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The Adrenal cortex and hypertension

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THE ADRENAL CORTEX AND HYPERTENSION

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THE ADRENAL CORTEX AND HYPERTENSION

I. Introductory Statement

A. The increasing interest in the adrenal as related to hypertension and unresolved controversy thereof.

II. History

A. Neusser 1897--first description of hypertensive changes secondary to an adrenal cortical tumor.

B. Josue 1903--first hint of possible relationship between adrenal glands and hypertension.

C. Oppenheimer and Fishberg 1924--commented upon the elevated blood pressure found in patients with adrenal cortical tumors.

D. Cannon 1929--showed the bodily changes in pain, hunger, fear and rage and showed hypertension to be among them.

E. Goldblatt 1937--initial discovery that bilateral adrenalectomy interfered with the development or maintenance of experimental renal hypertension.

F. Raab 1941--demonstrated an increase in adrenal cortical substances in the blood in cases of "renal" hypertension.

G. Selye 1946--whose adaptation syndrome theory brought some order to the mass of experimental work.

III. Theories

A. Renal

B. Neurohumoral

1. Selye's general adaptation syndrome

2. Blood sugar level

3. Desoxycorticosterone acetate

4. Nor-epinephrine

IV. Evidence

A. Pituitary gland

1. Effect of hypophysectomy on hypertension.

2. Involvement of pituitary in Cushing's syndrome.

3. Stimulation of adrenal cortex by pituitary cells.

4. Hypertrophy of adrenal cortex due to pituitary corticotropic hormone.

5. Increase of blood pressure by pituitary in sensitized animals.

B. Adrenal Cortex

1. Reduction of adrenal cortex reduces blood pressure.

a. Total bilateral removal

b. Irradiation

c. Denervation

d. Unilateral ligation of periadrenal blood vessels and tissues

2. Hypertrophy of adrenal cortex is associated with hypertension.

3. State of equilibrium of vasotropic principles.

C. Desoxycorticosterone acetate (DCA)

1. DCA increases blood pressure in animals.

2. DCA increases blood pressure in Addison's disease.

3. DCA increases blood pressure of normotensives.

4. DCA increases blood pressure of hypertensives.

5. Production of vascular lesions by DCA.

6. Use of DCA and NaCl together.

7. Use of DCA and adrenocortical extract.

8. Effect of cortisone on blood pressure.

9. Production of renal lesions by corticoids.

D. Sodium metabolism

1. Sodium metabolism in hypertension.

2. Effect of NaCl on blood pressure.

a. Animals

b. Humans

3. Presence of salt retaining hormone.

4. Reabsorption of salt from sweat.

E. Nor-epinephrine

1. Sympathin E and Sympathin I

2. Presnece in adrenal medulla tumors

3. Presence in normal adrenal medulla

4. Presence in sympathetic nerve fibers

5. Responses in man to nor-epinephrine and epinephrine

6. Epinephrine increases adrenal cortical hormone production

7. Effect of ACTH on epinephrine and nor-epinephrine

F. Hyperglycemia

1. Increases production of insulin

2. Increases stimulation of anterior pituitary

V. Summary

VI. Conclusion

I.

The adrenal cortex has been the object of increasing interest in many phases of physiology and pathology, among which the relationship to hypertension is prominent. The part played by the adrenal gland in hypertension is not fully appreciated, although the association of hypertension with tumors of the adrenal cortex and medulla is recognized.

II.

The first suggestion of a possible relationship between the adrenal glands and hypertension was made by Josue in 1903 (1). This was long before any actual evidence was discovered. Little attention was paid to hypertensive changes secondary to adrenal cortical tumors until Oppenheimer and Fishberg in 1924 (2) commented upon the elevated blood pressure found in patients with such tumors and contrasted it with the reduced blood pressure of Addison's disease.

Cannon in 1929 (3) first brought the idea of stress prominently before the minds of investigators. Although his own work led him more along the neurohumoral system, it was his thought that resulted in the realization that stress causes tremendous changes within the body.

Goldblatt (4) further involved the adrenal by his discovery in 1937 that bilateral adrenalectomy interfered with the development or maintainence of experimental renal hypertension.

In 1941 Raab (5) demonstrated an increase in adrenocortical substances in the blood in cases of "renal" hypertension with and without renal insufficiency. He found no clear relation between the blood level of adrenocortical compounds and the blood pressure, however, so concluded that these compounds furthered the development of arteriolosclerosis with secondary ischemic effects on vasomotor centers of brain and the kidneys.

