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THE PROBLEM OF HIGH BLOOD PRESSURE IN MAN*

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The question to be discussed here is central to the whole problem of human hypertension—namely, the nature of the agent raising the arterial pressure. Until we understand this no other question can be answered fully and satisfactorily. At the outset it is well to have clearly in mind the possibility that hypertension may originate differently in different clinical conditions. The following discussion will centre round so-called essential hypertension, but acute and chronic nephritis and coarctation of the aorta will be mentioned briefly.

Vasoconstriction

In all the maladies mentioned we may say that the rise in mean arterial pressure is due to vasoconstriction, for the other possible factors—raised cardiac output and increased blood viscosity—have been excluded by direct measurement. We do not yet know whether this vasoconstriction affects equally all vascular areas or some territories to a greater extent than others; but the evidence supports the idea that it is more or less uniform. Thus, if vasoconstriction affected some vascular territories more than others we should expect blood to be diverted from vessels that were more, to those that were less, constricted. We might therefore expect symptoms of ischaemia to arise from organs whose vessels were particularly narrow. Such symptoms are uncommon in the early stages, and when they occur in the later or more severe cases they are, in my opinion, nearly always due to local organic vascular disease. I am dissatisfied with the evidence for the view that so-called hypertensive encephalopathy is due to arterial spasm: hypertensive neuroretinitis may be, but the question of its origin is complex (Pickering, 1933-4) and the vascular territory small.

The normal blood-flows through the forearm recorded in chronic nephritis and essential hypertension by Prinzmetal and Wilson (1936) and by myself (Pickering, 1935-6b) support the conception of a generalized vasoconstriction, but the measurements perhaps require repetition in view of the recent demonstration by Grant and Pearson (1937-8) that the forearm plethysmograph used in both sets of observations receives not only blood entering the forearm from the arterial side but also blood returning through the veins from the hand.

On general grounds we would suspect that the vessels chiefly constricted in hypertension would be the small arteries and arterioles where the main vascular resistance lies. This idea is supported by the normal values for capillary pressure found by Ellis and Weiss (1929-30) in

essential hypertension and by the normal pressure gradient between brachial and digital arteries found by Oppenheimer and Prinzmetal (1937).

Nature of Agent Constricting the Vessels

It is probable that the disturbance underlying persistent hypertension in man is a more or less uniform narrowing of the small arteries and arterioles. Clearly there are three ways in which such narrowing might arise—namely, from a morphological change in the vessels, or from vasocostriction of nervous or of chemical origin. It is well recognized that anatomical changes in the small arteries and arterioles are almost invariable in long-standing cases of hypertension. In both chronic nephritic and essential hypertension fatty hyaline intimal thickening of these vessels occurs, usually in the kidney, and sometimes in other abdominal viscera and in the brain. But these changes are absent, or nearly so, from the large vascular territories of skin and muscle, in which regions the media is usually hypertrophied (Fahr, 1922; Fishberg, 1925, 1927; Kernohan, Anderson, and Keith, 1929). Most of those who have studied the histology hold that the intimal change in hypertension is not sufficiently widely distributed to account *per se* for the rise in pressure, and that the medial change represents a work-hypertrophy of the arterial wall analogous to that occurring in the heart. The indication from histological work that the vascular narrowing responsible for raised arterial pressure is a functional rather than an anatomical change is in accord with experimental observations suggesting that in human hypertension the vessels are capable of considerable dilatation. Thus, in the arm the vasodilator responses to circulatory arrest and to heat are of normal size in human hypertension (Pickering, 1935-6a, 1935-6b). Again, a vasodilator agent such as histamine produces in chronic nephritis and essential hypertension falls of arterial pressure that are similar to those in normal subjects when allowance is made for different initial pressures (Pickering, Kissin, and Rothschild, 1935-6).

So far in our argument there is fairly general agreement among different workers. The chief cleavage comes when we consider whether the abnormal vasoconstriction responsible for raised arterial pressure is due to overaction of the vasomotor nerves or to a chemical factor. In considering these rival hypotheses it is of great importance that we have a clear conception as to the question at issue. In the normal subject the blood pressure is maintained by the state of contraction or tone of the vessels taken as a whole. Normal vascular tone is undoubtedly in part of nervous origin, as is demonstrated by the vasodilatation which follows section of the sympa-

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thetic nerves, and by the profound fall of blood pressure which occurs when the spinal cord is destroyed. Completely denervated vessels are not, however, fully dilated, and it is probable that normal vascular tone is partly also of chemical origin. If we agree that normal vascular tone is partly of nervous and partly of chemical origin, then we must assume that vascular tone in hypertension has at least these two components, and what we have to find out is which of the two is abnormal. To prove that hypertension is due to vasoconstriction of nervous origin it is clearly not enough to demonstrate vasomotor nervous tone; it must be shown that this is excessive. Similarly, to demonstrate the chemical origin of hypertension an increase must be shown in the chemical component of vascular tone.

