HYPERTENSION AND RENAL DISEASE.

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I PROPOSE to discuss to-night two types of hypertension:—
(i) The transitory, seen in acute glomerulonephritis and in eclampsia, and subsiding with recovery.
(ii) The permanent, so-called essential hypertension which, when once established, persists. If we accept the German nomenclature, this type of raised blood-pressure may remain “benign,” or may pass over into the “malignant” form, and end, unless the patient’s life is terminated by cerebral haemorrhage, cardiac failure or intercurrent disease, in contracted kidney and uræmia.

Let us first consider the factors which may produce a rise in blood-pressure. Briefly, they are: (i) increased cardiac output—the peripheral resistance remaining constant; (ii) increased blood volume—plethora, or increased blood viscosity with increased frictional resistance; (iii) increased peripheral resistance, this resistance lying in the smaller arteries and arterioles.

We may dismiss increased cardiac output, and increased blood viscosity; in neither of these two types of hypertension do they play a rôle. Increased blood volume I shall discuss briefly at a later stage, but I shall assume that there is a general agreement that these two forms of hypertension result from an increase in the peripheral resistance, in a narrowing of the channel through which the blood is being forced.

Under normal conditions narrowing of one arterial region is compensated for by widening of another. An actual narrowing of the whole channel is conceivable as the result of: (i) a generalized anatomical change in the arteries; (ii) a generalized arterial spasm; (iii) a lack of interplay
between different arterial areas, contraction of one area not being accompanied by relaxation of another.

Certain differences would appear to exist between the two types of hypertension under discussion. In the transitory, glomerulonephritic form we notice, if we have the good fortune to follow a case from the beginning:—

(a) A gradual rise in pressure; (b) a plateau lasting possibly two or three weeks; (c) a fall usually gradual, sometimes abrupt and critical. At the height of the pressure, morning and evening blood-pressures show only slight differences, the evening exceeding the morning by 5 to 15 mm. Hg, about the normal swing in health. The pressure is very stable. In essential hypertension, on the other hand, especially in its earlier stages, the pressure is extremely labile. Differences of 30 to 40 mm. between the morning and evening pressure are common, and over a period of time extreme variations, 60 to 100 mm. Hg, occur. The lability is most marked in the early stages; later, especially with development of malignant hypertension, the pressure tends to run a higher and more stable course, though even here the chart shows much greater irregularities than we see in the plateau of the transitory form.

We will consider first the question of the causation of essential or permanent hypertension. The subject is perhaps best approached from the historical standpoint.

Bright noted cardiac hypertrophy in renal disease and attributed it to alterations in the consistency of the blood. No methods of clinical measurement of the blood-pressure were then available. With recognition of the rise of blood-pressure in "chronic interstitial nephritis," Cohnheim originated the theory that the rise was due to the increase of resistance in the diseased arterioles of kidney—purely mechanical view.

Experimental evidence was soon produced which told against this possibility. Katzenstein ligating the renal arteries, and Senator obstructing the renal arterioles with paraffin emboli, failed to produce a rise in blood-pressure. Since that time numerous workers have found that total or partial extirpation of the kidneys leads to no appreciable rise in blood-pressure. Anderson, for instance, has shown that removal of 70 per cent. of the renal substance with resulting prolonged renal insufficiency does not lead to hypertension. Conclusive evidence of the failure of occlusion of large arterial areas to produce a blood-pressure rise was also produced by Peters, who ligatured both femorals or the abdominal aorta without producing any appreciable hypertension.

At about the date at which Cohnheim advanced his theory, Gull and Sutton described the condition which they named "arterio-capillary fibrosis," a hyaloid intimal degeneration, with fibrosis of the coats of the arterioles, usually most marked in the kidney but involving numerous arteriole areas. Their findings removed the so-called interstitial nephritis from the position of a purely renal lesion to that of a part of a generalized vascular change. At about the same date, however, another view of the vascular lesion was advanced by Sir George Johnson, who found that the main change present was a hypertrophy of the medial muscle coat of the small arteries, and who attributed the rise in blood-pressure to a generalized active vaso-constriction rather than to an anatomic fibrotic change with resulting narrowing of the channel. Even at this time the three main theories of hypertension were thus staked out. A renal theory, an arteriosclerotic theory and a vasoconstrictive theory.

