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Etiology of essential hypertension

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ETIOLOGY of ESSENTIAL HYPERTENSION

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That arterial hypertension is a common disease or perhaps more properly, a symptom complex, has been appreciated by physicians for many years as an important cause of disability and death.

The true incidence of this disease has not yet been determined in any significant fraction of the earth's population. The general belief among observers, however, is that the incidence is increasing. To determine whether this increase is actual or apparent is, at the present time, impossible for several reasons. Ignorance concerning the true nature of the disease has been, and is yet, a barrier preventing the application of adequate classification upon which reliable statistics must be based. Because of the confusing terminology many deaths are listed under other diseases which in all probability caused, or resulted from, arterial hypertension.

Fahr in 1928 estimated that approximately 140,000 persons die each year from the consequences of high blood pressure. Of these he estimates about one-half are the result of heart failure due to hypertension. He states that these deaths are listed statistically under numerous headings, the most frequent of which were chronic myocarditis, arteriosclerotic heart and mitral insufficiency.
Janeway in 7,872 private patients found 11.1% to have systolic blood pressures of 165 mm Hg or more. Most of these he classified as essential hypertension.

E. J. Stieglitz estimated the incidence of hypertension in white male adults in this country to be 7.2%.

R. C. Weller states that essential hypertension is primarily a disease peculiarly frequent among Americans. He attributes this to the stress and strain of our mode of living especially of those engaged in the business world. This factor has been widely accepted by practicing physicians in general.

Fishberg, however, feels that the disease is, by no means, confined to the middle and upper classes stating, "I have observed that the incidence of essential hypertension is high among dispensary patients, particularly among women at or shortly past the menopause. Certainly if worry and other forms of nervous strain are contributory factors in the genesis of essential hypertension, this class of poor women should have its full share and more of the disease."

While the opinions of individual observers on the incidence of this disease show considerable variation
it is universally agreed that it is a major cause of
death during the most productive and useful period of
man's life. This together with the fact that the fun-
damental nature of the disease remains obscure even
after several decades of intensive study by the keenest
of observers not only stimulates the curiosity but
constitutes a challenge to every person associated with
the medical profession.

The object of this paper is to discuss the factors
that are believed to have some etiological significance
in essential hypertension.

The blood pressure level is generally conceded
to be the result of three major factors: 1. The
cardiac output per unit of time, 2. the "run-off"
from the arterial termination perhaps better designated
as the peripheral resistance to blood flow and
3. the viscosity of the blood, 4. the blood volume,
5. arterial elasticity.

Each of these factors is, of course, the resultant
of one or more mechanisms. The minute output of the
heart is the product of the heart rate and the stroke
volume. Peripheral resistance is determined chiefly
by the total cross sectional area of the arterioles
and to a much lesser extent the capillaries.
The blood pressure will also vary if the amount of blood filling the vascular tree varies.

Of all these mechanisms operating to maintain uniform blood pressure the peripheral resistance to blood flow is the one most pertinent to the subject under discussion.

Physiologists and clinicians alike are generally agreed that essential hypertension is the result of an increased resistance to peripheral blood flow. This conclusion was first supported chiefly by negative evidence. Nearly all investigators agree (certain rare cases excepted) that the cardiac rate in essential hypertension is within or below normal limits.

Radiological studies and post mortem examinations of persons dying in the early stages of essential hypertension show no significant cardiac enlargement. It would appear logical that the heart itself is not the basic cause of the hypertension. This has been confirmed by Plesch, Burwell and Smith, Lauter and Baumann and several other investigators.

It has been shown (Fishberg's book) that in normal persons the circulating blood volume may be greatly increased without any significant change in the blood pressure. Surgical experience, however has taught
us that the converse does not hold true.

As Fishberg has pointed out the blood pressure in polycythemia vera is usually within normal limits and yet it is known that the blood volume in this disease may be several times that in normal persons.

Although the methods for determining blood volume are not absolute in their accuracy comparative determinations using normal persons as controls satisfy the requirements in this problem. Hartwich and May, Van Slyke and Stillman and numerous others using the same and different methods in the study of blood balance in normal and hypertensive persons have concluded that the blood volume is not significant factor in initiating hypertension. However Miller and Williams have found that once hypertension is established the blood pressure may be considerably elevated by the ingestion of excessive amounts of water. The amount of water required to accomplish this, however, was far in excess of the average water intake of persons with hypertension.

That increased viscosity of the blood might be an important factor in the production of hypertension was suggested by Galadin and Mortinet, Harris and McLaughlin. Increased blood viscosity was found in 35 out of 40 hypertensives.
Brundage, Cantarow and Griffith made careful observations on 21 hypertensive patients. Their findings were as follows:

(1) The total plasma protein concentration in the 21 cases was within normal limits, the average being slightly higher than the average for the normal controls.

(2) The albumin-globulin ratio were approximately normal but in some cases the fibrinogen fraction was notably increased.

(3) The plasma viscosity in general was higher in hypertensives than in the control group but there was no correlation between degree of increased viscosity and the degree of hypertension.

(4) They found the concentration of fatty acids to be higher than in normals but state that lipid concentration of the plasma has no relation to viscosity.

From these studies it would seem safe to conclude that the viscosity of the blood has but little, if any, relationship to arterial hypertension.

That the state of elasticity of the arterial tree is not questioned. It is this quality of the conducting system that acts to maintain a comparatively smooth, even flow of blood activated or propelled by intermittent pulsations of the heart. This elasti-
city in function is analogous to the air chamber of a continuous-flow hydraulic pump. Both act as "shock absorbers" resulting in a much more even and continuous flow than if the fluid were being driven thru a system of rigid tubes. Also, as the air chamber of the continuous flow pump operates to maintain flow during the filling of the pump cylinder, so the elastic vessels of the arterial tree maintains the diastolic pressure during the filling of the ventricles. Were the arteries absolutely rigid the pressure during systole would rise to a much greater height and during diastole would quickly fall to zero.

From histological observations on the arterial bed it is seen that the aorta and its larger branches contain a predominant amount of elastic fibers in contrast to the smaller arteries and arterioles the walls of which are predominantly muscular and are incapable of much passive distention.

A decrease in the distensibility or elasticity of the great vessels such as may exist in advanced atherosclerosis tends to increase the systolic pressure, but to lower the diastolic pressure, disrupting the "one-two-three" relationship between pulse pressure, diastolic, and systolic pressure. A state of hypertension
does, then, exist, but it is not like that seen in essential hypertension where not only the systolic, but the diastolic pressure as well becomes elevated and in which the "one-two-three" relationship is not disturbed.

It would appear from these facts then that loss of vessel elasticity is not the change responsible for essential hypertension.

The foregoing facts exclude all mechanisms but that of an increased peripheral resistance as the immediate cause for essential arterial hypertension. The question naturally arises, "Where along the arterial conducting system does the increased peripheral resistance arise?" "How does it operate?"

