ESSENTIAL HYPERTENSION.

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I do not propose in the following pages to deal with the symptoms or course of the disease which we call essential hypertension—the condition is so common that we are all familiar with it in that aspect—but rather with the problem of its ætiology.

A raised blood pressure, like a raised body temperature or a raised metabolic rate is in itself merely a symptom. An increase in the bodily temperature was recognized at a very early stage of clinical medicine, and the diseases of which it may be a symptom have been gradually distinguished from each other. The measurement of the blood pressure is a relatively recent development in medical science, and our understanding of its significance is therefore less complete. If from a series of hypertensive patients we take out all those cases in which the rise of blood pressure can reasonably be regarded as secondary, that is cases of acute and chronic nephritis, eclampsia, and certain endocrine disorders, we are left with a group of cases in whom no obvious cause of the raised blood pressure is present. It is this group, which constitutes a large majority of all hypertensive patients, that we designate as “essential hypertensives”: they suffer from a disease, or from diseases, the only recognizable feature of which is the raised blood pressure, and the various lesions of the vascular system and the viscera which they present are apparently purely secondary results of the increased intra-vascular pressure. It must be admitted that to diagnose a patient as suffering from essential hypertension is as unsatisfactory as to make a diagnosis of “essential fever,” but at present no more precise diagnosis is possible.

Clinically the condition represents a well-defined entity, the symptoms of which we can all readily recognize, and the course of which can be predicted with some accuracy. The sequence of events is capable of rational interpretation. Briefly the rise of blood pressure leads to organic changes in the vessels; these changes, combined with vascular spasm, lead to ischæmia and consequent degenerative changes in various viscera: the patient's death ultimately results from (i) cardiac failure in face of the increased peripheral resistance, the failure of the cardiac muscles being often accelerated by coronary degeneration, (ii) thrombosis of rupture of degenerate cerebral vessels, (iii) failure of renal function owing to destruction of renal tissue by ischæmia, or (iv) peripheral vascular lesions and gangrene. Once given the rise in blood pressure, any or all of these results may follow and the condition therefore presents the characters of a definite disease. This superficial unity may, however, be more apparent than real. As we shall see, certain forms of hypertension due to endocrine and other dysfunctions will set in motion a similar chain of events, though there is every reason to believe that in these conditions the underlying causes of the hypertension are dissimilar. Again, even among so-called essential hypertensives, the disease may run a very variable course. The rapidly fatal malignant type of hypertension, for instance, which we see especially among the younger patients, carries an essentially different prognosis from the benign hypertension of the elderly patient, in whom the disease may not appreciably shorten life.

The two principal questions which present themselves in any study of essential hypertension are (i) What dysfunction of the vascular mechanism leads to the rise in blood pressure? and (ii) To what is this dysfunction due? The first of these

problems, that of the proximate cause of the raised pressure, may be regarded as solved: the second, the ultimate cause of essential hypertension, remains as far from solution as ever.

Pathogenesis.

A rise in the systemic blood pressure may theoretically be produced by an increase in cardiac output, an increase in the blood volume, or a raised peripheral resistance, which might again be due either to increased viscosity of the blood or by peripheral vaso-constriction. There is a general agreement that the blood volume and cardiac output of hypertensive patients are not increased and that the viscosity of the blood does not differ from that of patients with a normal pressure. We are driven, therefore, to the conclusion that the rise of pressure is due to an increased vascular tonus with a resulting increase in the peripheral resistance.

Such an increased tone might be generalized or might be limited to a single large vascular area without compensatory dilatation elsewhere. The splanchnic area has been incriminated in this sense by certain workers, the pathological changes of hypertension are well-marked in this area, and sudden occlusion of the splanchnic vessels leads to a temporary rise of pressure. Section of the splanchnic nerves has been advocated, and the operation has even been performed as a treatment in essential hypertension, but such procedures have been of doubtful benefit. Recently the question has been investigated by the plethysmographic method of estimating the blood flow through the fore-arm. Assuming that the cardiac output is normal and that an increased peripheral resistance is present only in the splanchnic vessels, the blood flow through the vessels of other areas, such as the fore-arm, must be increased. Actually it has been shown that this is not the case: the blood flow per 100 ccm. of arm tissue is normal. The vascular constriction, therefore, involves the fore-arm and is probably generalized rather than limited to a single area. Clinically there is every reason to agree with this conclusion, since the vessels of the retina, which we are able to inspect, are undoubtedly constricted and, since the peripheral and cerebral incidents of hypertension point in the same direction. Even in the acute exacerbations of the hypertension which are so characteristic of the disease, the vessels of the arm participate. Further, the constricted vessels were found to respond to the application of heat and to temporary occlusion with a reactive dilatation and a resulting increase in the blood flow through the fore-arm, much as do the healthy arteries.

