Endocrine glands and hypertension.

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ENDOCRINE GLANDS AND HYPERTENSION

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HYPERTENSION

The level of arterial blood pressure is relatively constant in normal people, and in a state of health is the resultant of a number of forces, among the chief of which are the contraction of the heart and the peripheral resistance provided by the arterioles along with the elastic recoil of the large arteries and the state of the capillary bed. Included in the capillary bed proper are the metarterioles, the precapillary sphincters, the true capillaries and collecting vessels. The metarterioles and precapillaries are the only structural components possessing contractile muscle elements and hence are a major factor in regulating the volume and extent of blood flow through the network of capillary vessels.

Still, its range of variation is wide and it is much influenced by both internal and external factors. The following circumstances are commonly associated with temporary, moderate to slight changes in blood pressure: 1. Meals 2. Emotion 3. Alcohol 4. Tobacco 5. Obesity 6. Muscular Effort 7. Posture 8. Environment 9. Climate and Temperature and 10. Pregnancy. Many other factors play a part just as one increase of arterial pressure does not mean that hypertension is present.

In spite of the fact that these varied factors are continually altering the several parts of the circulatory system, under ordinary conditions any sudden change in pressure is rapidly restored to normal. Should the pressure continuously be above the normal, the condition is called HYPERTENSION.
The rise in blood pressure involves not only the systolic but more importantly the diastolic level. The latter reflects the increased peripheral arteriolar resistance which is the fundamental hemodynamic characteristic of the disease.

I concur with others who believe that the normal range of arterial pressure is 110-140 systolic and 70-90 diastolic. The majority find that systolic, mean and pulse pressure rise gradually from 40 to 62 years, then rapidly from 62 to 85. The diastolic pressure seems to have little correlation with age.

Continued hypertension occurs as a result of a number of different conditions either caused by, or associated with a large number of diseases. The association of pyelonephritis, chronic glomerulonephritis, polycystic kidney, hyperthyroidism, adrenal tumors, poliomyelitis, pituitary tumors, thymic tumors, and many others may play an important part in producing it. What is not so evident is that what seems to be ordinary essential hypertension probably is also of multiple etiology, so-called because it is not dependent on disease of the kidneys or of any other known organs, and is by far the more common.

When benign essential hypertension reaches an advanced stage, necrotizing arteriolitis occurs. This is the so-called malignant phase of hypertension, which was formerly looked upon as a special form of the disease. This classification of benign and malignant hypertension was established before the experimental studies of Goldblatt and collaborators in 1934. Volhard in 1923 divided hypertension into the red and pale types. The former was found in plethoric individuals of pyknic habitus; examination revealed hypertension
alone, and no vascular renal or eye ground changes. The latter had a generalized vasoconstriction, and as a result there were changes in eye grounds, cerebral symptoms, and early renal insufficiency.

Fishberg in 1939\(^6\) divided hypertension into: a. that due to renal lesions, b. not of renal origin, or renal factor not demonstrable.


Schroeder and Steele in 1939 classified hypertension according to renal, endocrine, nervous and vascular factors. Weiss\(^9\) 1940 classified hypertension according to physiologic and clinical character, as follows: A. Hypertension of Vascular Origin with Renal Ischemia. B. Hypertension of Organic Vascular Origin without Renal Ischemia. C. Hypertension of Vascular Non-organic origin in which are included:

1. Endocrine Disorders (a) Pituitary Dysfunction and Neoplasm (Cushing's syndrome), (b) Adrenal Dysfunction and Neoplasm (cortical and medullary) (c) Certain Types of Toxemia of Pregnancy. 2. Nervous Disorders (cerebral trauma, cerebral neoplasm, poliomyelitis and rare vascular disease of the brain).

Page\(^10\) in 1939 classified hypertension into: 1. Renal a) affections of vessels, b) affections of parenchyma, c) affections of perinephric structures and d) affections of ureter. 2. Cerebral. 3. Cardio-Vascular: includes heart failure, arteriovenous fistula, heart block, coarctation of aorta, polycythemia and atheromatosis. 4. Endocrine:
pheochromocytoma, adrenal carcinoma, adrenal hyperplasia, chorion-epithelioma, adrenal-like ovarian tumor, Cushing's syndrome, pituitary basophilism, acromegaly, thymic carcinoma, hyperthyroidism, arrehenoblastoma, desoxycorticosterone overproduction. 5. Unknown: essential hypertension and malignant hypertension. Braun-Menendez, Fasciolo, Leloir, Munoz, and Taquini classified hypertension into: A. Hypertension of renal origin. B. Hypertension probably orenal origin, (1) essential hypertension (2) malignant hypertension. C. Hypertension of extrarenal or ill-defined origin, (1) endocrine (a) hypophysis (b) adrenal (c) ovary (d) toxemia of pregnancy. (2) nervous (a) trauma (b) neoplasia (c) cerebral inflammatory process (d) anxiety state. Page 195411 mentioned that if one thinks of the various systems in the normal body which control blood pressure, it is possible to divide arterial hypertension into renal, endocrine, nervous and cardiovascular panels.

Before starting to discuss each group I would like to mention some historical information concerning hypertension.

In 1836 Richard Bright observed the large heavy heart of the hypertensive person and published his view that some of the large heavy hearts of his patients with renal disease were not the result of intrinsic heart disease and that there was direct relationship between renal disease and large, heavy hearts. Johnson13 in 1868 recognised the existence of thick walled arteries, both large and small. He considered this condition secondary to Bright's disease and believed that when diffuse, such a thickening (hypertrophy of media) of the blood vessels could constitute a basis for increased peripheral vascular resistance.
Widespread organized organic disease of the arterioles was described in 1872 by Gull and Sutton who called it arterio-capillary fibrosis and concluded that it was a primary, organic, pathologic basis for increased vascular resistance. They regarded this vascular disease as independent of renal disease.

Toynbee in 1846 observed thickenings of the walls and diminution of the calibre of the renal arteries in his anatomical studies, and gave support to Richard Bright's idea of the renal origin of the cardiac hypertrophy of hypertension and arteriosclerosis. Kirks in 1855 had demonstrated a relationship between hypertension and arteriosclerosis. Mahomed from his clinical observation in 1872 led to the view that high blood pressure precedes the development of any clinical signs of Bright's disease.

Von-Basch in 1880 introduced the sphygromanometric method for measuring blood pressure in man. This method came into general use a few years later when Riva Rocci used the pneumatic cuff for compressing the artery. In 1893 Von Basch published the result of his experience and drew attention to the frequent absence of demonstrable signs of arteriosclerosis in patients affected with hypertension. In this way the disease which today is called essential hypertension took origin, and was subsequently studied in detail by Allbutt in 1895. Huchard 1889, Janeway 1913, Volhard and Fahr 1914, and Tigerstedt and Bergman in 1898 called attention to the fact that saline extracts of the kidney produce a rise in blood pressure when injected intravenously. Evans in 1921 combined the observations of Johnson, Gull and Sutton and described diffuse
hyperplastic sclerosis, which he found most commonly in the kidney. He regarded the lesion as a manifestation of active inflammation. He failed to observe any changes in the muscles. Kernohan, Anderson, and Keith in 1929 did describe stenosis of the arterioles due to hypertrophy of media and thickening of the intima in the muscles of hypertensive persons. Scott, Seegof, and Hill in 1933 and Andrus in 1936 described degenerative arteriolar lesions with fibrosis in the media without stenosis or thickening of the wall.

There is absence of renal lesions in many hypertensive cases in the early stage of the disease or complete absence throughout the entire course of the disease (as I will mention in discussing the mechanism of renal origin of hypertension later on in some detail). This absence of renal lesions drew the attention of some investigators away from the renal origin of hypertension, and numerous theories of etiology were evolved.

**NEUROGENIC ORIGIN THEORY**

Monakow in 1920 and Raab in 1929, 1931 considered that hyper-irritability of the vaso-motor centers was of importance. Kehler in 1924 attributed hypertension to activity of the hypothalamic centers and proposed the theory of primary central origin. This theory was adopted by Castex in 1929. The theory lacked pathological confirmation, according to Braun-Menendez in 1934 and Leiter and Grinker in 1934.

Koch and Mies in 1929 suggested the possibility of producing permanent hypertension by section of the depressor nerves. The changes in the responses of carotid sinus to various stimuli caused certain
investigators to suggest that diminution in the sensitivity of the
carotid sinus to various stimuli produced changes in blood pressure,
and was therefore concerned in the genesis of hypertension 15 in 1932, Heymans, Bouchaert and Regnière 15 in 1933.

However, the subsequent studies of Keele 15 in 1933 and of Cannon 15 invalidated this hypothesis. The neurosurgeons, Paet and Isberg 21 in 1946, and Grimson 22 in 1942 have suggested that hypertension may be initiated by emotional stress, and in time this neurogenic hypertension may lead to structural change in the renal vascular system to produce hypertension of renal origin. However, neurogenic hypertension in dogs does not produce morphologic changes in arterioles, Thomas 23 in 1944.

A few psychiatrists have attempted to find a characteristic psychiatric pattern which might have etiological connection with hypertension, but their results have not carried complete conviction.

ENDOCRINE ORIGIN

ADRENA L AND HYPERTENSION

The discovery of the pressor action of the adrenal medulla
(Oliver and Schaefer 1895 15) and of its active principal adrenalin by
Taharine 15 in 1901 and Aldrich 15 in 1905 aroused the interest of many
in regard to the relation of hypertension to this gland (Tosse, 1903 and
Vaquer, 1904 15).

However, the presence of adrenalin in the blood of essential and
nephritic hypertensives has not been demonstrated, even by using
methods of extreme sensitivity, Hulse 15 in 1922. Oppenheimer and
Fisher in 1924 commented upon the elevated and reduced blood pressure found in adrenal tumors and Addison's disease, respectively. In recent years a series of observations has appeared, each one relating the adrenal cortex in some way to the regulation of blood pressure or the hypertensive state.

The first attempts to relate the adrenal cortex to hypertension in man were morphological.

The clinical features of Cushing's syndrome listed by Albright in 1943 are associated with relatively severe nephrosclerosis, hypertension, and arteriovascular disease. The basic pathology varies for this syndrome; it may be adenoma or cancer of the adrenal or basophil adenoma of the pituitary, and in this condition it is usually associated with bilateral hyperplasia of the adrenal cortices. The cortices may be hyperplastic without other lesions and simple or nodular hyperplasia, even true adenomas of the adrenal cortex have been reported in association with hypertension. Rinhardt, Williams and Capeller in 1931, Sarason in 1943, Russi, Blumenthal and Gray in 1945 and Fisher and Hawley in 1947.

In general, the cells of the cortex in these conditions are hyperplastic and may show a high lipid content. On the basis of this finding and other evidence cited, it is suggested that hypersecretion of the adrenal cortex may in some cases be a factor in the genesis of essential hypertension.

The mean weight of adrenals, according to one of the workers mentioned already is 11.2 gms. in non-hypertensive individuals and 15.4 gms. in hypertensive individuals.
These findings have not been widely confirmed. Dempsey in 1942 in a series of unselected routine autopsies on adult subjects, reported that the average weight of the adrenal gland in cases of hypertension is not significantly higher than that in non-hypertensive control cases. Nodular or adenomatous hyperplasia of the adrenal cortex is not regularly found in association with essential hypertension, and it occurs with considerable frequency in non-hypertensives. Others supporting Dempsey in his observations include Castleman and Smithwick in 1943 in their studies of the relation of vascular disease to hypertensive states, which were based on renal biopsies of 107 hypertensive patients; Dublin in 1943 and Bruger in 1944, who reported that there is no difference in the incidence of hyperplastic or adenomatous changes in the adrenal cortex of hypertensive and non-hypertensive subjects, and the urinary excretion of 17-ketosteroids is significantly lower in hypertensive than in normotensive subjects offering some theoretical consideration to account for these findings. Moore has written that there is no established relationship between focal hyperplasia or adenoma of the adrenal cortex and hypertension. Commons and Callaway in 1948 from their data presented, fail to indicate that the morphologic abnormality is related to or indicative of pathologic changes producing hypertensive disease. Goldblatt in 1951 from his experience at the Institute of Pathology, Western Reserve University, mentioned that these adrenal cortical changes were by no means a constant finding in autopsy in cases of hypertension. They felt that these changes or abnormalities were uncommon or existed with equal frequency in normotensives.
Koehler\(^{37}\) in 1936 reported that the size and epinephrine content of the adrenal gland are not altered by a pre-existing hypertensive state and in some instances are less than the values usually considered normal (4 to 5 gms. for the weight of each gland and 3 to 4 mm. for the epinephrine content).

Oppenheimer and Fishberg\(^{24}\) reported that the great interest of the cases of hypertension associated with suprarenal tumors lies in the demonstration that in certain instances among 15 reported cases of chronic non-nephritic hypertension, the increased blood pressure is associated with an anatomically demonstrable lesion of the suprarenal gland. Although the precise mechanism of the production of the hypertension remains unexplained, one small group of cases is thus removed from the great group of essential hypertension and may well be termed suprarenal hypertension.

