The Etiology of hypertension

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# TABLE OF CONTENTS

I. Introduction ............................................. 1
II. Historical Background ..................................... 2
III. Types of Hypertension ................................... 3
IV. Essential Hypertension ................................... 6
V. Normal Blood Pressure Variants ......................... 8
VI. The Mechanism of Essential Hypertension ............... 10
VII. Age in Essential Hypertension ......................... 12
VIII. Sex in Essential Hypertension ....................... 14
IX. Heredity in Essential Hypertension ................... 16
X. Race ..................................................... 17
XI. Occupation as a Factor in Essential Hypertension .... 17
XII. Diet and Essential Hypertension ....................... 18
XIII. Obesity and Essential Hypertension .................. 21
XIV. Constitutional Factors in Essential Hypertension .... 22
XV. Minor Etiological Factors in Essential Hypertension . 26
XVI. Causative Agents of Essential Hypertension .......... 26

1. The Kidneys ............................................. 27
2. The Sympathetic Nervous System ....................... 31
3. Pressor Substances ..................................... 33
4. Endocrines and Allergy ................................ 36
5. The Central Nervous System .......................... 38
6. Respiration and the Lungs ........................... 39
7. Other Diseases and Toxic Factors ................... 40

XVII. Summary ............................................. 42
XVIII. Discussion and Conclusions ......................... 43

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THE ETIOLOGY OF HYPERTENSION

INTRODUCTION:

The first known case of high blood pressure, in all probability, was that of Adam when he ate the apple with fear and apprehension. Down through the ages this malady has been carried and now the greatest causes of death are very closely linked with a blood pressure increase.

High blood pressure or hypertension may be defined as an abnormal force of the blood on the vascular system due to changes in the relation of the circulation to the tissue: A higher pressure than normal.

We, in the average American or European family, find that cerebral accident, cardiac failure and renal pathology, that is, cardio-vascular-renal disease, has been common among our ancestors. Today the greatest single cause of death is cerebral hemorrhage (150) and the basis of it is hypertension. Furthermore, it has been stated that death from hypertension is greatly increasing (74). It is only right that our interest in this subject should be keen.

Unfortunately the field has proven too large to be completely covered here, yet an attempt has been made to present a well-based, modern, and fundamental conception of hypertension and with sufficient critical analysis to avoid the "quick-sands". One eminent author on this subject says, "there are few fields in medicine in which ignorance is more profound" (17).
HISTORICAL BACKGROUND:

Down through the ages, man has fought his enemies and attempted to prolong his own life. In the medical field, the acute diseases have naturally been the most engrossing. But when some control of them was possible, the chronic disorders took the attention of the scientific minds.

As early as 1476, Saliceto associated dropsy, scanty urine and hardened kidneys and several other writers mentioned similar findings, but it was not until 1827 that Richard Bright presented the idea so that the medical world listened. He grouped coagulable urine and dropsy with kidney pathology and his findings soon became common knowledge. (102) In 1836, he associated the kidneys with arterial hypertension (94), for the existence of blood pressure had been discovered in 1733 and the term "hypertension" was originated in 1828 (60). Although no adequate method for the determination of arterial pressure in man was advanced for many years, animal experimentation and venesection proved that it could be abnormally high.

"In 1856, Traube postulated that arterial pressure was elevated in cases of disease of the kidneys to overcome mechanical resistance against blood flow, thus...maintaining the efficiency of the kidneys as excretory organs" (121). In 1868, Johnson published results of pathological studies of the kidneys and again agreed with Bright and Traube, as likewise did Gull and Sutton later (78).
Meanwhile, von Basch announced a method of determining the blood pressure in men (57) and in 1896, Riva Rocci introduced the first sphygmomanometer (166). By 1901, the instrument was perfected so accurate readings could be taken. Thirty-five years have told us what we know about blood pressure today.

That the cause of hypertension was due to kidney changes was well accepted until 1896 when Allbutt in England said:

"Hyperpiesia is a malady in which at or towards middle life, blood pressure rises excessively; a malady having a course of its own, and deserving the name of a disease. Of hyperpiesia I have never offered an explanation or nothing more than a conjecture. I have been content to distinguish it as a clinical series from recognized forms of Bright's disease." (47)

This was a terse statement for all the effects it had. A multitude of men have attempted to ascertain the causes of hypertension. History ceased and investigative work began.

**Types of Hypertension:**

Starting from Allbutt's statement on hyperpiesia, hypertension has been found to be a symptom of certain disease conditions.

Glomerulonephritis has been very closely associated with hypertension since it was first known and has been proven to arise from this type of kidney pathology. (11), (22), (28), (31), (36), (84), (104), (106), (130), (133), (158), (160), (168), (95). These same writers find much hypertension to be unexplained though, on a renal basis entirely.
Suprarenal tumors and other forms of chromaffin cell
tumors and tumors of the retroperitoneal nerve have been definite-
ly associated with hypertension and in these rare cases may be the
causative agents. The findings of suprarenal glandular disorders
are also present. (34), (98), (120).

In pregnancy, the toxemias of pregnancy will show as
a prominent symptom a hypertensive state (144), (130).

Periarteritis Nodosa has been recorded as being associ-
ated with high blood pressure of an unexplained origin, but this is
a very rare disease entity. (56) (161).

Some case of pyelonephritis are accompanied with hyper-
tension (79), (22), (42).

Certain men report finding hypertension in polycystic
kidney (25), but it is the exception rather than the rule.

Lead poisoning has as one of its early signs, an in-
creasing blood pressure level, yet only when other symptoms of a
definite poisoning are found (25), (79), (94), (142), (160).

Antimony, mercury and copper in toxic amounts will have a similar
finding (79).

Increased intracranial pressure has been shown experi-
mentally by Starling to cause blood pressure rise (42) and occasion-
ally in certain intracranial diseases this reaction may occur (11),
(23), (126).

Recently hypertension has been found to be a prominent
symptom of certain basophil adenomas of the anterior lobe of the
pituitary, but the actual association of the two has only been in
the presence of other changes, namely, altered secondary sexual
characteristics, adiposity and osteoporosis (88), (40).

In arterio-venous aneurysm, blood pressure is increased,
supposedly to maintain a sufficient tissue oxygenation (164), (75).

A moderate elevation of blood pressure has been found
in thyrotoxicosis, for cardiac rate is increased and cardiac output
greater (79), (75), (22).

Urethral obstruction, clinically and experimentally,
will cause hypertension until relieved according to von Monakow.
(22), (23).

