5-1-1942

Acute pancreatitis : its etiology and pathogenesis

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PRESENT CONCEPTS OF THE ETIOLOGY AND RECENT ADVANCES OF THE TREATMENT OF ESSENTIAL HYPERTENSION

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Senior Thesis Presented to the College of Medicine, University of Nebraska

Omaha 1942

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INTRODUCTION

In many instances a disease process must be defined by exclusion. Such appears to be the case with essential hypertension. Essential hypertension is a term employed to indicate the existence of abnormally high systolic and diastolic arterial blood pressure in individuals who have neither inflammatory kidney disease, urinary tract obstruction, or other disorders which are known to result in elevation of the blood pressure. So goes the typical text-book definition. (1) Even though such a definition is an expression of ignorance it serves its purpose in that the noun expresses the dominant clinical manifestation and the adjective serves the double function of forewarning of our ignorance of the cause of the hypertension and differentiating it from nephritic hypertension.

Historically essential hypertension is a very young disease. The term "essentielle Hypertonie" was first introduced by Frank in 1911. (2) Before that time the condition was known though often thought to be the precursor of arteriosclerosis or frank nephritis. Thus in 1874 Mahomed described the "prealbuminuric stage of Bright's disease" and von Basch in the same year termed it "latent arteriosclerosis". However, it was not until the works of Allbutt (3) in England and of Huchard (4) in France that the medical profession

realized the high percentage of high blood pressures in the absence of clinical findings of kidney or of arterial damage. Allbutt called the condition hyperpiesia because the elevated blood pressure was the predominent finding whereas Huchard termed his "presclerosis" based on the idea that hypertension was followed by arteriosclerosis. Janeway (5) was one of the first men in this country to make an extensive study of essential hypertension and since his study there have been many others who have done comprehensive studies on the disease.

Since the diagnosis of essential hypertension is made by exclusion there have been several attempts to classify hypertensive disease as a whole. Perhaps one of the most complete is that done by Page.(6)

Renal

1. Affections of vessels
   - arteriosclerosis
   - periarteritis nodosa
   - arteritis
   - anommaly
   - obstruction (tumors, aneuyrism, arteriosclerosis, embolism, thrombosis)
2. Affections of parenchyma
   - acute nephritis
   - chronic nephritis
   - pyelonephritis
   - hydronephrosis
   - polycystic disease
   - amyloidosis
   - infarcts
   - tumors
   - hypernephroma

ectopia
toxemia of pregnancy
x-ray lesions
renal stones
hypogenesis
distopia

3. Affections of perinephritic structures
   perinephritis
   tumors
   hematoma
4. Affections of Ureter
   obstruction (pelvis, ureter, prostate, urethra)
   pyelitis

Cerebral

1. Increased intracranial pressure (tumors, trauma, inflammation)
2. Diencephalic stimulation
3. Anxiety states
4. Lesions of brain stem (ascending paralysis, poliomyelitis)

Cardiovascular

1. Heart failure
2. Arterio-venous fistula
3. Angina pectoris
4. Heart block
5. Coarctation of aorta
6. Lead poisoning
7. Polycythemia

Endocrine

1. Pheochromocytoma
2. Adrenal hyperplasia (?)
3. Adrenal carcinoma
4. Wilm's tumor
5. Cushing's syndrome
6. Pituitary basophilism (?)
7. Acromegaly
8. Thymic carcinoma
9. Hyperthyroidism
10. Menopause
11. Arrhenoblastoma

Unknown

1. Essential
2. Malignant

In other words there are forty-eight known syndromes with which hypertension is associated besides the unknown benign essential hypertension and its malignant form. Griffeth and his co-workers (7) attempted to establish certain objective criteria for the classification of hypertension. They made studies on the cutaneous capillaries, the minute vessel pressure, the cutaneous lymphatic flow, the blood volume, and the association of posterior pituitary substance in the blood, but their findings were neither definite nor consistent enough to be used as a classification.

In attempting to determine whether the so-called "malignant hypertension" should be classed with the essential group, Derow and Altschule (8) concluded, "It is usually impossible to decide during the life of a patient exhibiting the syndrome of malignant hypertension whether the hypertension is primary or secondary to some unrecognized morbid process." They believed that malignant hypertension is a syndrome which may occur, 1) with no evidence of previously existing hypertension, 2) as the end stage of essential hypertension with or without uremia, or 3) as the end stage of a miscellaneous group of conditions characterized by secondary hypertension.

All in all, hypertensive disease, of which 80 to

85 per cent are classed as essential by our present standards, is an extremely important disease, and as Hines (9) states, "The problem of the causation and treatment of hypertensive disease should be considered one of the major challenges to the medical profession. When it is considered that four times as many deaths result from the effects of hypertension as from cancer and that approximately a fourth of all deaths of persons past fifty years of age are due to the effects of hypertensive disease, the importance of this problem is evident."

With this in mind it is the aim of this thesis to present those etiological factors of essential hypertension which, today, are thought to be important and to briefly cover the recent advances in treatment.

ETIOLOGICAL FACTORS

A discussion of the etiology of essential hypertension should perhaps be started with a quotation from Janeway (5) who reviewed nine years of private practice on hypertension. "The range of such factors as were found in the life histories of these persons was so great as to demand an extensive critical study to yield anything more than the usual text-book catalogue of all the diseases and vices of the human race as the causes of any disease the origin of which is obscure. A discussion of the etiology seems likely to provoke the criticism made by Artemus Ward, 'It is better not to know so many things than to know so many things that ain't so.' " This statement seems to be about as true today as it was in 1913.

The several divisions that follow should be classed as etiological factors which are today considered to be important in the cause of essential hypertension. Many of them are theories as yet unproven or proven only in animal experimentation.

RENAL FACTOR

Frank kidney disease, such as glomerular nephritis, has long been associated with the elevation of blood pressure, however, until comparatively recently it was generally believed that most instances of hypertension were due to disease originating in some part of the body

other than the kidney, and the role of the kidney in the greater percentage of hypertensive patients was ignored. Then came the work of Goldblatt (10) which was published in 1934. The constant elevation of blood pressure which he obtained in his experiments forced the medical profession to delve more carefully into the function of the kidneys with regard to essential hypertension. Since his original publication, Goldblatt and his associates have done much with regard to the role of the kidney in hypertension and have started many others in the investigation of the mechanism of the elevation of blood pressure. Goldblatt produced a renal ischemia by use of specially made silver clamps around the renal arteries. The detail of the technic will not be described here but has been fully covered in some of his publications.(10,11) He and his associates succeeded in producing a persistent hypertension in the dog, monkey, sheep and goat with an elevation of both the systolic and diastolic pressures. If they produced a moderate constriction of the main renal arteries, there was no accompanying renal excretory insufficiency detectable by the usual means, but if the constriction was excessive, there was a definite disturbance of the renal excretory function and fatal uremia often resulted. In animals with hypertension without impairment of the renal excretory function, the only

changes that occurred in the cardiovascular system, even after several years of hypertension, are cardiac hypertrophy and some thickening of the media of the small arteries and arterioles in most organs in which the vascular system is subjected to increased tension. Simple intimal arteriosclerosis of large vessels and arteriolar sclerosis were not observed in such animals. In animals with hypertension and renal excretory insufficiency, especially if they developed fatal uremia, petechiae associated with hyalinization, fibrinoid degeneration, necrosis, and acute inflammation of the arterioles developed in many organs, chiefly the gastro-intestinal tract, pancreas, gall bladder and urinary bladder but not in the lungs or kidneys in which the vascular system is not subjected to increased tension. (12) Constriction of the aorta just above the origin of both renal arteries produced the same effect.(13) The rise in blood pressure occurred in twenty-four to forty-eight hours with the maximum being reached in about two weeks. If a collateral circulation is established to relieve the renal ischemia, the hypertension does not persist. If only one renal artery was constricted, the blood pressure rose but returned to normal in about six weeks which was thought to be due to the establishment of a collateral circulation and to the compensating effect of the other kidney. By

denervation of the kidneys, bilateral section of the splanchnic nerves and excision of the lower four thoracic sympathetic ganglia (14), section of the anterior nerve roots from the sixth dorsal to the second lumbar inclusive, and even pithing (15), they eliminated the possibility of any nervous reflex from the kidney as a cause of the hypertension since these procedures had no affect on the rise of blood pressure following the production of renal ischemia. They found that coincident occlusion of the renal veins prevented the elevation of blood pressure which ordinarily occurred following constriction of the main renal arteries. If the renal vein of an ischemic kidney was occluded, the elevated blood pressure returned to normal. In investigating the role of the endocrines in this type of hypertension, they removed the pituitary, thyroid, pancreas, gonads, and medulla of the adrenals and found that it had no detectable influence on this type of hypertension with the exception of the adrenal cortex. They found definite indication that the integrity of at least a portion of the adrenal cortex adequate to sustain life is necessary for the persistence of hypertension due to renal ischemia. The results of their work led them to believe that the hypertension was due to the development of a humoral substance supposed to be due to the deficient irrigation of the renal tissue with blood. (11)

Page (16) produced a renal hypertension in dogs which corresponded to that produced by Goldblatt but used a different technic. He had previously found, while attempting to prevent the development of a collateral circulation in the Goldblatt ischemic kidney, that the use of cellophane wrapping of the kidneys caused a marked fibrotic reaction. He then attempted to produce an ischemic kidney by the use of cellophane coverings for the kidneys without constriction of the renal arteries. The result was a marked fibrous capsule around the kidney and the resulting constriction producting renal ischemia. This in turn was followed by a persistent hypertension. He bore out Goldblatt's statement that the adrenal cortex was involved since he found that in his hypertensive dogs, complete adrenalectomy bilaterally, removed the hypertension but that the administration of adrenal cortex extract and sodium chloride sufficient to sustain life caused the return of hypertension.

Discussion arose as to whether or not the renal nerves had anything to do with the hypertension produced by renal ischemia. Although Page (17) thought the renal nerves had little to do with this type of hypertension, as did Collins (18), and Goldblatt's work had relagated the nervous component in this type of hypertension to a negative position, Glenn, Child, and Heuer (19) attempted

to settle the matter by transplanting a normal kidney from its usual location and vascular supply to the femoral area and using the femoral artery and vein. The femoral artery leading into the kidney was then clamped as with the Goldblatt technic. It was found that they could not get or maintain as high a blood pressure with this method though admitting that the operation itself might change the picture considerably. They conclude that there is the possibility that while the hypertension may be due to renal ischemia, it might be sustained by the nerves along the renal artery.

