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The etiology of nephritic hypertension

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THE ETIOLOGY OF NEPHRITIC HYPERTENSION

BY

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THE ETIOLOGY OF NEPHRITIC HYPERTENSION

INTRODUCTION

The question of hypertension in nephritis dates from the work of Richard Bright (1) in 1827, who noted the increased resistance which the arteries of diseased kidneys offered to injection. In commenting on the cardiac hypertrophy so often associated with renal disease, he (2) made the following oft-quoted statement: " The two most ready solutions appear to be, either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately, or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant subdivisions of the vascular system. " He thus seems to have realized that the cardiac hypertrophy of renal disease is related to hypertension as effect is to cause, and in this short quotation lies the basis for nearly all subsequent investigation of this problem.

Traube (3) in 1856 was one of the first to show that arterial hypertension formed the link connecting renal disease with cardiac hypertrophy. He was forced to estimate blood pressure by palpation of the radial pulse, for the first instrument for measuring blood pressure directly was not devised until 1876 by von Basch, who thus opened the way for the investigation of this circulatory disorder. Accurate determinations were not possible for another twenty years, until Riva-Rocci

invented the pneumatic cuff in 1896. However, it has been only in the last quarter century that blood pressure determinations have become an essential part of clinical examination. Galabin (4) and Mahomed (5), in the 1870's, by means of pulse tracings, demonstrated the existence of hypertension in acute and chronic forms of Bright's disease.

From the time of Richard Bright, there has always been some question as to whether hypertension is the result of renal disease or whether the converse is true. Many have asserted that hypertension is the cause rather than the result of renal disease, some even going so far as to say that all chronic nephritides are secondary to hypertension. Mahomed (5) first showed the presence of heightened tension in some cases of Bright's disease and scarlet fever before the appearance of albuminuria. Jares (6), Moschcowitz (7)(8), and Ophuls (9) tend to support this view and point out that when sclerosis of the renal vessels is found at autopsy, it is only part of a generalized arteriolar sclerosis. Allbutt (10), who is noted for his work on essential hypertension, also adhered to this view-point, as did Kylin (11), who stated that " all attempts to explain any hypertension secondary to kidney insufficiency are a failure. " In apparent substantiation of this concept, Cadbury (12), working with Cantonese students, made the interesting observation, that, while chronic Bright's disease is common in China, hypertension is rare; but he drew no conclusions from his observations.

The opposite view-point, in all probability, is held by the greater majority of clinicians. Romberg (13) stated that in every case with a maximum pressure constantly over 160 mm. Hg., kidney disease may be the cause irrespective of diastolic pressure. Bennett (14) believes that hypertension can in some degree be the direct result of nephritis and renal disease, but he opposes the statement of Romberg with the assertion that a very high pressure is strong evidence for the existence of an extra-renal factor. This view is also supported by Evans (15), Foster (16), and Christian (17)(18). Experimental work by Hartman, Balliger, and Doub (19), who produced nephritis in dogs by the application of high voltage x-rays to the kidneys, tends to sustain the contention of Romberg and others that the kidney may be directly responsible for a certain group of cases of hypertension and cardiac hypertrophy. In reviewing this problem, Jaffe (20) remarks: " more frequently, however, high blood pressure and hypertrophy of the heart are associated with diseases of the kidneys. " This aspect of the problem of hypertension has been fairly summed up by Holmes (21), who states that only 10% of hypertension is due to renal disease, and that far too much stress has been placed on kidney lesions as the cause of hypertension. Although only 10% of hypertension may be due to renal disease, it is a very important 10%, particularly in regard to experimental work, for it seems more likely that the cause for this type of hypertension will be forthcoming in the future than will the cause of so-called " essential

hypertension. "