Prinzmetal and Wilson in their ingenious experiments have supplied the answer to this very important question. Their work deserves a brief consideration.

Using the plethysmograph they measured the blood flow during the resting state in the arms of both normal and hypertensive patients. They found no significant differences in the two groups. This supports the concept that the increased peripheral resistance is generalized and is not confined to the splanchnic area. For if the increased resistance were confined
to any one area such as the splanchnic we would expect an increased amount of blood to be diverted into other channels such as the extremities.

The hypertensive patients also showed an increased blood flow in response to heat and reactive hyperemia equal in degree to that produced in normal persons. This tends to prove that the arterial channels in hypertensives are capable of considerable dilatation and that the increased resistance to flow is caused by hypertonus or spasm of the arterioles rather and not to organic changes in the vessel walls. If the walls had suffered organic changes there would be a decreased response to physiological dilatation as produced by heat.

They also deserved credit for the observation that sympathetic dilatation produced by the heat test produces no greater increase in blood flow in hypertensives than in normal persons. This suggests that the hypertonus is not of vasomotor origin.

Patients suffering from coarctation of the aorta in which the upper extremities and head only are subjected to increased blood pressure, show a greater increase in blood flow in the arm in response to the heat test. This they believed to indicate the presence
of vasoconstriction of sympathetic origin in coarctation as contrasted to essential hypertension in which the generalized constriction is due to inherent spasm of the vessels independent of the autonomic nerves.

Using novacaine they blocked the nerves of the extremities of both normal and hypertensive patients. In both they observed some increase of blood flow to the arm, but the changes were equal in the two groups. They reassured that if the vasoconstriction in hypertensives were due to over activity or hyper-irritability of the autonomic nerves blocking of these nerves in the hypertensives should result in a greater increase in blood flow than a similar procedure would produce in a normal person.

They concluded from this study that the arterial hypertonus is an intrinsic spasm of the vessels and that it is independent of the autonomic innervation.

Following these experiments Oppenheim and Prinzmetal performed some clever, and yet comparatively, simple experiments designed to locate the site of the increased peripheral resistance.

The possible sites are: (1) The arteries, (2) the arterioles, (3) the capillaries and (4) the veins. Ellis and Weiss had previously shown that neither
venous nor capillary pressure is increased in hypertension.

While it is well known that in a tubular fluid containing system peripheral constriction of the tubes causes a rise in pressure between the constriction and the driving source or hydrostatic head. The quantitative relationships involved are not so apparent nor generally appreciated.

Paiseville's laws of hydrodynamics state that the pressure relationship in such a system is a function of the caliber of the outflow tubes, but that the pressure varies inversely as the fourth power of the radius of the outflow tube. This means that only minute alterations in the diameter of the tube result in profound changes in the pressure. These men point out that such small changes in diameter of vessels were probably no greater than the inherent error in the method of measuring arterioles. For this reason they abandoned the methods of Kernohan, Andrus and Moritz in favor of direct pressure determinations.

Again, according to the laws of hydrodynamics laid down by the physicist Poiseulle, the propelling force being equal the pressure within the system is proportional to the resistance against which the fluid
volume must flow. They then set out to determine the pressure gradient between the large arteries (brachial) and the pre arteriolar arteries of the fingers in both normal and hypertensive persons. They made blood pressure determinations in the brachial and digital arteries. In comparing the results obtained from both hypertensive and normal persons they found that the pressure fall or gradient between brachial and digital arteries to be the same. From this they logically concluded that the radicles offering the increased resistance did not lie between the brachial and the digital arteries. Therefore, the point of resistance must lie between the digital arteries and the capillaries. Since the digital vessels are the smallest of the true arteries and are separated from the capillaries only be the arterioles they concluded that the increased resistance was caused by changes in the arterioles. Whether this change in arterioles was functional or organic they give no opinion.

Another mechanism serving to regulate endovascular pressure is the proprioceptive reflex mechanism which recently has been extensively studied by Heymans and his associates in an attempt to discover its relation, if any, to hypertension. The important points on
this subject have been recently reviewed by Heymants and
deserve, at least a brief, consideration.

It was shown first by von Cyon and Sudwig in 1866
and more recently by Anrep and Starling, and Ladon and
Heymants and others that the cardio-aortic portion of
the arterial tree is supplied with a "presso-receptive
reflexogenic innervation". Rise of pressure in the
left heart of aortic arch acts upon specialized nerve
endings in the walls of these structures causing affer-
ent impulses to be sent to the central nervous system
via the cardio aortic nerves. These impulses result
in cardiac slowing and peripheral vaso dilatation which
tend to reduce arterial pressure. Conversely when the
pressure within the left heart and aorta is reduced
the pressoreceptors in this area send impulses to the
central nervous system resulting in acceleration of
cardiac rate and minute out put and peripheral vaso
constriction-- all of which cause the endo vascular
pressure to rise. These two, oppositely directed
reflexes result in an equilibrium that acts to main-
tain a constant pressure.

Cooper, Marey and other workers have shown that
carotid-cephalic arterial pressure changes cause
cardiac and vasomotor reactions.
Occlusion of both carotids causes immediate cardiac acceleration and peripheral vaso constriction while increasing carotid pressure produces diametrically opposite effects on the heart and peripheral vessels. This mechanism was first believed to be due directly to changes of blood pressure acting on the central cardio-vascular centers.

Heymans points out that the theory of direct central control of blood pressure regulation was generally accepted until 1924 when Hering and himself revived the ideas of Pagano and others that the regulation was not directly central.

These workers showed that at the bifurcation of the carotid arteries-- the "carotid sinus" is endowed with special nerve endings in both the adventitial and sub endothelial portions of the wall, which transmit impulses to the central nervous system via the carotid sinus nerves. Heymans and his associates performed one beautiful experiment which demonstrated the function of this special vascular area.

They were able, to excise the carotid sinuses from both carotids of one dog in such a manner that these arterial segments were attached to the dog only by the carotid sinus nerves. The isolated segments
were then perfused by either blood from another dog or by a special perfusing pump, so that the pressures within the isolated segments could be altered at will and the blood pressure changes in the dog could be studied.

They found that an increase in the isolated carotid sinus caused a fall in arterial pressure of the dog. Conversely, reduction of pressure in the isolated segment caused a general rise in the dogs arterial pressure. They demonstrated that the mechanism was sensitive, to changes of any one mm Hg.

The rise of carotid sinus pressure produced a compensatory dilatation. Lowering of carotid sinus pressure produced reflex arterial and venous constriction.

Other experiments showed these vasomotor reactions to be confined chiefly to the splanchnic area.

In 1923 Bainbridge and McDowall showed that the zone at which the vena cavae enter the right auricle also possessed special innervation which acted reflexly to maintain equilibrium.

Since then the existence of similar specialized areas have been demonstrated in the pulmonary and in the coeliac zones, all of which operate to maintain constant pressure.
Increased pressure in the carotid sinus produces reflex reduction in adrenaline secretion and conversely reduction of carotid sinus pressure causes reflex increase in adrenaline out-put.

