BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 10 1943

THE CIRCULATION IN ARTERIAL HYPERTENSION*

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LECTURE II

In Lecture I it was seen that the circulatory changes which give rise to raised arterial pressure are not quite the same in the various diseases of which hypertension is a symptom.

In one type, of which essential hypertension is the chief example, the hypertension is due to arteriolar constriction; evidence of vasoconstriction has been found in the skin and in the efferent glomerular arteries of the kidney, and in both places it has been shown to be of non-nervous origin. In the skin the vasoconstriction is of an order such that when nervous vasoconstrictor tone is removed the skin blood-flow is, for that circumstance, normal or but slightly reduced. A balance-sheet of the circulation suggests that the vessels to most other tissues except muscle are also constricted; and, although there is no evidence as to the nature of the vasoconstrictor agent in these tissues, it is not likely to be different. So far as we know, coarctation of the aorta and chronic nephritis present a picture similar in its broad features to that of essential hypertension, but, particularly in nephritis, our information is less complete.

The second type is that of acute nephritis in which no vasoconstriction has been demonstrated in the skin of the hand and in which the renal blood-flow may not be reduced. The circulation in pregnancy toxæmia presents certain features which resemble that in acute nephritis, but there is still too little information to judge of its identity.

We may now proceed to consider to what extent these features of the circulation in hypertension can be reproduced by the activity of known pressor mechanisms.

The Vasomotor Nerves

Like most other unexplained disturbances of the circulation, hypertension, and particularly essential hypertension, has been ascribed to abnormal activity, in this case overaction, of the sympathetic nerves. This overactivity, when it has been accounted for, has in its turn been attributed either to a disturbance in the higher functions of the brain acting on the vasomotor centre or to a diminution in the sensitivity of the carotid sinus and depressor reflexes. The first of these hypotheses has never received any substantial proof: the alleged hereditary element in the aetiology of essential hypertension is compatible with it, but also with other hypotheses. The second hypothesis seemed to receive support when it was demonstrated that in the experimental animal a persistent hypertension could be produced by section of both carotid sinus and depressor nerves (Koch, Mies, and Nordmann, 1927). But Pickering, Rothschild, and Kissin were able to show in 1936 that the carotid sinus mechanism is active in essential hypertension, and the tachycardia which is a cardinal feature of the experimental lesion is absent in the supposed human example.

Most of the evidence with which the vasomotor nervous hypothesis of essential hypertension has been supported proves on critical inquiry no more than that the vasomotor nerves are active in patients suffering from the disease, as they are in normal subjects; and although there is a good deal of normal

variation in the responses to vasomotor reflexes there is no true evidence of their overactivity in hypertension.

From the evidence presented in the first lecture it is improbable that the vasoconstriction which underlies essential hypertension is of nervous origin; for we saw that the vasoconstriction present in hand and kidney is not of nervous origin. In fact, a review of the circulation in the several diseases revealed only one—acute nephritis—in which overaction of the vasomotor nerves seemed likely; and although Arnott and Kellar (1936) have found that in experimental acute nephritis hypertension is prevented by renal denervation no relevant reflex mechanism has yet been demonstrated.

Adrenaline

Adrenaline, first demonstrated by Oliver and Schäfer in 1894, proved a relatively simple substance, and a good deal is known of its action on the circulation of animals though much less of its action on man. Rein (1931) was, so far as I know, the first to point out that the most important action of adrenaline was that of a redistributor of blood, diverting it from gut and skin to muscle, brain, and heart. This is probably also its chief action in man (see, for example, Grant and Pearson, 1937-8). Thus in an unpublished experiment on myself on Dec. 12, 1936, adrenaline infused into the internal saphenous vein, at the rate of 1.6 c.cm. of a 1:100,000 solution per min., reduced heat elimination of one hand from an average of 224 cal. per min. to 35 cal. per min. while increasing the flow through the other forearm from 4.6 to 7.2 c.cm. per min. This dose of adrenaline therefore very considerably decreased blood-flow through skin while increasing it through the whole forearm and therefore through muscle; on another occasion in the same subject the arterial pressure was 120/75 before and 145/65 during infusion at a similar rate. We can, I think, be reasonably sure that adrenaline is not concerned in the genesis of the forms of hypertension considered in the previous lecture; for, although it seems to produce constriction of the efferent arterioles of the kidney, as Smith and his colleagues have shown, its constriction of the skin vessels is much too intense for the active agent in, say, essential hypertension. The simplest demonstration that it is not concerned in essential or chronic nephritic hypertension is one which Kissin and I described in 1936. It is common knowledge that the skin of the face is pink or red in many patients with essential hypertension and in some with chronic nephritis. The absence of constriction in these skin vessels indicates either that there is no excess of adrenaline circulating or that the vessels are insusceptible to it. We were able to exclude the second alternative, for we found that in both these kinds of hypertension the facial skin paled to a normal extent on intravenous injection of small amounts of adrenaline (2 to 2.5 γ).