Goldblatt's work was confirmed by Blalock and Levy (20) by a repitition of all of his experiments.

Recently Goldblatt (21) reviewed his work on experimental hypertension, and while he does not deny the possibility of sympathetic reflexes playing a part in humans, he questions the possibility since animal experimentations show no relationship of nervous reflexes.

There has been some question as to whether renal ischemia was the actual cause of experimental hypertension as it had been observed (10) that urea clearance was sometimes normal in experimentally hypertensive animals. It is known that the urea clearance in normal dogs parallels the rate of renal blood flow.(22) It was also observed (23) that the renal blood flow of phenol red, inulin, and

creatinine were in some instances not altered during the induction or course of experimental hypertension. Indirect measurements (24) of renal blood flow before and after compression of the renal artery in uninephrectomized dogs with single explanted kidneys have since shown that hypertension of moderate degree may be induced without any significant or lasting change in renal blood flow while in some instances renal blood flow may be reduced without the occurrence of an increase in arterial pressure. The explanation of the apparent paradox that compression of the renal artery sufficient to induce changes in the kidney which lead to hypertension need not always be associated with renal ischemia may lie in a consideration of the mechanism of blood flow. The balance between mean arterial pressure and peripheral resistance determines the rate of blood flow. If the arterial pressure is increased correspondingly with increased resistance, the rate of blood flow may remain unchanged. In any case Mann and his co-workers (25) have shown that a high degree of arterial occlusion is necessary in order to reduce mean arterial pressure and blood flow distal to the point of compression. Corcoran and Page (26) believe that since the initial effect of arterial compression is a reduction of pulse pressure distal to the point of clamping, while mean arterial pressure, and therefore, blood flow remain

unchanged, it would follow from these principles that arterial compression, as by the Goldblatt clamp, will nearly always result in a decrease of pulse pressure distal to the clamp. If the constriction were severe enough this would be followed by a decrease of mean pressure and blood flow, however, if the mean arterial pressure proximal to the clamp is simultaneously increased, and if the compression is not excessive, neither mean arterial pressure nor renal blood flow need be reduced by clamping. Other observations (27) support the view that renal hypertension may occur in the absence of renal ischemia since it was observed that mean renal arterial pressure in some experimentally hypertensive dogs is normal distal to the point of clamping. If the mean renal arterial pressure is not reduced by clamping, then probably the renal blood flow is not. Schroeder and Steele (28) have demonstrated that, following clamping of the renal artery, there is a tendency for renal blood flow, which initially had decreased, to return to or toward, normal levels. The results of these experiments suggest that if there is probably no renal ischemia following clamping of the renal arteries but that a decrease of pulse pressure does result, then possibly the decreased pulse pressure is the cause of the experimental renal hypertension. Kohlstaedt and Page (29) have

performed experiments in which isolated dog's kidneys were perfused with blood under conditions which were as physiologic as possible. A clamp was gradually adjusted on the renal arteries to a point where pulse pressure was greatly reduced while renal blood flow was either unaffected or slightly decreased. Arterial pressure was then increased proximal to the compression so that both mean arterial pressure in the renal artery and renal blood flow remained within normal limits. Under these circumstances, the perfused kidney liberated renin, the so-called renal pressor substance, into the renal venous blood. They conclude, therefore, that renal ischemia is not necessarily the cause of renal hypertension and suggest that the intra-renal reduction of pulse pressure may be the exciting cause. Reduction of renal blood flow cannot be ruled out since under the conditions of producing experimental renal hypertension, the intensity of clamping cannot be regulated so that pulse pressure is decreased and renal blood flow is not. No explanation of the mechanism by which a reduction in blood pressure would cause hypertension is known. It is known that organs perfused in the absence of pulsatile flow speedily become edematous, and that their cells may lose their normal permeability to vital dyes. (30) It has been suggested (29) that renal cells are normally impermeable to renin, as

evidenced by the absence of renin from normal renal venous blood, and that reduction of pulse pressure increases renal cellular permeability so that renin escapes.

Perhaps a discussion of the "supposed" normal function of the kidneys in many hypertensives should be undertaken before discussing the renal pressor substances. The knowledge that the renal clearances of urea, phenol red, inulin, and creatinine were normal in some hypertensives (10,123) as well as the absence of proteinuria and hyposthenuria led to the belief that the kidney was intact in many hypertensives, since it was assumed that an abnormality of renal function would be revealed by one or the other of these tests. However, proteinuria is not present unless there is damage to the glomerulus and hyposthenuria, when present in a mild degree, cannot be detected unless efforts are made to obtain urine of maximum specific gravity, as in the concentration and dilution tests of Volhard and Fahr (31). Corcoran and Page (26) have shown that when such efforts are made, the majority of hypertensives show definite impairment of the maximum ability to concentrate urine. By the use of inulin and diodrast clearance ratios they have also shown that even in early hypertensives there is evidence of constriction of the glomerular efferent arterioles,

and that even though the urea clearance is normal they can show a decreased diodrast clearance either with reference to surface area or with reference to renal mass. In other words the common methods of measuring urea or other products which are excreted by the glomerulus as a means of determining renal function are not accurate since these filtrates may be kept normal by increased filtration pressure even though the renal blood flow is decreased and the kidney is slightly ischemic as the result of the decreased flow. They claim that the increased intraglomerular pressure of hypertension is due neither to the high level of systemic arterial pressure nor to the dilatation of the afferent arterioles since either of these changes would of themselves increase the renal blood flow, which, in hypertension, is decreased. They conclude that both the decreased renal plasma flow and the maintenance of filtration rate in hypertension are the result of constriction, predominently of the glomerular efferent arterioles. However, they state, "It should be noted that the renal ischemia of hypertension is more probably a result of the action of the vasopressor system rather than a cause of it." To them the explanation of the apparent inconsistency of the fact that the functional pathology is in the efferent arterioles while the pathological findings of hyalinization and sclerosis are in

the afferent arterioles lies in the protection of the efferent arterioles from the elevated pressures by their constriction while the afferent arterioles are subjected to the higher pressures.

The liberation of the renal pressor substance, the so-called renin, has been explained by two theories. The production of renal ischemia with a change in metabolism or the reduction of pulse pressure causing the release of renin. Neither one has been proven. However, it must be admitted that the reduction of pulse pressure has the attractive theory that if it is the cause of the liberation of renin, the change in the renal cells should be found in a site normally exposed to a high pulse pressure; i.e., proximal to the glomerulus and probably in an area in close relation to the afferent arteriole. Such appears to be the case. Studies (32) have shown that the juxtaglomerular apparatus of the normal rabbit kidney contains afibrillar, basophilic granular and acidophilic granular cells which exhibit signs of cyclic secretory activity. The granular cells are present only in the juxtaglomerular apparatus of the normal kidney, but the afibrillar cells are present also in small numbers in the glomerular arterioles. In hypertension, produced by the Goldblatt technic, there is an increase in size and number of the acidophilic granular cells in the juxtaglomerular

apparatus, and all three types of cells, especially the acidophilic granular are present in the glomerular arterioles. It was suggested that these three types of cells form a developmental series having a probable origin from smooth muscle cells, and that the acidophilic granular cells were the source of the renal pressor substance. Donihue (33) produced cellophane perinephritis by Page's method and studied the cells of the juxtaglomerular apparatus. He found that the cells are increased as early as the third day after the application of cellophane to the kidney. The cells attained a maximum development in granularity, number and distribution prior to or simultaneously with the onset of hypertension and then subsequently decreased in number but probably never were reduced to normal values. He believed that the behavior of these cells was consistent with the suggestion that they were the source of renin. Goormatigh and Grimson (34,35) had previously studied these cells and their findings were essentially the same.

It has been assumed that the liberation of the renal pressor substance, or renin, somehow leads to the development of experimental and possibly clinical hypertension. The association of renin with hypertension will now be discussed.

The existence of renin, a protein-like pressor

substance, was first observed in extracts of the renal cortex by Tigerstedt and Bergman in 1898.(36) Various aspects of the original study have been confirmed and extended, largely as an aspect of the recent renewal of interest in renal hypertension. Methods of purification of renin have been described, (37,38) since crude extracts of kidney are contaminated by depressor substances. It was observed (39) that purer fractions of renin had little or no effect on the blood vessels of isolated organs perfused with Ringer's solution, while the addition of blood, plasma, or pseudoglobulins of plasma to renin in Ringer's solution resulted in prompt vasoconstriction. It was concluded that the pseudoglobulins of plasma contain a substance tentatively connoted renin activator.(40) Further work by Corcoran, Kohlstaedt, and Page (41) showed that renin is vaso-inactive unless permitted to interact with a pseudoglobulin present in blood plasma (renin-activator), and that the interaction of renin and renin-activator yields a crystallizable, dialyzable, thermostable product which they termed angiotonin. They performed experiments in which they measured the arterial pressure by auscultation, the effective renal blood flow by calculation from the hematocrit ratio and apparent plasma diodrast clearance, and checked the skin temperature in response to injections and infusions of angiotonin

intravenously in animals and humans. They found that doses of from .5 to 1 cc. of angiotonin raised both the systolic and diastolic pressures but they returned to normal within six to nine minutes. They could find no outward vasomotor changes such as change in skin temperature or pallor. In addition they found an increase of the filtration fraction occurring during infusion which they thought was evidence of increased intraglomerular pressure and since it was associated with decreased renal blood flow, indicated the constriction of the glomerular efferent arterioles. They conclude that hypertension might be the result of unopposed action of angiotonin in humans. Thus it is seen that angiotonin, unlike renin and renin-activator, is not a protein. Its action as a pressor substance is both prompt and of short duration and is unlike the slower rise and sustained increase of arterial pressure which follows injection of renin. It was shown that repeated injections of renin into normal animals results in a loss of pressor responsiveness (tachyphylaxis).(42) This was claimed to be due in part to a loss of activator by combination with the injected renin, however, restoration of activator by transfusion or injection of activator concentrates did not fully restore the pressor action of renin. Observations (43) on repeated injections of angiotonin showed