J. M. Rogoff and E. Marcus in a recent article review the relationship between the adrenal gland and blood pressure.

Before the turn of the present century Ascher experimenting with dogs reported that stimulation of the splanchnic nerves produced a rise in blood pressure and an increase in the concentration of blood sugar and adrenalin. These observations were confirmed by Cannon and Pay. The latter in further experiments on dogs observed that during emotional storms the adrenaline concentration of the blood accompanied the rise in blood pressure. It was from these observations that they formulated the well-known emergency theory of adrenal function. They also suggested that some functional perversion of the adrenal glands might be an important factor in clinical hypertension.

Following these reports Elliot suggested that under some conditions the adrenalin secreted might return to the adrenal glands via the blood and here stimulate them to secrete more adrenaline thus setting
up a vicious cycle. The hypothesis is analogous to that of creating a perpetual motion mechanism and has since been definitely proven to be untenable.

Dragstedt showed that continuous injection of excessive amounts, 10-15 times normal, invariably resulted in death of the experimental animal within a few days. Rogoff and Marcus showed by careful quantitative studies using reliable analytical methods that the adrenalin secretion is not changed during, or following parenteral adrenalin administration. They found also that injected adrenalin disappears from the blood stream almost immediately following injection.

These facts destroy Eliot's theory.

Another factor that bears a limited but consistent relationship to blood pressure is weight. This correlation holds in all age groups. Michael showed that even in children the blood pressure increased up to certain limits with the weight. Symonds, Alvarez and other investigators in examining large groups of men have also found that thin persons generally exhibit some degree of hypotension and that persons over weight nearly always have some elevation of blood pressure.

This is not surprising because we know that by
increasing the amount of body for the peripheral vascular area must also be increased. This constitutes an increase in the peripheral vascular surface which we have seen necessitates a compensatory rise in blood pressure. It has been demonstrated many times that weight reduction in both obese and normal persons results in a depression of blood pressure.

In the examination of the body of a person known to have suffered from hypertension three pathological findings are almost always present. These are: (1) Hypertrophy of the heart, (2) arteriosclerosis and (3) changes in renal structure. It is generally agreed among investigators that these three pathological conditions are also the immediate cause of death in persons with hypertensive heart disease.

It is the relationship of these findings to the disease process that has resulted in great controversy among workers in this field. In particular is this true of the relationship between sclerosis and hypertension--a question that is nearly as old as the study of the disease itself. Richard Bright was one of the earliest writers to comment upon the coincidence of cardiac hypertrophy and arteriolosclerosis.

Gull and Sutton advanced the theory that the sclerosis of the arterioles was the primary pathological
process and that the resultant narrowing of the vascular bed offered increased peripheral resistance to the flow of blood thereby producing an compensatory rise in blood pressure. These men believed the arteriolosclerosis was generalized and involved all arterioles in the body. More recent studies on this point by Jares, Fishberg, Fahr and others pointed out that the arteriolosclerosis was not universal but appeared in the bodies of hypertensives in regular and well established patterns.

Fishberg's studies gave the following incidence.

<table>
<thead>
<tr>
<th>Organs</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>100%</td>
</tr>
<tr>
<td>Spleen</td>
<td>66%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>49%</td>
</tr>
<tr>
<td>Liver</td>
<td>30%</td>
</tr>
<tr>
<td>Brain</td>
<td>19%</td>
</tr>
<tr>
<td>GI tract</td>
<td>9%</td>
</tr>
<tr>
<td>Myocardium</td>
<td>3%</td>
</tr>
<tr>
<td>Skeletal</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>0%</td>
</tr>
<tr>
<td>Lungs</td>
<td>0%</td>
</tr>
</tbody>
</table>

As seen in 72 cases.

In 1925 Jaffe published his pathological findings in hypertensive heart disease. He noted a moderate, but constant dilatation of the afferent arterioles of the kidney in the early stages of the disease. This, he believed, was followed by thickening of the media and proliferation of the intimal cells. In late stages subintimal hyalin masses appeared the enlargement of which caused marked reduction in the caliber of the vessel lumen. Search for similar changes in the brain, liver, pancreas and other organs was fruitless. They
were confined to the renal arterioles. From this he reasoned that the initial dilatation seen in the kidney, but not in other organs was not the result of a universal passive congestion.

Jaffe believed the afferent arteriole dilatation was caused by an increased resistance to blood flow beyond the afferent arteriole. In as much as there was no venous dilatation in the kidney he concluded that the partial obstruction existed in the glomerular tuft itself.

Careful inspection of the latter revealed that in many of the tufts only a few of the capillary loops were filled. In others hyalinization of the capillary tufts, and thickening of Bowman's capsule was apparent.

From these observations he was led to believe that in some way the glomeruli were injured. This caused the tufts to become spastic increasing the blood pressure in the afferent arterioles which caused them first to dilate and later to become sclerotic.

Kernohan and his associates took exception to this belief that the arteriolo-sclerosis was not generalized. They studied the arterioles from pectoralis muscle biopsies on living hypertensive patients. These men made careful measurements of the muscle arterioles
and found that hypertrophy of the media was very common and in some cases demonstrated intimal proliferative changes. Both of these histological changes were more marked and more frequent in the "malignant" than in the "benign" types of hypertension and they attributed the failure of earlier workers to find the same changes to the fact that they did not include the more severe or malignant types.

The work of Kernohan has been criticised on the ground that measurements of arteriolar lumina and walls following fixation does not indicate the true condition during life.

Moritz and Oldt, however, have shown by careful study that the relative dimensions of the arterioles are not distorted by histological fixation and staining methods and that such measurements are an accurate index to the lumen-wall ratio during life.

Having proven the accuracy of their method of measurement, they then studied the arterioles from one hundred cases of known hypertension and also the arterioles from 100 patients coming to necropsy in which there was no clinical nor pathological evidence of cardio-vascular disease.

In the hypertensive patients they found three different types of pathological changes in the arterioles.
(1) The most common change seen was initial hyalinization which consisted of a sub endothelial accumulation of homogeneous acidophilic which appeared to be identical to the ground substance between the medial muscle fibers.

(2) Medial hypertrophy and degeneration are also common. The changes in the media were of two types; one, an increased number of cells in the media; two, an increased amount of intercellular collagen in the muscular wall. These two types of change are frequently seen together.

(3) Endothelial hyperplasia was seen in vessels 50 microns in diameter or larger the endothelial proliferation apparently giving way in smaller radicals to intimal hyalinization.

In the non-hypertensive control group Moritz and Oldt found vascular changes qualitatively much like those in the hypertensive group. The distribution of arteriolar-sclerosis in these cases is as follows:

1. Spleen (highest incidence) 86%
2. Pancreas 43
3. Adrenal capsule 42
4. Renal sclerosis 7
The degree of arteriolo-sclerosis in the kidney was much less severe in this control group.