INCREASED CARDIAC OUTPUT

The earliest theory regarding the mechanism by which blood pressure is raised was that of increased cardiac output. Bright (2) considered this possibility as a likely cause for the cardiac hypertrophy noted in cases of chronic nephritis. Broadbent (22) in 1883 believed that increased cardiac output might play a small part in the production of hypertension. In more recent years, Bachmann (23) postulated on excessive stimulation of the heart by retained urinary constituents. This idea has often been brought forth, with many substances believed to be the stimulants of the heart, but is seldom entertained at the present. The fallibility of this hypothesis is shown by Burwell and Smith (24) and by Weiss and Ellis (25), who have demonstrated that the cardiac output is not increased in cases of hypertension. In addition, the minute volume and stroke volume of the heart have been shown to be normal in hypertension by Ringer and Altschule (26). Fishberg (27) also notes that the cardiac rate is usually slow and that the x-ray and autopsy often show no cardiac hypertrophy. Thus, it is evident that increased cardiac output is not a factor in the production of nephritic hypertension.

INCREASED BLOOD VOLUME

Another early theory was proposed by Traube (28) in 1870, that of an increase in blood volume. This view has had but few proponents, being briefly mentioned by Broadbent (22) as a possible factor, and it has been definitely discarded since Linder, Lundsgaard, Van Slyke, and Stillman (29) have shown that there is no gross increase in plasma volume in glomerulonephritis, nephrosclerosis, or in nephrosis.

INCREASED VISCOSITY OF THE BLOOD

Early in the investigation of this problem of hypertension appeared the concept of increased viscosity of the blood, first suggested by the statement of Bright himself on the cause of cardiac hypertrophy in chronic renal disease. (v.s.). Galabin (4) believed that an increase in viscosity of the blood played an important part in the production of hypertension, as did Allbutt (30) in more recent years. In 1930, Harris and McLaughlin (31) reported an increase in blood viscosity in thirty-five of forty cases of hypertension. They also demonstrated that this increase in viscosity was not due to carbon dioxide or to increase in size or number of blood cells, and thus supported Allbutt's view. In contradistinction to this theory, Austrian (32) found hypoviscosity

of the blood in many cases of hypertension, and Lucas (33) noted hypertension in only one-third of 189 cases of polycythemia. The most conclusive argument against this concept is furnished by Fishberg (27), who demonstrates by the laws of Poiseuille, which govern the flow of fluids in capillary tubes, that doubling of the viscosity of the fluid only doubles the pressure, whereas halving the radius of the tube increases the pressure sixteen times. Thus an increase in viscosity of the blood could produce some increase in pressure, probably only minimal, even were it possible to demonstrate a constant hyperviscosity of the blood in hypertension.

DIMINUTION IN ELASTICITY OF THE ARTERIES

Since the work of Gull and Sutton (34) in 1872 on the pathology of chronic Bright's disease, in which they described the so-called "arterio-capillary fibrosis", many men have believed that loss of elasticity of the arterial walls because of fibrosis was an important factor in the production of hypertension. Gull and Sutton, however, laid but little emphasis on the loss of elasticity, stressing more the hyaline fibroid change with contraction of the vessels. This view is no longer held, for it is well known that only the aorta and the larger vessels are elastic. Loss of their elasticity not only increases the systolic pressure, but also lowers the diastolic; such a condition, of course,

is not a true hypertension.

INCREASED PERIPHERAL RESISTANCE

A point of view differing from the aforementioned theories has been held by most investigators and is now generally considered to be the actual mechanism in the production of increased arterial tension. That view is that hypertension is produced by increased resistance to the arterial flow due to narrowing of the peripheral vascular bed. Bright (2), as mentioned above, considered this as one of the two possible mechanisms in the production of hypertension. Fishberg (27) demonstrates that, according to Poiseuille's laws (v.s.), halving the radius of a tube increases the pressure within sixteen times, and quotes the works of Hess, Tigerstedt, and others to show that this is a fairly accurate approximation. Most investigators are of the opinion that this increased peripheral resistance is encountered in the arterioles rather than in the capillaries.

