The RENAL ORIGIN of HYPERTENSION

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by

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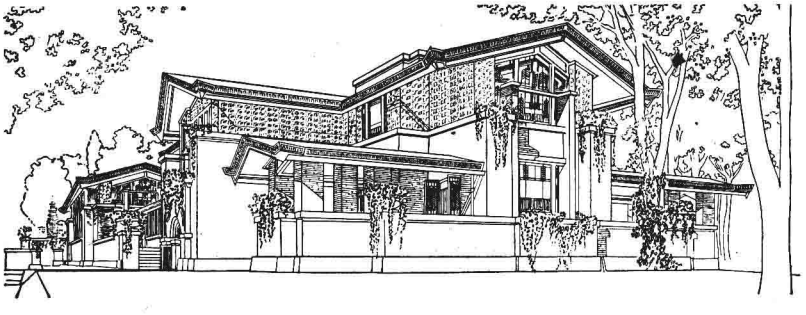

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PREFACE

In recent years, in several books (1-4), the present state of our knowledge of human and experimental hypertension has been described and discussed in great detail. It is legitimate, therefore, to question why a written lecture on this subject should be published at this time. My first impulse is to apologize for making this contribution, which is incomplete, and in great part repetitious, but, on second thought, I have considered that it may prove of some value to those whose interest is not sufficient to induce them to read the original papers or who do not have the time to devote to the reading of books on this topic. To me, the whole subject continues to be fascinating, and I consider that it should be of great interest to all students of medicine, and even to laymen. The justification for this statement is that: (1) the death rate from arteriosclerotic disease of the brain, heart and kidneys, associated with the symptom of hypertension, continues to be very high (about four times that of cancer); (2) fully 25% of deaths, at least in males over 50 years of age, is associated with the existence of this condition; (3) treatment has done but little to reduce these figures; (4) there are no known methods of prevention; and (5) the initiating cause or causes of the two associated conditions, arteriosclerosis and hypertension, are still obscure or unknown. It is my ardent hope, therefore, that the advances in our knowledge of the pathogenesis of human hypertension, based on the investigations of experimental renal hypertension, may yet lead to the prevention and cure of this condition which takes such a large toll of human lives.

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INTRODUCTION

Not infrequently medical historians find it difficult, or even impossible, to assign the origin of an idea to a single person. Although Richard Bright knew nothing about hypertension, because in his time blood pressure in man had not yet been measured, yet there is little doubt that to him should go the credit for the basic idea that hypertension may be of renal origin. Although Bright did not differentiate clearly between the various types of renal disease, and although he knew nothing of the important entity which is now called *essential hypertension*, yet he did make the important observation that in cases of cardiac hypertrophy, not obviously due to intrinsic cardiac disease, or extrinsic vascular abnormality, there is found, almost without exception, some disease of the kidneys. Basing himself upon this observation, with the intuition of a great clinician who was also greatly interested in pathology, he speculated that the increased weight of the heart (hypertrophy) might be related to the disease of the kidneys. Indeed, he went so far as to suggest that a chemical alteration of the blood resulting from the renal disease was probably the immediate cause of the cardiac hypertrophy, by effecting an increased action of the heart and, what is more important, by inducing what amounts to increased peripheral vascular resistance to the onflow of blood. The latter idea is nothing short of remarkable for the time, for if there is one thing that appears to be definitely settled about the basic mechanism of the state of hypertension in man, it is the existence of a state of increased peripheral vascular resistance. The specific parts played by arteriosclerosis and by generalized spasm of the arterioles, and the primary or secondary relationship of these changes to the hypertension, still constitute a controversial subject. What is not yet settled, also, despite all the work that has been done on the subject, is the question of the renal origin of the type of hypertension that is now usually referred to as *essential*, or *primary*.

In a normal animal, direct determinations of blood pressure had been made by Stephen Hales, in 1733, one hundred years before Bright; but in man, measurements of blood pressure were not made until the end of the nineteenth century. Although, on the basis of other indirect methods, particularly palpation of the pulse, pulse

tracings and other bloodless methods, the existence of a state of increased vascular tension in man had been recognized, yet it was not until the development by Riva-Rocci of a method to determine blood pressure (really bursting tension), by a pneumatic cuff and a mercury manometer, that the existence of elevated blood pressure in man was fully recognized, its significance appreciated, and the study of its pathogenesis undertaken.