a loss of responsiveness also, but this tachyphylaxis did not develop as rapidly as that due to injection of renin and plasma transfusion and injection of activator did not affect it. It was further found that bilaterally nephrectomized animals were sensitized to the pressor action of renin and angiotonin and did not develop tachyphylaxis to angiotonin and only slowly to renin. To these workers angiotonin tachyphylaxis and the residual inhibition of the pressor action of renin after restoration of activator seemed to be due to the liberation of an angiotonin inhibitor from the kidneys. Harrison, Grollman, and Williams (44) and Page and his co-workers (45) have been successful in attempts to extract such an inhibitor or antipressor substance from the kidneys. Both groups seem to be working with the same substance though the work has been done independently. In line with these observations Friedman (46) has found that the ability of normal systemic blood plasma to neutralize angiotonin is markedly decreased after circulation through a partially ischemic kidney. To summarize, the pressor system may be considered as originating in renin which, when released into the blood, combines with renin-activator to yield angiotonin. Angiotonin acts as the effective vasoconstrictor and pressor agent. Opposing or balancing the action of angiotonin, the kidney contains a substance which acts as

an inhibitor of the action of angiotonin. The relation of this pressor system to experimental and clinical hypertension is suggested by the following observations: 1) renin is present in the renal venous blood of hypertensive but not of normal animals (47), 2) the blood of hypertensive animals and human beings has properties which suggest that it contains less angiotonin inhibitor than normal blood (41), 3) nephrectomized and , possibly, hypertensive animals are more sensitive to the pressor action of angiotonin than are normal animals (43), 4) the peripheral blood of hypertensive animals and human beings contains a vasoconstrictor which, like angiotonin, is potentiated in the presence of blood from nephrectomized animals (48), and 5) the nature of the pressor action of angiotonin is not inconsistent with that of a substance which might participate in the genesis of hypertension. Braun-Menendez, Fasciolo, Leloir, Munoz, Taquini, and Houssay of Buenos Aires (49) have recently confirmed most of this work. They used a pressor substance which was probably renin and found that it interacts with a pseudoglobulin, the renin-activator, which they called, "hypertensinogen", with the liberation of an effector substance, similar in physiologic properties to angiotonin, to which they refer as hypertensine. The chemical similarity or identity of angiotonin and hypertensine remains to

be established. Indirect evidence has led them to the conclusion that there exists in normal kidneys an angiotonin inhibitor, called by them "hypertensinase", since it is their view that it may act by enzymatic destruction of hypertensine(angiotonin).

Other pressor substances have been described as originating in the kidney. Thus "perfusin" which, unlike renin and angiotonin, is potentiated by cocaine, has been obtained by perfusion of the kidneys of normal hogs and dogs with Ringer's solution.(50) A substance whose properties are not unlike those of renin, is found in the renal venous blood of completely ischemic kidneys and has been provisionally called ischemin.(51) It now appears that this substance is renin.(52)

Of interest is the recent work done on an entirely different substance. Observations of Mason and his co-workers (27) had shown that the ammonia production of the Goldblatt kidney was reduced which they thought was evidence of a decrease in deaminization. Following this Bing (53) observed that isolated ischemic kidneys or anaerobic kidney tissue in vitro as well as completely and partially ischemic kidneys in vivo form a pressor substance. He believed that amino acids were formed to pressor amines in the ischemic kidney. He perfused ischemic kidneys with l' dopa (l-dihydroxyphenylalanine)

and found that it produced a pressor substance which he thought was probably hydroxytyramine. Kidneys with normal blood flow failed to transform the dopa reagent.(54) This substance, like "perfusin", is potentiated by cocaine and may be similar to the pressor substance formed during the anaerobic incubation of kidney tissue which Victor and his associates (55) have observed. These observations seem to be confirmed by Schroeder's work (56) in which he found that the injection of tyrosinase, a phenolic oxidase obtained from mushrooms, consistently lowered the blood pressure of hypertensive rats and dogs. It also inactivated renin, angiotonin, adrenalin, and tyramine in vitro. However,the work of Levy and his associates (57) as well as that of Mason and his co-workers (27) have shown that the oxygen content of renal venous blood in hypertensive dogs, even in the presence of moderate renal ischemia, is within normal limits which puts the burden of proof on those who claim the existence of anaerobic conditions in the ischemic kidney.

The application of the experimental findings to clinical hypertension has not been extremely successful. A case of hypertension has been reported in which a mass of smooth muscle was found in the right renal artery with a resulting drop in blood pressure after removal of the right kidney.(58) Moritz and Oldt (59) studied 200

consecutive cases at autopsy, one hundred of which were known to have had chronic hypertension while the other hundred had no history of hypertensive disease. They found arteriolar sclerosis in most of the hypertensives with the medial hypertrophy and degeneration the most predominent. It was suggested that this was probably the mechanism of Goldblatt's experimental renal hypertension in humans. Another case was reported (60) in which an embolus plugged both renal arteries resulting in bilateral renal ischemia. Marked hypertension was present before death and immediately after death perfusates of one of the infarcted kidneys were used in animal experiments which revealed the presence of a pressor substance that seemed to be the same as that obtained from the ischemic kidneys of experimental animals. Farrell and Young (61) have recently reported a clinical case of hypertension which showed a pathological fibrotic condition around the kidney which was similar to that produced experimentally by Page. Therefore, there is more than fair clinical evidence that the kidneys may play a far more important role in hypertension than was heretofore realized. Perhaps the experimental renal hypertension is similar to or the same as clinical hypertension.

Another strong argument for the renal basis of hypertension is found in the reported success from the

use of the extracts of the renal antipressor substance in lowering the blood pressure of hypertensive animals and human beings. This will be covered under the section on medical treatment.

HEREDITARY AND CONSTITUTIONAL FACTORS

The relationship of heredity to essential hypertension is unquestioned though its importance is the subject of much controversy. Studies of its relationship are difficult. Sodeman (62) states, "Such a disease as this, not dependent upon a malformation or congenital defect, in which the tissues show no structural change until, or even after, the disease has developed, is often extremely difficult to evaluate genetically. Human matings lack the control attending the study of experimental animals; the life span is too long for one observer to study many generations; family data are notoriously inadequate, and families are not large; and environmental factors are often necessary as precipitating causes."

However, difficult though it may be, much work has been done on the hereditary factor. Janeway in 1916 (63) expressed the opinion that the belief in an inherited quality of the arterial tissues with a tendency to premature death from apoplexy, angina pectoris, or other local manifestations was too firmly grounded in clinical observation to be without basis. He thought that hypertensive

arterial disease should be looked upon as the type in which hereditary plays "the largest role". O'Hare, Walkers, and Vickers (64) found that 68 per cent of three hundred patients who had hypertension gave a family history of cardiovascular disease as compared with 37 per cent of 564 patients not suffering from hypertension who gave such a history. Hines (65) used a different method in determining the hereditary influence and percentage. He utilized his "cold pressor test" for determining vascular hyperactivity in hypertensive and non-hypertensive families. He used the term "vascular hyperactivity" to describe that condition which is manifested by marked variability of the blood pressure and by hyperreactive response of the blood pressure to a variety of, or perhaps all, forms of stimulation. This vascular hyperactivity can be estimated by determining the range of blood pressure at hourly or half-hourly intervals in which the patient is active and during periods of rest for a period of from twenty-four to forty-eight hours. Hines has described his cold pressor test (66) which he believes to be a satisfactory and much less time consuming method of determining the vascular hyperactivity. As to the question of what constitutes a significant response, "analysis of the results of a large number of tests has determined that an elevation above the basal level of more

than 20 mm. of mercury in the systolic pressure and of more than 15 mm. of mercury in the diastolic pressure indicates a hyperreactive type of response to the test. If the maximal value obtained is more than 140 mm. of mercury, systolic, and 90 mm. of mercury, diastolic, the patient is even more certain to have a hyperreactive vasoconstriction mechanism." He studied the reaction of the blood pressure to this standard stimulus in 608 cases in which the blood pressure was "normal", in ten pairs of twins and in 256 members of thirty hypertensive and non-hypertensive families. A study was also made of the family history of the 608 individuals who had a normal blood pressure and of the 267 patients who had essential hypertension. A positive family history of hypertensive cardiovascular diseases was found to be five times as frequent among the individuals who have hypertension or who are hyperreactors to a standard stimulus test than it is among individuals who react normally to the test. In his study of the twins and the family groups he found that the type of blood pressure reaction to the test followed an inherited pattern which he believed to be a dominent characteristic. In a later follow up study (67) of the records of patients who had returned to the Mayo Clinic ten to twenty years after the original examination by correlating data concerning the subsequent development

of hypertension with the original readings of blood pressure, he found that the majority (70.4%) of the patients who as a result of nervous stress--he believes that the psychic elevation of blood pressure often seen on the first examination can also be used as an indication of vascular hyperactivity-- had an original elevation in systolic and diastolic blood pressures above the upper ranges of normal, had hypertension ten or twenty years later, whereas only a small number (3.4%) for whom the original readings of blood pressure had been in the lower ranges or normal had hypertension ten to twenty years later. In studying the family histories of this latter group, 1374 patients in all, he found that the incidence of subsequent hypertension was approximately six times greater among those with a family history of hypertensive cardiovascular disease on the original visit as it was among those who did not have such a family history. Ayman (68) made a direct study of the blood pressure in 1524 persons in 277 families and found a tendency toward elevated blood pressure early in life in hypertensive families, a finding which was largely absent in members of normal families. Weitz (69) tried to circumvent the difficulties of following many generations through the often inaccurate histories of the patient by studying the collateral family groups. These individuals were

living and could be submitted to examination. His conclusion at the end of his analysis was that the predisposition to essential hypertension behaves in a majority of cases as a Mendalian dominent.

Even though there is much evidence that there is a strong hereditary factor in hypertension, there is also much controversial evidence. It has been found that hypertension is a disease largely confined to occidental civilization. Studies have been made on the blood pressures of African natives (70) which show that up to the age of forty the blood pressures of natives and europeans were similar but between the ages of forty to sixty the average blood pressure of the native declined, whereas the average blood pressure of the european rose steadily. Of 1800 patients in a native hospital not a single case of hypertension, arteriosclerosis, or chronic interstitial nephritis was encountered. In this country studies on the American negro (71,72) have indicated that hypertension is on the whole three times as common in the negro as in the white. Studies on the Chinese (73), on the Buddhist priests in Ceylon (74), and on Egyptians of the laboring classes (75) all indicate that hypertension is very rare among these peoples. Another interesting finding has been the discovery that the blood pressure of foreigners living in China(76) and the tropics (77) are lower than

when they are living in a temperate zone. All in all, these studies cast extreme doubt upon the importance of heredity in essential hypertension. Especially the work of Kesilman and of Schulze and Schwab on the American negro mentioned above (71,72), since it is acknowledged that the negro's ancestors did not have hypertension and yet the American negro has acquired hypertension in a period of two hundred years to a degree much more severe than the white man.

