one week) and late (two to three months), and with both mild and severe hypertension. In some instances samples were collected from the anaesthetized animals. In others a catheter was inserted into the renal vein via the external jugular vein, under ether, and samples were subsequently collected from the conscious animal.

In order to see whether we could detect renin infused into the rabbits so that their blood-pressure was raised to the same level as in renal-artery clamping, we performed another type of experiment. A catheter was introduced just within the mouth of the renal vein and a fine nylon catheter pushed through it right up to the kidney. Infusion of renin was made through this and the blood-pressure raised (Fig. 8). At no time in any rabbit with hypertension due to renal-artery clipping has it been possible to show the presence of renin, yet it has always been possible to demonstrate this substance when infusions were given in the way described, and blood was collected from the mouth of the renal vein. Fig. 9 shows a typical comparative experiment, and relevance is added when it is realized that the infusion experiments were done in animals treated in exactly the same way as those which did develop hypertension but in which, probably due to a too large clip, hypertension did not develop.

Again, it may be asked how it is that these negative findings were obtained when others have claimed the presence of renin in this sort of hypertension. The direct demonstration, I think, is the only one worth while, since all the other errors which may creep into the interpretation of indirect methods are avoided. In performing a direct investigation, the presence of artifacts has to be rigorously excluded, and in handling blood which has to be assayed elsewhere artifacts

FIG. 8.—Method for infusion of renin into the renal vein with collection of renal-vein blood mixed with renin. Renin infused through the fine catheter. Blood collected through the wider outer catheter.

FIG. 9.—Assay of rabbit plasma. Rat blood-pressure. All rabbits unilaterally nephrectomized with renal artery clamp on remaining kidney. Samples { vc=inferior vena cava below renal veins. r=renal vein. Animals { A=B.P. 32 mm. above baseline. B=B.P. 52 mm. above baseline. C=no rise of blood-pressure until renin infused into end of renal vein to give 30 mm. rise of blood-pressure. Sample taken from mouth of vein. Dose 0.1 ml.

readily creep in. Fig. 10 shows a typical artifact produced in human blood obtained from the renal vein, which has a long action like that of renin. Fig. 11 shows an artifact which is produced by incubating rabbit plasma and which is indistinguishable from hypertensin in its effects on the blood-pressure. Some reports of renin and hypertensin may be based on this sort of finding.

Tachyphylaxis

If successive doses of renin are given to certain animals the response dies away. This is especially so in the rabbit, and Taggart and Drury (1940) made use of this to determine the role of renin in the renal-clip hypertension. They injected renin into such hyperten-

FIG. 10.—Long-acting pressor artifact in human plasma. Rat blood-pressure. P=plasma. St.H=standard human hypertensin. Doses in ml.

FIG. 11.—The appearance of a hypertensin-like artifact in rabbit plasma on incubation at 37° C. for 20 minutes. H=standard. P=plasma. Doses in ml. The small effect before incubation is quite common.

FIG. 12.—Renin tachyphylaxis in the rabbit. The dark blocks represent infusions of renin given at a steady rate during the period indicated. It can be seen that after the first response there is no further response.

sive animals until the response was abolished, yet the animals remained hypertensive, suggesting that they could not be producing renin themselves to maintain the hypertension.

Goldblatt (1958b) has claimed that he has never seen tachyphylaxis in the dog, but it certainly occurs in the rabbit, even with purified preparations of renin, and Fig. 12 shows a typical effect.

Antirenin

Johnson and Wakerlin (1940) conceived the idea that, if it were possible to make an antibody to renin, injections of it into animals with renal hypertension and observation of the subsequent effects on blood-pressure would define the role of renin. They, and subsequently Goldblatt *et al.* (1951), have shown that such antirenin sera are capable

FIG. 13.—Effect on blood-pressure and pulse in man of an infusion of Asp-NH₂ ileu 5 octapeptide (H=5 µg./min.).

