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Essential hypertension : an etiological survey

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ESSENTIAL HYPERTENSION

An Etiological Survey

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Introduction

Before discussing modern theories relating to the cause of Essential Hypertension, it is necessary to set up some sort of a definition of this disease process.

In 1836, Richard Bright (1), while listing cases of Glomerulo-Nephritis, says, "I have certainly seen one or two cases, and have read statements of one or two more, in which the condition would have lead me to suspect albuminous urine, but in which it had not been found to exist."

In 1836, he practically described the modern conception of Essential Hypertension, for outside of the fact that he classified the symptom complex in his group of kidney conditions, Bright knew almost as much about the disease as we do today.

At the present time we consider hypertension to be the first clinical sign of a symptom picture which causes twenty-three percent of all deaths in the white in the age group of fifty years or over. (2) (3) Ernstene (4) of the Mayo Clinic, says that Essential Hypertension is characterized by a continuous, though often variable elevation of blood pressure, in the absence of Glomerulo-

Nephritis and other conditions known to increase arterial tension. He believes that the term, after 100 years, must still be interpreted to mean a disease picture rather than a disease entity.

There are two types of Essential Hypertension. It makes no difference whether the classification of the disease be according to pathological or clinical findings, Essential Hypertension is either benign or malignant in type. There has been much discussion as to just where the benign form ends and the malignant begins, but roughly it can be said that a hypertension, without known etiology, beginning in the second decade or earlier, progressing rapidly and terminating in a very few years, is of the malignant type. In the same manner, a hypertension beginning in the third or fourth decade, progressing slowly with frequent remissions, and terminating fatally in the age group of 50 to 80 years is the benign form of the disease. (5)

A study of the history of hypertension shows how the modern view has been built up.

The greatest difficulty in obtaining a clear view of the clinical picture of Essential Hypertension has arisen because of the tendency of medical and re-

search men to tie all types of hypertension together with renal pathology. Bright, in his original article, cites the "full hard pulse" of a typical glomerulonephritic patient.

Samuel Wicks (6), in 1851, voiced the opinion of the men of his time when he said, "There is a possibility that renal disease may exist without albuminuria."

He referred to what he called cases of Chronic Bright's disease.

The first element of doubt of the renal origin of the disease arose in 1872 when Gull and Sutton (7), working together, called attention to the frequent occurence of death by ingranescent apoplexy at the age of 45 to 50 years, and the fact that in many of these cases the kidneys were unaffected. They believed that the renal involvement was just a part of the general change and that necrosis in the epithelium of the kidney was secondary to the changes in and around the blood vessels.

Mahomed (1879) (8), built the first clinical picture of Chronic Bright's disease and its essential

symptoms. He said that albuminuria and edema are absent, that arterial pressure is first increased, and that there are late symptoms, arising insidiously of either heart, cerebral, or renal disease. He reported 61 cases of chronic kidney disease that did not show albuminuria and concluded that if high blood pressure can produce arterial and cardiac changes in the presence of renal disease there should be no reason why the arterial and cardiac changes cannot be produced by hypertension alone, without renal involvement. (9)

In 1893, von Basch (10) introduced the sphygmomanometer into clinical medicine and with its use described what he called a "latent angio-sclerosis." (11) This term, as well as Gull and Sutton's arterio-fibrosis and Essential Hypertension evidently mean the same thing.

Allbutt (1895) (10) (11), marked another milestone in clearing up this confusing problem when he noted varying degrees of severity of this process, which, he said, was characterized by changes in the small vessels. A possibility of a malignant form of the disease had not been considered until this time.

Between the years of 1895 and 1914 very little significant work was done. In 1914, however, Fahr and Volhard (12) classified and differentiated benign and malignant hypertension pathologically, basing their classification on kidney change. The malignant form showed productive endarteritis and necrotizing arteriolitis in the kidney. In the benign form the kidneys showed only arterial and arteriolar sclerosis.

Their work has been taken exception to many times since, chiefly because there are too many other kidney conditions that can present the same picture.(12)

From a clinician's viewpoint, the work done by Keith, Wagener and Kernohan (1924) (13) (14) is much more significant. They defined malignant hypertension as a clinical entity and classified it as a symptom complex characterized by: sustained high blood pressure, neuro-retinitis, and a short course, varying from one to five years after the onset of severe hypertensive symptoms.

It can be seen from the preceding paragraphs that the modern tendency has been to veer away from a potential renal background, as a possible cause of Essential Hypertension. It may be that the kidney is the

cause. It may be that the cause lies in some malfunction of another organ of the body. Today, the medical and research men are more or less open-minded concerning the etiology of this disease process. The accepted theory is that the primary high blood pressure is a representation of an arteriolar spasm and that the spasm persists as long as the initiating factor acts. Later in the process, however, secondary changes in the arterioles, such as hyalinization and hypertrophy of the walls make a continuous hypertensive state. (15) (16) (17) Although the afferent glomerular arterioles are the ones most deeply involved, it is the belief today that this is a result of the great amount of blood passing through them at a consistent high pressure. (18)

At any rate, it is the purpose of this paper to present a view of the potential etiological factors of this disease, and to give what evidence there is for and against each.