In coarctation of the aorta, a peculiar form of hyper-
tension is present, for the area above the stenosis, according to
blood supply, will have a very high blood pressure level and below
the narrowing the tension is normal. Life is compatible without
any appreciable disturbance (28), (58), (131), (79).

Within the last few years, a "Hypertensive Diencephalic
Syndrome" has been described as being a distinct form of hyperten-
sive disease. It is an irritation of the vegetative centers in
the brain stem, that is, of the vasomotor centers (124), (31).

In certain fevers, especially typhoid, there is found
to be an increase of blood level, but it becomes normal with the
abating of the fever. (79) Diabetes, chronic anemia, uterine
fibroids and aortic atherosclerosis may have a raised blood
pressure as a symptom (50).
A large group of hypertensions still are not found due to any of the above conditions. This constitutes the Primary Hypertensions.

A classification of the hypertensions then may be given as: (22), (23), (25), (42), (50), (67), (75), (147).

Secondary Forms:

1. Glomerulonephritis.
2. Suprarenal and chromaffin cells tumors.
3. Toxemia of pregnancy.
4. Periarteritis Nodosa.
5. Pyelonephritis.
7. Lead, antimony, mercury or copper poisoning.
8. Increased intracranial pressure.
10. Arterio-venous aneurysm.
11. Thyrotoxicosis.
12. Urethral obstruction.
13. Coarctation of the aorta.
14. "Hypertensive Diencephalic Syndrome"
15. Certain fevers, especially typhoid.

Primary Forms:

1. Primary, functional, or essential hypertension or hyperpiesia.
It can be seen that blood pressure is merely a symptom in the "Secondary Forms", but in cases with no demonstrable vascular disorder nor other pathology and in which the high blood pressure is the outstanding symptom and feature, it may be possible that it is an actual clinical entity. Let us consider this "Essential Hypertension".

**ESSENTIAL HYERTENSION:**

"It is difficult to define such an entity. Generally, it has been considered the increased blood pressure for which there is no detectable cause. The early hypertensive victim may be found to be, as far as our present methods of investigation are concerned, a perfectly normal person. Not only is it difficult to define essential hypertension, but it is equally difficult to define normal blood pressure. There is such a great variation in arterial tensions, even in identical age groups, that the best that can be obtained is an average figure for normal. The same difficulty, of course, is encountered in setting up normal weights, heights, and so forth... One is impressed with the variability of normal limits set by different writers as he reviews the literature on this very interesting subject. It is just this actual lack of unanimity of opinion regarding normal blood pressure, as well as hypertension, that accentuates the present concept of essential hypertension". (147)

However, reference to the so-called hypertensive states, as used here, has been limited to the raising of both the maximum pressure of the blood or the systolic and the pressure at its lowest ebb between heart beats or the diastolic. There has been no attempt to include conditions, such as aortic valvular insufficiency, which give an elevation of only the systolic. In fact, the diastolic pressure is believed by certain
men: to be the most important fact in essential hypertension because the arteries and the aortic valves must continuously bear this burden and "from which there is no escape", while systole lasts only a relatively short period of time in each cardiac cycle. (60), (114)

The average systolic which has been set as the arbitrary boundary-line between hypertension and normal in the majority of cases is about one hundred and fifty millimeters of mercury, although some feel one hundred and forty millimeters is a good estimate (7), (129), but one used one hundred seventy-five (24) and another even one hundred eighty systolic (4).

That such a condition as essential hypertension does exist was not accepted earlier, for many Continental investigators felt that the kidneys were the primary cause of the pressure changes and that only under nephritic conditions could such an abnormal state be present (42), (113). Yet today, they same men have published articles showing that there is a disease process known as essential hypertension, that is, an idiopathic or unexplained type of high blood pressure (162). A numerous group further substantiate the fact that hypertension due to an unknown cause is a present clinical entity. (21), (23), (75), (84), (121), (123), (156). The future may prove that all high blood pressure is a symptom or secondary to a variety of different pathological states, but at the present time, knowledge is too inadequate for this to be more than a supposition.
NORMAL BLOOD PRESSURE VARIANTS:

The body does not attempt to maintain blood pressure at a constant level (79). It serves as a stabilizer of the circulating blood in the body under varying conditions (110). In the normal individual, increase in both the systolic and diastolic are caused by emotion (14), such as pain, excitement and fear (160), (126). Even cool weather has been found to raise the blood pressure slightly (8). Fatigue, as little as is present after a day's work, they believe, will give an elevation (111). Another report is the finding of an increased systolic pressure on weekends from the excesses of "recreation" and a lowering during the week when moderation and rest are more prominent in the lives of city-dwellers (33). One group, when taking the blood pressures in a routine physical examination of a large number of cases, found that by repeating their check of the pressure, the percentage with systolics over one hundred forty dropped from seventeen per cent to nine and eight tenths per cent. They attributed this to eliminating nervousness and excitement (179).

These variations are known as normal vasomotor and psychic responses. They are associated with the mobilization of the body forces to meet emergencies by giving energy drive and strength in a changing environment.

Men in the middle of life have a slightly higher pressure than women and Caucasians are reported to always have a higher pressure than the Occidentals. With advancing years, blood pressure will increase slightly, too. (53)
Altitude has been claimed by some to give changes in the blood pressure. A German physician says he is subject to a higher blood pressure in high altitudes, as were several of his patients, and that the inhalation of pure oxygen returned his pressure to normal (85). A countryman of his also found that in his cases of essential hypertension that the inhalation of carbon dioxide caused a rise of blood pressure several times greater than normal, while in the hypertension of nephritis, normal responses were elicited (68). Yet, the report of high altitude lowering blood pressure and low altitude raising it has been made (83), (84). On the whole it is probable that, as others have found experimentally, there is no change of pressure by altitude (53).

These vasomotor and physiological responses of blood pressure are found in normal people, yet, in the discussion of essential hypertension, there shall be association of these factors. "The vasomotor instability in health becomes much more pronounced in hypertension" (140).