In the hypertensive group the incidence of arteriolo-sclerosis in the spleen and other organs, kidneys excepted, was about the same. In the kidneys, however, arteriolosclerosis was present in 97% in the hypertensive as contrasted to an incidence of 7% in the controls. Furthermore the sclerosis was invariably much more severe in the hypertensive kidneys. Moritz and Oldt concluded that the physiological state of the vascular system at the time specimens were obtained nor variation of histological technique in preparing tissues for section caused any significant changes in arteriolar dimensions.

Another important observation made by Moritz and Oldt was that the thickness of wall in relation to lumen was not uniform along the arterioles. Andrus was unable to confirm the findings of Kernohan and associates. He stated that post mortem measurements of arterioles did not give a true picture of their condition during life. The control experiments of Moritz have shown his objections to the method to be invalid.

Morlock, after studying a series of hypertensives
and a series of normal controls concluded:

(1) Arterioles of pancreas, spleen liver, G.I. tract of the normal person gave no evidence of thickening of the arterial wall and alteration of wall-lumen ratio due to age.

(2) Marked changes, thickening of the wall as compared quantitatively with normals, was seen in hypertensives of all ages.

He also quotes a personal communication from H. M. Odel who found similar changes in myocardial arterioles although not as severe. This confirms Moritz's discovery of cardiac arteriolar-sclerosis in 50% of his cases.

In conclusion Moritz states, "There is only one situation in which the presence of arteriolo-sclerosis was almost invariably associated with hypertension and where the absence of arteriolar-sclerosis almost invariably betokened an absence of high blood pressure. This was in the kidneys."

Fishberg after post mortem study of 72 hypertensives stated that terminal renal arteriolosclerosis was present in 100% of the cases. The splenic arterioles were involved in about 60%, the pancreatic in 50%, hepatic in less than 30% and cerebrals were involved in less than 20%. 
Arterioles of skin, muscle, myocardium, lungs, intestinal, and thyroid, were rarely and then only slightly involved.

Fishberg states, "The view that holds that hypertension is due to statically increased resistance offered by generalized organic lesions of the arterioles is untenable. A true generalized arteriolo-sclerosis does not exist in association with essential hypertension and therefore cannot be the cause of the latter.

Changes in the arterioles of a nature similar to the arteriolo-sclerosis of essential hypertension occur physiologically with advancing years. Arteriolo-sclerosis is a pathologic exaggeration of these physiological changes resulting from wear and tear incidental to the hypertension."

He goes on to state that, "The anatomic changes in the kidney cannot be reconciled with the theory that essential hypertension is due to a disorder of renal function.

Fishberg in his book on nephritis and hypertension emphasizes the difference between the arteriolo-sclerotic and arteriosclerotic kidney, pointing out that in the latter the larger renal arteries, not the renal arterioles, are sclerosed. This results in isolated
patches of scarring in the renal tissue as contrasted to the generalized, diffuse scarring in the arteriolar-sclerosis of essential hypertension. He does, however, admit that lesions of both types may be encountered in the same kidney.

He describes the histologic renal changes according to the phase of the disease process. In those dying early of cerebral hemorrhage he finds only arteriolar sclerosis with normal kidney parenchyma. In the next stage small isolated areas of parenchymal atrophy separated by large areas of normal kidney tissue are found in addition to the preexisting arteriolar sclerosis. As the disease progresses he finds more and more of these wedge shaped atrophic areas until they coalesce leaving only isolated areas of normal renal parenchymous tissue between.

He believes that glomerular obliteration appears early in the disease and progresses steadily onward until death. Various stages of hyalinization, sclerosis and complete obliteration appear in the same tissue specimen.

Contrary to Jaffe, Fishberg believes the glomerular pathology to be secondary to the arteriolar-sclerosis. The latter process by shutting off the blood supply to the tufts is responsible for the pathological
changes in these capillaries. Along with the hyalinization of the capillary tufts there may, or may not be, thickening and contraction of the glomerular membrane.

As a result of destruction of a glomerulus, the associated renal tubule becomes atrophic and ceases to function. This, according to Fishberg results from combination of failing blood supply and atrophy of disuse.

As the functional units become atrophic, round cell infiltration and fibrosis of the interstitial tissue occurs.

Fishberg, quoting McGregor states that serial sections of arteriolo-sclerotic kidney show the vas efferentia to be normal.

Not all investigators agree with Fishberg and Moritz on the incidence of arteriolo-sclerosis of the kidneys in essential hypertension. Numerous reports are found of normal kidneys being found at necropsy in persons who were known to have essential hypertension. Bell and Clawson claim that in 10% of their cases the kidneys did not show arteriolo-sclerosis, Moritz and Oldt found only 3% of their cases to have no arteriolo-sclerosis. Fishberg has seen only two
such cases. Paz, von Monakow and Kauffmann and others have reported similar observations. The discrepancy in statistics between Fishberg's and Bell and Clawson's reports may be explained by the fact that the latter do not include any arterial radicles larger than the pre glomerular arterioles whereas Fishberg includes interlobular arteries and Moritz included all renal arterial radicles up to and including those 100 microns in diameter.

Wallgren reported eight cases in which no changes other than normal physiological changes for the age group were evident.

Kauffmann reports a case known to be a hypertensive for twelve years that showed no abnormal vascular changes in the kidney. Oppenheim and Fishberg in a case of suprarenal tumor found only slight changes in renal architecture whereas the heart weighed 880 grams.

Shapiro in a very recent article describes a woman known to have suffered from essential hypertension for twenty-five years who died as a result of hemorrhage from a peptic ulcer. Upon post mortem examination the kidneys were found to be perfectly normal. Marked hypertrophy of the left ventricle was present.

It has been known for some time that hypertensive disease has markedly different incidence in the
various racial groups.

Cadbury examined Cantonese students and found the systolic pressure to be 20-30 mm Hg lower than the normal levels in Europe and the United States. The diastolic pressure was also 10-20 mm Hg lower. Cadbury states, "It is a remarkable fact that hypertension as a pathological condition in Chinese is very unusual. In an extensive medical practice of more than 12 years in Canton I have rarely met with hypertension either with, or without, signs of nephritis although chronic Bright's disease is very common. When met with marked hypertension has generally been associated with aortic valvular disease of the heart. Other observers in Canton have confirmed my findings."

He presents the following possible explanations for the absence of hypertension in Chinese:

1. The use of opium.
3. Deficient adrenal glands.
4. Predominantly vegetable diet.
5. Simplicity of life and lack of strain.
6. Tropical climate.

McCoy studied 500 male, adult Bengalis (Hindus from lower Bengal) whose systolic pressure range was from 90 to 105 mm Hg.
Donnison states that hypertension among negroes in Africa is extremely rare.

Blackford quotes Firestone to the effect that hypertension has about the same incidence among Eskimos as is seen in the United States. From this it would appear that a high protein diet is not a basic etiological factor.