Selye's introduction of the general theory of the adaptation syndrome in 1946 (6) brought some order to the mass of experimental work including experimental renal hypertension, if applied as a hypothesis to the etiology of hypertension.

III.

Theories of the origin of hypertension may be divided into two large groups: the renal theory and the neurohumoral theory.

\- Those who support the renal theory contend that all hypertension, including essential hypertension, is a renal disease.

The neurohumoral theorists suppose that essential hypertension is a disease, or a group of diseases, with continued arterial hypertension as one sign of its presence, that the sign may, and frequently does, precede recognizable organic change and that hypertension is due to one or more disorders of function in the neuropsychic, endocrine and renal systems.

The renal theorists say the kidney is the essential organ in the cause of continued arterial hypertension for the following reasons: reduction in the amount of functioning kidney tissue, especially if the remaining tissue is injured, results in hypertension; alteration of the renal circulation to produce ischemia in animals is almost always followed by hypertension; a substance (or substances) is elaborated by the ischemic kidney that causes elevation of the blood pressure, accompanied by vasoconstriction; the endocrine nature of the kidney, apart from its excretory function, has been demonstrated, (7) and (8) and humoral regulation of the blood pressure by the kidney in experimental hypertension, in shock, and possibly in normal states, is known to exist, (9, 10, 11) and, finally, the ischemic renal-pressor mechanism is independent of sympathetic or other innervation of the kidney, but requires the presence of the adrenal gland, if not as a primary, at least as a secondary participant.

The interpretation of essential hypertension as a general neurohumoral disease due to functional disorders with laboratory manifestations in the kidney may be stated best in terms of Selye's theory (the general adaptation syndrome). Challenge (psychic or physical stress, endocrine or electrolyte burdens, infections, congenital defect) leads to response, which is mediated by pituitary activity, which in turn stimulates adrenal activity. Adrenal activity causes renal vasoconstriction or renal ischemia. This leads to liberation of renin (acutely) accompanied or followed by one or more anti-enzymes or other pressor-depressor substances, which produce general vasoconstriction and organic change, especially in the small arteries.

Several variations have been suggested to the application of The general adaptation syndrome in the neurohumoral theory. Hyperglycemia normally produces an increased secretion of insulin which causes a stimulation of the anterior pituitary gland with the release of adrenocorticotrophic hormone.

Desoxycorticosterone acetate (DCA), whose role in the production of hypertension has been so frequently investigated, is only one of the several adrenocortical steroids produced by adrenal activity which according to the theory of the general adaptation syndrome so affects the kidneys as to cause production of pressor substances.

Nor-epinephrine has been shown to be given off by smooth muscles on contraction and by sympathetic nerve fibers as well as to be present in quantities in the adrenal medulla but how much is secreted in the human being and under what conditions is not known. Some believe this pressor amine to stimulate production of adrenocorticotrophic hormone, while others explain the hypertensive effect on the basis of direct action on the circulatory system.

In the application of the theory of the general adaptation syndrome to the etiology of hypertension, the renal mechanism is considered to follow the adrenal cortex and to depend upon its being affected in one of two ways. Either vascular change in the kidney is induced, with resulting hypertension, or general hypertension is caused, which induces renal vascular change.

IV.

According to the neurohumoral theory, the pituitary gland is the foremost of the mechanisms involved in hypertension. Stress may result in a catabolic process that causes elaboration of the pituitary corticotrophic hormone, which in turn increases adrenocortical activity. Removal of the pituitary gland prevents this stress hypertension and nephrosclerosis (7). Renal experimental hypertension is not affected by hypophysectomy according to Goldblatt (12), but is reduced to near normal according to others (13).

Some cases of hypertension often qualitatively resemble Cushing's syndrome in a number of respects including hypertension, central obesity, menstrual abnormalities, and low salt concentration in sweat. However, in general it is a milder and less easily recognized group of symptoms and may have no evidence of hirsutism, abnormal carbohydrate metabolism or osteoporosis (14).

It has been suggested by Heinbecker that pituitary degeneration is caused by depression of the hypothalamic nuclei and that the pituitary eosinophilic cells are thus stimulated. In turn, the adrenal cortex is stimulated with the release of cortical hormones causing various effects among which are constriction of efferent glomerular arterioles of the kidney with the release of renin which together with other reactions causes the hypertension (15, 16).