Nuzum and Dalton\(^{38}\) in 1938 added one case of their own to the group of hypertension ascribed to hyperplasia or tumor of the cortex of the adrenal gland. Marked hyperplasia of the adrenal cortex and a cortical adenoma were apparently responsible for the development of hypertension. The other case was a pheochromocytoma of the medulla, with complete disappearance of the symptoms following surgical removal of the tumor.

Apsahl\(^{39}\) in 1938 supported the idea of adrenal changes in hypertension and said that the incidence of such morphologic changes was greater than could be accounted for by the factor of age alone.

Hoskins and Freeman\(^{40}\) in 1933 observed ten schizophrenic patients initially presenting low blood pressure who were treated for ten weeks with glycerin extract of adrenal cortex, and found that the systolic
and diastolic pressures were increased in all cases. The blood pressure returned to approximately the initial levels after treatment was discontinued. There was a slight downward trend in the nitrogenous bodies of the blood.

Freeman, Forrest, Linder and Hoskins\textsuperscript{11} in 1933 made further studies on glycerin extract of adrenal cortex by mouth, and confirmed the previous observation on elevation of systolic and diastolic pressure. On another nine patients there was a slight residual pressure effect maintained during the intervals between medication periods. Freeman and Hoskins\textsuperscript{12} in 1934 administered glycerin extract of adrenal cortex to healthy male schizophrenics and to normal subjects and noticed that the incidence of the pressure effect was much higher in the patients than in the normotensives.

Looney and Darnell\textsuperscript{13} in 1936 and Hoskins and Freeman\textsuperscript{14} in 1937 reported that following prolonged administration of glycerin extract of adrenal cortex in man, hyperplasia gradually developed. Potent adrenal cortical extracts will not induce elevation of blood pressure above normal levels in either intact or adrenalectomized animals.\textsuperscript{15}

Pines, Perera, Vislocky and Barrows\textsuperscript{16} reported that adrenal cortical extract lowered blood pressure in three uncomplicated hypertensive vascular cases. A small rise in arterial tension was noted in one case. Wilhelmj, Gunderson, Darinka, Shaput, and McCarthy\textsuperscript{17} in 1955 in an experiment on eight dogs noticed that the administration of 2.5 gms. per kg. per day of cortisone had no effect on blood pressure.
In 1939 Loeb and his associates\textsuperscript{8} called attention to two patients whose arterial blood pressure exceeded normal limits in the course of treatment of Addison's disease with desoxycorticosterone esters. Since that time these observations have been confirmed and extended; Ferrebee, Ragan, Archley and Loeb\textsuperscript{19} 1939, Soffer, 1940, Engel, and Oppenheimer,\textsuperscript{50} McCullagh and Ryan, 1940\textsuperscript{51} McCavack,\textsuperscript{52} in 1941, Loeb\textsuperscript{53} in 1942, Thorn, Dorans and Day\textsuperscript{54} in 1942, Engel, Cohn and Soffer\textsuperscript{55} in 1942, Altschul and Zamcheck\textsuperscript{56} in 1942, and Perera, Knowlton, Lowell and Loeb\textsuperscript{57} in 1944, Perera\textsuperscript{58} in 1950 and Knowlton, Lowell, Perera, Knowlton, Lowell and Loeb\textsuperscript{59} in 1954.

Perera and Blood\textsuperscript{60} in 1947, Perera\textsuperscript{61} in 1945, Perera, Knowlton, Lowell and Loeb\textsuperscript{57} in 1944, and Perera\textsuperscript{62} in 1948 noticed that administration of desoxycorticosterone for long periods produced a transient or at times sustained increase in the resting blood pressure of hypertensive patients.

Although Goldman and Schoeder\textsuperscript{63,64} in 1948 recorded an immediate pressor effect after the intravenous injection of desoxycorticosterone acetate Perera and his associates\textsuperscript{57} were unable to reproduce this action using the glucoside. In their clinical studies the fact that the response occurred in a matter of days rather than hours was testimony against a direct humoral mechanism.

Desoxycorticosterone has been found capable of producing hypertension in some patients with hypoadrenalism and of raising the blood pressure in other patients without renal or endocrine disease, Perera.\textsuperscript{61}
In the field of animal experiments Goldblatt in 1937 mentioned that bilateral adrenalectomy interferes with the development and maintenance of experimental renal hypertension unless cortical hormone replacement therapy is instituted. Comparable reports were made by Blalock and Levy in 1937, Page in 1938, Collins and Wood in 1938, Diaz and Levy in 1939, Williams, Diaz, Burch and Harrison in 1939, Lewis and Goldblatt in 1942, Houssay and Dexter in 1942, and Zweifach and Shorr in 1949.

Some of these investigators noted that adrenalectomy was associated with a fall in the concentration of hypertensinogen and at times a reduction in the response to renin.

Adrenalectomy also modified the hypertension produced in dogs by the intracisternal injection of Kaolin, (Teffers, Lindamer and Lukens in 1937) in rats by auditory stimulation (McCann, Rothbailer, Yeakel and Shenkin in 1948) and by injection of dehydroxyphenylalanine in 1945. In 1939 Rogoff, Nixon, and Stewart claimed that the blood pressure remained high in three hypertensive dogs 4 - 19 days after adrenalectomy.

**Effects of the induced hypersecretion of the adrenal cortex on the kidney**

Dougherty in 1948 reported an extensive hypertrophy of cells of the juxta-glomerular region has been produced by administration of adrenotrophic hormone for various periods of time. The juxta-glomerular apparatus remained in this hypertrophic state for as long as six weeks but eventually was not prominent in spite of continued daily administration of this pituitary hormone. It does not seem likely that the
induced alteration in the juxta-glomerular apparatus played a role in the production of hypertension. Although there appeared to be a thicker wall of muscle in the juxta-glomerular region, cells of the afibrillar type were only rarely observed in normal mice. It is suggested that the appearance of a juxta-glomerular apparatus composed of afibrillar cells is correlated with pathological alteration of smooth muscle in afferent arterioles. Arteriosclerotic lesions similar to those produced by administration of large amounts of desoxycorticosterone acetate were observed following daily treatment with adrenotrophic hormone for a period of weeks. 78

Dougherty stated that Rich had observed a marked increase in the production of afibrillar cells of these structures in a patient having an adrenal cortical tumor. Goormaghtigh 79 according to his previous observation reported that afibrillar cells which contain polychromic granules intermingled with minute vacuoles are found in the superficial juxta-glomerular apparatuses of normal rabbits. He suggested that these indicate the existence of a glandular cycle, and possibly a stage in the formation of a vaso-pressor substance, perhaps an internal secretion of the afibrillar smooth muscle cell.

Becker 79 in 1938, in a study of the normal human kidney, described cells which lie close to the arteriolar wall and ascribed to them an endocrine function.

The term Goormaghtigh-Becker cells which Clara 79 gave them in 1938 is inaccurate, as the cells which Becker observed are probably part of the intercalated segment whereas the observations of Goormaghtigh have shown that the afibrillar granular cells occur
only in the arteries and arterioles. The proximity of the intercalated segment to the juxta-glomerular mass of afibrillar cells may imply some important functional relationship, and the observations described demonstrate that pathological changes in one are always accompanied by changes in the other.

As a treated control series, mice of the same strain and age were treated similarly to the adrenotrophic series already mentioned by daily administration of a non-adrenotrophic protein hormone (Prolactin). Hypertrophy of the afibrillar cells of the juxta-glomerular region was not observed in any of the control groups. However, epithelialization of the glomerulus, similar to the alteration produced by injection of testosterone propionate (Selye in 1939) was observed in both male and female prolactin-treated animals. Selye and co-workers in 1943 to 1946 first described the morphological changes produced by over-dosage of desoxycorticosterone acetate and salt. They reported that hyperplasia of the adrenal cortex, with depletion of the lipoid material in the cortex occurs in rats with experimental hypertension produced either by renal ischemia or by administration of desoxycorticosterone acetate and salt. Over-dosage of this material and salt induces the development of nephrosclerosis and hypertension, especially in the unilateral nephrectomized animals, which show hyaline necrosis in the arterioles of the kidney, nephrosclerosis, and generalized severe periarteritis nodosa or panarteritis. By these different animal experiments they were trying to relate the adrenal cortex to hypertension and the kidney.
Selye\textsuperscript{88} believes that various non-specific types of stress, acting by unknown pathways on the anterior pituitary, produce an increase of adrenal corticotrophic hormone. This in turn causes the adrenal cortex to produce an increased amount of (corticoid hormone) desoxycorticosterone-like substance, and this may act independently or synergistically upon the kidney. The adrenal cortical hormone may even stimulate the anterior hypophysis to produce a direct effect on the kidney.

Forster, Canterow, Herbut, Raschkio and Rakoff\textsuperscript{39} in 1946 noticed degenerative lesions in cerebral arteries in their case of Addison's disease which was treated with desoxycorticosterone acetate.

Carnes, Bagam, Ferrebee and O'Neill\textsuperscript{20} Selye and Hall,\textsuperscript{85} Selye, Beland and Sylvester,\textsuperscript{91} and Darrow and Miller\textsuperscript{92} have reported histological changes in animals following administration of large doses of desoxycorticosterone acetate and NaCl. Selye and Hall described alteration of the aortic arch as well as severe renal vascular changes. Selye, Beland and Sylvester described changes of cerebral blood vessels in rats treated with very large doses of the hormone and salt.

Selye's description of the many profound morphological changes which can be produced by large doses of desoxycorticosterone was antedated by the reports of rise in blood pressure in association with the injection of desoxycorticosterone esters by Loeb and his associates\textsuperscript{48,49,50,52,53,54,55,57,93} followed by Grollman, Harrison and Williams\textsuperscript{94} in 1940, and Rodbard and Freed\textsuperscript{95} in 1942. By their
injection of desoxycorticosterone acetate to normotensive, spontaneously hypertensive, and Goldblatt hypertensive dogs, they noticed the elevation of blood pressure in 9 of 12 animals. The blood pressure changes after cessation of injection of the DCA led a variable course. In some it remained high for a considerable period, in others it fell rapidly to control pressure levels.

The effects of desoxycorticosterone on blood pressure were denied by Mario Gaudino and M. Levitt in 1949 who reported that the effect of DCA and cortical extracts in the intact animal are transient, all physiological variations observed tending to return towards normal despite continued treatment in dogs. Braun-Menendez reported that when desoxycorticosterone is given in conjunction with sodium-deficient diet, there is no significant increase in the extra-cellular fluid. On the other hand, Braun-Menendez believes that all factors which favor the retention of sodium in the organism, whether due to an increased intake or to decreased excretion, facilitate the attainment of hypertension.

Summers in 1948 claimed that the blood pressure and weight of two dogs on a high NaCl intake were not affected by the intramuscular injections of large quantities of DCA given over a period of one month, each animal receiving a total of 2000 mgm. of DCA.

Others who confirmed the rise of blood pressure, often to abnormal levels, following the sustained administration of desoxycorticosterone esters include Green in 1949 and Hall in 1949, and Swingle, Parkins and Ramington in 1941. But Hall suggests that the rise of arterial hypertension after the administration of desoxycorticosterone esters is not dependent upon a renal mechanism for its maintenance.

Victor in 1945 produced hypertension in dogs by unilateral ligation of the peri-adrenal blood vessels and tissue.
Knowlton and her associates in 1946, employing much lower dosages of desoxycorticosterone acetate esters in rats, revealed no significant vascular lesions but some degree of cardiac and renal enlargement (even in the absence of hypertension). \(^{101}\) Incidentally, in the dosages employed, adrenal cortical extracts did not produce hypertension. \(^{94,101}\)

Selye\(^{83}\) noted that the degree of pathological response to desoxycorticosterone acetate was intensified by an increase in the sodium chloride. Knowlton and co-workers\(^{101}\) found that the action of the steroid desoxycorticosterone esters was potentiated by salt.

Friedman and co-workers\(^{102-3}\) in 1948 reported that DCA, particularly with sodium salt, resulted in an impaired renal function, and under similar conditions a decrease in the adrenal size. This was confirmed by Carnes and his associates\(^{90}\) in 1941. Whatever may be the mechanism responsible for the various changes induced by desoxycorticosterone acetate, it is obvious that they are dependent upon a bilateral supply of the sodium ion in the diet. \(^{101}\)

The presence of blood-borne vaso-excitator principle (VEM) in experimental hypertension (Goldblatt clamp) has been demonstrated. The detection and quantitation of VEM was based on the development of hyper-activity to epinephrine in the terminal arterioles and precapillaries of the meso-appendix of the test rat.

VEM appeared in the renal vein blood within 30 minutes after partial obstruction of the renal artery by a Goldblatt clamp. It disappeared from the blood when the blood pressure had become stabilized in the hypertensive range in dogs with two renal clamps or with one kidney clamped and the other removed. It also disappeared
when pressure had fallen to normal levels with one kidney clamped and the other intact. Renin and VEM assumed to be hypertensive substances, have also been demonstrated during the acute phase of hypertension. VEM, however, differs in certain vascular effects from both. 104

This appearance of VEM in the circulation is subsequently counterbalanced by increasing amounts of the hepatic vaso-depressor agents. 105

A similar state of equilibrium with high titers exists in patients with essential hypertension. 105

Adrenalectomy abolished or impaired the renal capacity to form the vaso-excitor materials (VEM) even in animals maintained on high salt diets, but the combination of desoxycorticosterone acetate and salt restores normal kidney behavior. 106–8

Briskin, Stokes, Reed and Mrazek 109 in 1943 on the basis of their rat experiment observations reported that the administration of desoxycorticosterone produces marked hypertension. It is suggested that this hypertensive effect is due to renal injury, since it could be abolished by the administration of renal extracts, and since the evidence points to changes occurring in the kidney following the use of these substances. 94

Grollman 110 in 1947 reported that the kidney is the site of origin of a humoral agent involved in the pathogenesis of hypertension.