"The above remarks on the physiological variations in blood pressure may, perhaps, serve to indicate the caution that is needed in the interpretation of a blood-pressure reading. Normal blood pressure is purely a relative concept. An arterial tension that is within normal limits for the individual under certain circumstances may not be so under others; a pressure that is distinctly pathological at one age or for a particular person may be physiological at another time of life or for a different individual. The actual estimation of the blood pressure is now, as Gallavardin points out, probably not subject to any greater error than the vast majority of clinical procedures. But in evaluating the significance of the
"pressure found, one must not set up rigid standards of normalcy which in reality are non-existent. The study of blood pressure is only one method of examination, and its results can be interpreted rationally only in the light of the complete clinical picture. There are many instances in which one is unable to decide whether or not the blood pressure of a given individual is abnormally high for him; protracted observation may be necessary to decide this point if it can be settled at all. Lack of adequate caution in interpreting blood pressures lying in the broad border-land between the normal and the abnormal has caused many a person to undergo unnecessarily fears and restrictions that the diagnosis 'high blood pressure' too often brings in its wake". (53)

THE MECHANISM OF ESSENTIAL HYPERTENSION:

Gallavardin made the statement that arterial blood pressure is a force originated by contractions of the heart, maintained by the reaction of distension of the arterial walls and regulated by the peripheral resistance (60).

The actual mechanical factors which can give origin to elevated arterial tension have been classed (60), (30), (79), as being:

1. The force of the heart beat.
2. The blood volume.
3. The blood viscosity.
4. Peripheral resistance.
5. The elasticity of the blood vessel wall.

Experimentation has shown that the circulating blood volume, the cardiac output per minute, the velocity of blood flow and the mean velocity of the circulation to be normal in arterial hypertension, but the average resistance of the arteriolar system
of the greater circulation was twice as great as normal. They concluded that an abnormally accentuated arteriolar resistance and a high arterial and arteriolar pressure are present, but that loss of elasticity of the great arteries, increased cardiac output, increased circulating blood volume or hypoventilation and decreased blood content of the lungs are not responsible factors in hypertension.

Other experimentation which has limited the mechanical state to an increased peripheral resistance has been done also. Hypertension is included in the findings of a research which was: "In no disease studied could a pathognomic alteration in the viscosity of the blood be demonstrated" (13). Another found total velocity to be unaltered (19). The cardiac output did not show significant differences in patients with abnormal blood pressures from those with normal (29), (50). Blood flow was found to be the same in both hypertensives and normal individuals (131). On the whole, increased peripheral resistance is well established to be the intermediate cause of essential hypertension.

However, increased peripheral resistance and changes in the elastic properties of the central arteries was found by another (163), but no confirmation of the elastic properties is found. The possibility of loss of elasticity in the large arteries as a late change has been suggested though (30).

The pulse wave velocity is increased, but not the total velocity of the blood (19), (62). This does not comply
with Marey's Law:

"Whatever increases or diminishes the resistance offered to the blood in passing from the arteries to the veins, will cause the velocity and the arterial pressure to vary in an adverse sense as regards one another." (141)

No explanation can be given for this apparent discrepancy.

Other studies have led to the statement:

"the most important factor leading to cardiac hypertrophy... is not increased work of the muscle per se" (51).

In 1925, a worker wrote:

"Because of the great elasticity of the lungs, their size must greatly vary the volume in their blood vessels" (165).

This was applied to hypertension and there followed several hypotheses that, even in the light of the above findings, cannot be overlooked. They apply as causative agents of hypertension, however, and will be discussed under that caption.

Mechanically, then, in essential hypertension an increased peripheral resistance is the only possibility from which such a condition can arise. It is not definitely known if the resistance is increased generally in the body or locally to certain areas (79). There may be a loss of elasticity in the larger arteries. Decreased lung activity as an established mechanical factor is questionable.

AGE IN ESSENTIAL HYPERTENSION:

It is generally accepted that in the senescent period of life, arteriolar constriction will occur (160). For this
reason, age has been held to be more important than other factors in giving origin to hypertension (79). Yet, because many live to a far-advanced age before developing abnormally high blood pressure, while another will die at fifty-five of the same cause, there does not seem to be the whole answer to the hypertension question in the span of years one lives.

The analysis of the records of one group of investigators showed that past fifty years of age, sixteen per cent of the patients in general practice are hypertension cases (24). Other confirmed this (22), but the statistics of another showed approximately thirty per cent over the same age had hypertension in his practice (47).

Autopsy records have been investigated and the age groups showing the greatest number of deaths computed. The findings of the various groups of writers are:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-60 years</td>
<td>420</td>
</tr>
<tr>
<td>61-70 &quot;</td>
<td>--</td>
</tr>
<tr>
<td>71-80 &quot;</td>
<td>401</td>
</tr>
<tr>
<td>60-68 &quot;</td>
<td>801</td>
</tr>
<tr>
<td>50-59 &quot;</td>
<td>96</td>
</tr>
<tr>
<td>Average age = 54.5 yrs.</td>
<td>485</td>
</tr>
</tbody>
</table>

The average of these figures is about 61-67 years, this being about the age of the greatest number of deaths from essential hypertension.
In three thousand, five hundred and ninety-eight cases of college students, ten per cent had systolics over one hundred and forty millimeters of mercury and two and twenty-five one-hundredths per cent over one hundred and fifty millimeters (125). In another college, of five thousand, one hundred and twenty-two cases examined, about sixteen per cent had systolics over one hundred and forty millimeters of mercury, but after excitement and nervousness had been ruled out, only ten per cent remained in the hypertensive group (179).

In six thousand, four hundred cases, a sudden rise in blood pressure was noted in the number of cases over forty years of age (8) and the same sudden jump in the number of cases after forty has been noted by others in clinical practice (134).

In general, then, hypertension causes many more deaths between sixty and seventy years of age than in any other age group, and from these above statements, the percentage of men with systolic blood pressures over one hundred and forty millimeters of mercury is not much lower in the twenty to thirty years age group than in the sixty to seventy years group, but it is asymptomatic and not consistently as high in the younger class (125).

SEX IN ESSENTIAL HYPERTENSION:

The accumulating of material as to the role of sex in primary high blood pressure is most confusing, except that it is conceded to be more fatal in men. From the findings established by necropsies, there has been one who reports a higher death
rate in the females than in the males (96), but others report:
Fifteen and six tenths per cent (47), three and two tenths (47),
and one and four tenths per cent greater frequency in males. As
high a report as five times as fatal a course in males has been
made (128).

Clinically, the statistical evidence is much more
varied. One author believes there will be three men to show
clinical signs of essential hypertension to one woman (138) and
another states that women are less apt to have arterial tension
than men (16). All others showed women more frequently affected
than males. In a large Eastern hospital, females were found to
show high blood pressure more than men (134). Another reports
twenty-two per cent more women than men (154), while several found
twice the number of women as compared to men (103), (25). At
puberty, women show a drop of blood pressure as compared to that
found in the average man and it remains lower until forty years
of age when women begin to show a high average systolic than men
(7) and other statisticians found the same comparison but not
until after fifty years of age did the female average surpass
the male (24). Finally, Cabot has reported finding fourteen men
with hypertension to five women (103).