Pituitary corticotrophic hormone causes hypertrophy of the adrenal cortex with production of adrenocortical hormones and, when the animal is sensitized by high-protein or high-sodium diets, causes hypertension via the kidney with salt retention and diffuse vascular change (7). Finally, certain tumors, or hypertrophy of the adrenal cortex as in Cushing's syndrome, are associated with hypertension; removal of the tumor, appropriate reduction of the hypertrophied adrenal cortex, or reduction of the blood pressure.

Hench(17) found that adrenocorticotropic hormone (ACTH) may raise the blood pressure of non-hypertensive patients as well as increase arterial tension in hypertensives.

The adrenal cortex is the second important mechanism in the physical basis of continued arterial hypertension according to the theory of the general adaptation syndrome because disease that diminishes or ablates the adrenal cortex lowers the blood pressure in a patient with hypertension and results in hypotension in the normal subject. Moreover, administration of the adrenocortical hormone restores the blood pressure to hypertensive or normal levels in such patients. (18)

Goldblatt (4) made the initial discovery that bilateral, but not subtotal adrenalectomy interferred with the development or maintenance of experimental renal hypertension. Comparable reports were made by Blalock and Levy (19), Page (20), Collins and Wood (21), and others (22-28). A decrease in sensitivity to renin was found following adrenalectomy when the vessels still reacted normally to hypertension. This was associated in some animals with a fall in hypertension precursor of the plasma (27).

The response was partially restored by substitution with adrenal cortical hormones (23, 24).

The possible relationship of the adrenal cortex brought forth many therapeutic attempts to modify the hypertensive state. Beneficial results were claimed after irradiation of the adrenals, (29-31) devervation or sub-total bilateral adrenalectomy (32-35). Dramatic effects following complete bilateral adrenalectomy, in a woman with severe hypertension and diabetes, have recently been reported by Green and his associates (36). Victor (37) produced hypertension in dogs by unilateral ligation of the periadrenal blood vessels and tissue. Others have attempted to repeat the experiment, but have obtained only equivocal results.

Certain tumors or hypertrophy of the adrenal cortex as in Cushing's syndrome, are associated with hypertension; removal of the tumor, appropriate reduction of the hypertrophied adrenal cortex, or reduction of pituitary corticotrophic hormone is followed often by reduction of the blood pressure (38-42). However, some have felt that adrenal hyperplasia existed with equal frequency in normotensives (43-46).

The vasotropic principles of renal and hepatic origins give rise to yet another example of adrenal cortical relationship in experimental renal hypertension (47). Shortly after the partial constriction of the renal artery by a Goldblatt clamp, vasoexcitor materials appear in the circulation but are subsequently counter-balanced by increasing amounts of vaso-depressor agents. A similar state of equilibrium with high titers is thought by some workers to exist in patients with essential hypertension (48).

Trueta (49) believes some people suffer from an excessive reactivity or exaggeration of the adaptation syndrome operating through the nervous-hormone complex of the hypothalmus-hypophysis-adrenal cortex. He describes the normally highly contractable arterioles of the renal cortex in these individuals as being more frequently subjected to constriction, either by the sympathetic or by the hormonic complex. The transient constriction provides the necessary conditions for the production of renin, VEM or other pressor substances, or for the inhibition of anti-pressor substances by the renal cortex. Thus the role of heredity would be explained on the basis of a tendency to react following a familial pattern rather than by the transmission of a disease. Trueta explains that as this mechanism repeatedly operates, structural changes take place; the arterial walls subjected to increased pressure thicken, the vessels of the renal medulla showing change earlier than those in the renal cortex. He suggests that psychic or physical rest, relaxing the tonus of the renal arterioles, might lower the arterial blood pressure to within normal limits if applied before the renal cortex arterioles show change.

It has been shown that there is a rise of blood pressure to hypertensive levels in animals implanted with desoxycorticosterone acetate (DCA) (6).

Elevation of blood pressure following administration of various sterols has been reported by some workers and denied by others (50-55).

The toxic effects of desoxycorticosterone esters in dogs were noted in 1939 (56). Other observers have confirmed the rise in arterial tension often to abnormal levels following the sustained administration of this steroid.(52-64).

DCA was the first of the adrenocortical steroids to be produced synthetically. Its use in Addison's disease, with the elevation of blood pressure as one of the results, led to its use in the study of hypertension (65-73). The slow increase in blood pressure could not be correlated with abnormal retention of the sodium ion nor with an increase in circulating blood volume (73). It was not dependent apparently upon an abnormally labile peripheral vascular system as measured by the cold pressor test.