Until fairly recently there has been no comprehensive study of the relation of constitutional factors to hypertension. Clinically it has long been recognized that the so-called degenerative diseases, of which hypertension in one, were more often seen in the short or stout individual but there was no factual evidence to support this clinical observation. Short and Johnson (78) studied the records of individuals applying for periodic health examination. They had 2850 cases of overweight men and 658 cases of normal weight for controls. They set 150 mm. of mercury for the systolic basic level and 90 mm. of mercury for the diastolic in determining the presence or absence of hypertension, and age was considered in the evaluation of the findings. Overweight was found to exert a positive influence on hypertension with a more marked influence on the diastolic pressure, but the incidence of hypertension

in the overweight was generally lower than they expected. The concluded that the influence of overweight on hypertension was generally over-rated. Robinson and Brucer in a series of studies (79,80,81) have attempted to show the relation of hypertension to body build, obesity, and heighth. They divided people into two main constitutional types, the lateral or broad build, and the linear build. In determining into which classification a person was to be put, they used a ratio determined by figuring the chest circumference in relation to height. Obesity was found to have no great influence on the blood pressure but was an accompaniment of the lateral or broad build as is hypertension and other cardiovascular disorders. In a follow up study of 3658 persons who came in for periodic health examinations they found that for every person of the linear build with hypertension, there will be seven of the lateral build with hypertension. Further studies revealed that as far as height was concerned the tall lateral person was more apt to have hypertension than the short lateral individual. They conclude,"The build is the gross morphologic expression of a deep seated genotypic change of the neuro-endocrine system and the biochemical reactions of the entire body."

It would seem, then,that there is an inherited constitutional factor which predisposes to hypertension.

NEUROGENIC FACTORS

Hines (9) has said, "The most evident characteristic of a person suffering from essential hypertension is a certain type of personality. The majority of patients who have essential hypertension are dynamic, hard-driving, non-procrastinating persons with the desire and ability to accomplish much in a short period. Careful questioning of the patient and his relatives will reveal the fact that this type of personality has not developed since the patient acquired hypertension, but that it represents the patient's natural tendencies and has been characteristic of the patient as far back as can be remembered."

Whether this so-called "personality type" should be regarded as a constitutional factor or as an environmental factor is not known. Palmer (82) explains the mechanism by considering essential hypertension as a state of "chronic emergency" which depends upon nervous strain in an individual with a constitutionally susceptable sympathetic nervous system. Fishberg (2) is in agreement with the idea that emotional and mental strains play purely an accessory role in the cause of essential hypertension, serving to precipitate or aggravate the increase in blood pressure in those individuals who have the inherited predisposition.

In contrast to the inherited predisposition is

the work of Kesilman (71) and of Schulze and Schwab (72) who showed the much higher incidence of hypertension in the American negro as contrasted with that of whites and the apparent complete absence in the African negro (70). This fact, they claim strongly suggests that the hypertension in negroes and white people is a manifestation of the body's effort to accomodate itself to a more exacting mode of living, and that it is more marked in the negro because he has had relatively much less time to adjust himself to it. Alexander (83) is in agreement in that he believes the early fluctuating phase of essential hypertension is the reaction of the individual to the complexities of our present living pace and civilization and is "the manifestation of a psychoneurotic condition based on excessive and inhibited impulses." Cannon (84) in dealing with this subject has opened the horizon to a trend in diseases, believing that the change in living pace is reflected in the predominent type of disease. Thus, the present trend is reflected in the diseases resulting from an overworked and overstrained organism, the so-called degenerative diseases of which hypertension is one.

The clinical substantiation for these theories rests in the reported successful results of treating essential hypertension by psychotherapy. These will be taken up under the section devoted to treatment, and it

will suffice to say here that psychotherapy for the hypertensive is one of the standard treatments for essential hypertension regardless of what other additional treatment is given.

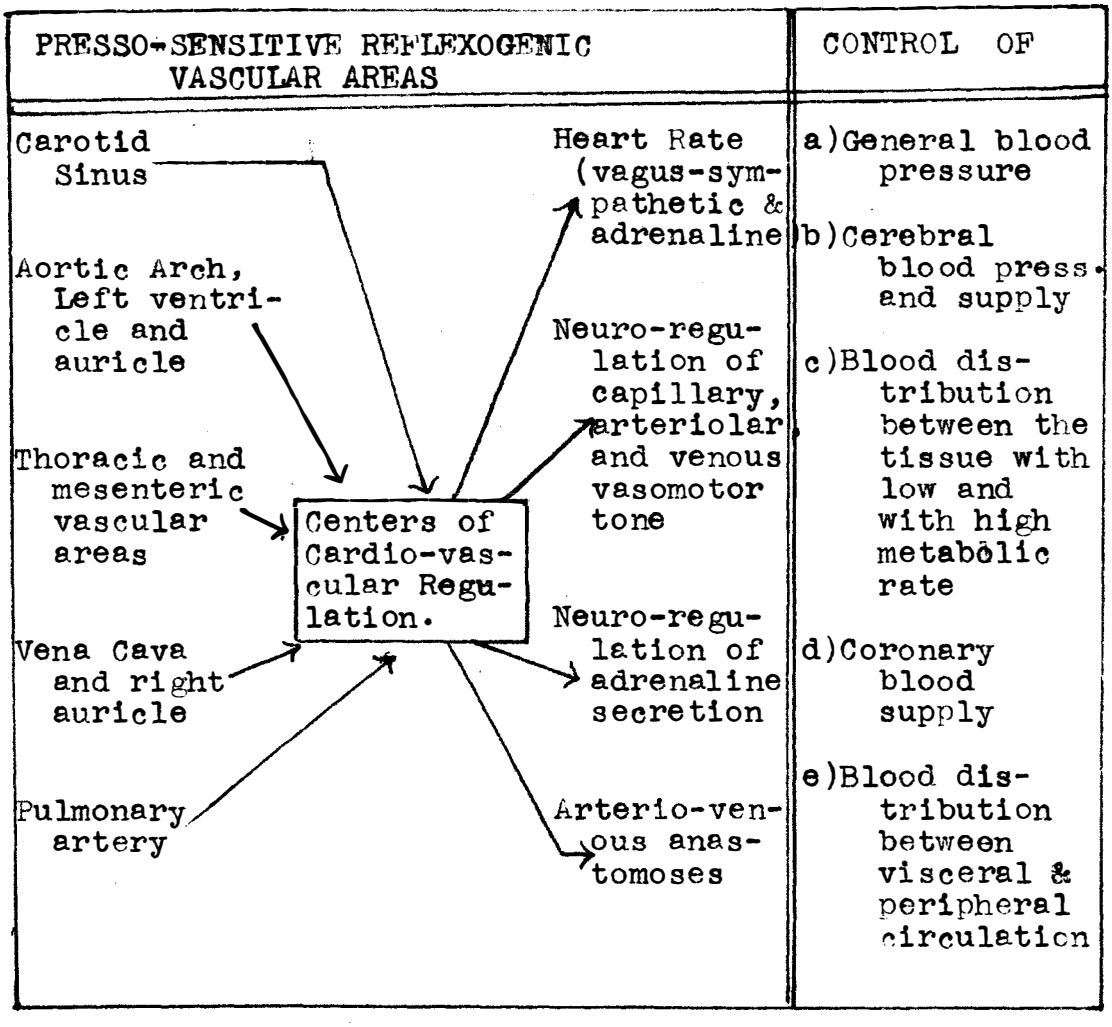
In relation to the emotional factors Page (85) has described a condition found occasionally in hypertensive patients which he referred to as "the hypertensive diencephalic syndrome" since the symptoms and signs somewhat resembled those seen in the decerebrate animal and referred to as diencephalic fits. The attacks were described as 1) a curious, irregular blotchy blushing, first of the face then spreading to the neck, the trunk and sometimes the abdomen, 2) spontaneous crying or watering of the eyes, 3) excessive perspiration often at the site of the blush, 4) palpitation of the heart and increase in cardiac rate, 5) rise in blood pressure, and 6) coldness of the extremities. The attacks were usually brought on by emotional stimuli in these patients but might occur spontaneously. Crisler and Allen (86) have reported four similar cases, only one of which had a blood pressure which was within the normal range. Schroeder and Steele (87) have reported on twenty-seven patients with all of the signs and symptoms of the "diencephalic syndrome" and on nineteen others who had most of them. The cause of this condition is not known, but it is significant in

that it shows a relation between emotional instability and increased sympathetic activity.

The long observed and well established fact that the majority of hypertensive individuals were of the nervous or high strung type with all the evidence of an overactive nervous system has naturally led many to experimentally investigate the role of the nervous system in hypertension. Thus, neurogenic hypertension has been produced by 1) bilateral excision of the carotid sinuses and complete denervation of the area, 2) injection of kaolin suspension into the cerebral ventricles or into the subarachnoid space, and 3) permanent decrease of the cerebral blood supply by ligation of the carotids, vertebral, and spinal arteries.

The method largely used is the excision of the carotid sinuses and cutting the depressor nerves of that area. This method was investigated soon after the role of the carotid sinuses in the regulation of blood pressure was determined. Before discussing the relation of the nervous system to hypertension it is perhaps wise to briefly review the proprioceptive mechanisms of the regulation of general blood pressure. The experimental work which led to an understanding of this mechanism has been ably reviewed by Heymans (88) and the following diagramatic chart is taken from his work: It has been

shown that the regulation of blood pressure is fundamentally an automatic, proprioceptive reflex mechanism. The homeostasis of the arterial pressure is effected mainly by the action of the pressor-receptor innervation of the different arterial and venous vascular areas. (see chart below)



The carotid sinus and cardioaortic nerves not only act as a reflex regulation of the general arterial pressure but also act as buffer or modulator nerves of the blood pressure. In theory this should mean that release of the vasomotor areas from the buffer action of these areas would lead to a rise of the vasoconstrictor tone and an increase in blood pressure. Experimentally, this has been shown to be the case. Heymans and his co-workers (88) have observed arterial hypertension maintained at 250 to 300 mm. of mercury, systolic, for periods of nine to twenty-six months after section of the cardio-aortic and carotid sinus moderator nerves. Nowak (89) obtained a maximum duration of hypertension for three years and four months.