After the discovery of the existence of elevated blood pressure in man, it was realized at once that the enlargement of the heart observed by Bright was a direct consequence of the hypertension, and the problem switched at once to the pathogenesis of the increased peripheral vascular resistance. What confused the problem was the previous discovery by Johnson and by Gull and Sutton of organic disease of the small arteries and arterioles, which consisted of thickening of the walls and reduction in the size of the lumen, an obviously possible organic cause of increased peripheral vascular resistance. The direct result of this was that one group of investigators, a minority group, contended, with Johnson, that the renal disease was the cause of the hypertension, the diffuse vascular disease and the hypertrophy of the heart, while the other group asserted, with the followers of Gull and Sutton, that the hypertension and consequent cardiac hypertrophy were the direct result of the increased peripheral vascular resistance caused by the diffuse organic disease which only incidentally involved the kidneys. This division of opinion has survived up to the present time, with one addition, namely, that the primary phenomenon is increased peripheral vascular resistance due to vasospasm (neurogenic or endocrinogenic), which results in increased peripheral resistance and hypertension, and that all the organic changes, vascular and cardiac, are secondary to the hypertension.

In more recent times it has been recognized that primary renal disease may be associated with hypertension and that a causative relationship between the two conditions may exist. In such cases the presence of the renal disease is recognized usually by reason of renal excretory functional abnormalities which result from pathologic changes in the kidneys. These include polycystic disease of the kidneys, glomerulonephritis (acute and chronic), bilateral obstruction of ureters, from any cause, bilateral chronic pyelonephritis, and other conditions which involve considerable reduction of renal parenchyma and in which disturbance of excretory function usually

occurs. After the recognition of essential hypertension, doubt was cast upon the frequency with which renal disease might be considered the cause of the initiation of the elevated blood pressure. As a matter of fact, renal disease characterized by disturbance of renal excretory function has always been excluded from the definition of essential hypertension. Dalton and Nuzum believe, however, that the critical statistical analysis of the data on renal excretory function in cases of essential hypertension in man does show, in most cases, some impairment of ability to concentrate urine and to excrete phenolsulfonphthalein. The fact that renal excretory functional abnormality frequently cannot be demonstrated for many years after the onset of hypertension, and even throughout the entire course of the disease, convinced many investigators that most cases of hypertension are not on a renal basis. As a result, hyperepinephrinemia, abnormal pituitary function, neurogenic stimuli affecting the vasomotor mechanism and diminution of the sensitivity of the carotid sinus are some of the conditions that have been considered at various times the cause of this type of hypertension.

Most students and investigators of the subject of essential hypertension are now in complete agreement that cardiac output, and the volume and viscosity of the blood are within the limits of normal in well established essential hypertension. It is, therefore, generally agreed that, with few exceptions, the ultimate cause of the elevated blood pressure is increased peripheral vascular resistance. Although there is still some division of opinion about whether the increased vascular resistance is ever on an organic basis, yet most investigators are of the view that peripheral vasospasm is the physiological basis for the phenomenon. That the organic changes in the peripheral blood vessels, especially the arterioles, are ever so widespread as to be a purely mechanical cause of hypertension is not supported by the anatomical findings of pathologists. Also, physiologists and clinicians have shown that the peripheral arterioles exhibit normal physiological responses to physical and chemical stimuli, for example, the normal vasodilator response of the vessels of the forearm and hand to heat and reactive hyperemia (Prinzmetal, Pickering) and the normal depressor response to an intravenous injection of 0.1 mg. of histamine acid phosphate (Pickering and Kissin). The process of vasospasm, therefore, can be adduced as the cause of the increased peripheral resistance.