We may conclude then that the raised blood pressure of the hypertensive is due to an active generalized vaso-constriction, rather than to obstructive organic change in the vessels, at any rate in the earlier stages of the disease, and that the vascular mechanism, while set at a higher level of pressure, is still adapted to respond to the physiological requirements of the body. Histologically this increased activity of the vascular musculature is evidenced by medial hypertrophy, a true work hypertrophy.

Ætiology.

The next, and as yet inexplicable, problem is the actual cause of this generalized vaso-constriction. We may conceive of it as due to a derangement of the central vaso-constrictor mechanism, as the result of pressor bodies acting peripherally, as due to the failure of nervous inhibitory mechanisms, or even as the expression of the absence of dilator, depressor substances, but as yet these are only hypotheses. All that we can say is that the ground has been to some extent cleared.

The clinical method of approach has yielded little information. We find indeed that the disease is often inherited, that it develops in most instances in middle and late middle life, and that it shows some correlation with obesity.

Renal Disease. Clinically, too, it has been recognized that the rise of blood pressure precedes any manifestation of renal damage, such as albuminuria. With destruction of renal tissue, the only method by which the glomerular filtrate can be maintained at the necessary level is by increase of the filtration pressure; this fact possibly accounts for the rise of blood pressure in certain types of renal disease and is presumably effected by a nervous mechanism. The exact methods of testing the renal function which have been evolved during recent years permit us, however, to state definitely that there is no impairment of this function during the earlier stages of essential hypertension: even when the rise of pressure is well established such functional tests as the urea clearance test yield entirely normal results. It might of course be argued that the integrity of the renal function was more apparent than real, any impairment of function being compensated and masked by an increased filtration due to the raised pressure head. That this is not the case has been demonstrated by Soma Wiess who has shown that if the blood pressure of the essential hypertensive be lowered by nitrites, the urea clearance remains at a perfectly normal figure. The blood pressure in the earlier stages of essential hypertension is not therefore raised to compensate for a latent defect in renal efficiency.

Nervous Origin. Another nervous mechanism, damage to which might conceivably be the cause of essential hypertension, is that of the aortic and carotid vaso-sensitive zone with their nervous connections. As is well-known, section of the so-called buffer nerves, arising from the aorta and the carotid sinus, will in the dog or rabbit lead to persistent hypertension, owing to the removal of their inhibitory influence on the medullary centres. It is of interest, as showing the essentially secondary character of the morbid changes in the hypertensive, that in such animals vascular and renal damage results, resembling that seen in the human hypertensive patient. The suggestion has, therefore, been made that in the human hypertensive a degeneration of the great vessels of the vaso-sensitive zone may lead to such a loss of elasticity that the buffer nerves are no longer stretched and stimulated by a rise of pressure. The sinus mechanism is well developed in man. In the human subject, for instance, any hypertension of rapid onset, such as we see in eclampsia or in acute nephritis, evokes a well marked bradycardia. With the slowly rising pressure of essential hypertension bradycardia is exceptional, though it occurs in some patients, and some increase in the pulse rate is frequently observed, even in patients in whom no suspicion of cardiac failure exists. It may be remarked that the tachycardia met with in hypertensive patients is by no means of the order seen in the animal with denervated sinuses, in which with a much smaller rise of blood pressure the pulse rate may more than double. It is difficult, too, to assess the probable response of the sinus mechanism, which is essentially adapted to deal with rapid changes of pressure, to a rise of pressure occurring slowly over a period of years. Pathologically changes in the sinus in man show no correspondence to the height of the blood pressure during life; extensive atheroma is often present in individuals in whom the blood pressure has been normal, and conversely. Abnormal sinus reflexes have indeed been reported in essential hypertension, but their significance is doubtful. Stimulation of the sinus by pressure from without, the usual method of testing, in no way resembles the physiological stimulus of an increase of pressure from within the vessel. In my own experience a sudden rise of blood pressure, such as may be

produced within the artery by an intravenous injection of adrenalin is as often followed in the hypertensive by definite bradycardia as in the normal individual. There is, therefore, little evidence that the sinus mechanism is at fault in essential hypertension. Recent work, too, tends to the conclusion that the increased vascular tonus of the hypertensive is not due to central impulses passing through vaso-motor nerves, but rather to a peripheral cause. If this proves to be the case, little is to be expected from the very extensive sympathetic resections which have recently been advocated in the disease.