A great deal of work has been done in an effort to determine the nature and causes of this increased peripheral resistance, and consequently numerous theories have been developed. These may be roughly classified into two main groups: 1.) Organic lesions of the peripheral vascular bed, and 2.) Functional or angiospastic conditions affecting the arteriolar circulation.

ORGANIC LESIONS OF THE PERIPHERAL VASCULAR BED

Under the heading of organic lesions may be listed the contributions of many of the earlier investigators in this field. As early as 1846, Toynbee (35) noted that the blood vessels of nephritic kidneys were thickened and contracted, and ten years later Traube (36), who first connected hypertension with renal disease, believed that it was due to the increased resistance in the kidney. Gull and Sutton (34) differed from this view in that they believed the increased resistance was due to a generalized arterio-capillary fibrosis, not limited to the kidneys alone. This latter concept was supported by Goodhart (37) in 1885. Loeb (38) in 1905 proposed an interesting theory of compensation, postulating that a central nervous system reflex produced sufficient increase in pressure to provide an adequate flow of blood through the kidneys to prevent retention of metabolites. This view has received support from Fahr (39), Evans (15), and, as late as 1931, from Garsky (40). Additional evidence supporting the theory of an organic lesion as the etiologic factor has been demonstrated by Arnott and Kellar (41), who have produced an experimental oxalate nephritis in rabbits with which is associated a hypertension. They offer no suggestion as to the mechanism by which the pressure is raised, but believe that it is associated with glomerular ischemia.

The arguments opposing the theory of organic vascular lesions

may be briefly enumerated. Traube's theory of increased resistance in the kidney has been disproved by experimental ligations of the renal arteries with no resultant hypertension. (Janeway (43).). Gull's and Sutton's theory is no longer entertained, for, as Fishberg (27) points out, arterial changes are seldom sufficiently widespread to cause hypertension, and also hypertension usually precedes arteriosclerosis. Loeb's theory of compensation was shown to have no anatomic basis by Jores (42), who studied serial sections of the kidneys of four nephritics and found that the two with the greatest cardiac hypertrophy and the highest blood pressure had the least extensive glomerular lesions. Janeway (43)(44) states that the greatest objection to this theory of glomerular change is that in amyloid disease of the kidney, there is almost invariably no change in the blood pressure. Longcope and McClintock (45) add farther evidence by showing that permanent constriction or gradual occlusion of the superior mesenteric artery and the coeliac axis in dogs for a period of five months produces no definite or constant hypertension. These arguments would seem to disprove any theories of an organic lesion producing hypertension, and, at the present time, very little importance is attached to any organic vascular lesion as a factor in hypertension.

FUNCTIONAL OR ANGIOSPASTIC CONDITIONS OF THE PERIPHERAL VASCULAR BED

The functional or angiospastic lesions of the vascular system

proposed as factors in the production of heightened arterial tension comprise the major work on the subject of hypertension. These theories are mostly based on the supposed presence in the blood of chemical substances acting as vasoconstrictors, but there are a few based on nervous or reflex stimulation of the vegetative nervous system with resultant vasoconstriction and increase in blood pressure. These latter concepts may briefly be considered as follows.

NERVOUS OR REFLEX CONDITIONS

In 1889, Tuffier (quoted by Bradford (46)) and later Bradford (46), showed that up to two-thirds of a dog's kidneys could be removed with no serious effects. These results were later confirmed by Pearce (47) in 1908. Pässler and Heineke (48) applied the results of Bradford's work to the problem of hypertension and concluded that, as a result of a kidney lesion, increased irritability of the vasoconstrictor apparatus occurred with consequent arterial spasm and increase of the peripheral resistance to the flow of blood. Janeway and Carrel (49) added some evidence to this view by producing hypertension by ligation of a branch of the renal artery, but also added that they believed there must be a retained poison of some kind. MacWilliam (50) in 1925 demonstrated disturbances in the vasomotor reflexes in cases of hypertension and also showed that Marey's law does not hold true in cases of hyper-