Perera (73) found DCA to increase the blood pressure of normotensives while others (74, 75) found no increased pressure in normotensive humans. DCA used on hypertensive individuals caused prompt rise in blood pressure which could not be ascribed to changes in salt and water retention alone as there were comparable transitory changes in the normotensive group (74,75). Neither was it believed that alterations in cardiac output were responsible for this pressor effect. However, Perera (76) found only slight increases in resting blood pressure of five hypertensive patients treated with DCA.

Selye and Stone (77) produced lesions in the kidneys and heart by continuous exposure to various kinds of stress, by treatment with anterior pituitary corticotrophic preparation, or by DCA but found that these agents were effective only when the diets contained considerable amounts of sodium chloride. Other work by Selye and his co-workers (59, 78, 6) have produced about the same results. Knowlton (79) produced hypertension in a matter of a few weeks in nephritic rats given DCA and sodium chloride. Other workers found that DCA, particularly in the presence of added sodium salts, resulted in an impaired renal function as measured by clearance techniques (63, 80). Perera (81,82) found that rigid restriction of sodium chloride masks the pressor response of hypertensives to DCA.

Knowlton and others (79) used DCA and sodium chloride in both nephritic and non-nephritic animals. Arterial hypertension developed only in the nephritic animals. These studies suggest that DCA produces hypertension only when the kidneys are abnormal. Altschule and Zamcheck (83) suggested the same development of hypertension occurs in the human being when the kidneys are damaged. Hall and Hall (84) gave evidence to show that the kidneys are not involved by showing that after total nephrectomy, animals treated with DCA pellets showed a rise in blood pressure. The Friedmans (85) obtained the same results but interpreted this as due to the function of the kidney in excreting and possibly inactivating the steroid.

Adrenal cortical extract caused an actual decrease in resting blood pressure in 3 of 4 hypertensive patients (86). DCA and adrenocortical extract given together caused minimal increase or an actual decrease in blood pressure (87). Others (52, 88) also found that adrenal cortical extract did not produce hypertension in normal or nephritic rats.

Inspired by the observations of Pines et al (86), Friedman and co-workers (89) undertook to determine whether the adrenal gland liberated a factor that opposes the action of DCA, but found adrenocortical extract did not modify the hypertensive effects of DCA.

Use of cortisone (90) caused a decrease in resting blood pressure in five hypertensive patients. The decline usually occured immediately after the discontinuance of therapy. No change was found in the blood pressure of normotensives treated with cortisone (90).

Selye (6) reported small doses of salt active corticoid acting over long periods caused definite renal lesions. It may be that chronic endocrine overdosage of this corticoid is the basis of arterial hypertension. Symington and Goodall (91) have attempted to correlate these findings in a diagram (fig. 1).

In searching for evidence of adrenocortical dysfunction in hypertensive vascular disease, increased sensitivity of hypertensives to small doses of methacholine has been reported (92), a situation also encountered in Addison's disease (93).

The adrenal cortex is intimately concerned with sodium metabolism. Although the mechanism of the depressor action of salt restriction in hypertensive disease has not been explained, animal studies have suggested that electrolytes and water may behave differently in the presence of hypertension. Rats with experimental renal hypertension show significant degrees of polydipsia and polyuria (94) and tend to reduce their sodium intake when allowed freedom of choice (95). Tissue studies in hypertensive dogs imply that muscle sodium may be elevated at the expense of intracellular potassium (96). Furthermore, rats with an elevated blood pressure induced by renal manipulation have an increased reaio of serum sodium to chloride (97).

In contrast to these studies, the addition of salt to the diet has been accompanied, except in chickens, (98,99) by slight or no increases in the blood pressure of normal animals (100).

As in the animal studies, sodium metabolism also enters the picture in human hypertension. Modification of the resting blood pressure may result from extremes of sodium withdrawal or supplementation (101). It is claimed that serum sodium-to-chloride ratios are elevated in proportion to the height of the diastolic pressure in hypertensives (102). Despite an otherwise constant regimen sodium restriction is generally followed by immediate significant weight loss and increased uring output in control subjects which are not evident in hypertensive patients (103). These observations are consistent with, but not proof of the view that the adrenal cortex may be implicated. Of pertinence is the fact that rigid restriction of sodium chloride masks the pressor response of hypertensives to DCA (81,82).

H. Selye and associates (104) have recently re-emphasized their previous evidence that the production of hypertension and nephrosclerosis in rats is dependent on administration of both DCA and the sodium ion. Neither DCA and a salt-free diet nor 1% sodium chloride without DCA resulted in nephrosclerosis or a significant change in blood pressure. These data are particularly pertinent in the light of Schroeder's (105) report of patients falling into this clinical syndrome who responded to a low salt diet by a fall of blood pressure. Other hypertensives did not respond to low salt diet with a significant fall of blood pressure. Similar results have been obtained by Grollman and associates (106).