The capacity of certain steroids to induce changes in the kidney and to elevate the blood pressure, as well as the changes in blood pressure induced by alteration in the sodium and water metabolism of the organism present problems of endocrine interest.
Hartman in 1931-33, Farrebee, Ragan, Archloy and Loeb find the pressor effect of the cortical hormones on the adrenalectomized animals was less marked than its other functions. On the other hand, Swingle and collaborators using various techniques, found a prompt and marked effect in adrenalectomized dogs. They regard the cortical hormones as the specific hormones for capillary tonus.

Swingle, Parkins, and Ramington postulated the important role of the local action of electrolytes in the maintenance of the vascular tone. In the meantime it was found that the slow pressor effect of DCA is enhanced by sodium injection.

These observations suggest that the sodium ion is fundamentally involved in the action of desoxycorticosterone.

Corcoran suggests but does not prove that the adrenal cortex is genetically concerned in essential hypertension in human beings. Relevant to the problem are the facts that some hypertensives respond to low sodium diets, some of these show abnormally high urinary formaldehydigenous corticoids in control periods, and some show abnormal tendencies to sodium retention.

Groep in his preliminary observations on the relation of the adrenal cortex to electrolyte metabolism in the rat, mentioned that in adrenalectomized rats, salt therapy in the conventional manner (1% NaCl) was not successful in maintaining life, although a lesser amount was of some benefit. Desoxycorticosterone acetate was more effective than salt in this regard and the electrolytes were not disturbed during the brief survival following removal of the adrenals.
Corey, Silvette and Britton were primarily responsible for the theory that the hormones of the adrenal cortex and posterior pituitary exert antagonistic influences in the metabolism of both sodium and water in 1939. Gaunt, Birnie, Boss, Eversole, and Osborn in 1950. There was much evidence to support this concept.

It has been shown that potassium chloride tends to correct the depression of potassium in the serum and the intracellular replacement of potassium by sodium, but has no effect upon the hypertension in nephritic animals nor upon the anatomical lesions.

Green observed the increased voluntary fluid intake of rats receiving the steroid, mainly because the intensity of the blood pressure rise could be related to fluid exchange, and he suggested that hypertension might be a compensatory mechanism to fluid and electrolyte changes.

Selye claimed that the concurrent administration of ammonium chloride tends to inhibit the development of vascular and renal damage.

Sahen and Green in 1948 reported that subcutaneous implantation of desoxycorticosterone in rats was followed by increases in fluid intake, blood pressure, and urinary output of antidiuretic factor. Substitution of isotonic salt solution for drinking water in animals not treated with desoxycorticosterone produced an increased output of antidiuretic factor unaccompanied by significant blood pressure elevation. The urinary output of antidiuretic factor was proportional to the degree of elevation of fluid intake. The evocation of antidiuretic factor excretion by desoxycorticosterone would appear to be a consequence of the disturbance in fluid exchange.
A direct relationship of this factor to the development of hypertension was not established. Kempner\textsuperscript{129} in 1944 described dramatic improvement in signs and symptoms of hypertensive disease with the use of low sodium, low protein and low fat diet.

Grollman and Harrison\textsuperscript{130} in 1945 obtained striking decreases in arterial tension in some instances on rigid restriction of sodium alone. Considerable evidence has been obtained from controlled studies, pointing to a salt and water disturbance in essential hypertension. Pines and Perera\textsuperscript{131} in 1949 suggested that blood pressure levels in this disorder may be at least slightly modified by extremes of restriction or addition of sodium.

Knowlton and her co-workers\textsuperscript{127} have observed that salt deprivation blocks the pressor activity of desoxycorticosterone acetate in nephritic rats and a similar basic phenomenon has been described in essential hypertension.\textsuperscript{132}

It is claimed that the ratio of serum sodium to chloride is elevated in proportion to the height of the diastolic pressure in hypertensives.\textsuperscript{133}

Perera and Blood\textsuperscript{134} in 1946 reported their observations on twelve control subjects and twelve patients with uncomplicated hypertensive vascular disease following the rigid withdrawal of sodium chloride for 24 hours. Sodium restriction in control subjects was followed by significant weight loss and increased urine output, which were not evident in hypertensive patients, regardless of variations in environmental temperature and physical activity. A disturbance in salt and
water metabolism exists in hypertensive vascular disease as judged by
the abnormal response to the abrupt and rigid restriction of sodium in
the diet. It is suggested that this difference in response may be
referable to primary renal changes, or more likely to changes in the
kidney mediated by the adrenal cortex. Of perhaps greater pertinence
is the fact that rigid restriction of sodium chloride masks the pressor
response of hypertensives to desoxycorticosterone.132

Others who studied the effects of high sodium intakes on all
forms of hypertension are Verney and Vogt in 1938, De Wesselow and
Page and Lewis in 1949 reported that renal hypertension
appears relatively resistant to sodium restriction in dogs, while a
fall in pressure can be produced in rats with renal artery ligation
by salt deprivation alone.130,1140 All forms of corticoid hypertension,
as far as is known, can be prevented by feeding a sodium-free diet.101,
103,119,120,59,121,122,127 It does not respond to very low sodium
diets when it has progressed into the permanent condition (meta-
corticoid hypertension).141

In the majority, low sodium regimes are without appreciable
influence on the blood of hypertensive patients, although a number
of them seem to be symptomatically improved without commensurate
pressure fall.112-114 Sodium retention is one of the most important
effects of cortical activity,145-118 and cholesterol is the mother
substance of steroids.149
Low-potassium diets are followed by a fall in Goldblatt hypertension to normal limits, whereas similar diets are without effect on blood pressure in metacorticoid hypertensive disease. In human hypertension low-potassium diets have resulted in a slight, although statistically significant, reduction in pressure.

The effect of both sodium or potassium on neurogenic hypertension has not been studied.

THE HORMONE OF THE ADRENAL MEDULLA

I have mentioned previously the pressor action of the adrenal medulla, its discovery by Schaefer in 1894, and isolation of the active principal by Takamine and Aldrich in 1901. Friedman determined its chemical composition in 1906, and Stolz and Dakin prepared it synthetically.

The most extensive action of adrenaline is exerted upon the vascular system, whose smooth muscular fibers react to it very sensitively, with vaso-constriction. Owing to the contraction and the rise in tonus of the vessels, blood pressure increases both in man and mammals. This rise of blood pressure is due in part to direct action upon the myocardium; ventricular systoles are accelerated and intensified, but only after the heart has been relieved from vagal inhibition by atropine. Small doses of adrenaline lower the blood pressure in dogs and cats. The action of the adrenal medulla was first studied by Goldblatt, Lynch, and Summerville in 1931 who observed that constriction of the renal artery produced marked elevation of blood pressure in two dogs in which the whole right adrenal and the left adrenal medulla had been removed, and the left
adrenal denervated by section of the splanchnics on that side. These findings were confirmed by Page in 1939. The problem of adrenalinemia has been much debated, and so far the investigations do not appear to have brought definite proof of its existence, either in normal subjects or in those with arterial hypertension. Trendelenburg and Fleischauer et al. The presence of adrenaline in the blood of individuals with essential and nephritic hypertension has not been demonstrated, even by using methods of extreme sensitivity.

Hogoff, Marcus, and Wasserman in 1933 were unable to demonstrate an increase in the secretion of adrenalin in dogs made hypertensive by constriction of the renal artery. Excessive adrenaline discharge as a cause of hypertension is clearly demonstrable in chromaffin tumors of the adrenals or other parts of the sympathetic nervous system. Hypertension which occurs in cases of adrenalin-producing tumors is usually of a peculiar intermittent nature, and accounts for spells spoken of as paroxysmal hypertension.

There is similarity between almost all clinical manifestations of essential hypertension and the syndrome of sustained pheochromocytomatous hypertension except for some specific tests for abnormal epinephrine secretion (histamine) adipolytic doses of benzodioxane and epinephrine assay.

All signs and symptoms disappeared when the tumor is removed. These indicate that in the case of pheochromocytomatous hypertension the responsible vaso-pressor sympathomimetic amines (epinephrine, sympathin, encephalin) originate entirely in the tumor, and reach the cardio-vascular structures exclusively by means of the blood stream. In essential hypertension, on the other hand, analogous
sympathomimetic, cardiovascular, and metabolic effects (including a frequently observed elevation of the basal metabolism) may be attributable to the excessive neurogenic sympathin discharge directly into the cardiovascular effector cells. This results from exaggerated central stimuli or is ultimately derived from an increased formation of hydroxytyramine in the ischemic cortex of the kidney.

Pressor substances in the urine of a patient with labile hypertension due to pheochromocytoma were demonstrated by intravenous injection of 1 cc. into a dog, thereby producing significant transitory hypertension in the animal. Urine from patients with hypertension due to other causes failed to affect the dog's blood pressure.

In the majority of patients with essential hypertension abnormally intense discharges of sympathomimetic amines (epinephrine, sympathin, encephalin) into the blood have been observed during exercise. Even normal amounts of epinephrine present in the blood of hypertensive individuals, can acquire an intensified vaso-pressor property due to contact with certain lipids or other activating substances.

The presence of vaso-constrictor substances in the blood of hypertensive subjects not identical with epinephrine or sympathin, but possibly with modified forms of the latter, has been claimed by several investigators, and was confirmed in the arterial blood of hypertensive persons. Abnormally high concentrations of epinephrine and sympathin were detected in the heart muscles of deceased hypertensive individuals. Enlargement of the adrenals, especially diffuse or nodular hyperplasia of the medulla, muscular hypertrophy
of the adrenal veins and increased adrenalin load of the glands emphasized the significance of medullary hyperactivity in hypertension, Goldzieher \textsuperscript{167} in 1928-1932.

Drake, Hibbard, and Lehwig \textsuperscript{168} in 1944 in a study of 26 cases of hypertension not associated with inflammation of the kidney, found that 24 cases showed histologic evidence of hyperfunction of the medulla. They support the theory that in the early stages of essential hypertension hormonal factors play a substantial and primary role.

Allen \textsuperscript{169} in 1929 observed hypertrophy of the muscular veins of the adrenals in hypertensive people. The total lumen of all veins is greater in cases of hypertension than in cases of normal blood pressure, and he suggested that this higher degree of vascularization probably indicates a higher level of functional activity.

The significance of hyperplasia of the medulla and muscular hypertrophy of the adrenal veins described by Goldzieher and Allen in hypertensive individuals is discredited by Goldblatt in 1951 and Dempsey \textsuperscript{30} in 1942. It may be concluded that the adrenal medulla plays no important role in the production or maintenance of hypertension from renal ischemia.

**PITUITARY GLAND**

The association of high blood pressure, occasionally of the paroxysmal type, with acromegaly brought attention to the importance of pituitary gland and its relation to hypertension. Hypertension is not invariably present in the eosinophilic variety of hyperpituitarism,
but Cushing's description of the symptom complex which he attributed
to basophilic adenoma of the pituitary body included high blood
pressure which was present in all the cases on record. Basophilic
cell hyperplasia is found almost constantly in cases of hypertension,
both of the renal and essential type. Thus anatomical changes of
the basophilic cells may well be the only consequence rather than the
cause of the increased pressure.

Life is possible even without the pituitary, but only under
conditions widely different from the physiologic. One of the results
of experimental removal of the pituitary gland is lowering of
the blood pressure, Pauulesco, 1907, Cushing 1912 and Collab, Camus
and Roussy, 1922, Aschmer, 1929, Crowe, 1910, Biedl, 1928, Bailey and
Bremer, 1921 and Dott, et al in 1923. Most animals do not survive
the operation for long, but some observations have been carried on for
eighty days and even more. Two cases at autopsy with complete absence
of pituitary had been seen by Zondek with no signs of pituitary
deficiency having been observed in their lifetime.

Wyman and Tum-Sudon, in 1934, showed that hypophysectomy in
normal animals was followed by a fall in blood pressure.

In normal dogs removal of the hypophysis produces a fall of
blood pressure as Braun-Menendez observed in 1934. Page and
Sweet in 1936-37 reported that hypophysectomy produces a variable
but large reduction in renal hypertension, although small degrees
of hypertension can be induced in the absence of the pituitary.

Williams, Diary, Burch and Harrison also observed a fall of blood
pressure in hypophysectomized rats, and greater sensitivity to renin
in hypophysectomized than in normal rats. They suggest that these results were due to the lower blood pressure of the hypophysectomized animals. Constriction of the renal artery in hypophysectomized dogs produces a rise in blood pressure. Houssay and Dexter in 1942 found that the injection of renin, adrenalin, and hypertension produced the same rise in hypophysectomized dogs as in normal controls.