There is, however, one form of hypertension not yet mentioned in which the presence of abnormal amounts of adrenaline in the circulating blood is the cause of the raised arterial pressure. This is the rare paroxysmal hypertension produced by a pheochromocytoma, a tumour of the adrenal medulla. In this condition occur paroxysms characterized by pallor and coldness of the skin, by hypertension, and in some cases by acute oedema of the lungs; between the attacks the patient is

* An abridged version of the Oliver-Sharpey Lectures delivered before the Royal College of Physicians of London on March 23 and 25, 1943.

normal. A substance which behaves like adrenaline has been demonstrated by Beer, King, and Prinzmetal (1937) in the blood during but not between the attacks; and the paroxysms are abolished by removing the tumour, which often contains excessive amounts of adrenaline. The differences between this and the other forms of hypertension support the view that it is the only one in which adrenaline is concerned; among other differences it is the only form of hypertension in which vasoconstriction affects the digital arteries, as Prinzmetal and Oppenheimer have shown; and it is the only one in which blood taken directly from a patient and perfused through an animal preparation produces vasoconstriction (Beer, King, and Prinzmetal, 1937).

Other Pressor Amines

Several pressor amines have been isolated from tissue undergoing putrefaction (Barger and Walpole, 1909), where they result from decarboxylation of amino-acids. These amines are not known to be present in living tissues, and for this reason are probably not the cause of any hypertension. Little is known of their detailed action on the human circulation, but in animals the action of tyramine bears some resemblance to that of adrenaline (Dale and Dixon, 1909).

Posterior Pituitary Extracts

Pitressin, the pressor fraction of post-pituitary extract, can be dismissed briefly. Theobald (1933-4) has pointed out that it is a feeble pressor substance but a powerful antidiuretic in man. In minute doses it produces intense blanching of the human skin. Its action clearly fails to reproduce the known conditions of the circulation in human hypertension.

Renin

Renin was discovered in 1898 by Tigerstedt and Bergman, who observed a prolonged rise of blood pressure in the rabbit after intravenous injection of saline and other extracts of kidney. They established many properties of the active substance, which they named renin. Unlike adrenaline, renin was to prove a most elusive substance. Despite its discovery only four years after adrenaline and by men no less eminent than Oliver and Schäfer, and despite the clinical relationship between raised arterial pressure and renal disease indicated by Bright, 40 years elapsed before the existence of renin was firmly established. During this interval only Bingel and his co-workers, Strauss and Claus (Bingel and Strauss, 1909; Bingel and Claus, 1910), were able fully to confirm the original observations. The failure to demonstrate renin was not entirely due to neglect. Notable among attempts to demonstrate it were those of Batty Shaw and of Hartwich and Hessel. In 1906 Batty Shaw, in his Goulstonian lectures to this college, described a series of very careful experiments on etherized cats in which he had been able to demonstrate a prolonged pressor effect in some experiments from intravenous injection of saline extracts of fresh kidney. But the results were so irregular—only a fall of pressure being obtained in some instances—that the investigation was not pursued. Nevertheless Batty Shaw had no doubt of the existence of renin, and his views on its possible relationship to hypertension are so like the theory current to-day that they may be quoted: "If a toxic agent leads to the liberation of sufficient renal parenchyma or if a sufficiently large district of renal tissue is newly cut off from the general circulation by extension of occlusive disease . . . the cells involved yield a pressor substance to the system and cause a rise of blood pressure above normal."