The one man who kept the idea of the possible renal origin of some forms of human hypertension alive was Volhard who believed that, in pale (malignant) hypertension, at least, the pathologic change in the kidney plays an important part in the development of the elevated blood pressure. He even sought, but failed to find, a vasoconstrictor substance in the blood of patients with this condition. Although there are those who still deny that the kidneys ever play a primary part in the initiation of hypertension, yet it is now quite generally admitted that some forms of renal disease may, in some way, be the cause of the hypertension. What is not generally admitted is that essential hypertension, especially the benign phase, the type of hypertension that is usually associated with widespread arteriolar sclerosis, and especially with nephrosclerosis, but without accompanying excretory functional abnormality, is of renal origin. The arguments usually given against the renal origin of essential hypertension are: (1) the frequent discovery of elevated blood pressure long before there is any recognizable sign of renal excretory insufficiency; (2) the absence of any recognizable signs of renal excretory insufficiency throughout the entire course of the hypertension in a large percentage of cases, and (3) the failure to find at autopsy significant intrarenal vascular disease in an occasional case of essential hypertension.

Experimental proof for the view that the kidneys play a primary part in the development of the increased peripheral vascular resistance and consequent hypertension had been sought in a variety of ways before our own experiments on this subject began, in 1928.

Production of Experimental Renal Hypertension By Various Methods

Unilateral and bilateral nephrectomy had been tried but had not resulted in hypertension in the rabbit, cat and dog. (Mosler, 1912, Bachman, 1916, Cash, 1926). Most experiments of a similar nature that have been performed up to the present time have been in agreement with the early results (Harrison, Blalock and Mason, 1936), but recently Grollman has asserted that hypertension may develop in dogs and rats as a result of unilateral nephrectomy.

Reduction of the amount of functioning renal tissue, by partial resection of each kidney, had been reported as causing slight hypertension in the rabbit, cat and dog, (Cash, 1924) and, since 1928, sev-

eral investigators have noted the development of considerable hypertension in the rat, but not in the dog, as the result of this procedure. (Ferris and Hynes, 1931, Chanutin and Ferris, 1932, Wood and Ethridge, 1933). In the light of our own studies on the dog, and because only the rat gave a pronounced effect, it is suggested that the cause of the elevation of the blood pressure in these animals was the hemodynamic disturbance in the small remnant of the kidneys, caused by the scarring from the surgical operation.

The effect of a nephrotoxic substance, such as uranium, had been tried on rabbits by Beckmann (1925) and Dominguez (1928), but elevation of blood pressure was not produced consistently. Since then other investigators, using the same and other nephrotoxic agents, have obtained contradictory results. Lead salts, sodium and potassium oxalate, mercury, bismuth, and streptococcus toxin are among the other substances that have given negative or equivocal results. The direct injection of trypsin into the renal artery (Freedman and Katz, 1938) failed to produce persistent hypertension. It has been shown that nephrotoxic heterologous antiserum to rabbit renal substance produces glomerulonephritis and renal excretory insufficiency, accompanied by slight elevation of blood pressure (Masugi, 1934). This has also been accomplished in the rat (Smadel, 1937) and confirmed for the rabbit; but Corcoran and Page (1941) failed to observe elevation of the blood pressure in the dog with glomerulonephritis produced by a nephrotoxic serum.

Irradiation with roentgen rays of the kidneys of dogs caused moderate elevation of blood pressure, but impairment of renal excretory function was an invariable accompaniment. (Hartman and collaborators, 1929). This was confirmed later by Page (1936), for the dog, but Hermann, Dechard and Erhard (1941), failed to observe indirect evidence (cardiac hypertrophy) of hypertension in the rabbit as a result of irradiation of the kidneys.

Occlusion of one or both ureters was first tried in 1929, by Hartwich, who observed some elevation of blood pressure associated with fatal uremia, in the dog, as a result of bilateral occlusion of the ureters. This result has been fully confirmed, but most investigators have reported failure to produce hypertension as a result of unilateral occlusion of a ureter. Constriction of one ureter, with contralateral nephrectomy, also did not result in hypertension in the dog (Eichelberger, 1938). In the light of our own experiments,

it appears probable that occlusion of a ureter may produce a hemodynamic disturbance similar to, but not as pronounced as, the effect of constriction of the main renal artery.