In investigations with careful analysis of the existent
conditions, sexually abnormal women were found in the greater pro-
portion of female hypertensions, averaging as high as ninety per
cent (9), (127). This is discussed under the role of the endocrines
as causative agents of essential hypertension.
One summation is: "Women may outlive life expectancy. Men never do". (24)

Sex factors in essential hypertension show that there is a greater mortality in men of a small to moderate degree. On the other hand, women are clinically more susceptible, especially at the age of involution (103), (36).

HEREDITY IN ESSENTIAL HYPERTENSION:

That heredity is a most important factor has been nearly unanimously accepted by all men studying hypertension and of those who call it not a hereditary factor say it is due to environment on a weakened tissue defect (46), (107).

First, it has been generally known for years that "strokes" have been commonly found in certain families and frequently at about the same age for different generations (53).

Secondly, many have found it very prominent in their series of cases. Reports from thirty-three per cent (24), (25), (47) to fifty per cent (41), (85), sixty-six per cent (36), (119), seventy-seven (5) to as high as ninety-eight per cent (57) give positive family histories.

From the careful analysis made by groups doing work in this phase of high blood pressure (15), (16), (119), stimulation has been given to determine if essential hypertension is a dominant characteristic and, although it has not been conclusively proven yet, that is the general opinion they have advanced (5), (66).
At present, heredity is the only universally accepted etiological factor in primary hypertension (9), (36), (67), (73), (79), (158), (162).

**RACE IN ESSENTIAL HYPERTENSION:**

Among the Caucasian race, blood pressure is normally higher than in the more sedative races, as has previously been stated. In the African Native, a high blood pressure is very rare and hypertension is not known at all (45). In the Greenland Eskimo there is a very small per cent of hypertension (149) and, likewise, the Orientals are as free as the native African from blood pressure elevations (23), (47), (53), (142). Mexicans have been reported to seldom have hypertension either (8). Nevertheless, Negroes and Orientals living in the United States are found to be as subject to this condition as the other races in America (33), (47), (142), (154) and the Egyptians in their own country are in no way more fortunate than Europeans or Americans (73). The Jews have been stated to be the most susceptible to hypertension (53).

In general, the only races in which essential hypertension is prevalent are those in the Americas, the Europeans and the Egyptians.

**OCCUPATION AS A FACTOR IN ESSENTIAL HYPERTENSION:**

Absolutely no relation between blood pressure elevation and the type of work and activity a person does has been found (23), (73), (142), (154), although there has been reported to be a higher percent in the medical profession (53).
DIET AND ESSENTIAL HYPERTENSION:

In the early twentieth century, German and French physicians emphasized the relation of nephritis to the ingestion of proteins and salt (3), (53) and many have subsequently applied this to hypertension.

A group of workers suggest:

"Diets containing an excessive acid or alkaline ash, necessitating the excretion of excessively acid or alkaline urines might, in themselves, over long periods of time, be responsible for degenerative blood vessel and kidney changes." (116).

Practically the same group of experimenters found that acid-base disturbance does not produce atherosclerosis later, but that excess proteins in the diet of rabbits will give increased blood pressure and atherosclerosis without an increase of cholesterol in the diet (117).

The results of another series of experiments, though, found:

"Hypertension is not caused in rabbits by renal insufficiency per se; nor by a high protein diet even in the presence of a low renal function; nor by prolonged retention of creatinin and urea in the blood ... The high protein diet given here results in a marked atherosclerosis of the aorta which does not extend to the small arteries". (10)

If the normal diet itself is deficient as has been claimed (116), how could it be of primary importance here more than in the innumerable other diseases also claimed to arise from a deficient normal diet? (126)
Other experimenters (158) and clinicians (3), (100), (158) agree that protein does not give origin to an elevation of blood pressure. There has been reported to be no excess of hypertension in the Greenland Eskimo who lives on a very high protein diet, while the Labrador Eskimo, on a more varied and general diet, is very susceptible to the vascular and renal diseases (149).

The only relation of protein to hypertension was expressed by others as being due to the overeating which would lead to obesity and a high blood pressure as a result from it. As the plasma protein is low (82), it is most questionable as a factor in causing blood pressure changes.

Cholesterol has been shown to be of import in arteriosclerosis and a small number feel the sclerosis will cause hypertension (11), (145). Others have associated cholesterol directly with hypertension (22), (117), (108), but as a dietary disturbance, hypercholesteremia may lead to arteriosclerosis and give rise to secondary hypertension, but not to the primary disorder (61), (79), (126), (157), (160).

This has led, since the finding of a definite arteriosclerosis and arteriolosclerosis is common in essential hypertension, to the belief that arteriosclerosis is a result of the blood pressure elevation (22), (23), (104), (106), (108), (158). Still others see no association at all between arteriosclerosis and hypertension (54), and as proof, there has been shown the absence of sclerosis in coarctation of the aorta (26), (58).
Calcium and phosphorus have been thought to be so altered that they could give rise to blood pressure elevation, particularly because of pregnancy, when calcium metabolism is so important, and the secondary hypertension in the toxemias of pregnancy. No experimental nor clinical confirmation could be found however. (6), (79), (144), (157), (160)

Salt has been found experimentally and clinically to give a definite blood pressure rise in the hands of one investigator (3), (4), yet the evidence of others was directly opposed to these findings:

"There is no definite evidence in the literature that sodium chloride raises blood pressure. The level of the blood chlorides bears no relation to blood pressure... In a series of experimental observations, the injection of ten grams of salt failed to raise the blood pressure in cases of hypertension" (110)

"Salt in blood, i. e., plasma chloride, was normal in hypertension or above normal, but no relation to blood pressure by variations was found" (118)

To this last statement, others agree (83), (142), (168).

Thus, the existence of salt is, at least, not a very important etiological factor in hypertension.

Alkalosis has been described as existing in hypertension and renal diseases with raising of the pH and the concentration of bicarbonate and lowering of the blood chlorides (155), but the above results on the halogen in the blood raise some doubt as to the importance of alkalosis.
The relation of diet in essential hypertension cannot, in the light of all findings, be expressed as being a very important (or clear) matter.