tension, for an increase in the blood pressure of hypertensives does not slow the heart rate as it does in normal individuals. He draws no definite conclusions, however, from these observations. Goldblatt, Lynch, Hanzal, and Summerville (51) produced hypertension in dogs by constriction of the renal arteries, and mentioned as a possible mechanism, a reflex causing general vasoconstriction. They also suggested that this theory could be tested by complete renal denervation. This was recently done by Elant (52) who found that hypertension produced by section of the depressor nerves and denervation of the carotid sinus could not be prevented or reduced by complete denervation of both kidneys. This work is apparently sufficient evidence against an entirely nervous reflex theory as a factor in the production of hypertension.

CHEMICAL CAUSES OF INCREASED PERIPHERAL RESISTANCE

The theories of the cause of renal hypertension which are dependent upon the presence in the blood stream of chemical substances exerting a vasoconstrictor action are numerous and varied. They have occupied a foremost position in the investigation of this problem since the time of Richard Bright, and in his famous statement concerning the altered quality of the blood lies the germ of their origin.

Johnson (53) in 1868 proposed one of the earliest theories of a chemical nature, believing that the blood was made impure with urinary

excreta which caused contraction of the vessels with resultant hypertension. Musser (54), reviewing the work on hypertension, concludes that it is due to a chemical urinary retention, and like uremia is an evidence of renal insufficiency. Jaffe (20) outlines the vascular changes in the kidney occurring in nephritis and shows how irritants will be collected in that part of the arterial system with resultant intensive action on its walls producing constriction and hypertension. Janeway (43), Rayer (55), Monro (56), Goldblatt, Lynch, Hanzal, and Summerville (51), and Volhard (57) agree with the above view-points in their general aspects, and all agree that some pressor substance is the cause of hypertension, but they make no definite conclusions as to the nature or identity of the pressor substance.

The chemical substances which have been considered are almost infinite in number and variety, all the urinary constituents having been considered at one time or another. To record the results of all the theories and experiments involving all these substances would not only prove to be uninteresting, but would not fall within the scope of this resume. Therefore only the more important concepts will be considered.

RENIN. One of the earliest substances investigated was a kidney extract called renin by its discoverers, Tigerstedt and Bergmann (58). They suggested that this substance was liberated by the diseased kidney and produced hypertension by its pressor action, for they had isolated

it from the rabbit's kidney and had produced a temporary rise in blood pressure by injecting it intravenously. This work was confirmed by Bingel and Strauss (59) in 1909. Shaw (60) proposed a rather similar theory, believing that kidney substance alone could be the cause of hypertension in renal disease. Pearce (61), in checking the work of Tigerstedt and Bergmann, obtained conflicting results and was unable to support this theory. Miller and Miller (62) were unable to get pressor effects from any organ extracts, including kidney extracts. Additional evidence opposing this theory is found in the fact that hypertension is most extreme in those cases of very chronic nephritis where kidney breakdown is minimal, if present at all. And finally, as Fishberg (27) points out, such a theory is untenable because there is no clinical parallelism.

EPINEPHRINE. Another substance which has often been considered as the pressor substance in hypertension is epinephrine. This idea was first proposed by Neusser (quoted by Biedl (63)) as a guess from a single case of chronic Bright's disease with carcinoma of one adrenal. This concept of hyperadrenalemia has been extensively investigated by a number of French workers. Vaquez (64) in 1904 showed autopsy material of hyperplasia and adenomata of the adrenals in cases of hypertensive nephritis. Landau (65), Pearce (66), Thomas (67), and Borberg (68), however, were unable to demonstrate any constant relationship between hypertension and anatomic changes in the adrenals. Hoskins and McClure