Hypophysectomy did not alter the renin content of rat kidneys according to Williams and others in 1939 nor the hypertensinogen content in the blood of dogs, according to Kohlstaedt, Page and Helmer in 1940. In 1941, Anderson, Page, Li and Ogden reported that ACTH reverses the effects of hypophysectomy in renal hypertension. It also slightly augments (self-sustaining post-DCA hypertension) metacorticotoid hypertension and essential hypertension.

Hypophysectomy prevents DCA-induced hypertension and is followed by slow recession to normal pressure if performed after the metacorticotoid hypertensive syndrome has become established, but does not restore the ability of DCA to induce hypertension after the pituitary has been removed (Saunders, McDonough, Wahlgren and Green in 1952 and Green, Saunders, Wahlgren, McDonough and Clampit in 1952).

Luft and Olevecrona in 1953 reported on the effect of total hypophysectomy in human hypertension. The patients who survived exhibited a fall in the blood pressure to normal, but died shortly thereafter of uremia.

The influence of the pituitary on blood pressure in both hypopituitary hypotension Simmonds' disease and hyperpituitary hypertension Cushing's syndrome is usually assumed to be mediated through the adrenal
cortex according to the following experiments. Selye et al. showed that injection of a crude lyophilized anterior pituitary extract (LAP) acted like DCA in producing hypertension, cardiac and renal hypertrophy and nephrosclerosis.

These changes with other signs could also be reproduced by STH (Somatotrophic Hormone), but not by ACTH (Adreno-corticotrophic Hormone).

The effect of LAP and STH was accentuated by ACTH or DCA (Desoxycorticosterone acetate), and prevented by adrenalectomy or cortisone-induced adrenocortical atrophy. Page and Sweet believed in the hypothesis that the secondary changes occurring in other endocrine glands in hypophysectomized animals might be responsible for the rise of blood pressure. However, they were unable to obtain rises of blood pressure in hypophysectomized animals by the administration of folliculin and antuitrin. The administration of thyroid extract by mouth produced a slight rise of pressure.

Leathem and Drill in 1944 reported that following hypophysectomy the blood pressure was lowered to subnormal levels, and the administration of desoxycorticosterone acetate failed to prevent this drop, although the same dosage was able to prevent the decline in pressure following adrenalectomy. On the other hand, adrenal cortical extract did effect a partial maintenance of blood pressure in the hypophysectomized rat. Hence they believed that although the subnormal blood pressure of the hypophysectomized rat is due in part to insufficient cortical hormone, there is another additional factor responsible for the lowering of blood pressure after hypophysectomy in rats. Attempts to restore the
the subnormal blood pressure of the hypophysectomized rat to normal with adrenal cortical extract, PCA, or growth hormone were unsuccessful. Growth hormone did not prevent the fall in blood pressure when administered immediately following hypophysectomy.

The fall in pressure produced by complete hypophysectomy is due to the removal of the anterior lobe, since extirpation of the posterior lobe or lesions in the region of the tuber do not greatly modify blood pressure in the dog. Griffith and Ingle in 1940 studied the relation of the posterior lobe to hypertension in the rat and showed that hypertension could be produced by subtotal nephrectomy in animals in which the posterior lobe of the pituitary had been removed.

Ogden, Page and Anderson in 1941 and 1944 found that in Goldblatt renal hypertension, extirpation of the posterior lobe had no effect on blood pressure and diabetes insipidus appeared. If damage was done to the anterior lobe, as indicated by gonadal atrophy or absence of diabetes insipidus, the blood pressure fell to the normal level.

Sattler and Ingram in 1941 obtained fall in blood pressure in five of eight hypertensive dogs by sectioning the supraoptic-hypophyseal tract.

CONCLUSION

Removal of the anterior lobe of the hypophysis produces a fall in pressure in animals with renal hypertension; the effect may be transitory. Renal ischemia produces hypertension in hypophysectomized animals. The posterior lobe of the pituitary does not appear to play any important role.
It appears that the hypophysis is capable of altering renal hypertension without being essential for its production. The anterior lobe appears to be responsible for the changes observed, since it has not been shown that the posterior lobe particularly alters this hypertension, except in Sattler and Ingram's experiments. Finally, in 1949 reported that evidence derived largely from Heinbecker's experimental investigation supports the view that hypertension and many allied disorders of aging are due to hypofunction of the neurohypophysis. Diminished secretion of this gland results in degeneration of the basophils of the anterior pituitary and their respective organs and in a state of increased tissue sensitivity to the combined action of various pressor hormones.

**THYROID AND PARATHYROID AND HYPERTENSION**

Thyroid gland insufficiency, produced by its removal or inhibition, or hyperactivity produced by administration of its secretory products in large quantities, in most cases produces but small and variable changes in blood pressure.

Glenn and Lasher concluded on the basis of their dog experiments, that total thyroidectomy in dogs does not affect either the production or maintenance of Goldblatt renal hypertension.

On the basis of the study of Mountain, Allen and Haines, in their study of 827 hypertension cases, basal metabolic rates were elevated to higher levels and more frequently in patients with higher blood pressures than in those with less marked hypertension. No adequate explanation of this phenomenon is given although they think that the thyroid gland itself is not responsible. Katz, Friedman, Robard and Weinstein reported that partial thyroid and parathyroidectomy did not affect the blood pressure in renal hypertension.
Page and Sweet found that the oral administration of thyroid extract (0.8 gm.) to hypertensive dogs in which hypophysectomy had reduced the hypertension, produced moderate rises of blood pressure. The administration of theselin (1cc. daily) or antvitrin (1cc. daily) had no effect. The influence of the thyroid in a total of 56 animals was studied by Green, Saunders, Wahlgren, and Craig. Eighteen served as controls, nineteen animals were given thyroxin and another nineteen animals received propylthiouracil. Thyroxin produced rapid and sustained increase in blood pressure with a little tendency to return to pretreatment levels until thyroxin administration was stopped. By contrast, propylthiouracil treatment produced a moderate fall in pressure. The influence of parathyroid was studied in a total of 177 animals. Eighteen received calciferol and exhibited a fairly prompt and sustained increase in blood pressure with reversion to control levels after treatment was concluded. The effect of parathyroid loss was studied somewhat indirectly: In 11 animals in which parathyroid-thyroidectomy was performed there was a transitory and moderate decline in pressure with prompt return to preoperative levels by the end of the second week.

Green, Saunders and Wahlgren reported that the blood pressure was reduced by propylthiouracil. Thyroid-parathyroidectomy was followed by a fall in the DCA hypertension. A small rise was produced by large doses of calciferol.

**GONADS AND HYPERTENSION**

Clinical experience directs attention to the gonads. Circulatory disturbances such as flushes, palpitation and attacks of dizziness and perspiration are outstanding complaints after castration and characterize
the climacterium. Hypertension is also associated with the post-
castrational and menopausal symptom complex. It would seem tempting
to ascribe to the gonad, particularly to the ovary, a blood pressure
regulating effect of the depressor type. Termination of ovarian control
would thus account for the prevalence of pressor factors. However,
hypertension and other vasomotor disturbances usually subside in the
course of time and only comparatively few cases develop permanent
hypertension. This observation speaks against the probability of a
hypotensive function of the ovaries and relegates these glands to
the secondary rank of indirect contributors.

The climacteric and postcastrational circulatory disturbances
are apparently due to the general imbalance of the vegetative
nervous system and become adjusted after complete extinction of
gonadal function.\(^{170}\)

Klopp, Young and Taylor\(^{199}\) report that the administration of
testosterone and testosterone propionate given during a period of
1 - 3 weeks in amounts presumed to be adequate for renotrophic effects
did not alter significantly the blood pressure in both hyper and
normotensive individuals. The normotensive individuals show slight
elevation of blood pressure while the hypertensive individuals show
slight depression of blood pressure.

The changes observed by Korenchevsky and Hall\(^{200}\) after injections
of androsterone, transdehydroandrosterone, testosterone and testosterone
propionate in the weight and histological structure of the organs were
in almost all cases similar in normal adult and senile rats. Testosterone
propionate in large doses was the only hormone which caused considerable
lipoid depletion. The presence of gonads therefore in most cases prevent
the changes in weight of the adrenal, no change in hypophysis except in two. The changes in weight and histological structure indicate a slightly stimulating effect of the hormones on the kidneys. No improvement was seen in the senile appearance and behavior of the old rats; the stimulation of the secondary sex organs of senile rats by testosterone propionate cannot be regarded as a rejuvenating effect.

This does not, however, upset the hypothesis that in combination with other cooperative factors, the sex hormones are important and possibly irreplaceable in the prevention of pathological senility.

MacKay reported testosterone propionate administration in male albino rats produced a marked increase in compensatory renal hypertrophy. Selye commented, "I think some emphasis ought to be placed upon the difference between the action of desoxycorticosterone and the other steroids." To my mind there is absolutely no correlation between the effects of desoxycorticosterone and the effects of other steroids. Indeed, we could not confirm the effects of any steroids except desoxycorticosterone as far as blood pressure is concerned. As far as the effect of salt is concerned, its addition in the diet with practically every steroid resulted in a rise of blood pressure.

Only desoxycorticosterone causes nephrosclerosis and only desoxycorticosterone among those steroids assayed by us has any salt retaining capacity. I may add that testosterone not only failed to cause nephrosclerosis and hypertension, but actually prevented the nephrosclerosis developing and it has a beneficial effect on the kidney, and by the effect prevented damage from desoxycorticosterone."

Propionate testosterone proved to be possessed by a puro renotropic action, while desoxycorticosterone, as I mentioned already, is nephrosclerotic.
The renotropic action of methyltestosterone (unlike the renotropic anterior pituitary lobe preparation) is not potentiated by administration of thyroxin, but the kidney stimulating effects of the two hormones are apparently merely summated.\textsuperscript{205}

Grollman, Harrison and Williams\textsuperscript{94} on the basis of their rat experiments reported that administration of estradiol, testosterone, desoxycorticosterone, progesterone and diethyl-stilbestrol to normal rats induced in some animals an elevation of blood pressure to hypertensive levels. It is suggested that this hypertensive effect is due to renal injuries since it could be abolished by the administration of renal extracts and since other evidence points to changes occurring in the kidney following the use of these substances.

They attributed the occurrence of hypertension in certain cases of Cushing's disease or of the adreno-genital syndrome to the formation of abnormal steroid products.

All the sex hormones display some degree of sodium-retaining effect, says Harrop.\textsuperscript{206} Estradiol and progesterone appear to be the most active substances. They suggest that estrogenic activity and the influences on retention of sodium are not necessarily parallel phenomena.

Appelrot\textsuperscript{207} and Handovsky\textsuperscript{208} each found that administration in large doses of vitamin D (which is also a steroid compound) induces hypertension.

Toldman and Schroeder\textsuperscript{64} reported their observations after intravenously injecting progesterone, testosterone, DCA, dehydroisoandrosterone acetate, \(\Delta^5\) pregnenolone and their effect to twenty patients. Of these substances only DCA acted as a pressor substance and then only in hypertensive subjects. Its pressor effect was prolonged.
The influence of gonads was studied in a total of 24 animals, 12 of which served as controls, while the remainder were castrated by Green, Saunders, Wahlgren and Cöig.\textsuperscript{197} The two groups did not differ significantly in blood pressure.

Page\textsuperscript{209} mentioned that neither the ovaries nor testes are essential for the maintenance of hypertension in dogs with their renal arteries constricted.

The degree of post DCA hypertension was not influenced by castration as noticed by Green, Saunders and Wahlgren.\textsuperscript{198}

Estrogen and testosterone had no significant effect on blood pressures of renal ischemic hypertensive dogs concluded Wakerlin.\textsuperscript{210}

It had been claimed that large doses of testosterone may exert antihypertensive actions. Certain recent observations intimate that these are further enhanced by simultaneous folliculoid treatment, but the data reported so far hardly suggest any great efficacy.\textsuperscript{211}

Relation Between the Various Hormones of the Steroid Type

The structural formulas of the ovarian, testicular and adrenal cortical hormones denote a near chemical relationship. Theoretically all may be derived from the cholesterol nucleus, but it is not known whether in the organism cholesterol actually is their mother substance. This close chemical relationship is shown also by a crossing of their biological effects.

Atrophy of accessory sex glands after castration is cured by cortico-trophic hormones. The same hormone induces a kind of estrus in infantile female rats.\textsuperscript{212-13}

Before this, Nice and Schiffer\textsuperscript{214} were able to obtain premature sexual development in immature female rats with implant of rat adrenals.
These experiments afford indirect evidence for the production of sex hormones by the cortex. Direct proof was given by the isolation of progesterone from large quantities of cortical extracts. Subsequently, Reichstein isolated hydroxyisoandrosterone and Beall oestrone from the extracts.

In a report on the increase in the excretion of female sex hormones with cortical tumor, it was found, patients suffering from adrenal tumor excrete very large quantities of sex hormones with the urine. In some cases where the tumor could be attacked by operation, or irradiation, improvement was shown by a fall in sex hormone excretion. A recurrence was established by renewed increase of hormone excretion.