The Kidneys and Essential Hypertension

Since the time of Bright, the kidney has been suspected to be the cause of all types of hypertension, whether or not renal pathology could be shown clinically.

In 1856, Traube (19) postulated that arterial pressure was elevated in cases of disease of the kidneys to overcome mechanical resistance against blood-flow, thus compensating for abnormal resistance and maintaining the efficiency of the kidneys as excretory organs. With this statement Traube opened up several possibilities.

There is a possibility that the kidney influences the blood pressure by means of a reflex mechanism. Another possibility is that the damaged kidney elaborates pressor substances or hormones which act directly on the blood pathways. Of course, there is always a possibility that the waste products, backed up in the blood stream by non-acting kidneys, might influence the pressure of the blood throughout the body.

Traube's original postulation often has been disproved since 1856. Just recently Page (19) compared the renal efficiency of humans during periods of high and low tension and found that the efficiency of the kidneys was not definitely altered in either case. Using the Urea Clearance Test of Moller, McIntyre and Van Slyke as a check of efficiency, Page noted that in patients suffering from Essential Hypertension the renal efficiency was not altered by a marked fall in blood

pressure. Inversely, he showed that the abnormal elevation of blood pressure in Essential Hypertension patients did not aid in kidney efficiency. It may be that in the cases studied there was enough permanent, though indemonstrable, kidney damage, so that the differences in blood pressure could effect no change.

In cases of Essential Hypertension it has been impossible to note loss of kidney efficiency either by urinanalysis or by blood analysis. In early cases of Essential Hypertension there is no albumin excreted in the urine. R. H. Major,(20) in 1928, checked the excretion of phenolsulfonephthalein and the blood chemistry in 330 cases of Essential Hypertension. Only a few of these cases showed a phenolsulfanephthalein excretion of less than 50% in two hours. The blood urea, non-protein-nitrogen, and creatinine were normal. He did find, that in 130 of the 330 cases there was a lessened excretion of creatinine. Keith and Wagener (13), as far back as 1924 noted no constant rise of blood urea, creatinine, uric acid, or chlorides in a survey of 14 cases of the disease. Their conclusion was that certain patients with high blood pressure showing a neuroretinitis, which, according to their own classification meant Malignant Hypertension, had little or no evidence

of renal insufficiency.

The proteins of the blood stream have also been examined as a possible etiological factor in this disease. Brundage, Cantarow, and Griffith (21) determined the amount of fibrinogen, globulin, albumin and total protein in normal and hypertensive subjects. They found that although in some cases the individual protein factors appeared to be slightly elevated, the total protein in the hypertensives was not. They attributed this variation to experimental error in measuring the separate protein classes.

Because Harris and McLaughlin (21), in 1930, demonstrated increased blood viscosity in thirty-five of forty hypertensives, Brundage and his co-workers tried to verify their results. They found, that instead of the blood viscosity being increased, it was decreased or normal in twenty-three cases of hypertension.

The most significant work, as far as the kidney is concerned has been done by those men who have produced renal hypertension on experimental animals.

Katzenstein (22), in 1905, opened the way by producing hypertension in rabbits with compression of the renal artery. Chanutin and Barksdale (27) in 1933 caused hypertension in rats by partial nephrectomy. This was confirmed by Wood and Ethridge (23) in the same year. Goldblatt (24) in 1934 perfected the silver clamp technique of compressing the renal artery and since that time,many tests and results have been run and recorded by means of this method. The definite results can be easily summed up. First, constriction of renal artery gives a permanent rise of blood pressure. Second, excision of one kidney does not give a blood pressure rise. Third, occlusion of one renal artery causes the blood pressure to rise. Fourth, occlusion or clamping of both renal arteries causes uremia and death. Fifth, partial removal of both kidneys results in a rise of blood pressure. (25)

This work has been confirmed by innumerable men, all of whom seem to agree that renal ischemia, or degenerate renal tissue, could build the set-up for a hypertension. (25) (26) The question which remains unanswered is whether or not there is any renal ischemia in Essential Hypertension, and whether or not there can be renal change without demonstrable renal pathology.

It is the belief of De Wesselow and Oxon (28) that there is no renal defect early in Essential Hypertension and that the old theory of increased renal vessel resistance setting up a high blood pressure demand is incompatible with common sense because there is a relatively small area involved. Goldblatt (25) himself, although believing the kidney to play some part in the Essential Hypertension picture, does not think mechanical resistance, set up by clamping the renal artery, is the cause of the experimental hypertension. He lists the work of Longcope and McClintock in 1910, which demonstrated that the constriction of either the splenic, the femoral, or the superior mesenteric artery has no effect on blood pressure.

Because of the fact that many of the men who produced hypertension believed there was a pressor substance elaborated by an ischemic kidney, Mason, Evers and Blalock(29)attempted to measure the difference in oxygen tension in a normal kidney and one in which renal arteries had been constricted. However, they were not able to show any change in renal arterio-venous oxygen tension in a kidney with a constricted artery. Again, it must be remembered that the venous blood in an organ as active as the kidney would demonstrate little oxygen

content in any case.