(69) further pointed out that the hypotension of Addison's disease did not bolster this theory, for they found that the adrenals apparently do not maintain the blood pressure at its normal level. A few years after Vaquez proposed his theory of hyperadrenalemia, Schur and Wiesel (70) developed a rather similar concept, prophesying that hypertension would be found due to increased activity of the chromaffine system, after having supposedly found increased epinephrine in nephritic serum. This theory enjoyed wide popularity for some time, although Schlayer (71) in 1879 had demonstrated that nephritic sera produced less vasoconstriction than normal sera. Fraenkel (72) and Trendelenburg (73), a few years later, failed to obtain greater constrictor effects on uterus suspensions and frog perfusions from the blood of hypertensives than from normal sera. Kretschmer (74), however, obtained positive results in acute nephritis and negative results in chronic nephritis. The constrictor effect noted by many of these investigators so closely resembled that of epinephrine that its presence in normal blood was accepted without question. The conclusions of these earlier investigators were disproved by O'Connor (75), who worked out a series of careful experiments. His work was a death blow to the great school of thought built upon Vaquez's theories, for he proved that the vasoconstrictor in defibrinated blood and serum was equally stimulating to peristalsis and was therefore antagonistic to epinephrine. He also demonstrated that this constrictor was not present in citrated blood, and therefore concluded that it was produced by the

process of clotting. Further evidence opposing this theory was added by Janeway (43), who pointed out that hyperglycemia is not constant in hypertension. In spite of these proofs, this theory continued to occupy a place of importance in the minds of many, especially the clinicians, as late as 1927, when Shapiro (76), in a careful study demonstrated that there is no relation between adrenal function and hypertension. Since that date, there has been little if any interest in Vaquez's theory, and the present consensus of opinion is that hyperadrenalemia, if there be such a condition, is not a factor in the production of hypertension.

INCREASE IN POTASSIUM - CALCIUM RATIO. Since the work of Jacques Loeb, Ringer, and Mathews on the biologic effects of various salt solutions and the antagonistic action mutually exerted by many of them, there has been considerable interest and investigation in the physiologic properties of the various salts. It has long been known that potassium salts exert a vagotonic action upon cardiac muscle and that calcium salts exert an exactly opposite action. This relationship of antagonism between potassium and calcium ions has been further demonstrated in perfusions of denervated salivary glands and other organs controlled by the vegetative nervous system. That these salts are necessary for normal function has been shown in the heart by demonstrating that potassium ions must be present in the heart for bradycardia to follow stimulation of the vagi nerves. The significance of these facts was

early recognized, and various attempts were made to apply the theory of antagonistic salt action to the problem of renal hypertension. Mathison (77) was able to produce an increase in tension by intra-arterial injection of potassium salts and showed their action to be antagonized by calcium salts. Mathison drew no conclusions from his observations, but Kylin (78) later proposed that potassium ions were increased and calcium ions decreased, - this change in potassium-calcium ratio causing a disturbance of the vegetative nervous system with resultant increase in peripheral vascular resistance. A similar theory was advanced by Reid (79), who suggested that a lack of calcium ions in the blood stream lessened vagal inhibition with the result that the pressor action of metabolites was then manifested. These views, however, received but little support from subsequent investigators. Stieglitz (80), in a study of the hypertensive conditions found in pregnancy, concluded that hypocalcemia was not an etiological factor in the production of arterial hypertension in pregnancy. In a careful study of seventy-five cases, Weinstein and Weiss (81) concluded that changes in the potassium-calcium ratio could not be considered as playing a fundamental role in the production of hypertension, such changes as did occur being a result rather than a cause. Further evidence opposing these theories may be found in reviewing the physiological actions of these salts. Potassium produces slowing of the heart whereas calcium increases the heart rate. In their effects elsewhere in the body, potassium salts are usually

vagotonic and calcium salts sympathotonic. Thus, by analogy, the effect of potassium on the blood vessels would be expected to be vagotonic, or dilating, and the action of calcium to be sympathotonic, or constricting. At the present time changes in the potassium - calcium ratio are not generally considered to be of etiological significance in the hypertension associated with chronic nephritis.