In 1932 Hartwich and Hessel, proceeding on the hypothesis advanced by Volhard that pale hypertension was due to a pressor substance of renal origin, obtained a pressor effect from intravenous injection of autolysed but not of fresh renal press-juice; the pressor substance in the autolysate was not renin, however, and was probably one of the putrefactive amines.

Interest in renin received a new stimulus from the demonstration in 1934 by Goldblatt *et al.* that a persistent hypertension could be produced by constricting the renal arteries in the dog. Work by him and by many others succeeded in demonstrating that this hypertension results from the release into the circulation of a pressor substance from the affected kidney. In 1936

Harrison, Blalock, and Mason, and Prinzmetal and Friedman, independently observed that saline extracts made from the ischaemic kidneys of dogs with hypertension produced a greater rise of pressure than did similar extracts of normal kidneys when injected into unanaesthetized dogs; the responses in both instances were peculiar in that they reached a maximum in 20 minutes or more. In 1938 the existence of renin was confirmed independently by workers from many laboratories, and since that date our knowledge of it has grown apace. The question as to why this substance should have eluded detection for 40 years is a fascinating one. It was not because the original account was wrong, for, as Prinzmetal and I showed in 1938, Tigerstedt and Bergman's account of the chemical properties of renin was correct. Depressor and interfering substances are certainly present in saline extracts, but both Tigerstedt and Bergman and Bingel and Claus described methods of removing most of these. Prinzmetal and I suggested that most of the difficulty had arisen from the use of anaesthetized animals as test preparations; for although, as we showed, pressor responses could be obtained in such, they were diminished at least in the rabbit. This has been confirmed by Scarff and Martin (1941), but not in other animals, and needs further work. Another possible reason has emerged from the important work of Kohlstaedt, Helmer, and Page (1938), Page (1939), Page and Helmer (1940a, 1940b), and Braun-Menendez, Fasciolo, Leloir, and Muñoz (1939, 1940), who independently showed that renin is not in itself a pressor substance, but that it is an enzyme acting on a constituent of the plasma globulins (hypertensinogen) to produce a third substance, hypertensin (Braun-Menendez, *etc.*) or angiotonin (Page and Helmer), which is the effective pressor agent. To produce a pressor response, renin is dependent on the presence of hypertensinogen in the blood.

We may now consider whether renin or hypertensin reproduces the circulatory conditions found in any form of human hypertension; if so, we may consider the substances in greater detail.

Effects of Renin and Hypertensin on the Circulation

Since renin acts through its capacity to produce hypertensin from hypertensinogen, the actions of renin and hypertensin, though differing in duration, should be similar in kind. This seems to be true in the experimental animal, in which intravenous injection of either produces rises of systolic and diastolic pressure which are not due to increased cardiac output and which may be inferred, therefore, to be due to vasoconstriction. This vasoconstriction differs greatly from that of most other known pressor substances in that it does not affect the skin vessels more intensely than those elsewhere in the body. Thus, in the unanaesthetized rabbit, renin in doses which double the arterial pressure produces only the faintest paling of the ear (Pickering and Prinzmetal, 1938) and no fall of skin temperature (Landis, Montgomery, and Sparkman, 1938), effects which are conspicuous with adrenaline and tyramine and posterior pituitary extract. That the ear arterioles do constrict to renin and hypertensin was determined by direct examination of them by Prinzmetal and me (unpublished) and by Abell and Page (1942).