It has been shown experimentally that the vascular reactions occurring as the result of the reflexes from the carotid sinus and cardioaortic areas take place largely in the splanchnic area.(88) This fact has led to the use of sympathectomies in animals with this neurogenic hypertension as an argument for the mechanism of the hypertension. Grimson (90) , Freeman (91), and others have shown that total sympathectomy in these animals will either prevent the rise of blood pressure or will cause a substantial drop in the elevated blood pressure of an already neurogenic hypertensive dog. They have shown that only a total

sympathectomy is effective and that partial sympathectomies have little or no effect. Heymans (88) explains the failure to produce a persistent hypertension in some of the animals by claiming the drop in blood pressure following the initial rise is due to the presence of accessory fibers of the cardioaortic nerves in the vagus, or because in certain animals the pulmonary and mesenteric intestinal presso-sensitive nerves may take over the moderator function of the cardioaortic and carotid sinus nerves.

The work which has been done on the other type of experimental neurogenic hypertension has been largely foreign.(92) The method was to inject a suspension of kaolin (a native hydrated aluminum silicate) into the cerebral ventricles or into the subarachnoid space. The mechanical compression thus produced led to cerebral anoxemia which particularly sensitizes the vasopressor centers to the stimulating action of carbon dioxide. Raab (93) has substantiated the belief that anemia and anoxemia may stimulate the vasopressor centers. Nowak (94) produced a permanent arterial hypertension through the mechanism of central anemia and anoxemia by ligation of the carotid arteries, vertebral and spinal arteries. It has been suggested that this type of hypertension might be produced in humans as the result of some anoxic process,

such as endarteritis, localized in the region of the vasopressor centers.(93) Prinzmetal and Wilson (95) disagreed with the idea that the vasomotor system had anything to do with hypertension. They believed the generalized peripheral resistance found in hypertensives was due to an intrinsic vascular tone with a normal vasomotor control superimposed upon it. Whether such drastic experimental methods have any related clinical conditions is not known and will have to wait for further investigation, though it must be remembered that Hines (65) has shown a vascular hyperactivity in most hypertensive or prehypertensive individuals.

Efforts have been made to relate the neurogenic type of hypertension to the renal variety which has been discussed previously. Heymans (96) believes the experimental neurogenic hypertension to be different from the typical nephropathic variety but believes it resembles more closely the essential hypertension found in humans. He suggests that a functional deficiency of the moderator nerves, either in the region of the vasoconstrictor centers or in that of the peripheral presso-receptors or in that or the peripheral vasoconstrictor nerves is the underlying cause for essential hypertension. Grimson and his coworkers (97) attempted to correlate the neurogenic and renal factors by first doing total sympathectomies in

dogs except for the adrenals and kidneys. They then cut the depressor nerves and excised the carotid sinuses and got an immediate elevation of blood pressure. They found that by denervating the kidneys this rise of blood pressure could be prevented. Goldblatt and his associates (98) found that excision of both carotid sinuses, with or without section of the cardioaortic inhibitor fibers, did not interfere with the development of hypertension produced by renal ischemia. On the other hand, Goormaghtigh (34) in studying the afibrillar cells of the juxtaglomerular apparatus found that there is hyperplasia of these cells following the hypertension produced by denervation of the carotid sinuses and cardioaortic zones. Such controversial views on the subject can lead to no generalizations but it would seem that the work of Grimson and the histological studies of Goormaghtigh shows some relationship between the neurogenic and nephrogenic experimental hypertension. Proof of disproof of this will have to rest with further studies.

ENDOCRINE FACTORS

The endocrine glands have been regarded for some time as possible causes of hypertension, and there is some basis for this regard. Several endocrine disorders are associated with hypertension, however, the vast majority of individuals with essential hypertension do not

reveal either clinical or post mortem evidence of disease of the endocrine glands. Whatever, if any, the influence of the adrenals, the pituitary, and the sex glands have come under discussion. The thyroid and the pancreas have also entered the field in attempts to relate diseases of these organs to the etiology of essential hypertension.

It was Vaquez (99) who first suggested that the increased secretion of epinephrine was responsible for hypertension. He thought he had observed a frequent coincidence of adrenal hyperplasia and hypertension. Since then there have been many who favored the theory though it must be admitted that the theory of hyper-epinephrinemia has had just as many opponents since its conception. The basis for the supposition was the known vasoconstrictor effect of adrenaline. Thus it was suggested that the hypertensive had a chronic emergency status with the almost continuous secretion of adrenaline into the blood. Huelse (100) in Germany devised a biological test for epinephrine so delicate that it revealed the presence of epinephrine in a dilution of 1 to 7,000,000. He was unable to find the substance in either the venous or arterial blood of individuals with either nephritic or essential hypertension. More recently, Dragstedt and his co-workers (101) studied the effect of continuous intravenous injection of epinephrine on the blood pressure

of experimental animals. They found that amounts which were sufficient to raise the blood pressure to hypertensive levels killed the animals within a short time because of the other effects of epinephrine; i.e., on sugar metabolism and gastro-intestinal motility. This has been substantiated by Rogoff and Marcus (102) who duplicated the experiments of epinephrine injection. They conclude, "existing experimental and clinical evidence is inadequate to support the view that epinephrine secretion is an important factor in the etiology and pathology of chronic hypertension."

These facts, of course, do not exclude those cases in which there is a definite tumor of the adrenal medulla and in which there is an excessive secretion of adrenaline. These pheochromocytoma or paraganglioma consist of chromaffine cells which are derived from the adrenal medulla or other chromaffine tissue. However, the hypertension associated with these types is usually of a paroxysmal nature with periods of normal blood pressure between the paroxysms. As such these cases do not belong in a discussion of essential hypertension. The only point of interest are those few cases which are due to pheochromocytoma and do not have paroxysmal hypertension but do have a chronic elevation of the blood pressure. These may be confused with the true essential hypertension,

and offer a problem of diagnosis. A case of this type has been reported by Binger and Craig in which the adrenal tumor was accidently discovered during a sympathectomy for the treatment of what they thought was a case of essential hypertension. (103)

Tumors of the adrenal cortex, such as carcinoma or adenoma, are also associated with hypertension. It is a chronic hypertension and the cause is not known. It is possible that the endocrine substance involved in this type of tumor may be related in some way to essential hypertension, however, it is improbable since these tumors are associated with clinical evidence of the other effects of the hormone. In childhood the clinical picture is known as pubertas praecox and in adults as Cushing's syndrome. (104)

The posterior lobe of the pituitary has also been implicated as a cause of essential hypertension. Here, too, the extracts are known to have a pressor effect. Cushing (105) was probably one of the strongest advocates of a pituitary factor in essential hypertension. He believed that the basophilic adenoma of the pituitary was responsible and even found basophilic infiltration into the posterior lobe in eclampsia. However, his syndrome has since been found largely due to adenomas of the adrenal cortex in which hypertension is a prominent

symptom. The work of other investigators (106,107), however, would tend to eliminate the pituitary since it has been found that frequently basophilic infiltration of the pituitary is present in the absence of hypertension. It would seem, then, that as far as present knowledge of the pituitary goes, it has neither clinical nor experimental relation to essential hypertension.

The work on the gonads in relation to essential hypertension has been largely confined to women in relation to the menopause. (108) It is true that the occurrence of essential hypertension is high at this time but the cause has never been established. Two possibilities have been suggested; 1) that at this time women are emotionally unstable and in those who are predisposed to essential hypertension, this serves to set it off, and 2) that some endocrine imbalance is to blame. Both are theories with little evidence to back them up though the emotional basis, which, in turn, may be due to endocrine imbalance is probably the most widely accepted as the cause of the higher incidence of essential hypertension during the menopause. Nothing has been done in relation to the male sex hormones as far as their role in essential hypertension, if any, is concerned.

The hypertension which is found associated with hyperthyroidism is not a true hypertension in that the

diastolic pressure is not elevated. As such it is not to be classed with true essential hypertension. Of interest is the work of Goormaghtigh and Handrovsky (109) who administered large doses of vitamin D_2 (calciferol) to thyroidectomized dogs and found that some of them developed a true hypertension. They also found a hyperplasia of the afibrillar cells of the juxtaglomerular apparatus similar to that found in the experimental renal and neurogenic hypertension. Just what the relationship of thyroid secretion, vitamin D, and arteriosclerosis to hypertension is, is not yet known.

The work of the pancreas has been largely confined to a study of the relation of diabetes mellitus to essential hypertension. Most authorities are inclined to doubt any relationship other than the fact that both are of the so-called degenerative diseases which tend to appear in certain types of people. Thus, both may have a common constitutional background but they are not related otherwise.

METABOLIC FACTORS

As in the case of most diseases the various foods and their metabolism have been accused of causing the disorder. This has been the case in essential hypertension. Much work has been done in relation to the metabloic factors though largely in the past, and as

Fishberg (2) has said, "the results of these investigations have been essentially negative inso far as clearing up the nature of essential hypertension."

As far as protein is concerned the original theory was that essential hypertension was primarily a disease of the kidney and that the hypertension was the result of failure of the kidney to excrete pressor substances which were thought to be the end-products of protein metabolism. Later, it was suggested that the hypertension was due to excessive ingestion of protein food. These theories have been discarded since the work of Mosenthal (110), of Struse and Kelmer (111), and that of Lieb (112) leave little room for protein metabolism in the etiology of essential hypertension.

Fat and lipoid metabolism have also been investigated in relation to essential hypertension. The role of obesity has previously been discussed. (page 31) Studies of cholesterol metabolism have also been essentially negative. (113)

Carbohydrate metabolism has been studied in relation to diabetes mellitus which, in turn, has been found to be a coincident occurrence in the constitutional type predisposed to essential hypertension.

Investigations into the role of salt metabolism have also been negative and is no longer regarded as

being of any importance in essential hypertension.

The higher incidence of essential hypertension in individuals with gout has led to investigation of purine metabolism in relation to hypertension. These studies have also been negative, and it is thought that, as in the case of diabetes, the relationship is one of a common constitutional type rather than any direct relationship.

TOXIC CAUSES

It should be sufficient to mention that intestinal auto-intoxication and the excessive ingestion of alcohol have been considered as factors in the cause of essential hypertension. These were merely fads at the time of their suggestion and received no serious support. Alcohol has been blamed largely by those who were opposed to the use of alcohol.