SODIUM CHLORIDE. For many years, clinicians have treated cases of chronic nephritis and hypertension with a salt-free diet. The results of this type of treatment have been fairly satisfactory, edema being controlled and the arterial tension checked to a greater or less degree. From these clinical results, Allen (82) has advanced the hypothesis that the pathological effects of chronic nephritis, including hypertension, are due to the osmotic influence or chemical stimulation of sodium chloride, following a primary infection or toxic injury. Mosenthal and Short (83), however, were unable to find any definite evidence in the literature that sodium chloride raises blood pressure. They also demonstrated that ingestion of ten grams of sodium chloride failed to raise the blood pressure in cases of hypertension. In view of this evidence, it seems improbable that increased arterial tension is related in any way to the salt content of the blood.

EXCESSIVE PROTEIN INTAKE. Another factor suggested by clini-

cal practices is that of excessive protein intake. It was formerly believed that this would produce hypertension, and many physicians still greatly limit the protein intake of patients suffering from chronic nephritis or even essential hypertension. The relations of plasma proteins and edema have been of considerable interest in recent years to many investigators, especially Krogh, Iversen and Nakagawa, Seiter, and Gorter, and it is through the work of these men that the osmotic influences of the plasma proteins have been demonstrated. It is now generally believed that loss of plasma proteins in renal disease, and also in other conditions such as malnutrition, is the cause of edema. Since the general acceptance of this concept, nephritic patients are no longer deprived of an adequate protein intake, but are given normal or slightly greater amounts of protein in their diets. The clinical results are justification of this explanation of edema, and in addition, no untoward effects are noted in regard to blood pressure. Further evidence that the earlier view of excessive protein intake producing hypertension is fallacious, is added by Mosenthal and Short (83) and by Strause and Kelman (84), who have shown that there is no relation between protein feeding and hypertension.

CHOLESTEROL. One of the more recent theories which has received considerable attention is that of hypercholesteremia. This substance was suggested as the pressor substance causing hypertension by Schmidtman (85)

in 1922, who observed a temporary rise in blood pressure in rabbits following prolonged cholesterol feeding. Following this lead, Westphal (86)(87), who noted that the blood pressure in experimental animals and also in man increased as did the serum cholesterol, postulated that cholesterol sensitized the muscular coats of the blood vessels which thereupon responded with increased contraction to substances in the blood serum. Further experiments on this problem were performed by Thomas (88), who found that the action of cholesterol was not immediate, but that it would produce a hypertension after repeated injections. This viewpoint was favored by many European investigators, especially the Germans, but the English and Americans were unable to confirm their results. Shapiro (76), Weiss (89), and Weinstein and Weiss (81) after careful studies concluded that there was no relation between cholesterol and hypertension. Additional evidence opposing Westphal's theory is brought forth by Harris and Lipkin (90), who find that there is no evidence that cholesterol increases blood pressure. Most investigators are now of the opinion that cholesterol bears no etiological relationship to hypertension, and that in cases of hypertension with increased serum cholesterol, the cholesteremia is the result rather than the cause of the hypertension.

GUANIDINE. Another substance believed by many to be a cause of hypertension is guanidine, proposed by Major (91)(92)(93)(94)(95) and his coworkers. He bases his view upon the experimental production

of hypertension in animals by injection of various guanidine compounds and upon the isolation of what he believes to be guanidine from the urine of hypertensives. Guanidine, however, has never been isolated from the blood, although Major has found a substance in the blood of hypertensives which gives the same color reactions as does guanidine. He also admits inability to decide whether there is an increased production of guanidine bases due to an error of metabolism or due to their faulty excretion by a damaged kidney. White (96) in 1927 demonstrated that the method used by Major in determining the guanidine in the urine was faulty, having obtained only considerable amounts of creatinine potassium picrate which Major mistook for dimethylguanidine picrate. He therefore concluded that there is no satisfactory chemical evidence connecting hypertension with the retention of guanidine bases. Since the appearance of this criticism of Major's work, there has been apparently no further interest in the possibility of guanidine bases as the factors initiating the pressor mechanism in hypertension. Major, himself, has apparently abandoned this viewpoint, for since 1927, he has reported no further work on the subject.