**OBESITY AND ESSENTIAL HYPERTENSION:**

"The majority of fat women who seek medical attention have hypertension" (14) is the observation made by a practicing physician who observed a group of obese women for one year. The statistical bulletin of a large insurance company reported that in sixteen thousand, six hundred and sixty-two examination: "Rate of high blood pressure per age group only showed significant increase in overweight groups" (100). Some clinicians agree (8), (44), (10), others, however, by analysis of their records do not find that obesity in itself will lead to hypertension (71), (73), (79), (125), (168). It has been stated that obesity may accentuate a pre-existing hypertensive state (97). The advancing that obesity is inherited (30) or that ninety per cent of obesity is endocrine in origin (99) places this problem in a class of other etiological factors.

Probably, excess fat forces the heart to do more work and by lowering the number of capillaries and arterioles, this load is somewhat relieved (99), (160), but at any rate, the relation does not seem to be a direct association.

"It appears evident that obesity in itself does not cause hypertension, for extremely obese individuals may have low blood pressure, even though there is no evidence of cardiac weakness. Obesity, like hypertension, is often an inherited characteristic,
and it seems probable that the same constitutional type is predisposed to both obesity and hypertension. Likewise, overeating tends to increase both weight and, apparently, blood pressure. The fact that reduction in weight in obese individuals may be accompanied by a reduction in blood pressure—though this is far from always the case—is not an indication that obesity causes hypertension, for dietary restriction may have a similar effect on the blood pressure of thin persons. (53)

**CONSTITUTIONAL FACTORS IN ESSENTIAL HYPERTENSION:**

The establishment of definite conclusions is most difficult in this field, but still, although facts are confusing and multiform, there is some enlightening to medical problems to be found in this consideration.

The physical type of individuals are: The asthenic, the pyknic, the athletic, the dysplastic, and the non-differentiated. In a large series of cases, the greatest number of hypertensives were in the asthenic and athletic types. The asthenic has been found by another clinician to be most susceptible (126), while in the examination of one thousand children between the ages of one and seventeen, the pyknic type was more prevalent and showed greater tendency to hypertension (87), and other have found the same in the adult (63). Another found tallness in the women was characteristic (128). This has led to the conclusion of some that no correlation exists (8), (18).

The description of four types of individuals seen in general practice with hypertension has been given as: The obese at the menopause, the thin or fat patient of about the same age
with nervous troubles, the business man with tension, and the youthful individual with a rapidly fatal course. The final decision, however, is that one should include the general person (91).

Contradictions are too frequent and numerous, one even finding in texts on this subject, contrary reports on different pages of observations (18), so that no conclusions can be advanced yet (8), (73).

The relation of tissue tonus to the hypertensive has been quite well accepted among those working in this field. In one hundred and forty-eight cases, a research expert found that persons with herniae or a low tissue tonus are much less susceptible to hypertension than those with a hyper-tissue-tonus (18). The same writer at another time says:

"However, with the idea of a constitutionally increased neuro-muscular tonus of the arterial system as the starting point in the study of essential hypertension, other more immediate questions must be taken into account" (17).

Others find constitutional hypertonicity of the autonomic, neurovascular control strikingly important (25), and there are other men who agree that a raised tissue tonus is present (65), (147). Conversely, another finds hernia frequently in hypertension (87) and the report has been made that in chronic diseases there is a lower tissue tonus (63).
Constitutional susceptibility (127) and an inferior vascular system (18), (23), (36), (130), (162) have been stated to give origin to hypertension. "Constitutional hypertension" has even been suggested as one type of essential hypertension (36).

Environment has been summarily considered as:

"It is believed that the germ plasm may contain determiners of abnormal traits as well as normal traits, and if the environmental factors are suitable for development of the abnormal traits, disease may result" (143);

"If emotional insults continue over prolonged periods, the functional reactions become more or less fixed... The problem remains of tracing the environmental influence that has created this vast and increasing race of hypertension" (108).

The problem still does remain.

The mental trend in the patient with hypertension has been remarked on many times. The hypertensive personality has been mentioned (16). The extreme conception is that there is almost a psychoneurosis present in many cases (66) and the description that has given of persons with arterial hypertension as being:

"Psychically they are the antithesis of the child. They do not play. They have no illusions. They are terse, are irritable and have single track minds. While their mental horizon is narrow, within this range they are terribly tense and pursue their aims with a grim desperation" (108).

"They are also the weak and unsuccessful men for whom the continued failure in the struggle for existence constitutes the life-long mental strain characterizing the victims of this disease" (126).
The Orientals (53) and the African Negro (45) are comparatively free of the mental tension so marked in the races in which hypertension is so common. Hypertension is not a new insult to the organism, but is simply an exaggeration of a normal phenomenon... it is a by-product of the "progress of modern civilization" (108).

Opposed to these findings are the reports of men who have found many of their patients with sedentary lives (158), (16) and in one well-written composium, the Egyptians were found to have high blood pressure regardless of the mode of living or environmental associations (73).

In the main, the psychic factors are of some importance is accepted by a great number of investigators of hypertension (23), (68), (126), even to the point that response to treatment may be entirely on a psychic basis (64). If secondary or primary, it is not known (160).

Since postmortem studies have proven disappointing, many feel that in the physiological fields, the answer to hypertension will be found (66). One writer even states: "The Continental School...taught, and still teaches, that morbid anatomy comes first and abnormal function follows", so one must not be misled by pathology, for in essential hypertension, pathological findings may be secondary (108).

Though "wear and tear" may be a very important factor (142), it is not possible, as was stated before (53), to be too
definite in statements on hypertension for it varies for the individual. If the psychic factor is primary in some cases, it may not be in others.

MINOR ETIOLOGICAL FACTORS IN ESSENTIAL HYPERTENSION:

Persons with primary blood pressure elevation have been ascribed to be in two of the four blood groups and also to be predominantly left-handed, but such findings are entirely unconfirmed and have had no further report than their first observation (53).

CAUSATIVE AGENTS OF ESSENTIAL HYPERTENSION:

One must "roll up his sleeves", so to speak, when an attempt is made to review the literature on agents giving rise to increased peripheral vascular constriction and essential hypertension (115), (131). "The current view regards essential hypertension as the primary phenomena and cardio-vascular-renal changes secondary" (108). Others are in agreement to this (28), (78). What causes this peripheral change?