With improved histological technique much work has been devoted to the study of the condition of the arterioles in the hypertensive. I need only mention the work of Jorés, Fahr and Evans. To summarize their findings, the media in these cases is found to be thickened and hypertrophied, the intima shows proliferation with subsequent degeneration. Different
stress is laid by these authors on the importance of the two conditions, but all appeared to believe that large arteriole areas escape, the lesion being most marked in the kidneys, spleen and pancreas, while the vessels of the skin, intestine and skeletal muscles are not affected.

It is obvious from what has been said above that if these large vascular areas remain intact, the rise in blood-pressure can hardly be connected with the changes noted. It is doubtful, however, whether the intestinal vessels and the arterioles of the skeletal muscles do actually escape. Brogstetter, for instance, has described marked medial thickening in the mesenteric vessels of hypertensive patients. A recent study by Kernahan, Anderson and Keith is of special interest, since pieces of the pectoralis major were removed in ambulatory patients and the condition of the arterioles examined. Medial hypertrophy and nuclear proliferation were found with proliferation of the endothelial cells and of the subendothelial tissue leading in some cases to almost complete occlusion of the vessel.

We may, I think, conclude that the vascular change is widespread and that both media and intima are involved. The medial change would appear to be of the nature of a pure hypertrophy.

What bearing have these findings on the development of hypertension? It seems reasonable to assume that the medial hypertrophy may be a purely functional hypertrophy—a work hypertrophy due to prolonged vaso-constriction. Can such prolonged vaso-constriction with the resulting rise in blood-pressure lead to intimal changes? In favour of such a theory we have the fact that constriction of the retinal arteries has been observed to precede sclerosis. We have also certain conditions in which increased intravascular pressure is accompanied by degenerative change in the intima, pulmonary atheroma as the result of mitral atenosis, sclerosis of the proximal aorta in congenital aortic stenosis, and the thickening of the endocardium of the left auricle in mitral stenosis. The predominance of the lesion in certain areas may perhaps be explained by differences in blood supply: the kidneys are known to have a particularly heavy blood supply, $\frac{1}{4}$ of the whole circulation, their weight being only $\frac{3}{10}$ of the body weight. If we accept these views the pathological findings are consonant with a primary medial spasm, resulting hypertrophy of the media and degeneration of the intima as the result of hypertension. The increased resistance leading to the blood-pressure rise would seem, at any rate at first, to result from muscular spasm rather than definite pathological change, though ultimately the intimal changes play some part.

In favour of such a causation of hypertension, we have the facts that hypertension is absent in the senile type of arteriosclerosis in spite of gross degenerative changes, and that the blood-pressure is exceedingly labile in the earlier stages of essential hypertension. As evidence of such lability I need only mention: (a) the frequent temporary return to normal of a high blood-pressure in the early period of essential hypertension; (b) the vascular crises, general with sudden and alarming rises of tension, or local, temporary cerebral or peripheral ischaemia; (c) the fall of pressure that occurs in febrile hypertensives.

I would point out that attempts to differentiate the spastic and anatomic factors in any individual case have not proved to be very successful. Actually advanced cases of hypertension respond less readily to vasodilators such as nitroglycerin than do early cases, as we should expect, if, in the initial stages, spasm predominates, while in the later irreparable anatomic change bulks largely in the production of the increased resistance. The results obtained are, however, conflicting and may vary in the same patient.

Assuming that in early essential hypertension we are dealing with a generalized
arteriole spasm, we have next to ask ourselves how this is produced.