FIG. 14.—Effect on skin blood-flow in man of Asp-NH₂ ileu 5 octapeptide, measured by thermocouple and hand calorimetry. The bottom two sections show the fall in heat output and skin temperature during the infusion.

of lowering the blood-pressure of the dog with renal-artery-clamp hypertension. There is no doubt about the observations, but I am far from convinced that this proves that the effect is due to the antirenin contained in the sera. These sera are not pure substances, and this indirect approach will require the use of pure renin to produce the antibodies before more credence can be given to this type of experiment.

Actions of Hypertensin

Knowledge of the actions in man of pure hypertensin may be expected to throw light on its possible role in hypertension. Sanderson, Pickering, and I (1958, unpublished), Bock and Krecke (1958), and Bock *et al.* (1958a, 1958b) have investigated these actions. Fig. 13 shows the typical effect on blood-pressure and pulse. As with noradrenaline, the pulse is slowed with rise of blood-pressure. With moderate rises of blood-pressure the subject is not aware of any unpleasant sensations, but with higher rises peculiar mental effects enter, difficult to define.

Skin Blood-flow

Intravenous infusions of hypertensin lower the skin blood flow as the blood-pressure rises. This is shown in Fig. 14. As the hand blood-flow is within normal limits in most forms of hypertension this suggests

FIG. 15.—Hand blood-flow in various forms of hypertension measured by calorimetry with body-heating to eliminate sympathetic tone (so-called maximal heat elimination). Shown are normals, unilateral renal disease (open circle represents renal-artery stenosis), pheochromocytoma before and after tumour removal, Cushing's syndrome.

immediately that if hypertension is playing a part considerable readjustment would have to take place in the circulation.

Hand Blood-flow in Hypertension

In view of the observations made and the effects of pure hypertensin in reducing the hand blood-flow in normal subjects, Dr. J. J. Brown has reinvestigated the hand blood-flow in

various forms of hypertension. This has especial relevance in that if one considers the state of the circulation in a patient with pheochromocytoma

where noradrenaline and adrenaline are circulating, the hand and skin blood-flow are found to be reduced, since these substances have special vasoconstrictor effects in the skin (Barnett *et al.*, 1950; Hamilton *et al.*, 1953). It has been commented that hypertensin infusions

FIG. 17.—Effect on urine flow and electrolyte excretion in man of infusion of Asp-NH₂ val 5 octapeptide (H). Left: High flow; H=4.5 µg./min. Right: Low flow; H=5 µg./min. The flow rate and electrolyte excretion are both greatly reduced.

led to a fall in skin blood-flow, and therefore we wondered whether we would find a reduced hand blood-flow in patients with renal hypertension, especially renal-artery stenosis.

Fig. 15 compares the hand blood-flow in various forms of hypertension. The low flow in the patients with pheochromocytoma is noted and is contrasted

with the normal flow existing in patients with renal hypertension, including renal-artery stenosis. In acute nephritis, Pickering (1936b) has previously found that the hand blood-flow was raised or had a high normal value, and that with decline in the blood-pressure the blood-flow also dropped. Readjustment of the circulation to noradrenaline does not seem to prevent the demonstration of its effects, whereas if hypertensin is responsible for the hypertension in patients with renal disease, it is perhaps surprising that their hand blood-flow is still within high normal limits. These arguments, however,

FIG. 16.—Effect on forearm blood-flow in man of infusion of Asp-NH₂ ileu 5 octapeptide (isoleucine) and Asp-NH₂ val 5 octapeptide (valine). The rise during both periods of infusion is shown.

are indirect, and I place much more emphasis on the direct methods described previously.

Forearm and Muscle

As the blood-pressure rises with infusions the forearm blood-flow also rises, and Fig. 16 shows the typical effects of infusion of two types of hypertensin. Bock *et al.* (1958b) have shown by direct measurement of muscle blood-flow that this rises. This is consistent with the findings on forearm blood-flow, which is a mixture of skin and muscle flow. Hypertensin is therefore not a very potent constrictor of muscle vessels.