Factors that may cause peripheral constriction are:

(76), (115)

1. Central nervous system changes.
2. Peripheral vascular changes, neurogenic or muscular.
3. Inherited qualities.

Essential hypertension has been clinically divided into benign and malignant type. Benign is the more chronic form and associated with less severe symptoms, while in the malignant
type, which is acute fulminating hypertension, the renal pathology is most marked (37), (75). Whether these are distinctly different conditions (37), (60), (75) or only varying degrees of the same pathological process (47), (112) is undecided. There has been a simile suggested from pathological studies that hypertrophic or benign hypertension is one form and degenerative or malignant is the other (21), (147). The suggestion is made that the renal pathology gives rise to the hypertension, but the pathology is probably a spasticity of the arterioles (23), (94).

I. THE KIDNEYS

The very earliest association of hypertension has been with the kidneys (79), (90), as has been previously pointed out. Furthermore, the greatest amount of pathology has been located within these organs (53).

Bright, Traube, Cohenheim (12), (23), (94), (121), and Gull and Sutton (78) explained that the kidney pathology gives rise to a compensatory increase of the blood pressure to maintain function of these vitally important excretory organs.

The vascular bed of the kidneys is very extensive peculiar unto itself, inasmuch as there is necessity for the filtration of one thousand to fifteen hundred liters of fluid per day through the glomeruli (79).

The close association of glomerulonephritis to hypertension, as was declared earlier, makes the kidneys particularly
suspicious. The pathology in glomerulonephritis is a swelling of the endothelium with narrowing and occlusion of the capillaries. Furthermore, in nephrosis, which is a cause of secondary hypertension, an occlusion of the circulation probably exists (23), (79). Since two-thirds of the kidney must be damaged before renal insufficiency will be apparent (168), then an occult and latent vascular disorder in the kidney may exist and give rise to hypertension long before it is suspected.

However, evidence has accumulated to indicate that the kidneys do not answer all the findings in essential hypertension.

A research experimenter concluded:

"Hypertension of various degrees is encountered in all animals with severe renal insufficiency. An estimation of the degree of renal damage cannot serve as a guide for the prediction of blood pressure" (32).

It is true, though, that constriction of the renal arteries and by application of roentgen rays to transplanted kidneys, artificial hypertension will be produced in experimental animals and extensive renal damage found at death (122).

However, in the contrary view, there has been found to be only an edema and temporary hypertension by others using a similar roentgen ray technic (22). Urethral obstruction and narrowing of the left renal vein gave a temporary blood pressure elevation only (23). No more positive results have been reported from partial or total nephrectomies (10), (22), (23); or by constriction (35) or occlusion (86) of the renal vessels; or even by renal denervations (35), (121).
Volhard separates hypertension into pale and red, pale being due to arterial constriction and is renal in origin, red being extrarenal and heredity, age and constitution playing the big part (162).

"Five years or more of hypertension is typical of essential hypertension and not of nephritis", says another (156).

In essential hypertension, blood and urinary findings are negative to minimal until the late stages, has been found by some clinicians (75), (79). There has been experimental work which found that kidney damage was not apparent and probably not present. No correlation between renal damage and the age of the patient, symptoms, or duration of the disease has been found by another (49). "Renal changes are lacking in about ten per cent of autopsies on hypertension" (11), (23).

The relation of renal changes giving rise to a sympathetic or hormonal or pressor substance retention that results in a general vascular constriction has been suggested (160). The capillaries are not known to constrict to such a degree that hypertension will result, but the inference is made that in shock a capillary dilatation occurs so there may be an opposite condition here (23). Possibly, like hypertrophy of the heart in cardiac compensation, the capillaries have a compensatory re-enforcement and hypertrophy (50).

In arteriosclerosis, a hypertrophy of the muscle
in the media and some in the intima with an elastic tissue hypertrophy in the intima and adventitia is reported (102). Arteriolar changes in hypertension has been described for many years and the media seems to show the greatest change, there being a muscular hypertrophy (75). Elastic tissue changes and intimal variations are apparently without established opinions (1), (75), (78), (90), (102), (105), (112). In the advanced and malignant type of cases, there has been the observation made in recent years, that skeletal muscle and generalized arteriolar changes are prominent (78), (1), (75), (90), (112). It has been reported that different arteries in the same tissue and varying segments of it are involved in varying degrees (105). By careful measurement of the lumina of arteries of normal tissue and that of hypertensives, the arterial lumen was found to be decreased in hypertension and in direct relation to the severity of the type of hypertension during life (75).

Yet, if essential hypertension is entirely due to arteriolar disease cannot be known before further investigation has shown more than has been discovered at the present. There has been found to be no elevation of blood pressure in dogs from the ligation of the main arteries (163).

The inability to correlate the degree of renal damage with other findings, as extensive lesions elsewhere, has caused the feeling that renal pathology is not the entire answer (79).
It has been stated that cardiovascular and renal changes are in no sense specific and are only secondary results (43). The kidney and the arteries in essential hypertension have not been ruled out nor have they been proved to be the causative agent, as yet.

II. THE SYMPATHETIC NERVOUS SYSTEM

Vasomotor instability has been shown earlier to be present in normal individuals and that an increased normal response is present in essential hypertension (33), (111).

The sympathetic nerves have been associated physiologically with vasoconstriction and their peripheral stimulation by various methods will give a blood pressure rise (22). The peripheral resistance is chiefly regulated by the vasomotor centers acting through the vasomotor nerves. (115)

Since the Hering-Brewer reflex has been found to control blood pressure by a depressor effect, there has been associated a loss of it in hypertension. Recently, there was announced the finding that endovascular pressure sensitizes reflexly certain vascular areas, namely the celiac and superior mesenteric arteries and maybe the thoracic and peripheral arteries, giving blood pressure changes. Total sympathectomy in the dog gave cessation of this reflex blood pressure control. (65)

Nevertheless, experimental destruction of the aortic and sinus nerves produces a permanent blood pressure elevation and this is the only experiment that does this, another group believes
They found the sinus mechanism normal in hypertension cases (43).

A hyperirritability of the vasomotor nerves (57) (68) or a vasomotor instability (12) have been accepted as being most important by some men. Others by association of menopausal findings believe that there is a close relation to the vegetative nervous system (35) and another by comparison of lowered sexual activity sometimes found, familial incidence, metabolic disturbance and neurasthenia, concluded that an alteration of the vasomotor activity was present (81).