Evidence for the Nervous Hypothesis

With these considerations in mind let us examine the evidence that has been advanced for the nervous hypothesis. One of the most complete hypotheses for the origin of hypertension was that due originally to Hering (1927) and later supported by Mies (1932) and Regniers (1930), and which supposed that the raised pressure was due to interference with the carotid sinus and aortic reflexes. This hypothesis is now generally abandoned, since it has been demonstrated that the carotid sinus reflex functions in hypertension (Gammon, 1936; Pickering, Kissin, and Rothschild, 1935-6), and since the hypertension produced in animals by section of the carotid sinus and depressor nerves differs considerably from that found in man. A second hypothesis put forward by Raab (1929) and others was that essential hypertension was due to ischaemia of the medulla and consequent increased irritability of the vasomotor centre. Raab's evidence has been partly though not wholly controverted, but his idea has won no general acceptance chiefly because the respiratory centre seems much more sensitive than the vasomotor centre to changes in gas content of the blood.

Those who now uphold the nervous hypothesis do not specify the way in which over-activity of the vasomotor nerves is brought about. They rely for their support mainly on the evidence derived from the cold pressor test and from the effects of dividing the sympathetic supply to the abdominal viscera. Hines and Brown (1932) consider that an unusually large rise of blood pressure in response to immersing one hand in water at 4° C. is characteristic of essential hypertension; a few subjects with normal blood pressure may show an equally large response, but these usually have a family history of hypertension and are regarded as potential or future sufferers from the disease. Hines (1937-8) has recently emphasized the significance of this test by showing that in families having a large response to cold hypertension is common, while in those having a small response hypertension does not occur. On the other hand, Kissin and I (Pickering and Kissin, 1935-6) found that a large response to cold was not peculiar to essential hypertension, being occasionally absent in the condition and sometimes present in subjects of comparable age with normal pressures and no family history of the disease; our series of patients was, however, small. Whether or not an exaggerated response to cold is peculiar to essential hypertension is a question of fact which will ultimately be decided by observation; purely for the purposes of argument, let us assume that it is so and consider its interpretation. The rise of blood pressure in response to cold is almost certainly due chiefly to vasoconstriction of nervous origin; an unusually large rise may be due to an enhanced irritability of the vasomotor centre, as Hines and Brown suppose, but it might

also be due to enhanced irritability of the peripheral vessels, or to a diminished sensitivity of the proprioceptive mechanisms regulating blood pressure, which would allow an unusually great change in pressure to occur. As evidence for the nervous origin of essential hypertension the cold pressor test is thus by no means unequivocal.

In considering operations for denervating the splanchnic area it is important to distinguish the therapeutic from the scientific implications of the results obtained. The operations, largely introduced by Adson and his colleagues, are of two kinds—section of the anterior spinal roots from about the sixth thoracic to the second lumbar, and section of the major and minor splanchnic nerves above or below the diaphragm with removal of the adjacent sympathetic ganglia—and there seems to be no doubt that they are successful as therapeutic ventures in certain cases. These two operations seem to produce similar effects on the arterial blood pressure in essential hypertensives (Allen and Adson, 1937-8; Freyberg and Peet, 1937; Page and Heuer, 1937); in some patients the fall of blood pressure is profound and persistent; in most a considerable fall is ultimately followed by a return to approximately the pre-operating level; and in a few the blood pressure is unaltered. The variability of the results obtained and the insufficiency of the control series make the interpretation of these results extremely difficult. From general considerations, and from the effects of similar operations on normal dogs (Grimson, Wilson, and Phemister, 1937) and on dogs with hypertension originating chemically from renal ischaemia (Goldblatt, Gross, and Hanzal, 1937), we may interpret those results in which a variable post-operative fall is followed by a return to the pre-operative level of arterial pressure as meaning no more than that normal vasomotor nervous tone has been removed from the splanchnic area. In those instances where the blood pressure returns permanently to normal this explanation may be insufficient, and we may suspect either that the hypertension was due to excessive vasomotor nervous tone, or that splanchnic denervation has produced its effects in an indirect manner such as by increasing the blood-flow through a previously partly ischaemic kidney. If this latter explanation were correct we should expect similar results to follow simple renal denervation; but this operation has not yet been performed on a sufficiently extensive scale.