Harrison, Mason, Resnik and Rainey (23) (1936) attempted to prove that the high blood pressure in experimental animals was produced by substances retained by damaged kidneys. They did bilateral nephrectomies on eight animals first. In these they could find no blood pressure rise in six of the eight. Then they did bilateral ureteral ligations on thirteen dogs and showed a blood pressure rise in all of them. From this set of data they concluded that malfunctioning renal tissue produced the blood pressure elevation.. They thought that the retention of substances by ureteral block caused renal damage, thus setting up a hypertension rather than setting up the increased tension directly.

almost

About the only conclusions that can be drawn from this experiemntal work are that the kidneys when damaged by infection or otherwise cause an increased blood pressure, but even today, just as one hundred years ago, the initiating factor is unknown.

The Nervous System and Essential Hypertension

In 1851, Claude Bernard (30) discovered that certain nerves caused constrictions of the peripheral blood vessels. The significance of these nerves was not considered until 1903 when Josue (31) thought that the adrenal glands might have something to do with hypertension. Friedman and Eisenberg (33) reported seven cases of Essential and Malignant Hypertension in which two of the patients died from adrenalin insufficiency. The significance of this finding arises from the fact that the suprarenal glands, as far as we know, are innervated by the sympathetic nervous system.

In 1913, George Crile (34) of the Cleveland Clinic, performed a unilateral adrenalectomy for high blood pressure. The result was rather disappointing. He noted a temporary fall in blood pressure with a subsequent rise back to and above the preoperative level. Crile at present believes that denervation of the adrenals helps only young subjects with hypertension, and then only for a duration of two to three years.

The possibilities of a complete sympathectomy were discovered with the introduction of spinal anaesthesia, which causes a sudden drop in the blood pres -

sure. The object of these sympathectomies has been to eliminate vaso-constrictor stimuli to certain parts of the arterial tree. (35) Results of these operations performed on a large scale during the last ten years have been more or less variable.

In 1931 Bradford and Cannon (36) extirpated the complete splanchnic sympathetic system in several stage operations and noted an immediate fall of tension after each stage of surgery. But there was a progressive return to normal. This work was confirmed by Bacq, Brouha and Hymans (37) in 1934. Since this time, sympathetic extirpation has been done on a large scale in cases of Essential Hypertension with the same results.

In 1936, Bisgard and Sharpe (38) of the University of Nebraska reported one case of a fifteen year old white school girl having a blood pressure of 230/140, in which they excised the tenth, eleventh and twelfth sympathetic ganglia and segments of the lesser and greater splanchnic-nerves on both sides. They noted at the end of the first year a permanent blood pressure level of 145/85.

The kidneys of this patient, which had previously shown some loss of function, returned to their earlier

functional state.

In 1937, Page and Heuer (39) reported seventeen cases of Essential Hypertension, treated by sections of the anterior nerve roots. Of these seventeen cases ten showed marked improvement in both blood pressure reading and symptomatology. In three others the symptoms alone disappeared, two died, and two showed no improvement.

Compare these seemingly excellent results with the majority of cases treated by sympathectomy. Crile (34) in 1936 reported 106 cases in which he denervated the adrenals and extended the operative procedure to include a resection of the major, minor, and lesser splanchnic nerves. In these cases only a few of the subjective symptoms were relieved. Allen and Adson (40) reported forty-five cases operated by subdiaphragmatic sympathectomies. The results were very poor.

Theorizing that there must be some effect on the nerves of the arterial tree by a hormone called sympathin, Crile extended the operative procedure, resecting the celiac ganglion, denervating the aorta and thus breaking up the sympathetic complex. During the operation the blood pressure of malignant hypertension was

reduced to normal, and, although it rose within a month following surgery, the pressure showed more stability and did not progress as rapidly as it did preceding operation.

In 1934, Goldblatt (41) found that by clamping the renal artery of rabbits and producing a partial ischemia in the kidneys, he could produce uniformly high blood pressure in these animals.

Page (42) in the same year confirmed his work in dogs and attempted to reduce this pressure by stripping the renal pedicle of its extrinsic nerve supply. He found that this did not reduce the pressure and thus these nerves did not appear to play a part in the genesis of renal hypertension. Freeman and Page (43) reaffirmed this work in 1937.

Goldblatt, Gross and Hansel (44) in 1937 attempted to show the effect of resection of splanchnic nerves of animals in which they had produced this experimental renal hypertension. They first clamped the renal artery. The blood pressure of the animals rose as expected and remained at a permanent level. They waited four years and did the complete splanchnectomy on all of these animals. Their results showed no permanent drop

in blood pressure.

The significance of these results is doubtful. It depends entirely on the fact that experimental renal hypertension stimulates the picture of essential high blood pressure, and not on the fact that it is essential high blood pressure.