The different types of individuals have been divided into the normal, those excessively stimulated by the sympathetics or the sympathicotonics and those which respond excessively to the parasympathetics or the vagotonics. The vagotonics are the hypertensives, who instead of getting a blood pressure rise from ephinephrin, show a fall (30), (68), (84), (166). However, others who have conducted research on this relationship of abnormal vasomotor responses to blood pressure find no demonstrable changes in the autonomic nervous system of the normal and the hypertensive individuals and "in general it may be said that ... the sympathetic nervous system is of little importance in the pathogenesis of hypertension and one must look elsewhere for an explanation of the etiology" (160).

"Cannon recently has shown that the sympathetics are relatively unimportant in cardiovascular, gastro-intestinal or secretory functions in cats" and the inference is made that the sympathetics are not too important in hypertension (79).
If emotion and pain will give an acute hypertension which is soon stabilized, the sympathetics probably would compensate for a more chronic condition (22).

The immersion of the hand in cold water has been found to raise blood pressure and maintain it much higher in the hypertensives than in the normal person but block anesthesia to the arm will stop such a reaction, while cervicothoracic or lumbar ganglionectomy will not (68). The same findings plus the absence of response during anesthesia led to the conclusion that an intrinsic spasm is the cause of the vascular hypertens (131).

Symptomatic relief but no permanent lowering of the blood pressure has been reported from the various neurological operations for hypertension, as in splanchnic resections (38), spinal divisions and ganglionectomy (38), (123), (124), (136), renal denervations (114), (122) or renal sympathectomies in experimental animals (101).

That the relation of the sympathetic nervous system to essential hypertension is not known must be concluded (126).

III. PRESSOR SUBSTANCES:

In 1890, Sir William Broadbent said the cause of hyperpiesia "can scarcely be other than some substance in the blood which acts directly upon the capillary wall" (94).

A pressor substance is some activator in the blood which will give rise to an intrinsic vascular muscle spasm. This has been accepted to be the primary cause of essential hypertension
by many researchers (19), (54), (79), (93), (95), (141), (142), (153), and others.

An American says:

"There are suggestions that intoxications resulting from abnormal metabolism may have a similar effect. These intoxications produce early only functional disorders chiefly referable to the nervous system. When persistent, they induce organic changes affecting the blood vessels and kidneys ... Hypertension as a purely mechanical factor is not adequate to produce arteriosclerosis. It is only operative when accompanied by a nutritional disorder" (54).

Epinephrin was the first pressor substance suspected, but then it was more or less disproved, as will be taken up under the following caption.

Sir Humphrey Rolleston states:

"Chronic inefficiency of the liver to deal with the metabolism of proteins has naturally been assumed to be a cause of high blood pressure" (142).

Hepatic disorders with decreased detoxifying action of proteins have been discussed (54), (153) and by using detoxifying tests on the liver in essential hypertension, hepatic impairment was found by one group (153), but others have found no liver impairment and concluded that, if a pressor substance is present, it must be retained because of renal damage (79), (160).

The proteins themselves have been found to play a questionable role in hypertension, but the protein cleavage products have been strongly suspected and were extensively investigated.

The protein cleavage products that have been ruled
out by the trial and error methods are: Indol and tyrosin (167) and those present in an extract of whole blood (43). There has been one substance, however, that an experimenter has found will give a hypertension in animals that is comparable to essential hypertension. It is guanidin (92), (93), (94). The findings were that sixty per cent of essential hypertension patients and one hundred per cent of chronic nephritics show an increase of guanidin bases in the urine (94).

"Our observations indicate that any great excess of guanidin is destroyed, although a part of this excess may be retained, probably fixed by the neuromuscular apparatus of the smaller blood vessels with the production of an arterial hypertension" (92), but whether it is a retention product of renal insufficiency or the actual causative agent, could not be stated (94). Another group gives these findings some confirmation, but because some cases of essential hypertension do not show guanidin bases in the urine and because changes in severity of the disease are not accompanied by changes in these excretory products, they are still a little dubious (70). Others criticise the experiment because of the large amounts of the substance that must be given and find the chemical methods used for its determination are questionable (160) and because the excretory products in essential hypertension are too variable (43).

Attempts to find a blood pressor substance have been, for the most part, futile (2), (39), (43), (168).
Urinary vasoconstricting substances have been found to be as potent in normal urines as in those of hypertension patients (160). Salt solution and sugar solution will give as prominent a blood pressure elevation in rabbits as any other chemical product (12).

A pressor substance in the blood gives only a temporary hypertension, for it causes an immediate equilibratory response (61).

The essential hypertension must be accompanied by a nutritional disorder (54) or that it is a metabolic disturbance (73) was advanced, but the statement is all that was given.

No pressor substances are known that will cause essential hypertension.

IV. ENDOCRINES AND ALLERGY

Epinephrin, described in the last of the nineteenth century, was shortly afterwards suggested to be the substance which is the causative agent of essential hypertension (166). At the present, paroxysmal hypertension is known to arise from suprarenal tumors (34), yet all chemical and physiological tests are not accurate enough to detect epinephrin in the blood of hypertensives, but because it cannot be determined even in normal blood, the exclusion of it should not be final (20). All others who have investigated this field find no association at all and
feel it should be discarded (53), (61), (166).

The administration of one cubic centimeter of adrenalin has been stated to relieve both asthma and high blood pressure (84). This opposes any belief that the hormone may play a role in hypertension, but indicates that allergy may be associated with primary blood pressure elevation. Because the angiospasm may be like that believed to be in anaphylaxis, heredity is prominent in both, and because a disturbance of the vegetative nervous system may be present in both allergy and hypertension, the two have been said to have common cause (83), (84), (152).

Fifty per cent of hypertension patients have been reported to have allergic manifestations (83). The comparison is not without merit, but further collaboration is necessary.

The statement that sexually abnormal women are more prone to hypertension has been made (9), (127) and the association of it with the involution period (50), (53), (78), (81), (113), (134) points to the gonads. The absence of axillary hair in most women and some men with hypertension has been reported (83), (84). Some have found hypertension in artificial menopause (22), but others have not (30). It has been stated that a short menstrual history gives greater possibility of hypertension (84). However, the ovarian hormone is definitely known to lower blood pressure (11), (53) and if the onset is when the hormones from the sexual glands decrease (9), (166), then the
opposing gland must give origin to the cause, that is, the pituitary.