Compression of the kidneys by an oncometer had been tried, in 1909, by Alwens, who reported slight immediate elevation of blood pressure in some brief experiments in cats. More recently, a similar effect on the kidney of a persistent type has been produced by Page and collaborators (1939) by the envelopment of the kidneys in cellophane or silk. The same effect has been obtained in rats and dogs (Greenwood, Nassim and Taylor, 1939, Hermann, Jourdan and Vial, 1940) by means of collodion painted on the surface of the kidneys and also by compression of the kidneys by means of a tape tied in a spiral form around the kidney (Grollman, 1944). These methods are supposed to act by direct compression of the kidney substance or by the compression and resultant ischemia caused by the thick perirenal scar which results from the perinephritis induced by the foreign material. The main drawback of the method is the frequent accompaniment of renal excretory functional disturbance and even fatal uremia.

Embolism by the direct injection of various substances (liquid paraffine, Berlin blue, charcoal) directly into the renal artery of cats and dogs had given consistently negative results (Senator, 1911, Cash, 1924). More recently, however, Maegraith, and McClean, (1938) reported the development of hypertension in the rabbit as the result of the injection of kieselguhr into the main renal artery of rabbits. The same substance failed to produce high blood pressure in the dog (Crestman and Blalock, 1939).

Passive hyperemia of one kidney produced by the constriction of the main renal vein had been reported by Pedersen, in 1927, as causing a transient elevation of blood pressure in the dog. This has been confirmed by Braun-Menendez (1933), Dicker (1937) and Friedberg (1944). It did not prove to be a method for the production of persistent hypertension on a renal basis because bilateral constriction of the main renal veins invariably resulted in fatal uremia.

Permanent occlusion of the main renal artery, vein, and ureter of both kidneys had failed to cause hypertension in the dog (Cash, 1926). Although Loesch (1933) did report hypertension in the dog as the result of intermittent occlusion of all the structures of the renal pedicle, yet there is reason to believe that the hypertension developed

only when constriction of some of these structures became permanent as the result of scarring.

Arteriovenous anastomosis had not been tried before 1928. In 1939, Weber and Rumold produced hypertension accompanied by uremia in the dog by arteriovenous anastomosis of one kidney and contralateral nephrectomy. This did not prove to be a method for the production of persistent hypertension.

Occlusion of the main renal arteries had been tried, in 1905, by Katzenstein, who reported an immediate slight rise of blood pressure, probably of reflex origin, in some brief experiments. Cash, in 1926, reported a rise of blood pressure in dogs that survived occlusion of both main renal arteries for several days, but died in uremia. This result has been confirmed since then by many other investigators, including ourselves. Although the animals develop elevated blood pressure, yet they die in uremia, so this is not a good method for the production of persistent hypertension. Although the animals die in uremia, as in the case of bilateral nephrectomy, yet, different from the latter, elevation of blood pressure does occur. This is understandable, in the light of our own experiments, on the basis that, although a state of profound renal ischemia exists, yet blood flow through the kidney does not cease altogether, and a pressor substance of renal origin may enter the circulation by way of the main renal vein or the lymphatics.

Ligation of branches of the main renal artery gave contradictory results and the hypertension, when it did occur, did not persist (Janeway, 1913; Mark, 1928; Hartwich, 1930; Friedmann and Wachsmuth, 1930; Wolf and Heinsen, 1935; Konzett and Unna, 1937; Verney and Vogt, 1938). Occlusion of the main artery of only one kidney also resulted in slight temporary elevation of blood pressure, in dogs, but all of these experiments were published after 1929 (Friedmann and Wachsmuth, 1930; Hartwich, 1932; Winternitz and collaborators, 1940). It is not a method for the production of persistent hypertension.

Constriction of the main renal artery had also been tried before 1928, but Katzenstein (1905) observed only slight elevation, probably of reflex origin, in a brief experiment, while Bridgman and Hirose (1916) reported no elevation of blood pressure in dogs as a result of the same procedure.

The administration of sterols (cholesterol) had also been tried