Levy, Wyman, Martin, Corey and Britton have demonstrated the cessation of estrus after adrenalectomy. Quantitative negative results were reported in ovarietomized rats and in hypophysectomized rats in attempts to produce estrus with adrenal extract.

An attempt to demonstrate any influence of a potent cortical extract on the sexual endocrine in normal and castrated rats failed.

**PANCREAS**

Pathological function of the pancreas has also been mentioned among the possible causes of hypertension, mainly on account of the frequent coincidence of hypertension and hyperglycemia. A fairly large percentage of diabetic patients, moreover, show increased blood pressure. No evidence is available, however, to prove that the lack of insulin production is a possible factor in hypertension. It is more likely that hyperglycemia associated with increased blood pressure
and coincidence of hypertension with diabetes express but an increase of the sympathetic tonus, which again directs our thoughts to hyper-function of the adrenal medulla and the thyroid gland. The latter is not consistently associated with increased blood pressure, particularly the acute stage of hyperthyroidism are likely to show hypertension. Incidence of normal or even subnormal pressure in hyperthyroidism is explained by complicating factors such as dehydration, loss of weight, vaso dilatation and occasionally cardiac impairment. 170

The frequent relation between hypertension and hyperglycemia was noted in 1910 by Neubauer 224 and since that time this subject has been discussed frequently. Some authors agree 225-7 with Neubauer while others 228-30 do not believe that the association of increased blood sugar and an elevated arterial tension is a common one. After it had become known that epinephrin could raise arterial pressure, and it had been established that this internal secretion mobilized glucose from glycogen and could thus elevate the blood sugar, Neubauer correlated these two facts and ascribed the simultaneous occurrence of hypertension and hyperglycemia to this common cause. During hypoglycemic coma, the systolic pressure rose as high 231 as 220 in a man whose arterial tension usually did not exceed 120. This rise in pressure is attributed to the liberation of epinephrin, a spontaneous attempt at the restoration of normal blood sugar. In Addison's disease, hypotension and lowered blood sugar are characteristic.

The relation of over indulgence in starch food, obesity, hypertension, arteriosclerosis and a high blood sugar has been stressed as a definite clinical diagnosis. 232 The over weight patients show a definite
reduction of blood pressure when the blood sugar is reduced; this does not occur in individuals who are of normal weight or of under weight. Hyperglycemia results in arteriosclerosis, even in juvenile diabetics.\textsuperscript{232} Mohlet\textsuperscript{230} accredits such vascular changes to the accompanying obesity. Mosenthal\textsuperscript{224} gave the following conclusions: An excess of sugar in the blood will not result in an increase in blood pressure over short periods of time and will not do so, as far as a limited clinical material permits the reduction for a period of seven years. This does not exclude the possibility of hyperglycemia in itself and indirectly, by inducing desiccation through polyuria, may not have a toxic influence favoring the development of such conditions as arteriosclerosis and cataract. Fifty per cent of patients with hypertension are obese.\textsuperscript{233} From 70 to 85\% of persons with diabetes\textsuperscript{234} are or have been obese.\textsuperscript{235} The influence of hyperglycemia is such as to hasten pathologic changes in the arteries,\textsuperscript{236-7} largely through inadequacy of complete fat catabolism. The frequent association of hypertension and diabetes is attributable to the coincident etiologic factors such as age and obesity.\textsuperscript{238} Other reports\textsuperscript{239} indicate that diabetes does not promote hypertension. Diabetes mellitus and arterial disease with hypertension are frequently observed in the same persons.\textsuperscript{240} Although hypertension is a frequent accompaniment of diabetic arteriosclerosis, but all the characteristic vascular lesions of diabetes (retinal hemorrhage, coronary occlusion, gangrene) are found in diabetics with normal blood pressure as well as those with hypertension, though presence of hypertension increases the incidence of these lesions. Premature and excessive development of vascular disease in the
diabetic occurs predominantly in muscular arteries under the greatest physical strain, especially in obese patients, and is due to metabolic changes of the diabetes itself; also, probably to a disordered lipid metabolism. Hypertension is an important contributory factor since it imposes additional strain.

The most characteristic renal lesion, however, is the glycogen deposition in the convoluted tubules, which is always pathognomonic of this disease. It is still doubtful whether the frequent association of hypertension and diabetes is secondary to such renal changes.

Renal Hypertension

The experimental work of Goldblatt and others suggests that renal ischemia may be the basic mechanism for essential hypertension. The absence of severe grades of arteriosclerosis in the kidneys of non-hypertensives, even though present in other organs, and the almost invariable presence of such lesions in the kidneys of hypertensives are taken by Moritz and Oldt to indicate that renal lesions are responsible for hypertension. Abnormalities in kidney function vary with the degree of renal arterial constriction from no demonstrable changes to marked reduction in all functions. The pathological finding includes moderate cardiac hypertrophy and varying degrees of arteriosclerosis, hyalinization and necrosis. These arteriolar changes are absent from the clamped kidneys even in the presence of advanced lesions elsewhere. If one renal artery is constricted, typical lesions will occur in the arterioles of the contralateral kidney. There are many other various methods of producing renal hypertension besides the Goldblatt method of partial constricting one or both renal arteries with metal clamps—i.e., an
alternative method is enclosing the kidneys in cellophane, silk or latex envelopes.254-6

Page 254 in 1939 was the first to demonstrate this technique which needs three to five weeks to elapse before marked elevations of blood pressure occur, while in the Goldblatt technic, some rise in blood pressure occurs within a few hours.257-8 Chanutin and Ferris259 in 1932 induced renal hypertension by removing one kidney and tightly constricting the other by means of a figure-eight ligature around the poles. It can be modified by using ligatures around both kidneys.260

It was demonstrated that the ischemic renal tissue released a pressor substance into the circulation which produced hypertension by a constrictive action on peripheral blood vessels, without material change in cardiac rate261 or output.262 In the early stage of renal hypertension the kidney releases an excess of an enzyme called renin.263 This renin has been extracted from renal tissue. The renin is a thermolabile substance which requires for its activity a protein-like substance produced mainly in the liver and present in normal serum called renin-activator or hypertensinogen.264 The product of interaction is angiotonin or hypertensin which is a pressor material265-7 and which produces a prolonged rise in blood pressure. The latter is in turn inactivated by hypertensinase.268 To date, immunologic counteraction in the form of anitronins269-70 appears to be the most promising lead. As a possible origin of renin, the juxtaglomerular apparatus and macula densa have been suggested.79,271 The renin could also be produced by Becker cells.272 It was noticed that in a human kidney these cells increase in hypertensive cases and increase with age. The enlargement of juxtaglomerular apparatus detected by many investigators273-4.
in renal damage occurs also in the contra-lateral normal kidneys of dogs made hypertensive through the unilateral constriction of the renal artery. Hence, they believe it is probably that the morphologic alterations in juxta-glomerular apparatus follow the production of hypertensive state and are not responsible for the chemical changes in the blood. Marked interference with arterial renal blood flow upsetting the vaso pressor system produces vas afferens arteriolaritis in the presence of normal arterioles and an arteriolar necrosis in the presence of sclerosed vessels analogous to human malignant nephrosclerosis. Changes in vas afferens reduce the tubular blood flow even more, resulting in acceleration of the process and producing a vicious circle.

There is no evidence that the kidneys liberate a specific hypotensive substance or release any specific agent that neutralizes or inhibits the action of renin. The protective action of the normal kidney in animals while the other kidney is made ischemic, may be accounted for on the basis of facilitating the urinary excretion of renin, assuring the function of the injured kidney and preventing the development of uremic poisoning which can aggravate the hypertensive state by interfering with the prompt destruction of renin by the tissue.

It is also mentioned, and well established, that renal hypertension is not due to the retention of nitrogenous wastes in the blood and bilateral nephrectomy results in a fatal azotemia but does not produce hypertension. Other factors may be involved besides the renin, renin activator and angiotonin mechanism in renal hypertension.

Pressor amines may be one of the factors in pathogenesis of experimental renal hypertension. The kidney tissue can convert amino
acids into pressor amines and there is no positive relation between
the metabolisms of amino acids by the kidney and the hypertension
resulting from renal ischemia.277

Primary renal changes underlie all hypertensive disease.278
Volhard279 always contended that the malignant type of hypertension
characterized by impaired renal excretion and elevated blood pressure
is of renal origin and refused to accept the benign phase of essential
hypertension as renal origin.

Another school of thought is that hypertension is one sign of
neurohumoral disease due to disordered function in neuropsychic,
endocrine and renal origin.110,280-1

It can be accepted that renal vascular changes are required for
most forms of sustained human hypertension. In kidney diseases, the
vicious circle is initiated in the kidney but in case of hypertension,
without renal excretory impairment what would be the factor for
initiation?

Primary renal arteriosclerosis is the probable cause of hypertension
in senescence.283 In other forms of hypertension the neurohumoral
mechanisms (eg. stress, stimuli from the vaso motor center)284 produce
temporary vas afferens spasms with resulting renin release initiating
the vicious circle of renal hypertension. The renal pressor mechanism
is dependent on the presence of the adrenal gland.
Materials, Methods and Results

1. ADRENAL CORTEX

The materials were derived from the records and routine autopsies at Massachusetts Memorial Hospitals and comprised of:

1. 120 hypertensives and 120 non-hypertensives. In every case a histological study of the adrenals and a careful review was made of the clinical history and general autopsy findings.

Heart weights of 500 gms. in males or 450 gms. in females were taken to indicate hypertension. Those weighing less than 400 gms. in males or 300 gms. in females were considered non-hypertensive.

Blood pressure readings of 150/100 or more were considered hypertensive for any age and no case was accepted as a non-hypertensive control if there was a record of a systolic pressure over 140 or a diastolic over 90 mm. of mercury. All cases of valvular disease of the heart were discarded. Cases where the adrenal was the seat of malignancy or tumor metastasis also was discarded. The investigations presented here were undertaken in order to determine the morphological character of adrenals in hyper and normotensive cases including the presence and absence of the cortical nodules, the amount of lipid in the cortex, and the thickness of the capsule. Cortical nodules are spherical, well defined, usually encapsulated masses of cells like those of the adrenal cortex, they occur in the cortex, capsule or in the peri-adrenal fat. The origin probably is the result of pinching off of its cortex either during embryonal and fetal development, or during subsequent growth. There is no sharp line of distinction between a cortical nodule and a cortical adenoma. However, the cortical nodule is usually multiple and smaller than the adenoma. While adenoma is usually single and larger than the nodule. It is suspected that a nodule may give rise to an adenoma.
Results: as shown in Table I

The 120 hypertensive cases include 74 females and 46 males with the age range between 24 - 79 years, 62 cases show cortical nodules and 38 cases are negative.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Cortical Nodules</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 females</td>
<td>range between 24 - 79 years</td>
<td>Positive for cortical nodules 68.3% (82)</td>
<td></td>
</tr>
<tr>
<td>46 males</td>
<td></td>
<td>Negative for cortical nodules 31.7% (38)</td>
<td></td>
</tr>
</tbody>
</table>

120 hypertensive cases

Table 2 shows the results in the normotensive cases.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Cortical Nodules</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>68 females</td>
<td>range between 26 - 81 years</td>
<td>Positive for cortical nodules 41.66% (50)</td>
<td></td>
</tr>
<tr>
<td>52 males</td>
<td></td>
<td>Negative for cortical nodules 58.34% (70)</td>
<td></td>
</tr>
</tbody>
</table>

120 normotensive cases

For purposes of visual estimation of the lipid content represented by the presence of the vacuoles, I classified the results in four groups.

1. Indicate the cortex is rich in lipid (+++)
2. Moderate amount of lipid (++)
3. Normal in lipid (+)
4. Poor in lipid (-)

These are shown in Table 3 for the hypertensive cases and Table 4 for normotensive cases.
The average thickness of the capsule in hypertensive cases of the adrenal was 73.7 μ and in the control series was 89.6 μ.

2. Frozen sections stained with red oil (Sudan IV or Scharlach R), sudan black of Ashbel methods were made from adrenals of some hypertensive and normotensive cases for the visual estimation of the lipid contents of the cortex.