The problem confronting the modern physician in the use of the surgical treatment of Essential Hypertension still remains prectically the same. Is peripheral resistance generalized throughout the body, or is it confined to the splanchnic system? (45) To what extent are vessels responsible for the increased peripheral resistance? Are they capable of dilatation, and what part does the vasomotor system play in the picture?

Longcope and McClintock (47) in 1910 obtained transitory elevation of blood pressure by sudden occlusion of splanchnic vessels. Princemetal and Wilson (46) in 1936 seemed to have progressed no further. They say that it appears that the arterial lesions in high blood pressure are most severe in the splanchnic area but that there seems to be no constant relationship. Basing an experiment on Poiseulle's law which states that the blood flow in any cross section of the vascular bed per

a given unit of time is directly proportional to the pressure and inversely proportional to resistance, they compared the blood flow and blood pressure in the arms of hypertensive and normal individuals. They found that the blood flow per unit of time was approximately the same in cases of both benign hypertension and normal blood pressure. However, in Malignant Hypertension and in secondary hypertension the blood flow was diminished.

Normal --- 1.65 cc/100 cc arm vol. per min.
Benign H.B.P. - 1.7 cc " " " "
Malignant H.B.P. 1.5 cc " " " "
Secondary H.B.P. 1.3 cc " " " "

They continued their experiments to find out to what extent the blood vessels of high blood pressure patients were capable of dilatation. Their results showed that in all forms of hypertension the blood vessels of the arm are capable of considerable dilatation, sufficient, in fact, to cause an increase in blood flow equal to that of normal individuals. Thus, it may be supposed that increased vascular resistance in early Essential Hypertension is not due to organic changes in the vessel walls. The fact remains, however, that hypertensive patients still exhibit greater peripheral resistance during exacerbations of the disease.

They also attempted to show the relation of the vasomotor nerves to hypertension. Upon the basis that vascular dilatation produced by heat is vasomotor in origin, they showed that in subjects with high blood pressure, the heat test produced no greater increase in blood flow than in normal individuals. This, of course, suggests that vascular hypertonis is not vasomotor in origin.

It can be seen from the surgical procedures and experiments listed that there can be no definite conclusions drawn as to the part the vasomotor system plays in Essential Hypertension. Although there does seem to be some transitory phase in the surgical procedure which causes a drop in blood pressure, there must be some complicating circumstances which we have not yet discovered.

There are some men today who insist that the cause of Essential Hypertension can be found in the general nervous make-up of individuals.(48) Some men refer to young people with vasomotor instability who show marked variations in blood pressure at a very early age. (50) (49) They believe that this type of individual, if not adequately controlled from a psychiatric standpoint, will

develop a full grown Essential Hypertension a little later in life.

Tolubejewa (51) lists three cases of individuals with high blood pressure that gradually dropped to normal over a period of months to years.

Palmer (52) of Massachusetts lists nervousness, varying from a feeling of inner tension to nervous breakdowns, as one of the prominent etiological factors of Essential Hypertension. It is his theory that the disease results from a constitutional susceptibility and the added strains of daily life. He suggests the possibility of a highly nervous individual developing a conditional reflex which will give him a permanent increased arteriolar tone.

He says, "The tone of arterioles are controlled chiefly by impulses conveyed by the sympathetic nervous system from the vasomotor center in the medulla, which in turn receives a constant stream of sensory impulses from the periphery. Finally, the reflex is modified or excited by influences from higher centers."

He states that at the onset of physical activity or of great emotional stress the reservoir above the

arterioles is reflexly increased either by a combination of arteriolar constriction and increased cardiac output or by maintained tone of arterioles with an increase in head of pressure.

Palmer and Thorpe (53) together, in a study of fifty-seven cases all under thirty-six years of age, found that the largest number of this group responded to rest and sedation. He concludes that the greater number of cases of Essential Hypertension under the age of thirty-six are really cases of vasomotor instability. It would be interesting to hear his conclusions regarding a large group of malignant hypertensives dying before the age of forty-five.

On the other hand, Gottlieb (54), in 1936, tested fifty-one cases of dementia praecox and found that their blood pressure was lower than normal, and that they had a static vascular bed. It was his conclusion that this failure of dilatation in the Schizo-phrenic was due to an unresponsiveness of the sympathetic nervous system, controlled reflexly by the higher centers.

Since the Schizo-phrenic has abnormal emotional reactions this would be expected.

Crisler and Allen (55) note a Flushing syndrome simulating diencephalic stimulation. This syndrome affects young women with hypertension and causes regional flushing, palpitation, perspiration over flushed areas, techychardia, salivation, slowing and deepening of the respiratory rate, and increase in the respiratory movement. This syndrome is supposedly brought on by severe emotional stress.

They concluded that either the diencephalon, or centers situated elsewhere in the central nervous system, may be unusually irritable to sub-threshold stimuli, or that the inhibitory threshold may be raised, or that the irritability of the peripheral effectors is increased.