The use of tobacco has also been implicated as a factor in the etiology of essential hypertension. It has been shown by many workers that nicotine is a vasoconstrictor, and that in the novice, smoking will produce some vasospasm which can be seen in the retinal vessels. The fact that hypertension is not present in many individuals who are excessive smokers condemns this theory, and recently Herrell and Cusick (114) found nothing which would indicate that the inhalation of tobacco smoke has anything to do

with essential hypertension. The restriction of tobacco in the treatment of essential hypertension is not based on the theory that tobacco is a cause of the hypertension but that in some it augments the nervous state already present and hinders lowering of the blood pressure by other therapeutic measures.

Infections and allergy have also been suggested as playing a part in the etiology of essential hypertension in case reports which occassionally appear in the literature. Here, again, it is found that the incidence of infections or a history of allergy is no greater in the hypertensives than in the non-hypertensives.

DISCUSSION

An attempt has been made to present those etiological factors which are thought to play a part in the cause of essential hypertension. Stress has been largely given to those factors which are today regarded as important, and those which have been discarded and are no longer regarded with any seriousness have only been briefly covered.

Perhaps the first thing to be corrected is the textbook definition of essential hypertension, which excludes the kidney in most instances. It is true that those cases of inflammatory kidney disease should not be classed in the essential hypertension group, but even here the actual cause of the hypertension may be the same as that in which there is no obvious kidney damage. In fact, is there such a thing as essential hypertension? Perhaps those cases which have no pathological kidney findings are still of nephritic origin. The work of Corcoran and Page has shown that more exacting tests on kidney function in the hypertensive will reveal a decrease of kidney function. Goldblatt and those who have duplicated his work have shown that the experimental renal hypertension resembles in many respects the so-called essential hypertension. The presence of a renal pressor substance has been definitely established, and

a consistent change in certain cells of the juxtaglomerular apparatus has been demonstrated. The difficulty, of course, lies in the application of experimental findings to clinical cases. Clinical cases in which a resemblance to the experimental renal hypertension was found have been reported, but these are as yet too few to form any basis for generalizations. The one thing that has been established, however, is that the kidney is of far greater importance than was formerly realized, and that in no case of essential hypertension can the kidney be definitely eliminated as a cause of the hypertension.

In relation to the hereditary and constitutional factors in essential hypertension it would appear that there is a hypertensive type of individual. The fact that essential hypertension is largely confined to the occidental civilization where mental stress is greatest does cast a great deal of doubt upon the hereditary factor. However, one cannot exclude the possibility that even in the more primative groups, such as the African negro, the predisposition to essential hypertension may be present but lacks the environmental stress and strain to bring it out. The field of genetics will have to be much more thoroughly mastered before one can do much more than generalize on the relation of hereditary to essential hypertension or in fact, to all of the degenerative diseases.

The relationship of the nervous system both clinically and experimentally has been discussed. It must be admitted that the experimental neurogenic hypertension can have little clinical application. It would be difficult to imagine a clinical condition in which the carotid sinus reflexes and the cardioaortic reflexes were thrown out as completely as they are in the experiments. The argument that since a total sympathectomy in the neurogenic hypertension will lower the blood pressure and that since sympathectomies in humans give some good results in essential hypertension, therefore, the process must be the same does not prove anything, for in all probably the results of the sympathectomies are effected through two entirely different mechanisms. In humans the good results seem to be mainly due to the orthostatic hypotension which results from the loss of constrictor control in the splanchnic region. In the experimental animals it appears to be due to the removal of abnormal constrictor impulses which result when the main blood pressure regulating centers are removed.

The emotional factor in the hypertensive on the other hand is an acknowledged fact. It seems, however, that the emotional instability is a part of the hereditary constitutional factor and not a cause of the hypertension. The evidence, then, is against a neurogenic origin.

The relationship of the endocrine glands has been briefly discussed. It is admitted that disorders of these glands may result in hypertensive states, however, this means that they no longer can be classed in the essential hypertension group since the cause is known. The only endocrine glands which may have some relation to essential hypertension are the adrenals and the thyroid. The adrenal medulla is involved in cases of paroxysmal hypertension and probably not involved in chronic hypertension. However, the adrenal cortex can produce a chronic hypertension when tumor tissue is present. Both Goldblatt and Page found that at least a portion of the adrenal cortex must be present to produce renal hypertension. Apparently the adrenal cortex plays some sort of an accessory role in this type of experimental hypertension, and it is possible that it plays an accessory role in essential hypertension. Even so, this does not mean that the adrenal cortex has to be functioning abnormally for the results have shown that only sufficient amounts necessary to sustain life are necessary.

The role of the thyroid in essential hypertension is doubtful. The hypertension associated with hyperthyroidism is a pseudo-hypertension, and there has been little evidence presented which would indicate an abnormally functioning thyroid in by far the majority of cases of

essential hypertension. It seems, then, that of all the endocrines probably the adrenal cortex is the only one which at present can be implicated in the cause of essential hypertension and that probably only a secondary role.

The metabolic factors which have been regarded in the past as having something to do with essential hypertension have also been briefly covered. Probably the metabolism of the various foods has nothing to do with hypertension. This can also be said of the toxic factors.

In conclusion, then, what can be said about the etiology of essential hypertension?

1. There is some doubt that there is such a thing as essential hypertension or at least the work of the next few years may remove it as a clinical entity.
2. The kidney with its pressor substances plays an important role and shows promise of becoming the established cause of the hypertension in cases which are now diagnosed as essential.
3. The hereditary factor lays the foundation for the development of hypertension once the environmental set up starts it off.
4. The endocrines, of which the adrenal cortex is probably the only one, play an accessory role.

RECENT ADVANCES IN TREATMENT

An attempt will be made to briefly cover the present modes of treatment of essential hypertension. Little attention will be paid to the development of these methods other than that which is necessary to explain the rationale of treatment and no attempt will be made to discuss the treatment of the hypertensive heart, cerebral accidents, or the other results of hypertension. The treatment to be covered is prophylactic in that it attempts to prevent the occurrence of those conditions.

The treatment of hypertension is not satisfactory and it is a mistake to speak of curing a patient of essential hypertension. Theoretically the treatment should begin in the prehypertensive stage so that the individual's life could be regulated in such a way as to eliminate as much as possible all strains on the vascular system. Practically, most physicians do not see the hypertensive patient until the disease is well advanced. With the knowledge that there are numerous conditions which are associated with hypertension, the physician should make a serious attempt to discover any primary causes, if possible. Even if found, the percentage of absolute cures is small. Those cases in which a pheochromocytoma or a unilateral reanl disease is found can receive tremendous benefit from surgery. Once the decision is made that there are no secondary factors which can be corrected, the

physician is faced with the necessity of determining the method of treatment; i.e., whether it is to be medical or surgical.

Before beginning the discussion of the present modes of treatment, I should like to quote the sarcastic remark made by Weiss (115) on the development of treatment. "What has been done in an effort to reduce the blood pressure? Because of an ill-founded idea that protein was responsible for hypertension and kidney disease, the patient was denied meat and eggs, especially red meat, which for some reason was looked upon with particular dread. His diet was rendered even more unpalatable by the withdrawal of salt. Sympathy would doubtless have been extended to this half-starved fellow except that he probably was not able to eat anyway, his teeth having been extracted on the theory that focal infection had something to do with hypertension. Even before this he had sacrificed his tonsils and had had his sinuses drained because of the same theory. In case some food had been consumed, the slight colonic residue was promptly washed out by numerous colonic irrigations, especially during the period when the theory of auto-intoxication was enjoying popularity. To add to his unhappiness he was often told to stop work and exercise. Of course, he was denied alcohol and tobacco as well as coffee and tea, and as a

climax to the difficulties of this unfortunate person, he may now fall into the clutches of the neurosurgeon, who is prepared to separate him from his sympathetic nervous system."

The medical treatment is divided into two lines of attack; the attempt to regulate the general psychic or emotional factor and an attempt to use specific drug therapy. Of the latter, the use of sulphocyanates and the experimental use of renal anti-pressor agents are the latest methods in use. Any attempt to evaluate the results of treatment is made difficult by the spontaneous variability of the blood pressure in hypertensives.(9)

One of the first to stress the psychic factor in treatment was Moschcowitz (116) who described a certain type of person in whom hypertension is very likely to occur. The importance of the psychic factor has come in for a great deal of discussion. Robinson (117) has reported a case of hypertension with an almost sudden disappearance of symptoms when the patient was relieved of an emotional strain but without any change in the elevated blood pressure. Even shortness of breath on effort, which was thought to be due to the organic condition, disappeared suggesting that dyspnea, at least in this case, was of psychogenic origin. This he thought emphasized the importance of not overlooking any psychic influences even when

a satisfactory explanation for the symptoms is found in an organic condition. Perhaps one of the largest attempts to treat the psychic factor is that done at Pratt's Clinic where the class method is used. (118) They depend upon the testimony of older members of the class, explanation of the pathological physiology of the hypertension and the fact that the symptoms of early hypertension are psychic in origin. They admit that the approach is largely psychologic and that some of the patients show no striking change in the level of their blood pressures, but that in two-thirds of those who have made three or more visits to the class a fall in pressure of from 18 to 46 mm. of mercury has been observed. Palmer(119) believes that symptomatic relief is obtained in ninety per cent of the mild cases of hypertension, seventy-five per cent of the moderate cases, and forty-six per cent of the severe cases. In a later article (120) he cites further instances of hypertension which were apparently due to some emotional maladjustment and which showed remarkable drops in blood pressure after psychic therapy and adjustment. However, he poses the interesting question, "Will these patients in middle life or later, with the strains and adjustments of that period, develop essential hypertension?"

Rennie (121) believes that some hypertensives reveal lifelong instability and emotional lability expressed in

easy depression and anxiety. He stresses the importance of recognizing this factor, when present, and taking it into consideration in the treatment. He warns of the poor results of fighting the patient's fears instead of seeking his cooperation.

Thus, it can be seen that this general therapy is an attempt to cushion the hypertensives vascular system from the additional insults of emotional maladjustments. Sedation is widely used, of which phenobarbital is perhaps the most commonly prescribed. The dosage varies with the individual and is regulated so that there is grossly imperceptable dulling of the mental abilities of the patient. The other forms of therapy, such as avoidance of over-eating, use of tobacco, special diets, etc., can be applied only when indicated. Thus the overweight hypertensive is advised to reduce, not because the obesity is the cause of the hypertension but because it produces an additional strain on the already overworked heart. Tobacco should be eliminated only if it is proven that smoking does increase the nervous tension of that particular patient. Its excessive use is to be condemned but this is true for all and not just the hypertensive. Special diets are not used unless renal failure or obesity are present. The restriction of salt is no longer considered to be of any value.