3. Twenty-seven cases of both hyper and normotensive, have been studied with Triphenyl Tetrazolium chloride (T.T.C) reagent. The same technique used by Shorr, et al.286

4. Cell counts of adrenal cortex of 27 hypertensive cases and 14 non-hypertensive cases were done by Dr. J. W. Godward287 using selected cases from our materials, as shown in Table 5.
# Table 5

<table>
<thead>
<tr>
<th>Case #</th>
<th>Sex</th>
<th>Age</th>
<th>B. P.</th>
<th>Ht. Wt.</th>
<th>Z. Glomerulosa</th>
<th>Z. Fasciculata</th>
<th>Z. Reticularis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-51-116**</td>
<td>♀</td>
<td>59</td>
<td>220/132</td>
<td>350</td>
<td>34.32</td>
<td>21.85</td>
<td>17.45</td>
</tr>
<tr>
<td>A-51-115**</td>
<td>♀</td>
<td>55</td>
<td>194/60</td>
<td>660</td>
<td>32.67</td>
<td>19.25</td>
<td>17.81</td>
</tr>
<tr>
<td>A-51-113**</td>
<td>♀</td>
<td>48</td>
<td>120/80</td>
<td>480</td>
<td>25.94</td>
<td>19.68</td>
<td>20.96</td>
</tr>
<tr>
<td>A-51-112*</td>
<td>♀</td>
<td>60</td>
<td>154/100</td>
<td>600</td>
<td>23.58</td>
<td>19.02</td>
<td>17.90</td>
</tr>
<tr>
<td>A-51-111*</td>
<td>♀</td>
<td>73</td>
<td>188/100</td>
<td>560</td>
<td>29.50</td>
<td>22.27</td>
<td>13.79</td>
</tr>
<tr>
<td>A-51-108*</td>
<td>♀</td>
<td>54</td>
<td>190/120</td>
<td>640</td>
<td>33.59</td>
<td>23.13</td>
<td>10.89</td>
</tr>
<tr>
<td>A-51-107**</td>
<td>♀</td>
<td>51</td>
<td>110/60</td>
<td>200</td>
<td>32.67</td>
<td>21.45</td>
<td>16.69</td>
</tr>
<tr>
<td>A-51-106*</td>
<td>♀</td>
<td>48</td>
<td>210/112</td>
<td>690</td>
<td>35.17</td>
<td>26.19</td>
<td>16.83</td>
</tr>
<tr>
<td>A-51-105**</td>
<td>♀</td>
<td>42</td>
<td>110/60</td>
<td>280</td>
<td>28.67</td>
<td>7.02</td>
<td></td>
</tr>
<tr>
<td>A-51-104**</td>
<td>♀</td>
<td>54</td>
<td>112/32</td>
<td>190</td>
<td>23.26</td>
<td>13.13</td>
<td>7.92</td>
</tr>
<tr>
<td>A-51-129*</td>
<td>♀</td>
<td>77</td>
<td>130/100</td>
<td>630</td>
<td>37.26</td>
<td>22.96</td>
<td>16.17</td>
</tr>
<tr>
<td>A-51-130*</td>
<td>♀</td>
<td>76</td>
<td>90/60</td>
<td>660</td>
<td>31.28</td>
<td>13.43</td>
<td>18.18</td>
</tr>
<tr>
<td>A-51-132*</td>
<td>♀</td>
<td>63</td>
<td>228/120</td>
<td>750</td>
<td>38.51</td>
<td>21.45</td>
<td>16.69</td>
</tr>
<tr>
<td>A-51-102*</td>
<td>♀</td>
<td>59</td>
<td>120/80</td>
<td>640</td>
<td>27.67</td>
<td>24.31</td>
<td></td>
</tr>
<tr>
<td>A-51-100*</td>
<td>♀</td>
<td>81</td>
<td>294/68</td>
<td>570</td>
<td>26.26</td>
<td>19.93</td>
<td>9.76</td>
</tr>
<tr>
<td>A-51-98*</td>
<td>♀</td>
<td>67</td>
<td>150/90</td>
<td>570</td>
<td>26.00</td>
<td>17.95</td>
<td></td>
</tr>
<tr>
<td>A-51-72*</td>
<td>♀</td>
<td>37</td>
<td>175/95</td>
<td>760</td>
<td>23.29</td>
<td>19.02</td>
<td>16.38</td>
</tr>
<tr>
<td>A-51-71*</td>
<td>♀</td>
<td>29</td>
<td>175/95</td>
<td>760</td>
<td>27.72</td>
<td>22.88</td>
<td>12.60</td>
</tr>
<tr>
<td>A-51-69*</td>
<td>♀</td>
<td>70</td>
<td>180/90</td>
<td>510</td>
<td>24.71</td>
<td>20.32</td>
<td></td>
</tr>
<tr>
<td>A-51-59*</td>
<td>♀</td>
<td>79</td>
<td>200/90</td>
<td>360</td>
<td>26.36</td>
<td>17.85</td>
<td></td>
</tr>
<tr>
<td>A-51-18**</td>
<td>♀</td>
<td>66</td>
<td>120/80</td>
<td>470</td>
<td>20.01</td>
<td>16.03</td>
<td>12.37</td>
</tr>
<tr>
<td>A-51-32**</td>
<td>♀</td>
<td>35</td>
<td>Normal</td>
<td>235</td>
<td>13.59</td>
<td>19.00</td>
<td>12.60</td>
</tr>
<tr>
<td>A-51-32**</td>
<td>♀</td>
<td>35</td>
<td>Normal</td>
<td>235</td>
<td>23.29</td>
<td>19.00</td>
<td>16.35</td>
</tr>
</tbody>
</table>
Table 5 (cont.)

Adrenal Cortex Cell Densities (per 10,000 square micro)

<table>
<thead>
<tr>
<th>Case #</th>
<th>Sex</th>
<th>Age</th>
<th>B.P.</th>
<th>Ht. Wt.</th>
<th>Z. Glomerulosa</th>
<th>Z. Fasciculata</th>
<th>Z. Reticularis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-52-14*</td>
<td>♀</td>
<td>69</td>
<td>220/110</td>
<td>520</td>
<td>50.49</td>
<td>37.02</td>
<td>36.89</td>
</tr>
<tr>
<td>A-46-69*</td>
<td>♀</td>
<td>62</td>
<td>270/134</td>
<td>71.0</td>
<td>48.4</td>
<td>19.6</td>
<td>21.4</td>
</tr>
<tr>
<td>A-46-95*</td>
<td>♂</td>
<td>35</td>
<td>231/150</td>
<td>320</td>
<td>41.98</td>
<td>31.57</td>
<td>33.16</td>
</tr>
<tr>
<td>A-46-33*</td>
<td>♀</td>
<td>208/150</td>
<td>700</td>
<td>35.9</td>
<td>24.1</td>
<td>32.46</td>
<td>19.94</td>
</tr>
<tr>
<td>A-46-7*</td>
<td>♀</td>
<td>280/110</td>
<td>400</td>
<td>34.2</td>
<td>15.6</td>
<td>36.82</td>
<td>15.7</td>
</tr>
<tr>
<td>A-46-16*</td>
<td>♀</td>
<td>290/168</td>
<td>130</td>
<td>26.76</td>
<td>22.78</td>
<td>18.60</td>
<td>18.84 18.68</td>
</tr>
<tr>
<td>A-53-32**</td>
<td>♂</td>
<td>59</td>
<td>110/70</td>
<td>370</td>
<td>42.8</td>
<td>23.31</td>
<td>20.82</td>
</tr>
<tr>
<td>A-52-96**</td>
<td>♂</td>
<td>76</td>
<td>110/60</td>
<td>340</td>
<td>43.24</td>
<td>21.50</td>
<td>27.09</td>
</tr>
<tr>
<td>A-53-43**</td>
<td>♀</td>
<td>122/78</td>
<td>240</td>
<td>47.4</td>
<td>29.9</td>
<td>13.38</td>
<td></td>
</tr>
<tr>
<td>A-53-29**</td>
<td>♂</td>
<td>76</td>
<td>100/60</td>
<td>500</td>
<td>34.1</td>
<td>27.02</td>
<td>27.6</td>
</tr>
<tr>
<td>A-53-19**</td>
<td>♂</td>
<td>54</td>
<td>200/105</td>
<td>360</td>
<td>32.55</td>
<td>18.86</td>
<td>13.38</td>
</tr>
<tr>
<td>A-53-37**</td>
<td>♀</td>
<td>120/80</td>
<td>210</td>
<td>31.6</td>
<td>22.4</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td>A-53-6*</td>
<td>♀</td>
<td>16</td>
<td>100/70</td>
<td>540</td>
<td>37.13</td>
<td>33.49</td>
<td>31.8</td>
</tr>
</tbody>
</table>

* Hypertensive
** Normotensive

14 Normotensive
27 Hypertensive
41 Cases
Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th># of cases</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>34</td>
<td>34 cases lipid increased</td>
<td>70%</td>
</tr>
<tr>
<td>II</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>28</td>
<td>36 either normal in amount or decreased</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

120 hypertensive cases

Table 4

<table>
<thead>
<tr>
<th>Group</th>
<th># of cases</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
<td>41 cases lipid increased</td>
<td>34.16%</td>
</tr>
<tr>
<td>II</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>23</td>
<td>79 lipid either normal or decreased</td>
<td>65.83%</td>
</tr>
<tr>
<td>IV</td>
<td>56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

120 normotensive cases

B. ADRENAL GLANDS

In the adrenal glands I am concerned with its weight in hypertensive and normotensive cases. The records of 200 consecutive hypertensive cases bearing the criteria for hypertension already mentioned and 200 normotensive cases already studied for adrenal weights, the results as shown in Table 6.

Table 6

200 Hypertensive cases 200 Normotensive cases
Average weight of both adrenals Average weight of both adrenals
(18.8 gm.) (14.1 gm.)
Age: range between 20 - 89 Age: range between 26 - 85
Sex: 84 females Sex: 90 females
136 males 130 males
C. ADRENAL MEDULLA

A. A study of the muscular veins

The tissue used for study has been removed at necropsy. Adrenal
slides from two groups of cases were studied, those with hypertension
and those with low or normal blood pressure. The age in the two groups
range between 21 - 82 years.

338 veins from 64 cases of each hyper and normotensive groups have
been measured.

The muscular veins were identified from or by greatly varying
thicknesses of their walls, irregular shaped lumen, absence of
circular muscle (usually found in artery), irregular distribution of
longitudinal muscle and absence of internal elastic lamina. In order
to determine as accurately as possible whether hypertrophy of the wall
of muscular vein was present in equal numbers (4 veins) of various
sizes were measured in each case. Care was taken that the vessels
of approximately equal size only should be compared and for comparison
of veins of equal size, they were divided into groups depending on the
mean of the external diameters as follows:

Group I—Mean external diameters 200-299 microns
Group II—Mean external diameters 300-399 and so on up to 3200-3299.

This is shown in Tables 9 and 10. Each group of hypertensive cases has
been compared with the same group of normotensive cases as shown in
Table 11 and Figures 1 and 2. Table 10 shows that the ratio of wall
to lumen of 211 veins out of 333 veins (63.3%) of various sizes of
hypertensive cases is more than the ratio of wall to lumen of 220 veins
out of 329 veins (66.8%) of various sizes of normotensive cases. The
ratio of wall to lumen of 122 veins out of 333 veins (36.7%) of various
sizes of hypertensive cases is less than the ratio of the wall to lumen
of 109 veins (33.2%) of 329 of various sizes of normotensive cases. The
ratio of wall to lumen of approximately 2/3 of the veins of hypertensive
FIGURE 1

Mean External Diameters

High blood pressure

Normal blood pressure
FIGURE 2

Mean Internal Diameters:
High blood pressure
Normal blood pressure
cases is more than the ratio of wall to lumen of normotensive veins.

B. Medullary changes

The cytologic and histologic study of the medulla of the adrenal gland in 12 cases of an equal number of hypertensive and normotensive cases has been done. The purpose of the investigation was to see whether there was any correlation between the structure and the function of the medulla, especially in deciding the possible role which the medulla plays in essential hypertension.

The great majority of the adrenal slides studied in this and other series have not enough medulla to fulfill our purposes, and for this reason few cases have been studied just to take some idea about this subject. The age in both hyper and normotensive cases range between 26 – 84 years.

The signs characterized increased function of the medulla.

(1) dilatation of the sinusoids, and intercellular excretory canal
(2) presence of vacuoles in the medullary cells
(3) enlargement of cells and nuclei with formation of giant cells.168

These served as guides to the evaluation of the activity of the medulla.