As far back as 1934, Leiter, Lewis and Grinker (56) were unable to distinguish between tracings of blood pressure in cortical, hypothalamic, or diencephalic stimulation. The obvious conclusion that may be drawn from this experiment is that if there be a higher vasomotor center it is still unknown to us. There may be such a center.

Before drawing any conclusions regarding the part the vasomotor system or any part of the general

nervous system plays in Essential Hypertension, it must be remembered that there could be intrinsic nerves in the blood vessels having their own particular threshold to stimuli. And it must be remembered that the nervous system may be a cause of a part of the cases now diagnosed as Essential Hypertension.

Thus, about all we can say regarding the part that the nervous sustem, vasomotor or otherwise, plays in this disease picture is that it does have effect on the blood pressure under certain conditions.

The Endocrines and Essential Hypertension

The three endocrines most commonly associated with hypertension are the adrenal, the pituitary and the thyroid glands. The possibility that they might cause Essential Hypertension is very slight, yet, because they do under certain conditions cause a rise in blood pressure they must be considered.

Neusser (57),in 1898, advanced the theory that excess adrenalin was responsible for hypertension. Hirsch and Thorspecken (58), in 1912, produced hypertension, experimentally, by repeated injections of adrenalin and demonstrated calcareous infiltrations in the blood ves-

sel walls. Wolf (59), in 1936, suggested that hypertension was due to arteriolar spasm throughout a large area and thought that Essential Hypertension was secondary to hyperactivity of the adrenal medulla.

Basing their work on these ideas, Friedman and Eisenberg (33) (1937) attempted partial bilateral adrenalectomy on seven patients with Malignant Hypertension. In four of these cases they noted a drop in tension that remained present for a period varying from one to two years. Two of their patients died of adrenal insufficiency, and one went the way many hypertensives do, dying of cerebral hemorrhage.

Beer, King and Prinzmetal (60) also report a case of elevated blood pressure, in which they demonstrated excess adrenalin in the blood stream pre-operatively. However, on operation, they found a paragangliomata of the adrenal gland. Removal of the gland did give complete relief of the symptoms.

The problem of Essential Hypertension would be simple if the physicians of today could point to any specific gland such as the adrenal, and say that there is the cause of Essential Hypertension. But about all the modern physiologists say is that by its secretion

it elevates blood pressure in times of hyperactivity.(61)

The pituitary gland also falls into the category of suspicious characters, because it, too, has been shown to cause a rise in blood pressure under certain pathological conditions. Berblinger (62) and Hoppler (63), in 1921, concluded that there was a definite increase in anterior lobe basophilic cells in renal disease but could find no cause. Cushing (64), in 1932, cites hypertension as one of the cardinal features in the classical picture of basophilic adenoma. In 1934, he stated that this hypertension resulted from basophilic extension into the posterior lobe of the gland. Biggart (65), however, said that posterior lobe invasion may occur without hypertension.

Because Cushing's work shows that basophilic overgrowth does cause hypertension,it does seem logical to believe that basophilic hyperplasia great enough to cause extension to the posterior lobe would cause hypertension.

In 1934, Kylin (67) demonstrated a remarkable amount of parallelism between the amount of gonadotropic hormone, excreted in the urine, and the amount of increased blood pressure.

Scharf and Israel (68) studied twelve cases of Essential Hypertension in an attempt to confirm Kylin's work. Because they knew that Essential Hypertension often manifests itself during the menopause when there is an increased amount of Prolan A in the urine, and because the sugar tolerance curve of the Essential Hypertensive is identical with that found in certain types of hyper-pituitaryism, notably Acromegaly, they thought it possible that the relationship might be constant. Their results did not confirm the work of Kylin.

The only experimental work done to show the relationship between experimental hypertension and the pituitary was done by Page (69) in 1936. He showed that in dogs, hypophysectomy does not prevent the development of hypertension produced by clamping of the renal artery.

Thyroid disease, also, has been commonly associated with hypertension. Plummer (70) (1915) felt that long continued thyrotoxicosis might lead to hypertension. Jones, Seabrook and Menne (71) (1932) reported a blood pressure rise in all of 835 cases of thyroid disease. Parkinson and Hoyle (72) (1934) reported a blood pressure of over 160, systolic, in one-hundred patients with long standing thyroid disease.

It is an interesting fact that although hypertension and thyroid disease are commonly associated there are very few men who will say that thyroid is the cause of Essential Hypertension. The general belief is that thyrotoxicosis might cause high blood pressure, and that in these cases thyroidectomy will relieve the symptom. (73) However, in those cases in which thyroid removal does not drop the pressure, as in a series of cases reported by Hurxthal (74) (1931), the thyroid disease is associated with Essential Hypertension. It may be that many cases of thyroid disease are mis-diagnosed, merely because of the blood pressure readings.

Pressor Substances and Essential Hypertension

It is a little hard to define just what is meant by pressor substances when speaking of them in the terms of the human body. In a broad classification, pressor substances might be any substances that cause an increased blood pressure by acting either on the blood vessels, on the heart, on the nervous centers, or on any part of the physiological set-up that controls blood pressure.