Fishberg believes hypertension to be more prevalent among poor Jewish people than in a corresponding group of gentiles.

Schulze and Schwab concluded from extensive studies of negroes in Texas that the incidence of hypertension among them was 2-5 times as high as it is among white people in this country. He does not believe that syphilitic infection can account for this striking incidence. Nor does he believe that dietary factors are of any importance in explaining the phenomenon.

The high protein intake of American negroes as compared to the vegetarian diet of the native African negro, according to these men, is not an important factor. This observation has been supported by Mosenthal and by Thomas. Lieb's report of a man who subsisted, in the arctic, for nine years on meat alone tends to support the idea that diet is not a
basic factor in the cause of high blood pressure.

Stengel and Albutt and others have maintained that over eating and obesity tend to produce hypertension. Schulze and Schwab admit that gluttony is characteristic of the American negro, but point to the work of Terry and others whose work indicates that obesity results in elevation of blood pressure but that these changes are limited physiological responses the nature of which are discussed in the section on physiology.

Schwab and Schulze attempt to evaluate their findings as follows: "Much has been written recently concerning the psychical characteristics of the hypertensive type of individual. The American business man who sacrifices all in his conscientiousness to attain success; worried, over ambitious and tense. To this psychical picture the American negro presents an exact antithesis; he is notorious for his lack of ambition, his indifference toward accomplishment and his slovenly, care-free, easy-going disposition. Yet the negro is by no means stolid nor does he have the platonic disposition of the Chinese. He is exceedingly emotional and syntonic, vibrating erratically with the environment. His responses to stimuli supplied by his surroundings are exaggerated and lacking in
restraint. These over reactions are evident in all of the emotions-- in fear he is panicky, in happiness he becomes hilarious, in love he is eratic, in reverence he is overly pious, and in anger he brandishes a weapon with intent to kill. On the other hand the native African negro is indifferent, unemotional, apathetic and disinterested.

Unlike the Mexicans and Chinese in this country, the American negro has attempted to emulate his white brother's modern manner of living-- that of "making life a problem rather than an art". Although statuabably free, racial prejudice dictates through custom, specific confines which are not insignificant additions to the intricacies of living like the modern American.

Moschowitz 42 agrees entirely with the ideas expressed by Schulze and Schwab. He is convinced that the psychic pattern of individuals is closely linked with hypertension.

The discovery of such a high incidence of hypertension among American negroes as contrasted to their hypotensive African brothers constitutes a significant blow to the heredity theory of hypertension.

Weiss and Prusmack 43 recently have studied 1,198 hypertensive negroes and compared their findings to
those from 989 white hypertensives. They found that hypertension occurred a decade earlier in the negroes than in the whites. Their series showed equal sex incidence among the negroes as compared to a slight preponderance of females in the white patients. They found that one or more of the major complications of hypertension—cerebral, cardiac and renal involvement occurred in 75.7% of the negroes as contrasted to an incidence of 66.2% in the white group. In both groups more males suffered these complications than females. The incidence of syphilis of both groups approximated the general incidence.

Nye in a recent paper gives his findings in 63 male and 40 female Australian Aborigines most of whom were grand parents, great grand parents or great great grandparents. Arterial hypertension was almost entirely absent the highest systolic pressure being 188 mm and the highest diastolic pressure 90 mm. There was no evidence of vascular sclerosis from which he concludes that this and high blood pressure are not normal in old age. He also noted a high incidence of focal infection among these people. This, and that they are almost entirely carnivorous are facts tending to refute the ideas that infection and high protein
intake are primary causes of high blood pressure. He concludes that their simple mode of existence is responsible for their freedom from high blood pressure.

That the incidence of hypertension is much higher in some families than the general incidence has been appreciated and commented upon by almost innumerable observers over a long period of time.

As Fishberg, in his excellent treatise on nephritis and Hypertension has pointed out, the sparsity of accurate geniological records in the literature is that this disease often becomes manifest only after middle age so that examination of the progenitors even one generation removed is impossible because the parents in many cases have died.

The cause of their death is often difficult to ascertain even by careful questioning of the patient. However, records of death by cerebral hemorrhage in three generations have been reported by Albutt. Nikitis showed a predisposition to arterial hypertension in three generations in the families of 32 hypertensive patients.

As pointed out before, the evidence to support these conclusions is often indirect and circumstantial in nature. One must therefore accept these with
some reservations even though the temptation is great to give such evidence face value.

O'Hare and Walker in 1924 reported several cases that they had observed in which heredity apparently played an important role. One male, age 42, was diagnosed as a cardiac infarct. The Wasserman was negative. The father of the patient had extensive generalized arteriosclerosis. The mother had chronic nephritis and hypertension. One maternal aunt had suffered a cerebral hemorrhage; another had died of angina pectoris and a maternal uncle had died of myocardial failure. The patient's sister showed marked vasomotor symptoms.

Janeway, one of the first to report any definite statistical data, concluded that while heredity is undoubtedly a factor it was only an accessory or subordinate influence in the production of hypertension.

The findings of O'Hare and Walker may be seen in the table below.

<table>
<thead>
<tr>
<th></th>
<th>Total Patients</th>
<th>AVE. AGE</th>
<th>% Positive</th>
<th>% Patients with Early Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>300</td>
<td>51.5</td>
<td>68.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Controls</td>
<td>128</td>
<td>45.0</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>436</td>
<td>36.2</td>
<td>37.6*</td>
<td>23.6†</td>
</tr>
</tbody>
</table>

* Vasomotor symptoms in 13%.
† Family history of vascular disease in 12.6%.
"We brought out one fact of importance, that is the high incidence of symptoms of early vasomotor disturbances as manifested by temperament, epistaxis, cold sweating, cyanotic hands, blushing and migraine. These usually appear in the second decade.

These men concluded, "The belief in an inherited quality of the arterial tissue with a tendency to premature death from apoplexy, angina pectoris and other local manifestations is too firmly grounded in clinical observation to be without basis. Hypertension must be looked on today as the type in which heredity plays the largest role."

Popper, from his study of 1,031 cases of hypertension concluded that heredity was by far the most important factor involved.

Barach in a very detailed study of a small number of hypertensive patients found positive evidence of an inherited factor in 95% of the cases. In this article he emphasizes the inadequacies of routine family histories upon which many statistics were based.

Glomset measured the blood pressure of 2,400 school children and found a positive family history of hypertension in 39% of those children with an elevated blood pressure as contrasted to a positive family
history in 10% of the children with normal or sub normal blood pressure.

Weitz decided that family histories were not a reliable guide in this problem. He made direct blood pressure observations on as many of the brothers and sisters of his hypertensive patients as possible. He found the incidence of elevated blood pressure much greater in the siblings of hypertensives than among the siblings of his control cases.