In certain anterior pituitary adenomas with characteristic secondary body changes, secondary hypertension is found (88). It has been claimed by a well-known endocrinologist that an increase of basophil cells in the posterior lobe of the neurohypophysis may be the cause of essential hypertension (40). Other clinical observers agree (18), (20), (72) that such an origin is possible, but the actual significance of the posterior pituitary pressor substance is unknown that the present (43). The report has been made that in some cases of very high blood pressure, no increase in basophilic cells is present and in very young, normal individuals an increase is prominent (20). Others agree that the pituitary is not the cause (138), (160). The question can only be settled by more knowledge.

Parathyroid has been found to play no part in the cause of idiopathic hypertension (61), (94), (144).

A general endocrine disturbance has been held to be present in Essential Hypertension (79), but others disagree (15), (53), (139).

V. CENTRAL NERVOUS SYSTEM

If the peripheral nervous system and pressor substances cannot be found to be the cause of Essential Hypertension, then, it has been reasoned, the central nervous system must be
the origin.

Since Cushing's (22) and Starling's (30) work on increased intracranial pressure have shown that it causes hypertension in experimental animals, there has been suggested that brain changes may cause this disease. Certain conditions of the encephalon will cause secondary hypertension, but not all Essential Hypertension can be included in this class (31).

A slow blood flow through the brain with a subsequent vasoconstriction elsewhere has been described by some, but work has shown slower even yet in other disease without hypertension (180).

Medullary sclerosis was found at autopsy in a high per cent of cases by several men (27), but others claim this is a late change and have discredited these findings (22), (30), (57).

Medullary disorders with a resulting spasm of the arteriocapillary bed is the "most universally accepted theory as to the production of hypertension" has been claimed by one author (83) and recently, by the action of epinephrin, the location of the vasoconstriction as arising centrally and not locally has been advanced (52). This is the latest trend in Essential Hypertension, but no significance can be attached until further work is done.

VI. RESPIRATION AND THE LUNGS

Starling, by experimentation, showed inspiration gave a more rapid return of the blood to the left side of the
of the heart. Hyperventilation then would give a better blood flow into the lungs and, secondarily, a prolonged hypotension results. With these facts, and of the opinion that most hypertensives are of the pyknic type with a high diaphragm and small lungs, a physician has claimed Essential Hypertension is solved. Since, what occurs is a large volume of blood is stagnant in the arteries which causes compensatory constriction and later hyperplasia and arteriolosclerosis, by increasing the blood flow in the lungs, better tissue metabolism results and blood pressure is decreased. (132)

By measuring the lungs in a large number of hypertension cases, another has found small lungs in the majority and feels that oxygenation deficiency is present (83). Others agree that the lungs are the key to hypertension (151).

The experimental work of others has shown that oxygenation is the same in both normal and hypertensive individuals (26) and general contradictions to the role of the lungs are strong (71), (108), (168) and leave doubt in one's mind.

VII. OTHER DISEASES AND TOXIC FACTORS

Diabetes and Essential Hypertension have been closely associated for heredity, age and obesity are common to both (72), but others have found no correlation at all (22), (79) and the experimental maintainence of hyperglycemia for as long as seven years has shown that there is no tendency for a blood pressure increase (109). The two are not closely enough related
to be clinically associated (53).

Syphilis was ascribed as causing hypertension by Stoll in 1915 and this was substantiated by Faught in 1916, but recent work has shown that the relation is only casual (69), (79), (83).

Infections as a direct cause of Essential Hypertension has been propounded for many years. Some state all infections have an important bearing (130), (143), others stress acute infections (74), or infections early in life (59) or low grade processes that do not break down tissue vitality directly but lower its resistance (56). Bacterial filtrates have shown that the typhoid group and many strains of the streptococci have an ephinephrin-like behavior (80). Typhoid fever will give a secondary hypertension, it has been found and a history of it is frequently found in the person with Essential Hypertension, one author asserts (79). Then, too, hypertrophic arthritis and pernicious anemia have been associated with Essential Hypertension (37), as have previous cardiac infections, but they are only believed now to be secondary factors (79).

In over sixteen thousand cases, infections were found to be without significance (100) and others give no value to the infections in idiopathic hypertension. In the Aboriginal African, oral sepsis, tonsilitis, chronic arthritis and rheumatoid conditions are very common but hypertension is nil (45). Because of the few to no remissions in the treatment of Essential
Hypertension, another writer believes toxins are not the cause, for variation in their absorption would occur on a restricted regime. (73)

Infections in themselves are at the most secondary to the cause of Essential Hypertension.

Coffee, tobacco and alcohol play no part in causing hypertension (8), (79), (84), (96), (100), (142), (60).

SUMMARY:

1. Hypertension is a symptom in many pathological states.
2. Blood pressure elevation is a physiological process in the normal individual.
3. Hypertension may be found as a clinical entity with no known cause. This is essential, primary or idiopathic hypertension.
4. Essential Hypertension is mechanically due to an increased peripheral resistance.
5. Essential Hypertension is commonest after forty-five years of age and the greatest mortality is between sixty and sixty-eight years of age.
6. Primary Hypertension is more fatal to men and probably more prevalent in women.
7. Primary hypertension has a hereditary basis and may be a dominant characteristic.
8. Essential Hypertension is found principally in the Caucasian races.

9. Occupation and diet are insignificant etiological factors in idiopathic hypertension.

10. Obesity is a secondary factor in idiopathic hypertension.

11. The essential hypertension patient may show a prominent psychic factor.

12. The cause of Essential Hypertension is unknown.

13. Likely primary factors in Essential Hypertension are: Renal Pathology, the sympathetic nervous system (more likely central), the pituitary gland or some unknown pressor substance.

14. The lungs possibly are the mechanical causes of Essential Hypertension.

15. Diabetes, syphilis and infections probably are only secondary factors in Essential Hypertension.

16. Coffee, tobacco and alcohol play no part in hypertension.

DISCUSSION AND CONCLUSIONS:

There are many schools of thought on the subject of hypertension and very little solid ground for any of them to stand on.
Conclusions cannot be made with any impunity. In experimental work, the clinical field is forgotten, while clinical studies are inadequate and biased, so misinterpretation of the findings of both is possible and only chaos is left.

I am impressed that this field of medicine is as close to the metaphysical as science can come, yet there is no other way than for all the observations to be collected. Clear heads, scientific minds and clinical observations of note are among the mass of material on this subject and in time Essential Hypertension will be found to either be a symptom of a number of different pathological states or the cause of it will be discovered and established as a known clinical entity. Already there has been a separation of some of the causes of hypertension from the chaff.

Hypertension, the commonest finding in the causes of death in Europe and America today, is a challenge to the medical science.
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