Let us first consider Volhard's views, since he is the chief exponent of the renal theory. In his opinion the underlying cause of hypertension is obstruction to the blood flow through the kidney. If the circulation through the great water excreting organ is impaired, a generalized arterial spasm results. The resulting blood-pressure rise is compensatory: the essential cause of this rise is the "throttling down" of the renal arterioles. In glomerulonephritis, for instance, the glomerular capillaries in the early stages are open but empty—a condition due to constriction of the renal arterioles. At the same time the skin is pale owing to generalized cutaneous vaso-constriction. Later degenerative changes appear in the glomerular capillaries as the result of ischaemia. Once the hypertension is established, lesions in the other vascular fields follow. As evidence for the essentially renal character of hypertension he quotes cases of hypertension in complete anuria after removal of the only sound kidney, in prostatic retention and in cystic disease of the kidney.

Whether hypertension is invariably in these conditions is, at least, doubtful. In cystic kidney the pressure is often normal. In prostatic obstruction the blood-pressure rise, when present, has been attributed to a bladder reflex, and, in any event, the age incidence of prostatic hypertrophy and hypertension largely overlap.

What objections can be raised to this theory of Volhard? In the first place the theory is to some extent in itself inconsistent. The underlying noxa is apparently assumed to attack the renal arterioles only; changes in other vascular fields occur, but are assumed to be purely secondary. If the toxic substance can attack the renal vessels, why should it leave untouched the other vascular areas, the involvement of which is assumed to be purely secondary through the agency of reflex vaso-constriction.

Secondly, the evidence of a primary renal involvement is not apparently so overwhelming as Volhard's theory would demand. In numerous instances, which I need not detail here, the renal vessels have been found to be normal, even in very long standing hypertension.

Thirdly we have a great weight of clinical evidence against a primary renal origin of the condition. In any series of hypertensives a large number show no evidence of any kind of renal involvement. We have all watched such cases of essential hypertension without albuminuria change over into malignant hypertension with every evidence of advanced renal failure; broadly speaking the longer the duration of the disease, and the higher the blood-pressure, the higher the percentage of renal involvement. It is obvious that prolonged arteriole spasm is likely to lead to damage to the glomerular epithelium. Transitory albuminuria may be noted in the "hypertensive crises," the temporary rises of pressure which occur in essential hypertension, and Volhard has noted the appearance of albumin and casts in the urine of a sound man after adrenalin injection.

Lastly, it is difficult to understand why, if the renal arteriole lesion plays the prominent part ascribed to it by Volhard, the majority of these cases do not die in uremia. Actually only about 20 per cent. at most die in the uremic state. Clinically the disease presents itself as hypertensive cardiac failure, glycosuria possibly with so-called diabetic gangrene, interstitial nephritis, cerebral haemorrhage, or softening, or as a combination of any of these conditions.

Of late years investigation of the condition has largely been directed to the search for some toxic body capable of producing a generalized vascular spasm. The direction of research has to some extent been biased by the renal theory, and attempts have been made to correlate hypertension with the accumulation of various waste products in the blood. The best known nitrogenous
waste products—urea, uric acid, and creatinin—have no definite pressor action. The only waste product which we have any grounds for incriminating is guanidin. In health about 100 mg. of this substance are excreted daily; in hypertension Major found that this quantity was considerably diminished, while on examining the blood of hypertensives he obtained readings as high as 0'68 mg. per 100 c.c., the maximum in the normal being 0'2 mg. He has also shown that, when injected into animals, guanidin exercises a marked and prolonged pressor effect, the blood-pressure being doubled and trebled, owing to a peripheral vasomotor reaction, and the rise persisting for as long as four hours. In his most recent paper (1929) he arrives at the cautious conclusion that “certain hypertensives show a body in the blood giving the same colour reactions as guanidin, and having certain of the chemical properties of that body.” He frankly admits that normal guanidin contents may be found in the blood of some patients who show a very high blood-pressure. Guanidin is then a substance which cannot be ignored in the study of hypertension, but the case against it remains non-proven.