Evidence is shown against a hyperactivity of the salt retaining hormone of the adrenal cortex being present in a majority of the cases of essential hypertension (14) yet the same authors show evidence for existence of a type of hypertension in which there is an abnormal reabsorption of salt from sweat probably mediated through adrenal cortex.

Cannon in 1933 (107) described a material called "sympathin" given off by the smooth muscles in any area of the body when they are made to contract. He concluded that there were two kinds of sympathin, sympathin E (excitatory) and sympathin I (inhibitory). This laid the ground work for much that has been done in the last several years.

Tumors of the adrenal medulla have been examined for nor-epinephrine and epinephrine (108-110) and varying amounts of the two pressor amines have been found in the different tumors. Pleochromocytomas are tumors of the chromaffin cells of the adrenal medulla. In view of the fact that some investigators are of the opinion that chromaffin cells secrete considerable amounts of nor-epinephrine as well as epinephrine (109,110), one must consider any abnormal aggregate of such cells as a potential source of increased circulating pressor amines. Holton (109) postulated that since nor-epiniphrine ("arterenol") has greater pressor activity than epinephrine, it might be the cause of the attacks of hypertension. Blacklock et al (111) described a persistent as well as a paroxysmal type of hypertension occurring in chromaffin tumors. While these workers showed conclusively that the paroxysmal type is due to the liberation of adrenalin directly into the blood sinusoids, the cause of peristent hypertension associated with these tumors is still unknown. The actual importance of nor-epinephrine as well as other pressor amines in the development of essential hypertension remains to be worked out.

Not-epinephrine has been shown to be present in the normal adrenal medulla (112) and to be secreted by sympathetic nerve fibers (113) but how much is secreted in the human being and under what conditions is not known.

In 1948 Goldenberg (114) reported on the differences in response in man to nor-epinephrine and epinephrine, and suggested that nor-epiniphrine was related to the problem of hypertension.

Swan (115) confirmed his observations that epinephrine increased cardiac output, increased systolic pressure only, dropped peripheral resistance, increased pulse rate and increased mean pulmonary arterial pressure whereas nor-epinephrine decreased cardiac output, increased both systolic and diastolic pressures, increased peripheral resistance, decreased pulse rate and increased mean pulmonary arterial pressure. Barcroft and Konzett (116) found epinephrine caused tachycardia and nor-epinephrine bradycardia. Both produced an increase in blood pressure but nor-epinephrine caused a more gradual rise that persisted longer. Further studies on the hemodynamic effects of epinephrine and nor-epinephrine by Goldenberg et al (108) confirm the above observations.

That epinephrine injection is followed by an enhanced output of cortical hormone has been described by Vogt (114,111). Davies and Clark (14) feel that stimulation of the production of the adrenocorticotropic hormone by epinephrine must be considered as one possible mechanism in the etiology of the endocrine hypertensive syndrome.

Hyperglycemia normally produces an increased secretion of insulin, which, according to Vogt (115), causes a stimulation of the anterior pituitary gland with release of adrenocorticotrophic hormone. Other investigator's results have been similar (116).

V. Summary

The renal and neurohumoral theories of the etiology of hypertension have been described and explained. Evidence supporting the neurohumoral theory is presented as well as evidence detracting from the neurohumoral theory's importance in the etiology of hypertension.

Removal of the pituitary gland prevents stress and experimental hypertension. Pituitary corticotrophic hormone causes hypertrophy of the adrenal cortex and production of adrenocortical hormones.

Reduction of the adrenal cortex reduces blood pressure, whether the reduction be by total removal, irradiation or denervation. Hypertrophy of the adrenal cortex is associated with hypertension.

Desoxycorticosterone acetate (DCA) has been shown to increase the blood pressure of animals, normotensives, hypertensives and in Addison's disease as well as produce vascular lesions. Use of NaCl has seemed to potentiate the action of DCA while adrenocortical extract has markedly diminished the action of DCA. Yet cortisone has been shown to increase the arterial pressure of hypertensives although it does not change the blood pressure of normotensives. Persistent use of the corticoids has produced definite renal lesions.

Sodium restriction or supplementation may cause modification of the blood pressure. Many believe that animals and humans with elevated blood pressure have an increased ratio of serum sodium to chloride. Rigid restriction of sodium chloride does mask the pressor response of hypertensives to DCA.