Pressor Bodies. When we turn to the discussion of the possible presence of peripherally acting pressor bodies in the blood of the essential hypertensive, two methods of investigation are possible. In the first place we may examine the effect of injections of the blood of hypertensives or extracts of that blood on the blood pressure of animals—the broadest possible method of attack—or again we may attempt to identify some particular substance of known pressor activity with the noxious agent which produces the raised blood pressure. Among such known pressor bodies are the two great natural hormones—adrenalin and vaso-pressin, certain normal products of metabolism which are known to be capable of raising the blood pressure, such as guanidin, or lastly products of disintegrating tissue, such as tyramin.

We may say at once that there is as yet no satisfying evidence that any of these bodies is the causative agent in hypertension, or even that hypertensive blood, or blood extracts, are capable of producing a rise of blood pressure in animal experiments. In spite of this disappointing position, it is not improbable that the solution of the problem will be found along these lines and for that reason alone the subject requires further consideration.

(A) *Of Endocrine Origin.* At the outset I would emphasize one extremely important fact—certain forms of endocrine dysfunction are now clearly recognized as producing permanent hypertension with all its characteristic sequelæ. First of these is the paraganglioma, a tumour derived from the chloraffin cells of the adrenal medulla and containing very large amounts of adrenalin. In patients suffering from these tumours, the rise in blood pressure is at first paroxysmal and associated with all the phenomena of adrenalin discharge—tachycardia, albuminuria and glycosuria; later, however, the hypertension becomes fixed and permanent and the typical secondary results of hypertension follow—vascular nephritis, arterial degeneration and retinitis; with these are often associated tachycardia and glycosuria, typical adrenalin effects. The post-mortem findings, with the exception of the adrenal tumour, are those of essential hypertension. We may conclude that hyperadrenalism may produce permanent hypertension, a conclusion which is borne out by the fact that operative removal of the tumour during the early stages of the disease is completely successful. Curiously enough permanent hypertension may also be a symptom of certain cortical adrenal tumours: no pressor body has been as yet discovered in this portion of the gland, and the cause of the raised blood pressure remains entirely unexplained.

Another instance of endocrine hypertension is met with in the Cushing syndrome. In this remarkable condition, which would, in certain cases at least, appear to be the result of a basophil adenoma of the anterior lobe of the pituitary, hypertension is marked and may be the cause of death, through failure of the left ventricle. The post-mortem findings include vascular nephritis and advanced arteriosclerosis. Here again the cause of the raised blood pressure remains unknown: vaso-pressin is produced by the posterior lobe of the pituitary and

the raised blood pressure is not the result of the adrenal cortical hyperplasia which is frequently present, since it may occur in cases in which the adrenals are atrophic. Lastly, certain forms of hypertension associated with endocrine dysfunction are the apparently abnormally high incidence of hypertension in long standing cases of thyrotoxicosis, and the alleged frequency of hypertension in acromegaly.

There is therefore ample evidence that hypertension may accompany and presumably result from endocrine disorders, and that the terminal vascular pathology in these conditions may resemble that of essential hypertension. The very similarity of the vascular lesions in such different conditions as sinus denervation and pituitary basophilism suggests that no conclusion as to the homogeneity of the group of "essential hypertensives" can be drawn from the post-mortem findings.