In man the action of renin on the circulation has not been fully investigated because animal renin fails to act on human hypertensinogen and is therefore inactive in man, and human kidneys are a poor source of renin. But hypertensin has been prepared by Helmer and Page in a form suitable for injection into man, and its effects have been investigated by Corcoran, Kohlstaedt, and Page (1941), Bradley and Parker (1941), and Wilkins and Duncan (1941). Hypertensin by intravenous injection or infusion produces a rise in systolic and diastolic pressures, and a slowing of the pulse which is absent or slight in the infusions. The cardiac output is reduced, the heart size is increased, and the venous pressure rises. Corcoran, Kohlstaedt, and Page state that, unlike adrenaline, hypertensin produces no paling of the skin, but Wilkins and Duncan sometimes observed this. No measurements of skin blood-flow have been made with the influence of the vasomotor nerves eliminated, but Wilkins and Duncan tabulate figures for the blood-flow through the hand of the warm subject in 36 experiments in which hypertensin was injected intravenously. In 22 of them

the blood-flow after hypertensin varied between limits above and below the resting; in 8 it was increased and in 6 decreased. Although a final conclusion should await a more deliberately planned experiment, these results suggest that the hypertension produced by hypertensin is not accompanied by any pronounced change in skin blood-flow. The effect of hypertensin on the renal circulation has been investigated by Corcoran, Kohlstaedt, and Page by the methods mentioned in the previous lecture. Hypertensin in doses sufficient to raise the arterial pressure by about 40 mm. Hg reduces the effective renal blood-flow by about 50%, but lowers the glomerular filtration rate to a much less extent—changes which are attributed to efferent glomerular vasoconstriction.

Wilkins and Duncan concluded from their investigations that the changes produced in man by intravenous injection of hypertensin resembled most closely the hypertension of severe acute nephritis in that both may show the manifestations of cardiac failure—i.e., dilatation of the heart and raised venous pressure, features not observed in essential hypertension except in the terminal stages. These changes are, however, precisely the changes induced in a normal heart by a sudden rise of arterial pressure, as Starling showed decisively on the heart-lung preparation 30 years ago. That the heart may behave similarly in acute nephritis and after the injection of hypertensin would thus seem to be due to their both representing the behaviour of a normal heart to an acute hypertension; and the difference in behaviour of the heart in the chronic hypertensions is readily linked with its pronounced hypertrophy in such conditions. So far as we know them, the changes in the peripheral vessels in acute nephritis are not the same as those after injection of hypertensin. Thus as yet there is no evidence of any humoral vasoconstriction in the skin vessels in acute nephritis nor of efferent glomerular constriction, both of which are produced by hypertensin. The absence of efferent glomerular constriction in pregnancy toxæmia again excludes this agent in that condition.

But in essential hypertension, and probably in the other related forms of persistent hypertension mentioned in the first lecture, the chief changes noted in the behaviour of the vessels are similar to those induced by hypertensin, which alone of the known pressor substances is a conceivable causative agent. For although, as Goldring, Chasis, Ranges, and Smith have pointed out, a variety of agents such as adrenaline and tyramine, as well as renin and hypertensin, produce constriction of the efferent glomerular arteries of the kidney, only renin and its product hypertensin produce hypertension without so constricting the vessels of the skin that much blood is diverted from it. So far as our knowledge goes—and it is clearly incomplete—they are the only agents known which reproduce the circulatory conditions of essential hypertension. Since there is thus a *prima facie* case for the view that the renin-hypertensin system may be concerned in the genesis of essential and related forms of human hypertension, we may proceed to examine it in greater detail.

Renin, as Tigerstedt and Bergman showed, is found in the cortex and not in the medulla of kidney; it has not been obtained from any tissue other than renal cortex. It is present in all mammals and birds examined, but not in cold-blooded vertebrates. Prinzmetal and I found that it is destroyed at 60° C., by strong acids and alkalis, and by alcohol above freezing-point but not at -10° C.; it is non-dialysable, salts out in the globulin protein fraction, and is probably a protein. It is an extremely unstable substance, and Butler and I found it became so progressively when purified. It has not been isolated.

Hypertensinogen, the name given to the substrate on which renin acts, is also a protein, and is found only in plasma. It is also a globulin (Muñoz *et al.*, 1940). Evidence from animal experiments suggests that the liver (Page *et al.*, 1941) and adrenals (Houssay and Dexter, 1942) may be concerned in its production, but the part, if any, played by other organs is obscure.

Hypertensin, the product of the reaction of the foregoing, is a simpler substance than either. It is stable to heat, dialysable, and soluble in alcohol (Page and Helmer, 1940a; Braun-Menendez *et al.*, 1940). It is destroyed by peptic or tryptic

digestion, and is therefore thought to be a proteose or polypeptide (Muñoz *et al.*, 1940; Edman *et al.*, 1942).