Evidence for the Chemical Theory

The interpretation of changes in blood pressure due to experimental interference is rendered hazardous by the complexity of the factors involved. It occurred simultaneously and independently to Prinzmetal and Wilson (1936) and to me (Pickering, 1935-6b) that the question of the nervous or chemical origin of hypertension could be settled by the following simple experiment. In any organ the blood-flow is proportional to the perfusing pressure divided by the resistance offered by the vessels. In persistent hypertension the blood-flow through the upper extremity seems to be normal—that is to say, the increased perfusing pressure is balanced by increased vascular resistance. Supposing that we completely remove vasomotor nervous tone from the vessels of the hand, then if the abnormal factor constricting the vessels is nervous it should disappear under these circumstances and blood-flow through the hand would be greater in the hypertensive than in the normal subject, since increased arterial pressure would no longer be balanced by increased resistance. If, however, the abnormal factor is not nervous, then it will not disappear with the removal of vasomotor

nervous tone: increased blood pressure will still be balanced by increased resistance, and in hypertensive patients blood-flow may be no greater than in normal subjects under comparable circumstances. To measure blood-flow Prinzmetal and Wilson used Hewlett and Van Zwaluwenberg's plethysmographic method with Lewis and Grant's forearm plethysmograph, reference to which has already been made. I used Stewart's calorimetric method on the hand as an index of its blood-flow, removing vasomotor nervous tone from the hand by raising the body temperature. Evidence was obtained that the calorimetric method provided a reliable index of blood-flow and that the degree of body warming employed was sufficient to remove entirely vasoconstrictor nervous tone from the hand. As regards essential, malignant, and chronic nephritic hypertension we agreed in finding normal blood-flows after removing vasomotor nervous tone.

In these conditions, therefore, the experiment suggests that the abnormal factor in the peripheral resistance is not nervous and is presumably chemical in origin. In coarctation Prinzmetal and Wilson found abnormally large flows and I found normal flows. Several possible reasons for this discrepancy may be advanced, but these have not as yet been investigated. I was forced to conclude that the increased resistance in the upper limb in coarctation was also of non-nervous origin. On the other hand, in four of six cases of acute nephritis in the hypertensive phase I did find increased flows through the hand from which vasomotor nervous tone had been removed, and the increase was of the order to be expected from a simple increase in arterial pressure. In these cases, therefore, there was no evidence of non-nervous vasoconstriction in the hand during the hypertensive phase, a result consistent with hypertension being due to vasoconstriction of nervous origin. As yet no pressor reflex mechanism has been demonstrated from the kidney.

To return to essential hypertension, the suggestion from these experiments is that the raised blood pressure is of chemical origin. A pressor substance has often been sought in the blood, but experiments in which extracts or ultra-filtrates of blood are tested and found negative are all open to the interpretation that the pressor substance was present in the discarded fraction. Accordingly I measured the changes of blood pressure produced in anaemic patients receiving blood from normal donors and from donors with essential hypertension (Pickering, 1935-6a). No appreciable rises of blood pressure occurred even when 600 c.cm. of blood from a hypertensive donor was introduced in six minutes. Prinzmetal, Friedman, and Rosenthal (1936) made similar observations in malignant hypertension, and found no pressor response from transfusion of as much as 2,300 c.cm. of blood from a hypertensive donor. It is evident, therefore, that if a circulating pressor substance exists in benign and malignant hypertension it is present in surprisingly small quantities. If the chemical theory is correct, then the agent would appear to be one which is relatively stable in the body and which is fixed by the vessels on which it acts. The strongest clues point to the kidney as a possible source of such a pressor substance. Thus in chronic nephritis there are many reasons for supposing that the kidney is the seat of the primary disturbance which results in hypertension. Again, Goldblatt, Lynch, Hanzal, and Summerville (1934) have shown that a persistent hypertension, which resembles essential hypertension in the maintenance of a relatively normal renal function, may be produced in the dog by constricting the renal arteries. More recently Goldblatt (1938) has shown that when the

constriction is severe, albuminuric retinitis, arteriolar necroses, and renal failure occur as they do in the malignant phase of human hypertension. Wilson and I (1937-8) have also reported the occurrence of widespread necrosing arteriolar lesions in rabbits with severe hypertension from renal artery constriction. From these observations there is no doubt that something very similar to the benign and malignant phase of essential hypertension may be produced in animals by renal artery constriction. And there is little doubt that this experimental hypertension is chemical and not nervous in origin. Finally, Moritz and Oldt (1937) have produced histological evidence suggesting that renal arteriolosclerosis is the primary lesion in essential hypertension.

The question arises, Are essential and chronic nephritic human hypertension due to the release into the circulation of a chemical substance by the kidneys, and perhaps its subsequent fixation by the vessels? We know that a protein-like pressor substance is a normal constituent of the renal cortex. It was described by Tigerstedt and Bergman (1898). The failure of many workers to find it is probably due chiefly to its action being reduced or abolished by anaesthetics (Pickering and Prinzmetal, 1937-8). Whether this substance is concerned in the production of experimental or human hypertension is a question which it is as yet unprofitable to discuss, but there is no doubt that evidence for or against the hypothesis will accumulate in the near future.

Conclusion

In this account I have attempted to develop a line of thought rather than to prove a scientific hypothesis. Proof will not come until we can demonstrate in detail the mechanism whereby the arterial blood pressure is raised in man. But in looking for such a mechanism we must have some guide, and it seems to me that on the available evidence the most profitable line to explore is that which I have tried to indicate here.

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