The nuclei and cells were measured in every case similar to the method used by Drake.168

The morphological criteria of hyperfunction were absent or minimal in the great majority of our cases. The diameters of the cell nuclei were between 4 to 6 microns; the diameters of the cells were between 5 to 11.5 microns in the hypertensive cases and 3.5 to 7 microns diameter of nuclei and 4.5 to 12.7 microns diameter of cells in normotensive cases. Vacuoles in the cytoplasm and rare giant cells seen in both hypertensive and normotensive cases were noted.
Table 7

17 Normotensive Cases and Pituitary Count Data

<table>
<thead>
<tr>
<th>Status</th>
<th>Age</th>
<th>Sex</th>
<th>B.P.</th>
<th>Ht.Wt.</th>
<th>Total</th>
<th>A</th>
<th>B</th>
<th>Amp</th>
<th>C</th>
<th>Hr</th>
<th>Hb**</th>
<th>Fields</th>
</tr>
</thead>
<tbody>
<tr>
<td>-51-31</td>
<td>50</td>
<td>m</td>
<td>128/72</td>
<td>425</td>
<td>10,484</td>
<td>19.7</td>
<td>22.4</td>
<td>28.9</td>
<td>27.6</td>
<td>1.4</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>-49-12</td>
<td>34</td>
<td>m</td>
<td>78/50</td>
<td>470</td>
<td>9,762</td>
<td>53.9</td>
<td>11.4</td>
<td>11.7</td>
<td>16.2</td>
<td>0.9</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>-46-2</td>
<td>59</td>
<td>m</td>
<td>134/80</td>
<td>1400</td>
<td>11,893</td>
<td>30.1</td>
<td>25.0</td>
<td>20.3</td>
<td>23.3</td>
<td>1.3</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>-37-115</td>
<td>68</td>
<td>m</td>
<td>100/60</td>
<td>260</td>
<td>8,991</td>
<td>52.1</td>
<td>17.1</td>
<td>12.5</td>
<td>17.8</td>
<td>0.5</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>-55-70</td>
<td>64</td>
<td>f</td>
<td>N.</td>
<td>350</td>
<td>10,243</td>
<td>43.2</td>
<td>17.4</td>
<td>17.8</td>
<td>19.9</td>
<td>1.6</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>-55-57</td>
<td>50</td>
<td>f</td>
<td>115/70</td>
<td>450</td>
<td>9,618</td>
<td>47.1</td>
<td>17.5</td>
<td>13.6</td>
<td>21.1</td>
<td>0.7</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>-51-122</td>
<td>43</td>
<td>f</td>
<td>118/70</td>
<td>310</td>
<td>10,551</td>
<td>39.6</td>
<td>25.3</td>
<td>7.4</td>
<td>25.0</td>
<td>1.3</td>
<td>1.3</td>
<td>80</td>
</tr>
<tr>
<td>-50-64</td>
<td>43</td>
<td>f</td>
<td>120/90</td>
<td>230</td>
<td>15,028</td>
<td>28.5</td>
<td>12.2</td>
<td>32.2</td>
<td>21.6</td>
<td>5.3</td>
<td>0.1</td>
<td>131</td>
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<tr>
<td>-49-154</td>
<td>23</td>
<td>f</td>
<td>135/90</td>
<td>230</td>
<td>7,746</td>
<td>42.7</td>
<td>14.4</td>
<td>16.5</td>
<td>24.5</td>
<td>1.2</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>-49-119</td>
<td>21</td>
<td>f</td>
<td>110/86</td>
<td>300</td>
<td>7,888</td>
<td>51.9</td>
<td>30.3</td>
<td>1.7</td>
<td>16.3</td>
<td>0.3</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>-46-113</td>
<td>60</td>
<td>f</td>
<td>118/72</td>
<td>350</td>
<td>8,660</td>
<td>40.1</td>
<td>16.3</td>
<td>20.3</td>
<td>22.7</td>
<td>0.5</td>
<td>&lt;0.1</td>
<td>51</td>
</tr>
<tr>
<td>46-110</td>
<td>31</td>
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4 males
13 females

A: Acidophils
B: Normal basophils
Amp: Amphophils
C: Chromophobes
Hr: Hypertrophic amphophils
Hb: Hyaline basophils
Table 8

17 Hypertensive Cases and Pituitary Counts*

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2 males
15 females
Table 9

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<th>Mean Thickness</th>
<th>Wall to Human</th>
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Table 10

Normotensive Cases

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<th>Wall to Human</th>
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see next page
Table 10 (cont.)

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Table 11

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<th># of vessels</th>
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<td>1500-1599</td>
<td>3</td>
<td>9</td>
<td>0.209</td>
</tr>
<tr>
<td>15.</td>
<td>1600-1699</td>
<td>6</td>
<td>9</td>
<td>0.260</td>
</tr>
<tr>
<td>16.</td>
<td>1700-1799</td>
<td>No veins found</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>1800-1899</td>
<td>2</td>
<td>3</td>
<td>0.275</td>
</tr>
<tr>
<td>18.</td>
<td>1900-1999</td>
<td>2</td>
<td>2</td>
<td>0.263</td>
</tr>
<tr>
<td>19.</td>
<td>2000-2100</td>
<td>2</td>
<td>6</td>
<td>0.178</td>
</tr>
</tbody>
</table>

TOTAL VEINS | 329 | 333 |

* Ratio to Normotensive case is more...
D. The pineal bodies obtained from consecutive autopsies of 16 hypertensive and 19 normotensive cases have been examined grossly and microscopically. The weights have been recorded as shown in Table 12.

The purpose of this examination was to recognize any morphological changes if any in the pineal bodies of hypertensive cases. Sixteen cases were females and nineteen males. Their age range was between 16 and 85 years.
Table 12

Pineal Body Weight In Normotensive And Hypertensive Cases

<table>
<thead>
<tr>
<th>Autopsy Number</th>
<th>Age</th>
<th>Sex</th>
<th>B. P.</th>
<th>Ht. Wt.</th>
<th>Pineal Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-55-12*</td>
<td>58</td>
<td>♂</td>
<td>220/130</td>
<td>705 gms.</td>
<td>40 mgm.</td>
</tr>
<tr>
<td>A-55-83</td>
<td>53</td>
<td>♀</td>
<td>160/90</td>
<td>450</td>
<td>150</td>
</tr>
<tr>
<td>A-55-43</td>
<td>70</td>
<td>♂</td>
<td>190/105</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>A-55-48</td>
<td>85</td>
<td>♂</td>
<td>180/90</td>
<td>190</td>
<td>120</td>
</tr>
<tr>
<td>A-55-82</td>
<td>54</td>
<td>♂</td>
<td>210/110</td>
<td>225</td>
<td>70</td>
</tr>
<tr>
<td>A-55-86</td>
<td>38</td>
<td>♂</td>
<td>150/100</td>
<td>260</td>
<td>19</td>
</tr>
<tr>
<td>A-55-93</td>
<td>39</td>
<td>♂</td>
<td>200/110</td>
<td>750</td>
<td>110</td>
</tr>
<tr>
<td>A-55-37</td>
<td>59</td>
<td>♂</td>
<td>590</td>
<td>1400</td>
<td>90</td>
</tr>
<tr>
<td>A-55-107</td>
<td>64</td>
<td>♂</td>
<td>170/100</td>
<td>810</td>
<td>220</td>
</tr>
<tr>
<td>A-55-109</td>
<td>82</td>
<td>♂</td>
<td>150/100</td>
<td>380</td>
<td>480</td>
</tr>
<tr>
<td>A-55-110</td>
<td>58</td>
<td>♂</td>
<td>220/80</td>
<td>440</td>
<td>250</td>
</tr>
<tr>
<td>A-55-115</td>
<td>75</td>
<td>♂</td>
<td>170/100</td>
<td>510</td>
<td>250</td>
</tr>
<tr>
<td>A-55-122</td>
<td>77</td>
<td>♂</td>
<td>160/80</td>
<td>600</td>
<td>80</td>
</tr>
<tr>
<td>A-55-90</td>
<td>66</td>
<td>♂</td>
<td>120/80</td>
<td>600</td>
<td>135</td>
</tr>
<tr>
<td>A-55-95</td>
<td>73</td>
<td>♂</td>
<td>140/90</td>
<td>530</td>
<td>60</td>
</tr>
<tr>
<td>A-55-116</td>
<td>59</td>
<td>♂</td>
<td>90/50</td>
<td>530</td>
<td></td>
</tr>
</tbody>
</table>

*Hypertensive cases

<table>
<thead>
<tr>
<th>Autopsy Number</th>
<th>Age</th>
<th>Sex</th>
<th>B. P.</th>
<th>Ht. Wt.</th>
<th>Pineal Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-55-113***</td>
<td>85</td>
<td>♂</td>
<td>150/70</td>
<td>400</td>
<td>110</td>
</tr>
<tr>
<td>A-55-8</td>
<td>75</td>
<td>♂</td>
<td>154/70</td>
<td>490</td>
<td>290</td>
</tr>
<tr>
<td>A-55-9</td>
<td>48</td>
<td>♂</td>
<td>110/70</td>
<td>330</td>
<td>410</td>
</tr>
<tr>
<td>A-55-11</td>
<td>25</td>
<td>♂</td>
<td>120/80</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>A-55-34</td>
<td>75</td>
<td>♂</td>
<td>80/60</td>
<td>310</td>
<td>100</td>
</tr>
<tr>
<td>A-55-59</td>
<td>60</td>
<td>♂</td>
<td>100/60</td>
<td>300</td>
<td>38</td>
</tr>
<tr>
<td>A-55-61</td>
<td>47</td>
<td>♂</td>
<td>120/70</td>
<td>120</td>
<td>21</td>
</tr>
<tr>
<td>A-55-72</td>
<td>16</td>
<td>♂</td>
<td>120/60</td>
<td>260</td>
<td>80</td>
</tr>
<tr>
<td>A-55-80</td>
<td>25</td>
<td>♂</td>
<td>120/84</td>
<td>310</td>
<td>170</td>
</tr>
<tr>
<td>A-55-84</td>
<td>49</td>
<td>♂</td>
<td>110/80</td>
<td>130</td>
<td>100</td>
</tr>
<tr>
<td>A-55-83</td>
<td>45</td>
<td>♂</td>
<td>110/70</td>
<td>380</td>
<td>110</td>
</tr>
<tr>
<td>A-55-85</td>
<td>38</td>
<td>♂</td>
<td>120/90</td>
<td>260</td>
<td>25</td>
</tr>
<tr>
<td>A-55-87</td>
<td>58</td>
<td>♂</td>
<td>110/70</td>
<td>310</td>
<td>100</td>
</tr>
<tr>
<td>A-55-92</td>
<td>64</td>
<td>♂</td>
<td>115/70</td>
<td>350</td>
<td>90</td>
</tr>
<tr>
<td>A-55-97</td>
<td>71</td>
<td>♂</td>
<td>110/30</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>A-55-106</td>
<td>85</td>
<td>♂</td>
<td>110/70</td>
<td>310</td>
<td>320</td>
</tr>
<tr>
<td>A-55-112</td>
<td>76</td>
<td>♂</td>
<td>160/40</td>
<td>420</td>
<td>60</td>
</tr>
<tr>
<td>A-55-118</td>
<td>75</td>
<td>♂</td>
<td>110/74</td>
<td>400</td>
<td>310</td>
</tr>
<tr>
<td>A-55-124</td>
<td>78</td>
<td>♂</td>
<td>120/60</td>
<td>370</td>
<td>175</td>
</tr>
</tbody>
</table>

***Normotensive cases
Discussion

Adrenal Cortex: There are many observations which suggest that in hypertension in man there are associated changes in the adrenal cortex, although there is no general agreement as to the nature or frequency of these changes.

Philpot, Oppenheimer and Fishberg, Rhinehart, et al. and Russi et al, Sarason and Fishberg observed that diffuse hyperplasia and circumscribed adenoma are common in the adrenal cortex in hypertensive patients. In essential hypertension Rhinehart found almost regularly a grossly thickened and nodular cortex with microscopic hyperplasia of the adrenal cords, which were usually well filled with lipoid droplets. The mean weight of the adrenal in essential hypertension was 4.2 gms. more than in their controls. Fisher and Herm 51 likewise observed increased lipid content of the adrenal cortex in hypertensive. Rather found the adrenals enlarged in rats with experimental hypertension. Contrary to the fact, Dempsey and others found no correlation between hypertension and hyperplasia or adenoma formation in the adrenal cortex.

In view of these observations, I decided to obtain further data. The data presented here succeeded to indicate that the morphologic abnormalities under study were related to or indicative of hypertension. Eighty-two cases or 68.3% of 120 hypertensive cases are positive for cortical nodules and 84 cases or 70% are either rich in lipid or have moderate amounts and more than the normal adrenals. The interpretation of this finding concerning the lipid can only be tentative because an increase in lipid per se does not prove that there is definite altered adrenal function, but it is reasonable to take the view that the increased
cortical lipid is an indication of altered cortical endocrine activity. This interpretation is supported by and consistent with the known facts relating adrenal cortical activity to the blood pressure. Since it was considered that the cortical lipids might reasonably be related to the elaboration of the steroid hormones and that if microscopic changes were found to be present they would be a strong indication of a disturbance in the elaboration of these hormones.

In 1942, in feeding experiments on guinea pigs it was pointed out by Blumenthal and Loeb that the degree of mitotic activity in the adrenal cortex is in inverse ratio to the number of lipid vacuoles present in the fasciculate cells. It has been also noted by Dosne and Dalton as well as by Selye that the amount of cortical lipid definitely decreases as the adrenal glands enlarge with increased activity. Sarason observed a cortical enlargement associated with decreased amount of lipid in inflammatory diseases, cachexia, etc.

This evidence suggests that under these conditions there occurs a discharge of lipid into the circulation and the cytoplasm of cortical cells changes from the vacuolated to the more solid or granular state. However, Sarason was unable to explain the observation that in hypertension there was a cortical enlargement associated with an increased amount of lipid. Injection of pituitary adrenotropic substance produces a distinct lowering of the adrenal cholesterol level in rates of 3 hrs. after injection. Repeated injections over a period of three days results in an increase in adrenal cholesterol concentration above that of control animals. In interpreting the preponderance of vacuolated
cells associated with hypertension, I agree with the suggestion of Russi et al\textsuperscript{28} that there may be a relatively weak but persistent stimulus similar to repeated small injections of pituitary extract in the experimental situation and that while the storage of lipids exceeds the rate of discharge, the latter may still be greater than in the normal adrenal cortex. Although the mean weight of both adrenals in hypertensive cases was 18.8 and in normotensive cases was 14.1 and the difference between these is obviously significant, a finding which agrees with Sorasan\textsuperscript{27} and Rinshart, et al\textsuperscript{26} and contrasts with Dempsey's\textsuperscript{30} findings, I am not satisfied with these results since the routine examination of the adrenal glands during autopsy is not sufficiently accurate due to the presence of fat or incomplete removal of the glands. This gives rise to inaccurate results in weights. Although the sudanophil and other fat-staining methods are particularly valuable in determining the distribution of ketosteroids and cholesterol, and correspond closely with the intensity of sudanophil material in the human adrenal cortex, I found no significant difference between the amount of sudanophil materials in normo and hypertensive cases.