Such a broad classification would include the hormones elaborated by the endocrine glands and certain drugs, which by their stimulatory action raise the tension of the vessels and stimulate heart action. Because, as has been shown, the action of the endocrines and of those substances backed up in the blood stream by a non-functioning kidney have no constant action in Essential Hypertension, further consideration is not necessary.

However, the possibility that the blood stream may carry some substances of unknown origin or chemistry, or some substances that are mal-metabolized or in abnormal ratio has also been considered by experimental and clinical men.

Shattock (75), in 1908, demonstrated atherosclerosis in the mummy of King Menephtah, and Ruffer (76) in 1911, observed the mummies of the eighteenth to twenty-seventh Egyptian dynasties and proved the plaques in the blood vessel walls to be made up mainly of cholesterol.

Pribam and Klein (77) (1924) said that eighty-seven patients with high blood pressure had hypercholesteremia. Weil, Guillamis, and Abricoff (78) (1928) confirmed this work. Alvarez and Neuschloss (79) (1931)

found that hypertensive blood was saturated with cholesterol.

As far back as 1926, Westphal (80) advanced the theory that hypercholesteremia resulted in cholesterol deposition in the smooth musculature of the arterioles so that they cannot relax spontaneously. Being a "hydrophobe substance" cholesterin is supposed to condense the superficial layer of the smooth musculature, diminishing its permeability and preventing the action of certain ions in the blood steam.

Leary (1935) (81) takes a different view of the subject. He implies that pathological cholesterol causes hypertension, but not by its effect of lessening the elasticity of the walls. Instead, he believes it to have a direct effect on the vessel.

Damrau, (83) treated eight patients of Essential Hypertension with iodine, merely because he believed that Leary's ideas were sound. His results coincide with those of about any clinical man who treats hypertension in this way. That is, some of the patients were relieved of their symptoms, but in the majority of cases the blood pressure drop was slight, and if marked, subject to remissions and the usual progression.

If we are to take these findings seriously, the evidence points toward cholesterol as one of the factors causing hypertension. However, the pathological findings of typical cases of Malignant Hypertensives coming to autopsy do not show cholesterol depositions in the arteriolar walls, nor does a typical case of early Essential Hypertension show hypercholesteremia. In other words, atherosclerosis is not arteriolar sclerosis. (84)'

Certain electrolytes in the blood stream might possibly play some part in the etiological picture of Essential Hypertension. Apperly and Cary (85) (1937) checked the chloride content of the blood of Essential Hypertensives. They found that the chloride content in the blood plasma of hypertensives was normal but that the red cell content was fourteen percent higher. There was no significant difference between the blood pH or the erythrocyte volume index. About all that can be said concerning this work is that if confirmed, it may lead to more extensive research along the same lines. As yet no conclusions may be drawn.

Another group of men (86) (1936) tried injecting certain electrolytes into the cisterna magna and noting their effect on blood pressure. Their results

showed that the potassium ion as well as certain anions, notably phophates, oxylates and citrates, caused increased blood pressure, but that they were all antagonized by the calcium ion. Again, this work has not been confirmed, and its significance is lessened by the fact that the blood chemistry picture in Essential Hypertension is, as far as we know, within normal limits.

Now let us consider the more obscure pressor substances that might act in Essential Hypertension.

Since 1911, men have been trying to show that the blood of Essential Hypertensives contained some element that might so affect the arterioles that there would be a generalized vaso-constriction.

In that year, Stewart (87) could not demonstrate vaso-constricting elements in the blood stream of hypertensives. In 1931 and in 1933 Bohn (88) demonstrated and checked the fact that alcoholic extracts from the blood of malignant hypertensives caused a rise in tension of from ten to twenty millimenters when injected into cats. Marx and Hefke (89) checked the work and obtained the same results with the blood of epileptics.

In 1936 and 1937 there have been several attempts to demonstrate the pressor effect of hypertensive blood in transfusion experiments. (90-91-92-93) The general result has been that hypertensive blood produces no greater rise of blood pressure than normal blood. Consider, however, the great element of variation in such an experiment. Reduced blood volume, the state of shock, and the possibility of sustained hemorrhage all tend to reduce the worth of this type of experiment.

Brown and Dodds (94) (1936) checked the blood pressures on three babies born of pre-eclamptic mothers. Each of the mothers had a pressure of two-hundred systolic and one-hundred and ten diastolic. The babies' pressures were never above normal limits. This would appear as if either there were no pressor substances carried in the mother's blood stream, or that the babies excreted such substances as fast as they received them.

Prinzmetal and Friedman (95) (1936), turning back to the old possibility that kidneys, when damaged, may produce pressor substances, extracted all the possible combinations from patients who had died of Essential Hypertension and injected them into dogs. They found that the average rise was twenty-eight millimeters

of mercury as against twelve millimeters from the control extracts. There seemed to be no correlation between the amount of renal damage and the rise in pressure. Considering the fact that a mere partial clamping of the renal artery will cause hypertension, the lack of correlation is not significant. The picture is not as yet completely explored.