The findings of Weitz were confirmed by Ayman in one of the most extensive and best controlled studies yet made on this problem. He personally examined 1,524 persons in 277 families. He found that in 780 members of the second generation whose ages ranged from 14-39, 148 had blood pressures definitely above the normal. He also found two families in which hypertension was found in three consecutive generations. He also observed that the so-called "emotional hypertension" of young adults occurred almost wholly among the children of hypertensive families.

He found that in families in which neither parent had hypertension the incidence among their children of elevated blood pressure was 3.1%. In families in which one parent was hypertensive the incidence among the children rose to 28.3%. Among children whose
fathers and mothers both exhibited hypertension the incidence was 45.5%.

Examination of 70 brothers and sisters of patients showed that 37.3% had elevated blood pressure. Similar examinations of 86 brothers and sisters of hypertensive patients showed that 86.3% had elevated blood pressure.

Frost obtained a family history of cardio-vascular disease in 28% of 400 young adults showing high blood pressure.

Backer in discussing the problem of etiology of hypertension concluded that the search for any one etiological factor is a hopeless task in view of the multiplicity of physiological mechanisms that are known to produce increased peripheral resistance. He then suggests that a more general predisposing cause be sought. His train of thought is as follows:

"The vascular resistance is the result of a certain neuro-muscular tonus of the arterial walls. This tonus equals the difference between two antagonistic energy potentials, namely those of the sympathetic or pressor, and the parasympathetic or depressor innervation respectively. Either one of these energy potentials varies normally within certain limits, under the influence of many interdependent regulatory
mechanisms and of a variety of stimuli, some of which alter the balance in favor of the sympathetic, some others in favor of the parasympathetic innervation. Under average circumstances, however, these variations of the energy potentials are not excessive. They are temporary and usually purposeful; the balance between such energy potentials is identical with normal blood pressure. Under abnormal conditions one of the two potentials is preponderant, its response to stimuli are excessive and purposeless. Depending upon the preponderance of either one or the other energy potentials the balance shifts from a state of equilibrium either in favor of an increase or a decrease of blood pressure. Thus in a case of essential hypertension, the energy invested in the pressor component is disproportionally greater than normal. This favoritism accorded one or the other innervation is a specific, constitutional characteristic.

He goes on to state that such a balance may be altered in either direction by exposure to environmental factors which augment the stimulation of one or the other types of innervation, but that the primary deviation from the norm is inherited and will manifest its preponderance regardless of environment.
"In this respect the writer believes as does Julius Tandler and his school that one's constitution is his somatic fate predetermined by the combined heritage of all the qualities and potentialities of the given two gametes."

Whether this tendency to hypertonus is a single inherited characteristic or if it is associated or correlated with other somatic and physiologic manifestations he does not know, but suggests that a search for other correlating be made.

Bauer in reviewing his cases of essential hypertension states that he found no characteristic physical pattern or habitus common to persons with high blood pressure. Nor could Ludwig Braun discern any physical build in which hypertension appeared with significant incidence. Kylin from similar studies arrives at the same conclusions.

Zipperlen, on the other hand, examined a series of hypertensives and reports an overwhelming prevalence of the hyperasthenic, pyknic or opaplectic types.

Barr in discussing Cushing's theory of hypophyseal basophilism as a cause of hypertension states that the number of basophilic cells in hypertensives is greater than in persons of asthenic build. Conversely, Fossier
maintains that persons of hyposthenic habitus are more frequently found to be hypotensive.

From such contradictory reports it would appear that either these opinions are based on poorly standardized criteria of physical type or that hypertensive disease is not closely correlated to any very specific body pattern.

Backer admits that it is true that cases of hypotension in the asthenic, and hypertension in the asthenics are reported, but believes further search will uncover certain characteristics closely related to, or linked with, hypertension. He states, "The specific question is: Does the strength of the original mesodermal foundation (from which the vascular system is derived) manifest itself in due time, and of inevitable necessity, in a certain strength of tonus of the mesenchymatous derivatives including the smooth arteriolar musculature? If this be so, the generally blamed, but, so far unclarified immediately responsible blemish, of increased peripheral resistance in the arteriolar bed of essential hypertensive patients shall be eventually be and its significance irrevocably linked with the somatic fate of its bearer."

In his search for these obscure and elusive factors Backer studied 148 cases of spontaneous hernia
in which traumatic etiology had been carefully excluded. He then compares the incidence of high blood pressure in these patients with the figures presented by Gager purporting to represent the general incidence of hypertension.

In males of all ages Backer found in his patients an incidence of 5.3% as compared to an expected incidence, by Gager's standards, of 15.2%. Backer found systolic hypertension in 6.2% of his cases as compared to an incidence of 12.6% in Gager's series.

Hines and Brown of the Mayo Foundation in search of a practical, clinical method of detecting early and "latent" hypertension devised a test that they consider suitable. In the light of their findings the test deserves description.

The subject is placed at rest for 20-30 minutes, during which blood pressure readings are taken at five minute intervals until a basal level is reached. One hand is then immersed up to the wrist in ice water for one minute. Determinations of pressure every 30 seconds show that the blood pressure, both systolic and diastolic, rises, then returns to the basal level within 1-2 minutes.

They found that using the foot or more than one
extremity did not alter the results in any way. Of great importance is the fact that even though venous return of the immersed extremity was blocked by means of a tourniquet the results did not vary. These results were found in normal persons.

Further application of this test to normal and hypertensive persons revealed some very interesting facts which are tabulated below.
<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>40</td>
<td>17-50</td>
<td>8.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Other Diseases sans Hypertension</td>
<td>14</td>
<td>18-45</td>
<td>10.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Potential Hypertension</td>
<td>8</td>
<td>19-44</td>
<td>30.1</td>
<td>21.1</td>
</tr>
<tr>
<td>Hypertension:</td>
<td></td>
<td>26-64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preorganic types</td>
<td>7</td>
<td></td>
<td>32.0</td>
<td>21.4</td>
</tr>
<tr>
<td>Organic types</td>
<td>11</td>
<td></td>
<td>38.4</td>
<td>22.5</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td></td>
<td>55-91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sans Hypertension</td>
<td>8</td>
<td></td>
<td>13.1</td>
<td>10.8</td>
</tr>
<tr>
<td>With Hypertension</td>
<td>5</td>
<td></td>
<td>29.1</td>
<td>16.0</td>
</tr>
</tbody>
</table>
The effect of various therapeutic agents on this vasomotor reaction were measured by this "cold-pressor" test. Sodium amytal in doses of 3-6 grains depending on the weight of the patient and dose lowered the pressor response 60-100%. Alcohol 1cc per Kg of body weight lowered the response 40-60%. General anesthesia completely inhibited the pressor response.

In group studies using this test Hines and Brown found eight persons that exhibited a hyper-response to the test even though no other evidence of hypertension was apparent.

They failed to find any known hypertensives who did not exhibit a hyper reaction to the test. They concluded that the mechanism of the reaction was nervous in nature.

Another report by Hines and Brown in 1936 shows that of the original eight hyperreactives found four years previously, three have developed clinical signs and symptoms of hypertension.