Of other clearly-defined bodies which might produce hypertension, we must first consider adrenalin. Hypertension has occasionally been noted with certain adrenal tremors. The difficulty of estimating the adrenalin contents of the blood is very considerable, and it will suffice to say that all recent work suggests that the adrenalin contents of hypertensive blood is normal. Assuming a normal adrenalin content, it has been suggested that certain bodies may circulate in the blood of hypertensives which sensitize the arterioles to the action of adrenalin. Westphal and others have incriminated cholesterol, but in Westphal's own series of eighty cases, only fifty show a cholesterol content in excess of normal, and in no case was a very high value found. The rises in blood-pressure which he produced by feeding rabbits with cholesterol were slight and inconstant, and we know of numerous conditions in man in which hypercholesterinæmia occurs with a normal blood-pressure, e.g., nephrosis, pregnancy and obstructive icterus. Hulse claims that the vessels are sensitized to adrenalin by the presence of excess of peptone-like bodies, but I know of no confirmation of his theory. In any case, the degenerative changes produced by adrenalin injections in rabbits are not the characteristic changes of the human hypertensive.

The inorganic constituents of the blood appear to play little part in the production of hypertension. Allen's statement that in the patient suffering from high blood-pressure the sodium chloride of the blood is raised, has received no confirmation. His treatment with exceedingly salt-poor diets, containing less than 2 grm. sodium chloride per diem, has met with little success in the hands of other observers, and probably any fall of blood-pressure that occurs is the result of the general prostration and weakness induced. It is also doubtful whether he makes sufficient allowance for the fall in blood-pressure which in most cases follows hospitalization and rest in bed.

Kylin attributes hypertension to a disturbance of the calcium potassium ratio in the serum and the resulting "disturbance in the vegetative system in the sense of Krause, that is the endocrine system and the vegetative nervous system both largely controlled by the ionic balance of the blood." As evidence of the part played by the endocrine system, be instances the association of the hypertension with the climacteric (ovary), the frequent occurrence of glycosuria in hypertensives (thyroid and adrenals), and the appearance of hypertension in Graves' disease.

There is undoubtedly evidence that hypertension not infrequently appears at the climacteric. In a large series of cases from a German source the average systolic pressure in the two sexes ran as follows:—
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At 40 ... ♂ 132 ♀ 133
" 50 ... ♂ 142 ♀ 152
" 60 ... ♂ 148 ♀ 139

It is conceivable, however, that this rise is the result of psychical disturbances at the menopause; for the connection of a raised blood-pressure with states of worry and anxiety is undoubted.

The association of glycosuria with hypertension is of more interest since it has been variously attributed to over-activity of the chromaffin system and to degenerative changes in the islets of Langerhans. Glycosuria is apparently more frequent in hypertensives who show impairment of the renal function, that is cases in which the parenchyma of various organs is undergoing degenerative changes as the result of vascular lesion. Marked changes in the pancreatic arterioles have been described, and Keith has recently observed degeneration of the islets in hypertension. It does not therefore seem necessary to invoke adrenal over-activities as a cause of the rise in the blood-sugar so frequently met with in the hypertensive.

At present, therefore, the search for a pressor substance as the cause of hypertension must be admitted to have been unsuccessful. The sequence of events as suggested by pathological and clinical findings would appear to be a generalized spasm of arterioles, at first characterized by extreme lability, later development of definite hypertrophic and degenerative changes in the arteriole wall, and ultimately secondary ischaemic changes in the parenchyma of the various organs affected. In the earlier stages we have spastic, labile "benign" hypertension. In the latter malignant hypertension, fixed, with retinitis and frequently with renal functional failure. Malignant hypertension is the final stage of the disease in a certain proportion of the benign cases.

As yet no evidence is forthcoming that a pressor substance is actually present in hypertensive bloods; and the only permissible attitude in discussing the cause of hypertension appears to be a pure agnostic-ism. In any theory of the disease account must be taken of the influence of psychic disturbances in blood-pressure, and of the very strong familial incidence of the disease.

We will now turn to the equally obscure question of the transitory hypertension of acute glomerulonephritis.

How important a symptom of the disease this rise in blood-pressure is may be inferred from Volhard's statement, "The pathognomonic symptom of typical acute glomerulonephritis is the rise in blood-pressure."