Major and Weber (96) (1927) noted the presence of an excess amount of guanidine in the blood stream of hypertensives, but,here too, there was no relationship between the amount of guanidine and the height of blood pressure. He confirmed this work in 1932.

It seems very possible that there may be pressor substances elaborated somewhere in the body that might work together with other factors to cause Essential Hypertension.

Depressor Substances

In 1928 Frey and Kraut (97) prepared an insulin free extract of the pancreas with which they produced a transitory fall in blood pressure in rabbits. They also used this substance to antagonize the pressor effect of adrenalin. Because of the fact that it did

not produce a fall in blood pressure, they theorized that the blood stream of normal individuals might carry a definite amount of this substance as a stabilizer of blood pressure. They thought that it was elaborated by the pancreas as needed by the human body.

In 1934, Elliot and Nuzum (98-99) extracted this substance from the urine and attempted to show that there was a lessened excretion of this substance in Essential Hypertension. They found that in fifty cases of elevated blood pressure the excretion of the substance called Kallikrein was less than that of normal individuals.

In 1937, Nuzum, Elliot and Bischoff (100) in reviewing nine patients, showed that the daily urinary output of Kallikrein was not changed by medical treatment which lowered the blood pressure. However, they found that Kallikrein was in low concentration in the urine of young hypertensives.

Because of the similarity of this substance to acetyl choline, Page (101) attempted to treat hypertensive patients with the drug Acetyl-beta-methyl choline. He found in one case only that the blood pressure dropped from 210/140 to 96/70, but that the toxicity of the drug

was so great that vomiting and other evidences of choline poisoning immediately set in. The blood pressure drop was accompanied by flush, slow deep respiration, sweating, and salivation, typical of the Flushing syndrome occuring in hypertensive crises.

In 1936, Hunt and Renshaw (102) demonstrated the effect of choline ethers as opposed to the ethers of methyl choline, and found that while acetyl choline gave a marked drop in blood pressure, the phenyl ether gave a marked rise in blood pressure. No significant conclusions can be drawn from these results.

Constitutional Factors and Heredity

Constitutional factors in many cases mean the background, the foundation on which any disease process is built. In Essential Hypertension, as in other diseases of known or unknown origin, the peculiar susceptibilities of the individual mean much, sometimes too much, to the clinician in etiology, diagnosis and prognosis of the disease process.

Along the same line of thought, the transmission of these susceptible characteristics,also play a large part in the knowledge of any potential pathology involving the human body.

These factors naturally fall into two classes, those visible to the eye, and those not observed by the examiner. Of the first group, the height, weight, and general build of the person are the more concrete evidence of his type. The more abstract are those factors concerned with the individuals general reaction to environment. Of the latter group, the physiological phenomen, the actions of the various organs, the internal structure, all of which are as much constitutional factors as those of the external form, are the most important.

Obesity has always been considered as a contributing cause in Essential Hypertension. It is the contention of nearly every physician that a high blood pressure patient must reduce in weight. There are two reasons for this. One is that the heart, placed under a severe burden in order to maintain the high tension must work harder to maintain the high pressure throughout a larger area of blood vessels. The other reason is that many believe that obesity may be the cause of the hypertension. The reason for this is, I believe, obvious. A practicing physician, unless picking up the hypertension during a routine physical examination, or sees a Malignant Hypertension in which the symptoms set

in early, never sees a hypertensive individual until severe cardiac, renal, or cerebral signs have occured. And these usually do not occur until the individual has passed the climacteric stage when the change in the endocrine set-up allows the person to become more or less obese. (103)

Of course there are other possible reasons why obesity may occur with Essential Hypertension. Obesity may be associated with Essential Hypertension because of the stimulating effect of the sympathetic-adrenal system on carbohydrate metabolism, or because of underlying endocrine disturbances which in themselves have been suspected of causing high blood pressure. (53)

There are many arguments today over what type of person is susceptible to the disease. Bauer (104) and Braun (105) say that there is no particular type.

Fossier (106) says that the tall, thin, hypertonic individual is the hypotensive type, and inversely, that the square, blocky type of individual is the hypertensive type.

Kylin (107) believes that the asthenic individual is apt to show either hypotension or hypertension,

both phenomenon being variations of the same disease. It is interesting to note that the Chinese are, almost without exception, asthenic individuals, yet high blood pressure in the people of this race is very rare. (108)

Before attempting to state definitely what type of individual may have a hypertension, note that the cases listed throughout this paper have shown no specific qualities as to build.

There is, supposedly, a greater prevalence of high blood pressure in the American negro than in the average American white man. To date, there have been no listed cases of Essential Hypertension in the African negro. (109) This opens up quite a realm of theoretical possibilities. It would seem, superficially, that either the type of life, the type of climate, or the type of food in this country as compared with tropical Africa might have some effect on the elevation of blood pressure. Yet the Eskimo, who lives in a cold climate and eats a high protein diet, shows no tendency toward hypertension. Of one-hundred and forty-two adults studied in Greeland, the average blood pressure was 129/76 - far from a hypertensive pressure. (110)

What about the psychic possibilities of the change in the form of living in a race such as the negro? Transported from Africa, and in some places with very little intermingling of the races, the tendency toward hypertension has become, as listed, greatly increased.