They also state that in those persons showing hyperreaction to the test 78% gave family histories of hypertension as contrasted to the group of normal reactors in which a positive family history was obtained in only 14%.
Another report (1937) by Hines after studying the family histories of 608 normal persons and 257 hypertensive persons show that hypertensive cardiovascular disease is five times as common in hyperreactors than in normal reactors to the cold pressor test.

The pressor test was applied to seven sets of identical twins. The response of one twin was always approximately the same as in the other.

Applied to three sets of fraternal twins a different response was shown in two sets.

Thirty families including 256 persons were studied each member's response to the test being recorded. In 12 of the families there was no evidence of hypertension. In 18 families definite evidence of hypertension was found.

(1) When both parents were normal and showed a normal pressor response all of their children were normal reactors.

(2) If both parents were hypertensives or hyper-reactors 95% of the children were also found to be hyperreactors.

(3) If only one parent showed hypertension or hyperreaction only 43.4% of their offspring showed hyperreaction.
Because of the close relationship between renal disease and hypertension it was to be expected that numerous attempts should be made, along experimental lines, to clarify this relationship.

Goldblatt, 1932 was the first investigator that was able to produce hypertension in animals regularly. Using special clamps he found that partial occlusion of the renal arteries in animals would invariably produce a marked hypertension that closely resembled the hypertension in man. He noted that partial occlusion of one renal artery would also produce a rise in blood pressure though somewhat more transient in nature. By partially occluding the aorta above the renal arteries produced similar results whereas a clamp placed just distal to the renal arteries had no effect on the blood pressure.

His results were confirmed by numerous investigators and his methods are widely used in producing hypertension.

In further studies Goldblatt found that complete renal denervation would neither prevent nor cure the hypertension. Partial and complete sympathectomies done before the application of the arterial clamps failed to prevent hypertension from developing.
The same operations had no significant influence on the blood pressure of his hypertensive dogs.

Excision of one adrenal with denervation and destruction of the medulla of the other adrenal gland were also without effect.

Partial occlusion of the arteries of transplanted kidneys also resulted in hypertension.

It has also been shown that ligation of renal veins in these experimental animals caused a reduction in blood pressure.

Acute experiments in which complete renal artery occlusion was done failed to show a rise in blood pressure.

Decapsulation of the kidneys invariably lowered the blood pressure of the hypertensive dogs.

From these facts Goldblatt concluded that the mechanism must be on a hormonal basis-- that in the ischemic kidney an "effective substance" is formed which, when returned to the blood stream, caused a constriction of the arterioles.

That the mechanism was not nervous in nature was proven by the ineffectiveness of partial and complete sympathectomy. Any adrenal influence was excluded in a similar fashion.
Decapsulation of ischemic kidneys permitted the development of a collateral renal circulation, the efficiency of which determined the degree of fall in blood pressure.

Attempts to isolate this "effective substance" have thus far failed. Goldblatt admits that the evidence supporting the idea that the ischemic kidney releases a pressor substance causing hypertension is indirect but at the same time very convincing.

Levy and Blalock and associates demonstrated that ligation of one ureter also produces hypertension in animals. Further they found the blood flow through the associated kidney to be definitely reduced. From this they concluded that renal ischemia does produce some substance resulting in hypertension.

Attempts to isolate this substance yielded contradictory results.

These men extracted both normal and ischemic dog kidneys and injected them into normal dogs. Ischemic extracts caused a greater increase pressure than normal extracts, however, the presence of depressor substances in the extracts could not be excluded and therefore no valid conclusions were drawn.

Blalock and Levy in a six stage operation on
dogs gradually occluded the blood supply to the intestine in an attempt to produce hypertension in dogs. They concluded that intestinal ischemia does not produce hypertension. By similar experiments they failed to produce hypertension in any fashion other than from ischemic kidneys.

Freedman and Hortley have reported a case of hypertension that appears to be the clinical equivalent of Goldberg's experiments. A man 57 fell from a ladder rupturing his right kidney which was removed on the same day. Recovery was complete. Sixteen months later he reentered with a blood pressure of 230/140. Previous determinations had shown it to be normal. Over a period of several months he developed a severe hypertension and died in uremia. At necropsy an atheromatous plaque was found to be almost completely occluding the renal artery, one centimeter from the aorta.

The "compensatory" theory of hypertension states that hypertension is a mechanism designed to maintain adequate circulation in a diseased kidney. Although it really explains nothing it has enjoyed considerable popularity.

Page made numerous kidney function tests in a series of hypertensives to determine basal values. He then
lowered the blood pressures of these patients with thio cyanites and colloidal sulfur which he had previously proven did not affect kidney function in the doses used. He saw no evidence of decreased renal function. He concluded that the abnormally high pressure does not appear to assist in maintaining renal efficiency.

Cutler found the arteries in brain stems from eight hypertensives to be moderately sclerosed. He suggested that the sclerosis resulted in restricted blood flow in this region and that hypertension created an anemic state of the vasomotor center.

Cushing found that the blood pressure varied directly with experimental variations in the intracranial pressure. He believed the rise in blood pressure following increase in general intra cranial pressure was the result of anemia of the vasomotor center in the medulla.

Dixon and Heller produced similar results by injecting kaolin in the fourth ventricle of the brain of rabbits causing pressure anemia.

Koch and Mies and later Heymans and his workers produced hypertension very similar to that in men by cutting the aortic and carotid depressor nerves. Blood
pressure in these dogs rose as high as 300 mm and was maintained at elevated levels for over three years.

While the recent experimental work, especially that done by Goldblatt and Heymans and their assistants, is extremely interesting from the physiological point of view it must be born in mind that there is no proof of their relationship, if any, to essential hypertension.

The evaluation of Goldblatt's work must await progress along the lines investigating the nature of pressor substances in general.

Before Heymans experiments assume any clinical significance the carotid and aortic nerve reflexes must be proven to have a more definite bearing on essential hypertension.

The concept that hypertension is the reaction of the vascular system to the presence of some pressor substance in the blood stream was first voiced by Johnson in 1868.

He proposed this theory as the cause merely on the basis of his clinical observations. The theory has enjoyed considerable popularity by some investigators since that time.

Broadbent believed the substance to be some nitrogenous product of incomplete oxidation.
Neubauer pointed to the rather frequent occurrence of hyperglycemia among hypertensives.

Fishberg and Westphal blamed uric acid and cholesterol respectively. Dragstedt demonstrated that renal tissue extracts contained some pressor substance which he named "renin" that produced an increase in blood pressure. Since then an enormous amount of work has been done along the lines indicated by Dragstedt's experiments, but so far no definite conclusions have been reached.

It was only a short time after the demonstration of the pressor-secreting function of the adrenal gland that Neusser reported two cases of essential hypertension in which, at necropsy, he found neoplasms involving the adrenals. He believes the neoplasms responsible for an increased adrenalin secretion which resulted in hypertension. Since that time reports have appeared with some regularity in which adrenal neoplasms are associated with hypertension.