It is only during the last few years that the true significance of this statement—a significance hardly realized by Volhard—has been recognized. We can now definitely state that in certain cases of the disease which we know as acute glomerulonephritis a rise of blood-pressure is the only symptom. A more careful study of the disease has revealed the fact that the sequence of events is a rise of blood-pressure and the appearance of oedema, which last for some days before the presence of albumin can be found in the urine. Nonnenbruch and Kylin have reported cases in which oedema, hypertension and even "uremic" fits occurred, but in which albuminuria was absent, or only appeared some days after the convulsions. Lundberg has also shown that in post-scarlatinial nephritis the blood-pressure rise definitely antedates the albuminuria, and cases of eclampsia without albuminuria are on record. We have then a very different conception of acute glomerulonephritis from that of ten years ago. We are entitled to regard the disease as a primarily vascular disturbance, in which definite evidence of a renal lesion in the shape of albuminuria appears relatively late and may not appear at all. In both acute glomerulonephritis and in interstitial nephritis the emphasis has shifted into the vascular change and the renal lesion has receded into the background.

What then is the cause of the rise of
blood-pressure in acute glomerulonephritis? The theory of a reflex hypertension arising from obstruction to the glomerular capillaries seems to me to be untenable. Glomerular ischaemia should produce early damage to the delicate glomerular epithelium and albuminuria, but albuminuria may be absent. The suggestion that the pressure rise may be due to hydramic plethora has also received its quietus; blood volume estimates show that the blood volume is normal, and the low red cell counts met with at the height of the disease are, according to Ashe, the result of a true anaemia.

Kylin’s view is based on his belief that in acute glomerulonephritis the capillary blood-pressure is raised. Taking the normal capillary pressure, as estimated by his visual method, at 100 to 200 mm. H₂O, he finds pressures in acute nephritis in excess of 500 mm. In mild cases the capillary pressure rises in proportion to the arterial. In essential hypertension, on the other hand, the capillary pressure is normal unless cardiac failure and stasis occur. The cause of the pressure rise is therefore different in the two conditions. In benign hypertension the increased resistance lies in the contracted arterioles; in acute glomerulonephritis in the capillaries. Kylin suggests that a generalized capillary lesion is present, due to the toxins, usually streptococcal, which produce the disease. As evidence of this lesion he cites the oedema and the high protein content of the oedema fluid, an indication of increased capillary permeability. Albuminuria, if present, is merely the expression of the involvement of the glomerular capillaries in the generalized capillary lesion, “capillaropathia acuta universalis.” Later, he believes that the capillary lesion may lead to reflex generalized arteriole spasm. He quotes the work of Dale and Laidlaw on histamin, which in weak concentrations produces capillary damage with exudation, in stronger arteriole constriction.

While admitting the great value of Kylin’s work in emphasizing the probably generalized character of the lesion in so-called acute glomerulonephritis, and in calling attention to the pre-nephritic stage of the disease and to the appearance of oedema before albuminuria, his theory seems to present certain difficulties.

In the first place direct observation of the capillaries in vivo has produced no evidence of definite pathological change in acute glomerulonephritis. No typical alterations in the capillary flow can be detected. In the kidney the earliest change appears to be a capillary ischaemia, due to arteriole constriction; histological changes in the capillaries appear later.

Secondly, it is not impossible that the high capillary pressures observed by Kylin may result from changes in the compressibility of the skin overlying the vessels, the result of latent oedema. Changes in the elasticity of the skin and subcutaneous tissues are known to occur even in the absence of obvious oedema and can hardly be left out of account in his compression method. Are the capillaries capable of standing up to the pressures observed? Acute glomerulonephritis rarely shows signs of actual capillary rupture, petechiae.

As you will see, I am quite unprepared to offer any satisfactory explanation of hypertension and its connection with renal disease. As I see the position, opinion is shifting more and more away from the kidney as the cause of hypertension either in essential hypertension or in acute glomerulonephritis, but as yet no satisfactory alternative has presented itself.
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