The possibilities of systemic changes in hypertensive types have also been investigated. The onset of hypertension in males supposedly occurs in much younger age group than in females. Barach (111) says that this is due to the different psychic and physical pictures after the puberty ages. The males, from adolescence to middle life, show an effort syndrome. It is Barach's belief that the reaction of the male to life is the result of amibions, worries, and financial pressures not common to the female. The whole train of cardiovascular manifestations stamp a few of these as being subnormal. Fatigue, exhaustion, tachychardia, and cardiac arrhythmias result from this tension. It is this type of individual that develops neuro-circulatory asthenia and tends toward hypertension. He also believes that the most hectic change occurs in the female at the menopause, and that if strain and fatigue are minimal at this time, their chances of developing high blood pressure is remote.

Barach's ideas cannot be disproved, but the factor underlying the susceptibility to strain and fatigue is the factor we are looking for.

Gay (112) advances the idea that certain food allergies may cause the sign of Essential Hypertension as well as Eczema, Asthma, and Hay Fever. Basing his statements on the theory that Gastro-intestinal allergy is merely a symptom complex produced by the response of the mucosa to food or foods to which the individual has become sensitized, he says that it is not illogical to believe that a person may develop hypertension as a manifestation of an allergic reaction. He cites one case of a woman whose blood pressure was dropped from 205/105 to 135/75 merely by the exclusion of certain foods.

Liston (113) (1937) lists four cases of high blood pressure which he cleared up, by checking their food allergies. All of these patients were over sixty-five years of age,and it seems extremely doubtful if the blood pressure was of any standing, or if there was any arteriosclerosis, that their blood pressure would drop as miraculously as this. However, there may be some cases of Essential Hypertension that really are results of some allergic phenomenon, and if checked by competent

and honest men may give a lead for the future.

Sooner or later, in any discussion of disease, it becomes necessary to question the part that heredity plays in the transmission of the disease.

The most complete work that has been done along this line in Essential Hypertension transmission, was done by David Ayman (114) in 1934.

He studied fifteen-hundred and twenty-four members of two-hundred and seventy-seven families. He found that in families whose parents had no hypertension, the incidence in the children was only three and one-tenth percent. In families in which one parent had Essential Hypertension the incidence in the children rose to twenty-eight and three-tenths percent. In families in which he could demonstrate high blood pressure in both parents, the incidence in the children was forty-five and five-tenths percent.

Of seventy brothers and sisters of these parents who had normal blood pressure, thirty-seven and three-tenths percent had high tension, whereas eighty-six brothers and sisters of the parents having arteriolar hypertension, sixty-three and three-tenths had

high blood pressure.

These figures are rather astounding. They almost prove that the predisposition to Essential Hypertension is transmissible. They tend to put the cause of Essential Hypertension on a constitutional basis and eliminate any infectious cause.

Hines, (115) in 1936, in the Mayo Clinic, tested the reactional blood pressure of four-hundred school children to a standard heat stimulus in an attempt to see whether an excessive vasomotor response is indicative of a prehypertensive state. He checked these results with the parents reactions. He concluded that the hyperactivity of the blood pressure to a standard stimulus may be seen in children as young as six years of age, and that the reaction of blood pressure increases in pre-puberty and puberty ages. Of these four-hundred school children he tested,there were six pairs of identical twins, each pair showing identical reactions.

Chronic infections, Syphilis, lead poisoning, Pneumonia, and Typhoid Fever also have been cited as early factors in cases of Essential Hypertension. Of these, only Syphilis would seem to have any legitimate right to be classed as a factor in this type of high

blood pressure because it does attack the small vessels. (116) The general consensus of opinion is that none of these,not excluding Syphilis,cause Essential Hypertension. (109-103-117-118)

Summary

1. The position of the kidney, as a causative factor of Essential Hypertension, remains as much a problem today as ever. Recent work makes it appear possible that in the kidney there may be the mechanism or part of the mechanism behind mysterious rises in blood pressure.

2. The nervous system does not appear to play a part in Essential Hypertension. The failure of neurosurgery to aid hypertensives, as well as the failure of experimental workers to demonstrate a relationship between the two, makes it extremely doubtful if the cause lies in the nervous system.

3. Endocrines may cause hypertension, but not Essential Hypertension. Endocrine disease and Essential Hypertension, however, may occur simultaneously in the same person.

4. Pressor and Depressor substances may cause Essential Hypertension, but as yet no confirmation has been obtained.

5. Essential Hypertension may occur in any type of person. Figures seem to bear out the fact that a susceptibility to the disease is handed down from generation to generation, and that this susceptibility is more of an intrinsic rather than an extrinsic constitutional factor.

6. Allergic phenomenon are said to be associated with some cases of Essential Hypertension.

7. Chronic infections, major infections, and metallic poisonings have been listed as causative agents of the disease.

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