Vaquez believes that diffuse hyperplasia of the adrenal tissue caused hypertension in some of his cases in which he found hyperplastic adrenal cortex.

These theories all held that excessive secretion of adrenalin was the immediate cause of the high blood pressure and pointed out the fact that some
hypertensives are known to be hyperglycemic, a fact fitting in nicely with the theory of hyperadrenalinemia.

The low blood pressure found in Addison's disease of the adrenals has been attributed, but not proven to be, a deficient secretion of adrenalin by the diseased glands.

Claims were made by Schur and others that quantitative tests for adrenalin in the blood of hypertensives revealed an increase in epinephrin concentration. O'Connor, and more recently Rogoff have shown that the methods used by Schur and collaborators were unreliable. Dragstedt also concluded that excessive adrenalin concentration was probably not a cause of hypertension.

The theory, erroneously attributed to Cannon, that excessive adrenalin returning to the adrenals augments further secretion thus forming a vicious cycle resulting in hypertension has been discredited by Rogoff and Marcus.

Goldblatt failed to demonstrate any relationship between the hypertension in dogs produced by renal ischemia and the adrenal glands.

While it has been shown that hypertension is not due to an increase of adrenalin in the blood, the
close relationship between adrenal tumors and hypertension has not been explained. Volhard and more recent observers have reported cases in which hypertension disappeared following removal of hypernephroma.

Hypertension often appears in women at the menopause and was first commented upon by Huchard. The vasomotor instability so characteristic of the menopause is attributed by Fishberg to be the result of ovarian senescence. He further states that removal of the ovaries in young women is sometimes followed by hypertension.

Hyperthyroidism is usually accompanied by a moderate elevation of systolic pressure while the diastolic pressure tends to remain within normal limits. The hypertension associated with Graves disease does not resemble the syndrome of essential hypertension closely enough to be included in this group. The existence of the two together, however, is not a rare condition.

A very mild degree of arterial hypertension is usually seen in cases of pituitary adenoma. This is associated with plethora of the face and neck. The clinical picture, however, does not bear much resemblance to that of essential hypertension and at present
the pituitary gland is not believed to be an important factor in hypertension.

H. F. Dunbar in his book reviews some 2000 articles on the relation of psychic to somatic processes some of which are pertinent to the subject at hand.

Weber observed that anticipation of motion alone causes increased blood flow and pressure. Persons under hypnosis showed blood pressure rises of 148-210 mm on the hypnotic suggestion of work even though the subject remained passive.

That blood pressure is markedly increased in subjects awakening from bad dreams has been observed. Such a mechanism may explain the high incidence of cerebral hemorrhage during sleep.

It is common knowledge that single blood pressure readings may be elevated as much as 60 mm above the true resting level.

Fahrenkamp observed one patient in whom merely mentioning her unhappy marriage raised her systolic pressure 50-60 mm in a few minutes. He does not believe psychic factor is the basic cause of hypertension, but states that it is an important accessory factor the control of which deserves more attention in treating hypertensives.

Moos states "We know that daily life confronts
us constantly with frightening experiences which may produce blood pressure rises if continued over a long period of time, hypertension may lead to lasting alterations of the cardio-vascular system. He cites a case of a man with a systolic pressure of 280 mm with pulmonary edema which resisted all treatment. After a free discussion with his wife concerning a great wrong he had committed his blood pressure dropped to 130 mm, his pulmonary edema disappeared and he no longer had any of his subjective symptoms of hypertension. Muller saw the patient several years later and found him to be quite normal.

Alkan believes certain persons inherit a sympathetic nervous system that is hyper reactive to emotional stimuli which are usually predominantly sympathetic, rather than parasympathetic in nature. This results in contraction of the arterioles which tend to become with the passage of time progressively more spastic.

Alkan also maintains that the mortality from conditions which result from hypertension, increases during times of stress.

Alvarez in studying the blood pressures of university freshmen noted that during the World War the
average of these students rose. Following the war the blood pressure averages again fell to approximately the same values obtained before the war. He believed the tension and stress during this period might well account for the changes.

Alkan states "Hypertension is a pure neurosis, in many cases acquired, but doubtless also hereditary and familial, at least to the great responsiveness to exciting stimuli. The vegetative nervous system, as in every neurosis takes part in the manifestation of essential hypertension; not as a cause, but as a mechanism and pathway to localization."

Roemheld and Fahrenkamp believe hypertension to be a disease of three phases. The first phase is purely functional and during rest the blood pressure returns to normal. In the second phase the blood pressure does not return completely to normal levels after rest and the disease has gone beyond the completely reversible stage.

The third and terminal stage is characterized by an elevated blood pressure that is but little changed by rest or drugs. The functional component is no longer demonstrable. Irreparable organic changes have occurred and these dominate the picture as the functional component dominated the first stage of the disease.
Blood pressure determinations on medical students immediately before examinations reveal significant rises in the systolic pressure in many cases.

Moschowitz maintains that the personality pattern of many essential hypertensives is quite characteristic. They are easily worried, quite irritable, and manifest a tense, strained manner.

Fishberg is entirely in accord with these findings but points out that not all hypertensive persons exhibit this type of personality pattern. Indeed, many hypertensives appear to be quite stolid and phlegmatic.

Syphilis was believed, at one time to be a very important factor in essential hypertension. This was probably due to the influence of Stoll, Omblard, Grenet, and others who reported an extremely high incidence of lues among hypertensives. More recent reports of group studies tend to indicate that syphilis is of about the same incidence in hypertensives as in the control groups.

Alcohol and tobacco likewise were indicted by earlier writers as causative agents. As with syphilis, recent observations have failed to establish any causal relationship between them and hypertension. Tobacco, however, is known to be an inciting agent in some of
the peripheral vascular conditions such as endarteritis oblitterans. Alcohol, on the other hand, is pharmacologically classified as a depressor substance which acts as a vasodilator.

Lead poisoning is an established cause of high blood pressure both in man and in experimental animals. In humans suffering from either acute or chronic plumbism hypertension is present in a high percentage of cases.

Experiments performed by Tscherkess on rabbits proved that lead salts in high dilutions produced vasoconstriction by direct action upon the vascular muscle. Some believe that lead colic is the result of intestinal ischémia produced by mesenteric arterial spasm.

Since the recognition of lead as a cause of intoxication in man protective methods have been developed in nearly all industries using lead which have greatly reduced the incidence of poisoning among employees. The replacement of lead by other pigments in the paint industry has also been of importance in reducing the incidence of plumbism.
CONCLUSIONS

1. That the hereditary nature of essential hypertension constitutes the most important basic, etiological factor.

2. That the most important immediate mechanism responsible for essential hypertension is the narrowing of the arterioles due either to central nervous control or to inherent vessel spasm, or both.

3. That essential hypertension is not a disease entity, but a common syndrome presented by several conditions the most important of which is hereditary hypertension.
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