Epinephrine and the more potent pressor amine, nor-epinephrine, are shown to be present in significant quantities in adrenal medullary tumors, in normal adrenal and to be secreted by sympathetic nerve fibers. These pressor amines increase production of adreno-cortical hormone and also increase arterial pressure by direct action on the circulatory system.

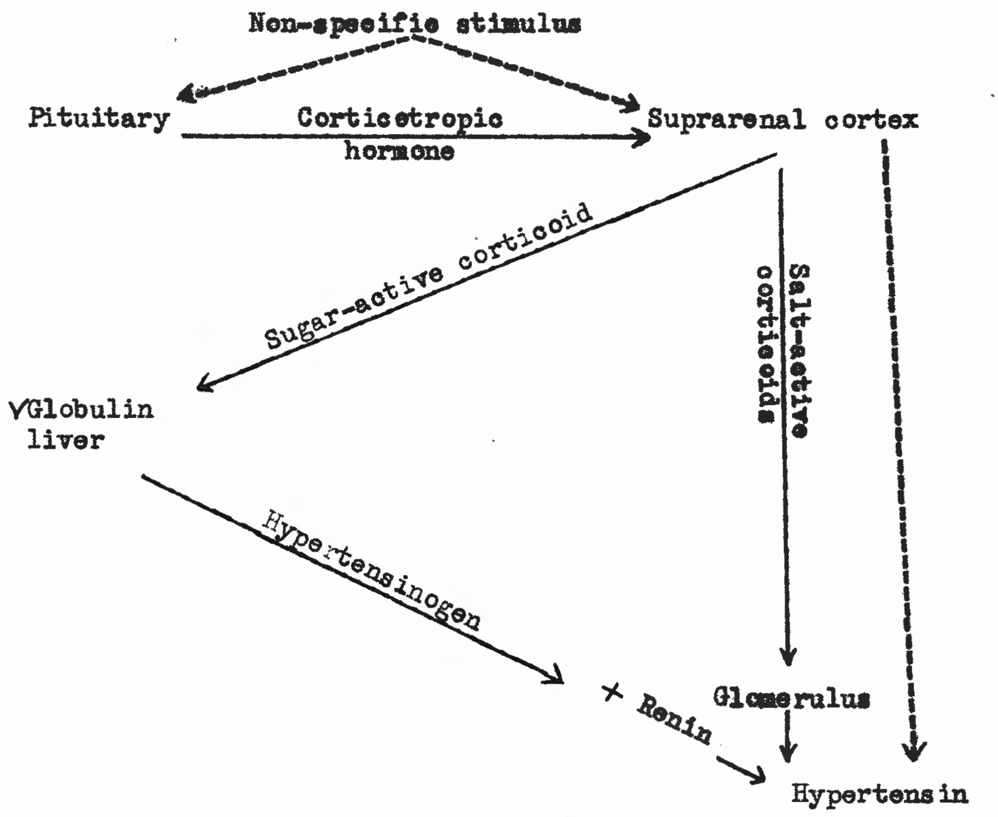
Hyperglycemia may stimulate the anterior pituitary gland to release adreno-corticotropic hormone.

VI. Conclusion

Much remains to be explained in the mechanisms in the etiology of hypertension. We do not know how the steroids achieve their effect, whether by modification of the pituitary release of adreno-corticotropic hormone or by peripheral action. We do not know whether adrenal products alter the reactivity of vessels and smooth muscle to other pressor and depressor agents. We do not know whether an excess of pressorhormone or a deficiency of a depressor hormone exists in the hypertensive syndrome. Adrenal cortex and sodium ion do appear to be related in some way to the regulation of blood pressure, whether this be by primary or secondary mechanisms.

The pituitary and adrenal activity in the adaptation syndrome probably plays a part in some but not all cases of the hypertensive syndrome.

Figure 1



The initiating mechanism is not definitely known, but it is presumably of the nature of a non-specific stimulus having a sympathetic-like action. This factor may activate the pituitary by liberating corticotropic hormone or directly on the suprarenal cortex by liberating corticoids. Sugar-active corticoid is believed to affect the γ-globulin which is the precursor of hypertensinogen (6). Salt-active corticoid may produce hyalinization of the glomerular afferent arterioles with narrowing of the lumen and consequent renal ischaemia. The renal humoral mechanism may be set off and the hypertensin formed may act as a further non-specific stimulus activating the suprarenal cortex. (91)

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