Effects on Kidneys

Of extreme interest are the effects on the kidney, since, as was discussed above, there are changes in hypertension leading to an increased output of water and sodium. In the normal subject the consistent effect is greatly to reduce urine flow and electrolyte excretion. This occurs with only moderate rises of blood-pressure, and with larger rises in blood-pressure it is possible

FIG. 18.—Effect in man on inulin clearance (C in.) and P.A.H. clearance (C p.a.h.) of infusion of Asp-NH₂ val 5 octapeptide (H) 5 µg./min. Both are reduced, as is the urine flow.

FIG. 19.—Effect of an infusion of Asp-NH₂ val 5 octapeptide (H) 4 µg./min. on the urine flow and electrolyte excretion in a patient with severe renal hypertension. Both factors rise in contrast with the normal subject.

almost to stop urine flow. This effect is shown in Fig. 17, and occurs at high and low rates of urine flow. That it is a direct effect and not one mediated through antidiuretic hormone is suggested by the experiment we performed in a patient with diabetes insipidus (Dr. de Warden, St. Thomas's Hospital), where the effect was shown to be the same as in the normal subject. In addition, we have noted a fall in inulin and P.A.H.

clearances, pointing to a vasoconstriction in the renal arteries (Fig. 18). These effects, of course, are not like anything seen in any form of hypertension, except perhaps acute glomerulonephritis, but it must be remembered that acute experiments do not necessarily give valid information about chronic states in man, and Dr. J. J. Brown (1959, unpublished) has repeated these observations in patients with severe renal hypertension and discovered that in many, with infusions of small amounts of hypertensin, sufficient to slightly raise their blood-pressure, the urine flow and electrolyte excretion rise in contrast to the normal (Fig. 19).

It is difficult to believe that in these patients the hypertensin that was infused was being added to endogenous hypertensin responsible for the high blood-pressure and the existing normal renal excretion of water and electrolytes.

The circulatory effects thus seem to be that pure hypertensin is vasoconstrictor in most areas where it has been studied and that the findings do not fall into line with anything that is known of renal hypertension, except perhaps the effects on the kidney in acute nephritis. These findings must be contrasted with the claims of Kahn *et al.* (1952) in patients with malignant hypertension where the blood was said to contain up to twenty times as much hypertensin as normal, and with the similar claims of Gollan *et al.* (1948) and of Skeggs *et al.* (1951) in dogs with renal-artery-clamp hypertension, where hypertensin was similarly incriminated as the cause of the raised blood-pressure. Immediately one must say that there is a discrepancy here which requires explanation. One cannot transfer arguments from dog to man, but the onus of proof of a high order seems to me to be fairly placed on those making the claim, and I do not think that the evidence of the presence of hypertensin is sufficient. The demonstration of a pressor action in an extract should be backed up by other methods—for example, parallel pharmacological assay or physical separation—so that we may at last bring clarity.

Summary and Conclusions

An examination of the morbid anatomical and histological changes in the kidney in hypertension shows no consistent relation to the level of blood-pressure. In man the often-found ischaemic change in the tubules is not uniform and is by no means paralleled in the experimental situation.

That arterial obstruction to one kidney may lead to hypertension in man, as well as in the animal with a Goldblatt kidney, has been well established by the demonstration that reconstruction of the stenosed artery or removal of the kidney beyond may return the blood-pressure to normal. The diagnostic criteria and investigation of function of the kidney in this condition are discussed and emphasis is laid upon the necessity for proper investigation before over-enthusiastic surgery is performed on arteriographic appearances.

Some possible roles of the kidney in hypertension are considered critically, and an attempt is made to distinguish those changes which occur as a consequence of the high blood-pressure as opposed to those which may have a causal role.

Special emphasis is given to a consideration of the role of vasoconstrictors emerging from the kidney and an assessment of the renin-hypertensin system made. Investigations and experiments performed in man and in the rabbit are described, which lead to the conclusion that renin cannot be wholly, if at all, responsible for the type of hypertension studied, which included clinical and experimental examples of renal-artery obstruction. The use of pure synthetic hypertensin peptide in human investigation is described and the qualitative and quantitative considerations which argue against its role in hypertension of the sort studied are considered.

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