Shorr et al in histochemical studies of the adrenal glands found that the normal adrenal cortex on incubation with triphenyl tetraazolium chloride (TTC) deposited red formazan quite uniformly through out all three cortical zones. In the presence of enzyme inhibitors, such as fluoride and Malonate, there was a suppression of the TTC uptake in all three zones. The adrenal cortex in experimental renal hypertension also took up TTC in all three cortical zones, with some suggestion of an intensified uptake in the zona glomerulosa.
The significant difference between the adrenals from normotensive and hypertensive animals was that in the latter, incubation with fluoride or malonate failed to exercise any significant suppressive effects on the uptake of TTC by the zona glomerulosa.

The adrenals of 27 human cases including both normotensive and hypertensive persons have been incubated in TTC, and six of these with fluoride inhibitor. The technique in our experience gives variable formazan staining, dependent on postmortem interval and unknown factors. Among the six completely studied, three were hypertensive and these were recognizable by the same criteria given by Shorr. However, three normotensive cases gave irregular staining, or was unaffected by inhibitors, and the results were not clearcut.

Among the whole group of cases studied, histochemical testing with TTC was so irregular in results, most cases failing to stain, that it has not proved a useful method for recognising adrenals in essential hypertension.

The possible association in man between abnormal cortical steroids production and hypertension is supported by the evidence of the pressor effects of desoxycorticosterone, \( \text{aldosterone} \), and other related steroids.

The results of comparisons of adrenal cortical counts which were done by Dr. Goddard as shown in Table 5 reveals that there is no significant difference in the counts between the normo and hypertensive cases. This lack of correlation may be due to the alteration of the adrenal picture by other factors other than the hypertension. This finding was found to be true of the pituitary cell counts which were done by Dr. Sheldon Sommers as shown in Table 7 and 8.
Medulla: The results of my studies on the adrenal muscular veins revealed that about 2/3 of the muscular veins of various sizes in the hypertensive cases have a thicker wall than approximately 2/3 of the veins of normotensive cases. The cause of hypertrophy of musculature of the veins is possibly due to the increased functional activity of the adrenal gland, increased activity of the general sympathetic nervous system or a reaction to noxious substances in the blood stream. 169 Goldzieher and Sherman 167 demonstrated hypertrophy of the musculature of the veins in cases of hypertension and concluded "our results add new and weighty evidence to the theory which links hypertension and allied diseases with functional disturbances of the supra renal glands and they believed that contractions of the muscles of the adrenal veins in cases of hypertension might occlude the normal channels of venous drainage of the gland and force the venous flow back through the kidney and liver. Its effect might then be primarily on the kidney and secondarily on the systemic blood pressure. These observations and opinions suggest the constant but increased liberation of epinephrine as a cause of hypertension. Such a condition has no experimental foundation. 111,153,156

The problem of adrenalineria has been much debated and so far the investigations do not appear to have brought definite proof of its existence, either in normal subjects or in those with arterial hypertension. 152

The presence of adrenaline in the blood of individuals with essential and nephritic hypertension has not been demonstrated even by using methods of extreme sensitivity. 155

In my opinion hypertrophy most commonly indicates overwork and there is some logic in the supposition that the hypertrophied musculature in cases of hypertension indicates an increase in the liberation of
adrenal cortical hormones, i.e. desoxycorticosterone or aldosterone. It is only fair to assume that hypertrophy of the musculature in the adrenal veins expresses an accommodation to a constant strain to which the vessel wall has been subjected.

The adrenal vein is looked on as the excretory duct of the glandular organ. The presence of strong muscle bundles in the wall and particularly about the orifice of the smaller vessels which lead into the centrally located larger sinus-like spaces, suggests a relationship of these muscle bundles to the regulation of the glandular discharge. The fact that the blood collected by the small cortical capillaries empties through small veins in those larger sinuses is accepted. It is within reason that the active substance, discharged from the cortical cells will reach the sinuses on the way described and will mix therein with the discharge of the medullary cells. The central vein, after collecting the whole output of the glandular organ, liberates its blood into the vena cava.

It seems reasonable to assume that such hypertrophy is the result of constant over excretion resulting from the attempt to regulate and hold back the excessive liberation of the glandular discharge.

The frequency of an increase in size of the adrenals in hypertension and so are changes in the structure of both adrenal veins and the cortex.

It has not yet been generally accepted that the changes described prove conclusively the connection of a disturbed or excessive adrenal function as the cause of hypertension and its sequelae.

Drake et al. in a study of 26 cases of hypertension not associated with inflammation of the kidney found that 24 cases showed histologic evidence of hyperfunction of the medulla. They support the theory that in the early stages of essential hypertension hormonal factors
play a substantial and primary role. They found the diameters of the cell nuclei were between 8.2 and 10.2 microns and the diameters of the cells were between 15.2 and 19.8 microns. Compared to my hypertensive series, 4 to 6 and 5 to 11.5 microns respectively.

The nonhypertensive (6 cases in my series) show different measurements more or less than the hypertensive 6 cases and the average was more in both the nuclei and the cell measurements than that of hypertensive cases.

Although the study of a few cases is not reliable, the results of these few cases were not encouraging to carry on the investigation and I was not able to confirm the view held by Drake et al that hypertension of the medulla were present in hypertension. But the study of these few cases, does not exclude the possible role of the medullary action in hypertension, though average measurements in cases of normal blood pressure were not significantly higher than that in hypertensive cases. Medullary hyperplasia of the adrenal is not regularly found in association with essential hypertension and it occurs with considerable frequency in non-hypertensives.

According to the literature reviewed concerning the significant relationship between the pituitary gland, adrenals and hypertension mentioned previously, I was interested to see such relationship in the cytological examination and counting of the pituitary cells done by Dr. S. Sommers. Thirty-four cases of equal number of normotensive and hypertensive cases and shown in Table 7 and 8 have been studied. No significant difference in the counts between the two conditions has been found. This lack of correlation does not rule out the relation
between the pituitary gland and hypertension. It might be due to alteration of the morphological and cytological picture by other factors than the hypertension which leads to the death of the patient.

Hypophysectomy in animals was followed by a falling of the blood pressure, the same result seen in human hypertension. ACTH reverses the effects of hypophysectomy in renal hypertension and slightly augments metacorticoid hypertension and essential hypertension but does not restore the ability of DCA to induce hypertension after the pituitary has been removed. The posterior lobe of the pituitary does not appear to play any important role.

Attempts to restore the subnormal blood pressure of the hypophysectomized rat to normal with adrenal cortical extract, DCA, or growth hormones were unsuccessful. This experiment led to the belief that although the subnormal blood pressure of the hypophysectomized animal is due in part to insufficient cortical hormone there is another additional factor responsible for the lowering of blood pressure after hypophysectomy. Some authors believe secondary changes occurring in other endocrine glands in hypophysectomized animals might be responsible for the fall of blood pressure.

It has been well established by several investigators that the adrenal cortex is a necessary part of the mechanism by which renal hypertension is produced and sustained. Since the adrenal cortex is one of the target glands under the influence of the anterior hypophysis it is to be expected that hypophysectomy which is always followed by a decrease in the function of the adrenal cortex would
lower the blood pressure of renal hypertension. All these investigations indicate that there must be cytological and morphological changes in the anterior hypophysis, in essential hypertension.

The preliminary studies and the cell counts in both adrenal and pituitary do not uncover these pathological changes and further studies on this subject might lead to a good result.

No relation between the pineal glands and hypertension has been reported in the literature. I was interested to find out if a relationship existed, like there is with other endocrine glands. The study consisted of gross and microscopic examination of the glands of 35 hypertensive cases and 19 normotensive cases. The age range was between 16 - 85 years. There were 16 females and 19 males. There was no significant difference either in the weight of the gland nor in the histological appearance and in both normo and hypertensives indicating the neutral position the pineal gland takes with regard to hypertension.
Abstract

Literature Review: The definition, history classification types, and possible etiological factors of hypertension have been reviewed in detail. The theories of neurogenic origin, endocrine origin (including adrenal cortex, medulla, pituitary, thyroid, parathyroid, gonad, pancreas), and renal origin have been presented. The relationship between the various steroids produced by different endocrines is reviewed.

Material, Methods and Results: Heart weights of 500 gms. in males or 450 gms. in females or more, were taken to indicate hypertension. Those weighing less than 400 gms. in males or 300 gms. in females were considered non-hypertensive. Blood pressure readings of 150/100 or more were considered hypertensive for any age and no case was accepted as normotensive controls if there was a record of a systolic pressure over 140 or diastolic pressure over 90 mm. of mercury. All cases of valvular disease of the heart were discarded.

I. Adrenal Gland

A. Adrenal Cortex: 1. The investigations presented here were undertaken in order to determine the morphological character of adrenal cortex in hyper and normotensive cases including the presence and absence of cortical nodules, adenomas, the amount of lipid in the cortex and thickness of the capsule. In 120 hypertensive cases, which include 74 females and 46 males with the age ranging between 24 and 79 years, 82 show cortical nodules or adenomas and whereas 50 of 120 normotensives showed cortical nodules or adenomas as shown in Tables 1 and 2.
For purposes of visual estimation of the lipid content represented by the vacuoles, I classified the results in four groups: rich in lipid, moderate lipid, normal lipid and poor lipid as shown in Tables 3 and 4.

Eighty-four cases out of 120 hypertensive cases or 70%, the lipid is increased and 41 cases out of 120 normotensive cases or 34.16%, the lipid is increased.

2. Frozen sections stained with red oil, sudan black or Ashel methods were made from adrenals of hypertensive and normotensive cases.

3. The 27 adrenals of human cases including both hyper and normotensives have been studied with Triphenyl Tetrazolium Chloride (TTC) reagent. Six of these cases were treated with fluoride inhibitor. The results are discussed.

4. Cell counts of adrenal cortex in 27 hypertensive cases is compared with the cell counts of 14 normotensive cases as shown in Table 5.

B. Adrenal: The mean weight of both adrenals in 200 hypertensive cases is compared with the mean weight of both adrenals in the same number of normotensive cases. Results showed that in the former group the mean weight was 18.8 gm. compared to 14.1 gms. in the latter group.

C. Medulla: This investigation presented here is undertaken in order to determine: (1) presence or absence of muscular hypertrophy of veins in both hypertensive and normotensive cases and (2) to study the morphological and cytological picture of the cells of the medulla which indicate its activity. Regarding the first point, the
ratio of wall to lumen of 211 veins out of 333 veins (63.3%) studied
of various sizes of hypertensive cases is more than the ratio of wall
to lumen of 220 veins out of 329 veins studied (66.8%) of various
sizes of normotensive cases. The ratio of wall to lumen of 122 veins
out of 333 veins (36.7%) of various sizes of hypertensive cases is less
than the ratio of the wall to lumen of 102 veins (33.2%) of 329
of various sizes of normotensive cases. This shows that in approximately
2/3 of the cases studied, the ratio of wall to lumen is more in
adrenal veins of the hypertensive cases than in the normotensive ones.
Concerning the second point, in hypertensive cases the diameter of
the cell nuclei was between 4 to 6 microns, and the diameter of the
cells was between 5 to 11.5 microns; whereas in normotensive cases,
the nuclei varied between 3.5 to 7 microns in diameter and the cells
varied between 4.5 to 12.7 microns in diameter. Vacuoles in cytoplasm
and rare giant cells were seen in both hypertensive and normotensive
cases.

II. Pituitary Gland

Cell counts of the pituitary gland of 35 cases has been done
through the generosity of Dr. Sheldon C. Sommers.

The cases comprised both hyper and normotensives. The results are
shown in Tables 7 and 8.

III. Pineal Gland

The pineal bodies of 35 cases of both hypertensive and normo-
tensive obtained from consecutive autopsies have been examined grossly
and microscopically. The weights have been recorded as shown in
Table 12.
We have shown the presence of some changes in the adrenal cortex associated with hypertension. The literature is filled with controversy as to the presence and significance of these changes. Hypersecretion of the adrenal cortex, has been shown in our study to be one persistent phenomenon and of significance in hypertension.

The histochemical studies of the adrenal gland utilizing TTC and fluoride inhibition were demonstrated to be of questionable value in such study. Frozen sections of the adrenal gland stained for fat and lipid are also shown to be of questionable value in this study.

The etiology of the hypertrophy of the adrenal veins is discussed in the text. The significance of such a change is also discussed. The findings of this study supports the theory that adrenal hyperactivity is associated with hypertension. That the adrenal cortex is responsible for this demonstrated adrenal hyperactivity is suggested by the fact that medullary hyperplasia is not a constant finding in hypertensive cases occurring more frequently in normotensive in our series. Adrenal and pituitary cell counts, as done in this study fail to uncover the role played by these two organ in producing hypertension.

No significant histological changes were found in the pineal glands of hypertensive cases, thus indicating that this organ is not related to hypertension.
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