The use of sulphocyanates, either the sodium or potassium salt, did not come into its own until the work of Barker (122) in 1936 when a method of accurately determining the blood level of the sulphocyanate and an explanation of the reason for the previous untoward toxic reactions were introduced. Barker believed the toxic reactions were due to the variability of different individuals in the ability to clear the cyanate from the blood stream. The untoward symptoms includes skin eruptions, rhinitis, nausea, vomiting, gastro-intestinal pain, diarrhea, marked weakness, increased nervousness, mental confusion, aphasia, hallucinations, and angina pectoris. These toxic reactions may appear suddenly and without apparent relation to the daily or total dosage. (123) Knowing that psychic therapy had a pronounced influence on the symptoms of hypertensives as well as the actual lowering of blood pressure in many instances, the claim by many oponents of the sulphocyanate therapy was made that the knowledge by the patient that a drug was being given for his disease was the predominent factor in the successful results reported. Massie, Ethridge, and O'Hare attempted to eliminate the psychic factor. (124) They observed a number of patients during a three months control period to establish their usual blood pressure level. The patients were then put on sulphocyanate therapy for a period, and then without

telling the patients only the vehicle for the drug was given. In the majority of cases during the period of active therapy, there was a drop of blood pressure on an average of from 66 to 21 mm. of mercury, systolic, and an average of from 33 to 8 mm. of mercury, diastolic. They noted that during the period when only the vehicle was given, the original complaints reappeared and the blood pressures gradually rose to approximate those of the original control period. Massie (123) recommends that a five per cent solution in any vehicle, such as aromatic elixer and syrup of wild cherry, be given. Of this solution he gives three daily doses of .2 Gm. (4cc.) for four or five days; following this he gives the same dosage twice daily for a similar period. After that, the amount given for the maintenance dose will depend upon the blood level of the sulphocyanate. The optimum level, first established by Barker (122), varies between 8 and 12 mg. per 100 cc. of blood. Kurtz and his co-workers (125) report eleven years of study on fifty patients with essential hypertension in which potassium sulphocyanate was used. They found good subjective improvement in 63 per cent; fair in 20 per cent; and disappointing in 17 per cent. Flexner (126) disagrees with the idea of an optimum blood level. He has found that a level of as low as 3 mg. per cent can be effective in some patients. He feels that the

optimum blood level must be determined for each patient and not judged by set standards.

The contraindications for use of sulphocyanates are not well established. It has been stated that no one over sixty years of age should be treated with this drug (123) but this has been ridiculed by others. (126) Most authorities agree that the patient whould be cooperative and fairly intelligent since the drug is poisonous and fatal results have been described (127) though these were before the use of blood level checks. A history of a recent cerebral accident or heart attack has been suggested as a contraindication.(123) Renal studies should be made since the renal function should be fairly normal if the drug is to be used.

Here, again, we are presented with a mode of therapy which is not curative but palliative. It serves as a check on the progress of hypertension in those cases in which it is successful. No guarantee of its effectiveness can be made. The rationale of its use is purely clinical since the mode of action has not been determined.(123)

Recently there has been a great deal of experimental work on the treatment of hypertension with renal extracts. The idea is not new, in fact, the earliest studies were made by Brown-Sequard and d'Arsonval in 1892 when it was reported that nephrectomized animals were improved by

crude renal extracts. This was also reported by Meyer the following year. (128) The earlier work which as done on the hypotensive action of renal extracts did not receive much attention mainly because there appeared to be no rationale for their use. The work of Goldblatt that started new investigations into the role of the kidney in hypertension also stimulated the more recent work on the use of kidney extracts in therapy.

In the original work of Tigerstedt and Bergman (129) it was pointed out that renin produced a greater rise in blood pressure in nephrectomized animals which was thought to be due to a failure to excrete some pressor substance. Merrill, Williams, and Harrison (130) found that the increase in sensitivity did not appear immediately after nephrectomy but only after a number of hours had elapsed. This led these authors to believe that normal renal tissue might form some substance which was distributed in the body and which had the property of limiting the pressor effect of renin. Other observers (131,132) have also noticed the increased sensitivity of nephrectomized animals to the renal pressor substance. The work on renal ischemia had shown that a unilateral ischemia produced only a temporary hypertension but that removal of the remaining normal kidney would produce a persistent elevation of the blood pressure.(43) This fact along with

the observations of Katz and his co-workers (133) that renal hypertension is dependent on the ratio of ischemic to normal kidney tissue was more evidence for the theory that the kidney produced a renal anti-pressor substance. It was known that the blood pressures of hypertensive animals showed a marked decline during the last months of pregnancy and that the blood pressure returned to the previous high levels following delivery. (44) This was explained by the possibility that either the placenta or the fetal kidneys produced some substance, anti-pressor in nature, which was lacking in the hypertensive mother.

Johnson and Wakerlin (134) claimed to have produced antisera in hogs, rabbits, and dogs against the renal pressor substance of the other animal. They used precipitan reactions as the basis for their theory. Later this was disproved by Winternitz, Mylon, and Katzenstein (135) who claimed that the precipitan reactions obtained previously were due to the renin protein or the proteins accompanying renin and not to the renin itself. They demonstrated that repeated injections of renin would not diminish the blood pressure of hypertensive animals. Grollman, Williams, and Harrison (136) prepared an extract of renal tissue which they first tested in rats and dogs. They found the oral administration was preferable to the parenteral route because of the fewer toxic reactions even

if larger dosages were needed. What toxic reactions that were seen were thought to be due to the ischemia resulting from the reduction of the blood pressure in the presence of the sclerotic vessels of a long standing hypertension. Several hypertensive patients with advanced or severe hypertension were treated by oral administration of the extract. They obtained a reduction of blood pressure in most of the patients treated and showed a rise to previous hypertensive levels within a few days after the discontinuation of the extract. The extract had no effect on the blood pressure of normal animals. Page, Helmer, and others (137) demonstrated the effects of extracts of kidney and muscle on eight patients with hypertension as well as in animal experiments. In all a sharp prolonged fall in arterial pressure occurred whether the hypertension was of the malignant or essential variety. The drop in blood pressure was observed in from twelve to forty-eight hours after injection depending upon the dasage. Experimentally it was noted that the extracts had the ability to reduce the activation of renin by plasma. Corcoran and Page (26) in their studies with diodrast and inulin clearances noted that the decreased arterial pressure following sympathectomy or the use of sulphocyanate was not usually associated with the undoing of the efferent arteriolar constriction; i.e., increase in

the diodrast excretion. The action of the renal antipressor extracts, on the contrary, was found to be associated with relaxation of the efferent arteriolar constriction, a finding which, to them, suggested that these extracts inhibit the action of angiotonin and the renal vasopressor system in hypertension.

The use of renal extracts in therapy is as yet too new to be judged. The rationale for their use is good since the work of the past decade has assigned the kidney an important role in essential hypertension. The active principle of the extracts is as yet unknown, but it is to be hoped that future work will solve some of the present problems of its use.

SURGICAL TREATMENT

The progress of the surgical treatment of essential hypertension can be followed in line with the developing concepts of its etiology. Thus, when focal infections were thought to play a part in the etiology of essential hypertension, surgical removal of the foci of infection was attempted when found. On the assumption that the hypertension was the result of overactivity of the adrenal glands, the partial removal of the normal organs was once practiced though this was done largely in France. The application of X-Rays over the pituitary and adrenal areas has been advocated in this country (138) but no further

work has been done on this form of treatment not only because it lacks any rationale but also because the procedure is dangerous.

The main attack on the surgical treatment of essential hypertension has been through the practice of splanchnectomies. This was first suggested by Danielopolu in 1923. The experimental work on neurogenic hypertension as well as the knowledge that the vascular reactions took place largely in the splanchnic area (88) formed the basis for its clinical application. The surgical technic which is used varies with the individual surgeon though there are several main types of operation. Successful results have been claimed for each type and in this line of thought Goldblatt (139) has stated, "It is also noteworthy that only the originators of each operation have been enthusiastic about the beneficial results of their operation and have reported poor success or failure with other methods. As in the case of other methods of treatment, factors other than the level of the blood pressure, such as disappearance of headache, and other subjective symptoms have been used in the evaluation of the effect of the treatment. The unreliability of such criteria need not be stressed. It is a striking fact that no matter what the type of surgical operation on the nervous system, the percentage of cases in which a significant lowering of the blood pressure has

been reported is about the same for all. After all the operations, the percentage of cases in which there is a return of the blood pressure to normal is relatively small." Goldblatt's statement is perhaps, over critical but it does express a basic fault in most of the reported success in the treatment of essential hypertension by surgery.

Recently de Takats, Heyer, and Keston (140) published a comprehensive study on the various types of sympathectomies, and the following classification has been taken from their work:

1. Supradiaphragmatic Splanchnic Nerve Section. In this operation one interrupts the splanchnic nerves above the diaphragm and excises the ninth to the twelfth sympathetic ganglions. The operation does not permit the examination of the kidney and the adrenal gland and cannot interrupt the lumbar sympathetic nerves.

2. Infradiaphragmatic Splanchnic Nerve Section. The splanchnic nerves are severed below the diaphragm, together with a small slice of the celiac plexus. In addition, the first and second lumbar ganglions are removed. Regeneration of the splanchnic nerves, which was described in animals by Cuthbert and de Takats (141), is difficult to prevent after this operation. In obese patients or in those who have a retroperitoneal lymphadenopathy, the identification of all the splanchnic trunks may be difficult.

Finally, branches that are given off toward the periaortic plexus from the splanchnic nerves and the sympathetic chain above the diaphragm are missed by this operation.

3. Transdiaphragmatic Splanchnic Nerve Section. This operation combines the advantages and eliminates the disadvantages of the two previous operations. It is a complete resection of the major splanchnic nerve, removing it from the fifth dorsal root down to its entrance into the celiac ganglion. In addition the sympathetic ganglionated trunk is removed from the ninth dorsal to below the first or occasionally the second lumbar ganglion. In order to obtain this exposure, the diaphragm must be incised and sutured. Through this approach the renal artery, pelvis, ureter, renal parenchyma, and adrenal glands may be inspected and palpated. The technic of the operation has been described by Smithwick. (142)

4. Omental or Muscular Graft Into the Kidney. After decapsulation and scarification of the kidney a one inch deep incision is made along the whole convexity of the kidney and an omental flap or a pedicled muscle flap is sutured into the incision. This operation has been described by Bruger and Carter.(143)

5. Nephrectomy. This is done for unilateral renal disease associated with hypertension when there is no detectable impairment of function in the opposite kidney.