In a simple mixture of the two renin acts as an enzyme and hypertensinogen as the substrate (Muñoz *et al.*, 1940). That is to say, the amount of hypertensin produced in unlimited time is determined only by the amount of hypertensinogen, and during the reaction hypertensinogen disappears while renin remains. The amount of renin determines only the rate of the reaction. It is obvious, therefore, that the amount of hypertensinogen available is an important factor in determining the intensity of the response to renin, and *in vivo* no response to renin is obtained if the hypertensinogen has been used up (Page, 1939). In the intact animal the amount of renin entering the circulation is also an important factor, for Prinzmetal and I (1938) found the response to renin injected intravenously was proportional to the logarithm of the dose. The intact animal may also be affected by agencies which destroy renin and hypertensin. In 1942 Prinzmetal, Kelsall, and I showed that renin injected intravenously into rabbits could be recovered from the arterial blood after ten minutes but not after an hour, and that the lost renin could not be recovered from the tissues, nor was it destroyed in that time by blood *in vitro*. It is probably slowly destroyed by the tissues, but in a manner at present unknown. Hypertensin is destroyed by an enzyme, hypertensinase, which is most abundant in extracts of kidney and gut, and least in plasma (Houssay and Braun-Menendez, 1942).

Role of the Renin-Hypertensin System

It is probable that the renin-hypertensin system is the effector mechanism in experimental hypertension resulting from renal-artery constriction, for the cumulative efforts of many workers (see Blalock, 1940) have excluded a cause other than chemical, and renin has been demonstrated in the renal-vein blood after renal-artery constriction (see Houssay and Braun-Menendez, 1942). Nevertheless some facts are not easy to reconcile with the hypothesis (Taggart and Drury, 1940; Dock, Shidler, and Moy, 1942), and the chapter is by no means closed. In man there is little direct evidence for the participation of the renin-hypertensin system in hypertension, but the absence of positive evidence does not invalidate the hypothesis. Thus in man it was shown that transfusion of blood from patients with essential or malignant hypertension does not raise the pressure of the recipients (Pickering, 1935-6; Prinzmetal and Friedman, 1936); the same is true in the dog with experimental hypertension (Collins and Hoffbauer, 1937), unless massive cross-transfusions are used (Solandt *et al.*, 1940). The kidneys of patients with benign essential and chronic nephritic hypertension seem to have a renin content no higher than normal (Landis, 1941), but the kidneys of rabbits with chronic hypertension due to renal-artery constriction also have a normal renin content (Pickering, Prinzmetal, and Kelsall, 1942). The crucial test for the presence of renin in the renal-vein blood in man has yet to be performed with the methods successful in the dog.

We may now consider very briefly a further aspect of the hypothesis and inquire whether there is any condition present in essential hypertension which might lead to the liberation of renin from the kidney. Here again the facts are few, and what follows is to be regarded purely as a contribution to a working hypothesis.

The constant presence of renin in the kidney of most mammals examined, and its enzyme-like action on blood, suggest that it performs a definite function in the animal economy. Accepting the interpretation of inulin and diodrast clearances, the chief action of renin or hypertensin on the kidney is to constrict the efferent glomerular arterioles,* and on the circulation to raise arterial pressure without greatly influencing the distribution of blood to organs other than the kidney. Thus we see that the renin-hypertensin system raises intraglomerular pressure by its action both on the renal vessels and on the circulation generally. I would suggest, therefore, that the func-

* Prinzmetal and I (Pickering and Prinzmetal, 1940) found that small doses of renin in the unanaesthetized rabbit reduce urine-flow and the creatinine clearance rate. With larger doses, well above the threshold for the pressor effect, renin produces a pronounced diuresis, in which the sodium and chloride contents of the urine approximate to those of plasma. The significance of this finding is not yet apparent.