PEPTONE. Following up the work of Vaquez (64) and others on hyperadrenalemia, some German investigators, especially the students of Volhard, proposed a theory that a peptone present in the serum of nephritics sensitized the peripheral sympathetic nervous system to the action

of epinephrine with resultant vasoconstriction and increase in arterial pressure. Kato and Watanabe (97) had shown that the serum from chronic nephritics sensitized the peripheral sympathetic fibers in animals to the action of epinephrine in direct ratio to the height of the blood pressure in the patients supplying the serum. Hülse (98) showed that hypertension was not due to hyperadrenalemia and also demonstrated that nephritic serum augmented the effect of adrenalin. Later Hülse and Franke (99) proposed cholamine as the pressor substance, having demonstrated that cholamine chlorhydrate injected intravenously into curarized cats produced a sustained and marked rise in blood pressure. A similar view is held by Bohn (100) who was able to produce a rise in blood pressure in cats by the injection of alcoholic extracts of the blood of patients with chronic nephritis. Extracts of the blood of patients with normal blood pressure and of patients with essential hypertension exhibited no pressor effects. Bohn believes this substance has a peripheral action, for section of the cervical cord of the experimental animals had no effect on the rise in blood pressure, but he also stated that nothing is known of the chemical nature of this pressor substance. As in the case of cholesterol as the pressor substance, the English and American investigators were unable to confirm the results of the German workers. Page (101) was unable to confirm Hülse's theory, suggesting that Hülse's results were partially due to the fact that repeated injections of epinephrine normally increased the vascular response of anaesthetized animals. Jackson, Sherwood, and

Moore (102), investigating Hülse's results, concluded that there was no convincing evidence to show that the blood peptide nitrogen in hypertension rises sufficiently to be of etiological importance. Further opposition to the German theory is provided by Curtis, Moncrieff, and Wright (103) who were unable to find evidence of a pressor substance in the blood of patients with hypertension. There still remains, however, considerable doubt on this question, for Bohn's work has as yet to be confirmed or disproved.

SUMMARY

In this analysis of the problem of etiology of nephritic hypertension, the attempt is made to consider the more important theories with the evidence tending to confirm or disprove them. That one of the aforementioned concepts may be the correct one is still a possibility in spite of the rather overwhelming evidence against them all. The majority of investigators now favor a theory postulating a pressor substance circulating in the blood stream and producing a continued state of vasoconstriction with hypertension, although none has produced incontrovertible evidence supporting any one substance as the active factor. Very little emphasis has been laid on the possibility of physico-chemical changes in the blood producing vasoconstriction, such as the suggestion of Stieglitz (104) that changes in the acid-base equilibrium of the blood

due to renal injury may produce hypertension. This field of investigation has, perhaps, greater promise in the quest for the cause of hypertension than has been realized, but the future alone can show its value. The fact that hypertension is more often not produced by renal disease leads one to the idea that it may be caused by some factor unassociated with renal damage even in cases of chronic nephritis, the renal damage also being a result of the condition causing the hypertension. However, the consensus of opinion is that in at least 10% of all cases of hypertension renal damage is the causative factor. We have advanced no further in solving this problem in respect to positive results than Richard Bright, who said that the altered quality of the blood affected the peripheral vascular bed in such a way as to require greater action of the heart to force the blood through its subdivisions. His statement practically comprises the sum of our knowledge of this subject except for the many factors known to be of no etiological significance.

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