Another type of operation that has been used in section of the anterior spinal nerve roots of the thoracic and lumbar areas but this operation is so extensive that the operative risk has prevented its use except by a few men.

As with the other methods of treatment certain criteria have been established to determine which patients are more apt to be benefited by operation. At the Mayo Clinic (9) operation is advised only for patients whose blood pressure responds satisfactorily to the following standard tests: 1) slow and intermittent intravenous injection of a five per cent solution of pentothal sodium to a stage at which decrease in the blood pressure no longer occurs; 2) administration of $\frac{1}{2}$ gr. of sodium nitrite at half-hourly intervals until six doses have been given; 3) administration of 3 gr. of sodium amytal each hour for three successive hours; and 4) hourly determination of blood pressure during rest and sleep for a minimum of twenty-four consecutive hours. If the blood pressure decreases to normal or to nearly normal as a result of all these measures, the patient may be considered a satisfactory candidate for operation. In addition to the unfavorable response of the blood pressure to the above tests, contra-indications are as follows: age greater than fifty years, congestive heart failure, angina pectoris, marked renal

insufficiency, and advanced arteriosclerosis. Spasm and apparent sclerosis of the retinal arteries, retinitis, moderate enlargement of the heart, inversion of T waves in the electrocardiogram, albuminuria and slight reduction in renal function, or a cerebrovascular accident from which recovery has been satisfactory are not, in themselves, regarded as contraindications by the Mayo Clinic.

A rather comprehensive preoperative classification has been compiled by de Takats and his associates (140) which they took from criteria previously reported by Wagener and Keith(144) and Palmer and Smithwick(145). The classification may be found on the next page. They feel that those patients who fall into grade 4, the malignant nephrosclerosis, are not benefited by any of the operations. Those who can be classed in groups 2 and 3 are greatly improved if complete splanchnic nerve section is performed, and those in group 1 have a fair chance for a "cure".

Rytand and Holman (146) believe that the various criteria for operation are worthless as far as prognostic significance. They think the main role in deciding the outcome is played by the presence or absence of malignant hypertension as evidenced by renal and retinal lesions.

Just what the value of the criteria is, is not definitely established. It is known that some patients remain in one classification for years while others may

TYPE	GRADE I Early or Mild	GRADE II Moderate	GRADE III Late Benign	GRADE IV Malignant
Symptoms	Early morning headache, vertigo; or no symptoms	Same	Nervousness, headache, dyspnea on exertion	Nervousness, visual disturbances, severe headaches, muscle pains.
Retinal Changes	No change or minimal narrowing of arteries	Arteriovenous compression, moderate sclerosis of arteries	Recurrent angiospasm, arteriolar sclerosis, hemmorrhage exudates; no papill-edema	Same as III plus papill-edema
Blood Press.	200/120 to 150/100; occasionally normal at rest	250/130 to 170/100; lower at rest but never norm.	almost always over 170/110; fluctuates upward	Diastolic very high; fluctuates upward
Heart	Minimal if any change	Slight enlargement; left ventricular preponderance; good funct.	Enlarged; actual or impending congestive failure; sometimes angina	Congestive or anginal failure often present
Urine	Normal	No change or mild albuminuria & casts	Albumin, casts; often rbc	Albumin, casts, and rbc
Renal Funct.	Normal; urea clearance may be slightly decreased	Slight decrease; urea clearance 30 to 40cc.	Impaired; urea clearance 20 to 30 cc.	Poor; urea clearance 7 to 20 cc.
Five Yr. Mortality Percent.	30	46	80	99

rapidly progress from a mild hypertension to a severe form. However, on the basis of the results of using these criteria for operation most men feel that they have a definite place in selecting patients for sympathectomy.

Evaluation of the type of operation which is most successful is difficult since most of the reported percentages of success are about the same regardless of the type of operation. Crile (147) prefers the bilateral celiac ganglionectomy which he claims has a mortality rate of only 2.8 per cent if done correctly. He finds the blood pressure is reduced to normal in 17 per cent, and partial or complete symptomatic relief in 87 per cent twelve months after the operation. Allen and Adson (148) report excellent results in reduction of the blood pressure in approximately 13 per cent of their cases and fair in about 18 per cent. In 30 per cent of the cases the blood pressure was not affected, and in 39 per cent they got good immediate results which lasted for weeks or months, but the pressures returned to preoperative levels. Regardless of the effect on the blood pressure, they claim 80 per cent symptomatic relief. Their operation is section of the major, minor, and lesser splanchnic nerves, with partial resection of the celiac, and resection of the upper lumbar sympathetic ganglions. Crane (149) uses a total sympathectomy and claims symptomatic relief in 75 per cent

of his cases and a good lowering of the blood pressure in 42 per cent. Craig and Adson (150) in a report on 237 cases treated by subdiaphragmatic sympathetic denervation claim relief of headache in 85 per cent, of nervousness in 71 per cent, precordial pain in 75 per cent, and fatigue and dyspnea in 45 per cent. They obtained a significant drop in the blood pressure in 52 per cent. Bruger and Carter (143) who used the renal graft method in attempting to establish a collateral circulation did not obtain successful results since they found that the drop in blood pressure after operation and relief of symptoms only lasted from two to six months.

The rationale or basis for the treatment is still under discussion. Experimentally it has been shown that only a total sympathectomy is effective in reducing the blood pressure of the neurogenic hypertension (90, 91) and that the sympathetic nerves apparently had nothing to do with the renal hypertension. (17,18,19,20,21) Corcoran and Page (151) studied two patients preoperatively and postoperatively by diodrast and inulin clearance tests and found that renal hyperemia was not produced by sympathectomy. They suggested that the beneficial results were due to: 1) decrease in splanchnic tone causing a decrease of venous return to the heart, especially in the erect posture, 2)this resulting in decreased arterial pressure because of

limited cardiac output which, 3) tends to slow down any arteriosclerotic process which may in turn in the kidney also slow down the production of renin and delays the hypertension. This theory has also been suggested by Leonard and Oughterson (152). De Takats and his associates (140) have drawn an analogy between the surgical treatment of hypertension and that of cancer in that, in both, it offers at least palliative relief. They suggest that the sympathectomy by decreasing the renal ischemia in some way inhibits the formation of the renal pressor substance. In addition to this they claim that postoperative studies with diodrast and inulin show a relaxation of the glomerular efferent arterioles which is in direct contrast to the results reported by Corcoran and Page. In an effort to explain the mechanism by which relief is brought about they suggest six possibilities: 1) actual lowering of the blood pressure, 2) pronounced polyuria, with diminished excretion of protein and improvement in renal function, 3) postural hypotension with consecutive decrease in venous pressure and effective circulating blood volume with decrease in papilledema and improvement in cerebral circulation, 4) decrease in reflex nervous irritability due to adrenal denervation, 5) sensitivity to epinephrine diminished and sensitivity to insulin increased, and 6) palpitation of the heart and dizziness disappear.

It must be admitted that the foundations for the rationale of the surgical treatment of essential hypertension are none too steady and that the reports are in too much disagreement for a convincing argument. Even more damaging was the work of Volini and Flaxman (153) who studied the records of Cook County Hospital and showed that the symptomatic relief and reduction in blood pressure in hypertensives resulting from non-specific operations (hysterectomy, prostatectomy, cholecystectomy, etc.) were similar to and sometimes better than those obtained by specific prodedures, such as sympathectomy, performed especially for those purposes in the treatment of essential hypertension. More work of this nature will have to be done before the surgical treatment of essential hypertension can be condemned, especially since good results are reported by recognized surgeons.

DISCUSSION

Those methods of treatment which are now in use have been presented. Perhaps the chief criticism of all of these methods in there lack of any real rationale and the palliative rather than curative results.

The medical treatment always consists of an attempt on the part of the physician to prevent additional shocks to the already burdened cardiovascular system in the hypertensive. This is accomplished by psycho-therapy and the use of sedatives. It must be admitted that the almost miraculous cures of hypertension by psycho-therapy are probably over-rated. However, such over enthusiastic reports serve their purpose in that they prevent the practicneer from over-looking the emotional factors in each case of essential hypertension, or in fact, any type of hypertension. They serve to guard against the idea that so many grains of phenobarbital daily is a cure for essential hypertension. Lastly, it must be remembered that a great number of patients are not suited for any of the so-called specific measures and the only hope of helping the patient lies in the psycho-therapy.

The use of sulphocyanates has been discussed, and the dosages and methods of administration have been given. There is no known rationale of treatment and the results are not too encouraging. The difficulty lies in the

necessity of constant blood level checks at least until the optimum dosage for the particular patient has been determined. This is not only costly to the patient but time consuming for the physician. Thus, if the patient is willing to undergo this form of treatment with the knowledge that it may do him no good, the physician should probably attempt to lower the blood pressure by use of sulphocyanate. Here, again, one is presented with a serious disease condition and any method of treatment is worth trying so long as it offers even a slight chance of being successful.

The use of renal anti-pressor extracts is the new method of attack on essential hypertension. As was discussed earlier, if the group of so-called essential hypertensions, is actually a renal condition, then this form of therapy is specific. As yet the use has been too limited to form any definite conclusions, but to date, the results are encouraging. Perhaps the day is not far when the "dread disease of hypertension" will no longer rank in the leading causes of death.

The surgical treatment of essential hypertension has been presented with the various types of operation now in use. Surgery offers at least, some palliative relief though the claims of some surgeons would indicate that it promises a cure. Surgical removal of the splanchnics

does give a fairly high percentage of relief from subjective symptoms of hypertension but it does not offer much promise in lowering the blood pressure. The mortality from the operation itself is not high enough to be a contra-indication, but in many instances the expense of the surgeon and hospitilization is enough to prevent its use. If the surgeon can offer a chance of relief from symptoms for even a few years to a patient in whom other methods of treatment have failed, the operation should be performed providing, of course, the condition of the patient does not contra-indicate surgery.

The treatment of essential hypertension is, indeed, analagous to the treatment of cancer in that the physician is presented with a disease process about which he knows little and has no specific mode of therapy. He is offered several types of treatment, none of which can offer more than palliative relief. Small wonder that the medical profession is watching the recent developments with the renal anti-pressor extract which may become another candidate for the scrap pile or may revolutionize the treatment of hypertension as much as the sulfanilamide compounds have revolutioized the treatment of infection.

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