tion of renin is to maintain the head of pressure in the glomeruli on which glomerular filtration, and thus the secretion of urine, depends. This hypothesis is in harmony with the peculiar features of the renin-hypertensin system. Were the effector agent secreted by the kidney near the glomeruli, then under conditions of defective renal blood-flow the renal vessels might receive an undesirably powerful dose of it, leaving little for the vessels elsewhere. But hypertensin is not released until renin has acted on the blood of the general circulation, and so it happens that although the kidney sets the mechanism in motion it receives no more than its due share of the active agent. Goormaghtigh (1939) has suggested that renin originates from afibrillary cells on the afferent glomerular artery close to the glomerulus, and his finding of hypertrophy of such cells in the three weeks following renal-artery constriction is in harmony with the finding of an increased renin content in the first eight days (Pickering *et al.*, 1942).

The hypothesis is also compatible with our knowledge of the mechanisms regulating the arterial pressure. Thus two of the most important organs of the body, the brain and heart, have in close relation to them sensitive vascular areas, the carotid sinus and aortic arch, which are known to play a part in the reflex regulation of the arterial pressure. It is important that both of these organs should at all times receive an adequate supply of blood at suitable pressure, and the advantage of a quickly responding reflex mechanism is obvious. From the circulatory point of view the kidney is also an important organ, since it receives as much as one-third of the cardiac output; but its importance to the organism as a regulator of the internal environment depends more on its action over a long than over a short period of time. A chemical regulating mechanism with a prolonged action is thus highly suitable.

On this hypothesis we should expect renin to be released from the kidney by any change tending to lower intraglomerular pressure. Evidence has been provided that renin is released (a) when the arterial pressure is reduced by haemorrhage or histamine (Hamilton and Collins, 1942); (b) when a clamp constricts the renal artery (see Houssay and Braun-Menendez, 1942; (c) after occluding the renal artery for some hours (Leo, Prinzmetal, and Lewis, 1940). A vasoconstrictor substance which resembles renin in producing tachyphylaxis (Verney and Vogt, 1938) and in having an accentuated action 48 hours after nephrectomy (Govaerts, 1939) is also released from the experimentally perfused kidney.

A Hypothetical Factor

We may ask, then, if any factor is present in essential hypertension that tends to reduce intraglomerular pressure and thus create conditions which, on the above hypothesis, might be favourable to the release of renin. Attention has already been drawn to the frequency of structural changes in the afferent glomerular arteries in essential hypertension. The hypothesis that these represent the causes of the raised arterial pressure is not new, and led Goldblatt to try to produce hypertension by constricting the renal arteries. His success, and in particular his demonstration that by varying the degree of constriction the chief characteristics of either benign or malignant hypertension could be produced, seemed to provide strong evidence in its favour (Goldblatt, 1938a, 1938b). The work of Goldring and his colleagues (1941), discussed in the first lecture, has, however, shown that the chief feature of the circulation in the kidney of essential hypertension is that of increased rather than reduced intraglomerular pressure. The hypothesis need not therefore be abandoned. For the kidney is an aggregation of nephrons, and it is still conceivable that the afferent arteriolar narrowing is sufficiently widespread to release renin in amounts requisite to raise the arterial pressure, while the overall picture of the circulation through the kidney is dominated by the effects of the renin-hypertensin system on the intact nephrons.

Such, then, is a hypothesis concerning the mechanism of essential hypertension. A rather similar hypothesis might be developed for coarctation of the aorta and for chronic nephritis, on which, however, our information is even more fragmentary. In acute nephritis and pregnancy toxæmia hypertension is probably of quite different origin, but beyond this it is not profitable at present to speculate.

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The interesting calculation has been made that the sewage from 5 million people is equivalent to 17,000 tons of rock phosphate in a year. This, as Dr. E. F. Armstrong points out (*Discovery*, March, 1943), happens to be the quantity present in the annual export of meat from New Zealand. According to him the population of Great Britain gets rid in the form of sewage of the equivalent of 150,000 tons of rock phosphate, most of which reaches the sea. The population of the United States rejects into the sea yearly an equivalent of 60 million tons of rock phosphate. Mineral deposits of phosphate are limited in amount and may become exhausted; and many of the agricultural soils of the world are short of them, with a consequent impairment to their crop qualities.