Attempts to trace the origin of essential hypertension to dysfunction of some member of the endocrine series have, up to the present, failed. Goldzieher, indeed, believes that there is definite evidence of hypertrophy of the adrenal medulla in hypertensive subjects, and that this is accompanied by an increase in thickness of the muscular coat of the adrenal veins which he regards as evidence of prolonged adrenal hyperactivity: certain French authors, too, have claimed that a nodular hyperplasia of the adrenal cortex occurs commonly in essential hypertension. It need scarcely be pointed out that it is by no means easy to estimate the actual size of such an irregularly shaped organ as the adrenal medulla, and that any attempt to determine the activity of a ductless gland from its size and histological appearance is obviously open to gross error. The more direct method, the actual determination of the amount of circulating adrenalin in the blood of hypertensive patients also presents grave difficulties: the most careful work upon the subject, that of Brandt and Katz, who used the three physiological test objects—the rabbit's ear vessels, the intestinal strip and the enucleated frog's eye—led to the conclusion that no demonstrable adrenalin was present in the blood of the essential hypertensive except during the so-called vascular crises. Similarly, attempts to demonstrate the presence in hypertensive blood of some substance sensitizing the vessels to adrenalin have failed. An excess of cholesterol, which it is claimed sensitizes the vascular muscle to adrenalin is indeed frequently present in the blood of hypertensive subjects, but such excess of cholesterol is frequently found in other morbid conditions in which the blood pressure is at a normal level. There is therefore no evidence which would incriminate the adrenal medulla in the causation of the disease.

As for possible dysfunction of the pituitary, though both unduly high and unduly low blood pressures are met with as concomitants of pituitary disease, no definite evidence has been obtained that excess of vaso-pressin is present either in blood or cerebro-spinal fluid in the hypertensive state. It is to be remarked that pituitary blood pressure disturbances are only known to occur in connection with lesions of the anterior lobe while the vaso-active substance of the pituitary, vaso-pressin, is obtained from the posterior lobe of the gland. Cushing, in the basophil adenomata, notes a basophil invasion of the posterior lobe, and suggests a "basophil activation" of the pars nervosa, the hypertension apparently being assumed to result from overproduction of vaso-pressin. There is, however, no evidence of such synergism between the two lobes of the hypophysis, and the alleged occurrence of an excess of basophil cells in the anterior lobes of patients suffering from essential hypertension is becoming increasingly doubtful. With better control, it has been shown that the accumulation of

basophil cells in the anterior lobe increases with age, and that invasion of the posterior lobe is frequently present in patients in whom no hypertension was present during life. An endocrine origin of "essential hypertension," while remaining a fascinating possibility, has therefore as yet no basis in fact.

(B) *Other Pressor Bodies.* In default of these known pressor bodies, search has been made for substances in hypertensive blood, capable of raising the blood pressure of animals under experimental conditions. Of such substances **guanidin** has been suggested by Major as a possible cause of essential hypertension, and more recently Govaerts has brought forward evidence that with the development of the malignant stage of the disease, tyramin, derived from the disintegrating kidney tissue, is responsible for the raised blood pressure. It would seem that an excess of a substance which in its colour reactions resembles guanidin, is frequently present in hypertensive blood, but its amount is not correlated with the height of the blood pressure, nor are its fluctuations in the individual patient associated with corresponding rises or falls in the hypertension. Further, the exact nature of this body is as yet undetermined, and since some guanidin derivatives are actually depressor in their action, it is obviously unjustifiable to assume that it is necessarily pressor.

The evidence that excess of **tyramin** is present in the blood in certain hypertensive states is at present unconvincing and, if it is in fact derived from degenerating renal tissue, the substance need not be discussed as a possible factor in the production of essential hypertension, since in the early stages of the disease the kidney is still undamaged.

If we take the broadest view of the question and ask ourselves whether the blood of hypertensives or extracts of that blood are capable of producing pressor effects when injected into animals, we can only reply that the findings of different workers are so conflicting that no definite answer can as yet be given.

Equally unsupported is the suggestion that the raised blood pressure results from the absence of a normal quantum of depressor substances in the blood. On physiological principles such a suggestion would appear to be highly improbable; though such bodies can be extracted from the tissues and chemically identified, their function would appear to be the production of a local vaso-dilatation, rather than a general fall in blood pressure. Their sphere of action is essentially regional, that of the pressor bodies general.

Conclusion.

Our conclusions are thus essentially negative; we are at present completely in the dark as to the cause of this common and disastrous disease. The ground is being slowly cleared; certain suggestive analogies can be recognized: there is no reason for pessimism. We must, however, clearly realize that we do not even know as yet whether we are dealing with a single entity or with a pathological state produced by various underlying causes; and that until this problem has been solved, a rational concept of its ætiology is impossible.