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THE ADRENAL CORTEX AND HYPERTENSION*

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THE rôle of the adrenal cortex, in the last few years, has been assuming tremendous proportions. Abnormal responses to stress, emotional disturbances, cancer, congestive failure and arthritis are but a few of the disorders which possess adrenal implications as judged by a perusal of current literature.

I have been asked to review the evidence concerning a relationship of the adrenal cortex to arterial hypertension. I am most grateful for this opportunity, for it will permit me to summarize our knowledge as well as to remind you of its many gaps and inadequacies.

As is so often the case, the first hint of a possible relationship between the adrenal glands and hypertension was made many years ago, forty-seven to be exact,[1] long before its substantiation by factual data of any kind. The first description of hypertensive changes secondary to an adrenal cortical tumor had been reported even earlier (1897),[2] although

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little notice was given to this association until the more extensive observations of Oppenheimer and Fishberg in 1924.[3] These authors commented upon the elevated blood pressure found in patients with such tumors and contrasted it with the reduced blood pressure of Addison's disease. Today it is common knowledge that many patients with hyperadrenocorticalism may exhibit hypertension, and that with hypoadrenalism one frequently observes hypotension, even after restoration of water and electrolyte balance by appropriate therapy.

In recent years a series of separate observations has appeared, each one relating the adrenal cortex in some fashion to the regulation of blood pressure or the hypertensive state. Let us review this material first as developed in animal experimentation, then as studied in the human.

Animal Observations

Goldblatt[4] made the initial discovery that *bilateral* (but not subtotal) *adrenalectomy interfered with the development or maintenance of experimental renal hypertension.* Comparable reports were made by Blalock and Levy,[5] Page,[6] Collins and Wood[7] and others.[8-18] Adrenalectomy, some of these workers noted, was associated with a fall in the concentration of hypertensinogen and at times a reduction in the response to renin. The administration of desoxycorticosterone restored the hypertension, and one investigator observed a similar restoration of the blood pressure on giving cortisone.[17] Adrenalectomy also modified the hypertension produced in dogs by the intracisternal injection of kaolin,[19] in rats by auditory stimulation[20] and, again in rats, by the injection of dehydroxyphenylalenine.[21]

Despite the apparent consistency of these results, Rogoff, Nixon and Stewart[22] claimed that the blood pressure remained high in three hypertensive dogs four to nine days after adrenalectomy. It is difficult to maintain the weight and sometimes the well-being of animals after adrenalectomy. Hence the possibility must be borne in mind that earlier experiments were too acute or included animals that were in poor condition. It is still conceivable that at least some forms of experimental renal hypertension can be achieved in the absence of the adrenal glands.

Even the *juxtaglomerular apparatus of the kidney* has been related to the adrenals. Goormaghtigh[23] suggested that this apparatus might secrete renin or some other vasopressor material. He also reported that the hypertension, produced by section of the depressor nerves, was asso-

ciated with thickening of the adrenal cortex together with an increased adrenal cholesterol content.[24] Dougherty[25] has remarked that large dosages of adrenocorticotropic hormone may stimulate the development of the juxtaglomerular apparatus, and stated that Rich had observed a marked increase in the production of the afibrillar cells of these structures in a patient having an adrenal cortical tumor.

The recently-described *vasotropic principles of renal and hepatic origins* give rise to yet another example of adrenal cortical relationship in experimental renal hypertension.[26] Shortly after the partial constriction of the renal artery by a Goldblatt clamp, vaso-excitor materials appear in the circulation but are subsequently counterbalanced by increasing amounts of vaso-depressor agents. A similar state of equilibrium with high titers exists in patients with essential hypertension.[27] Adrenalectomy abolishes or impairs the renal capacity to form the vaso-excitor materials under anaerobic conditions *in vitro* even in animals maintained on high salt diets, but the combination of desoxycorticosterone acetate and salt restores normal kidney behavior.[28-30]

Victor[31] produced hypertension in dogs by *unilateral ligation of the periadrenal blood vessels and tissue.* Although others have attempted to reproduce the experiment, there has been as yet only equivocal support of this interesting study.[32]

That *epinephrine injection is followed by an enhanced output of cortical hormone* has been described by Vogt.[33] This deserves mention here only because of the fact that chronic as well as paroxysmal hypertension may be evident in patients with pheochromocytomata.[34] Studies on the hemodynamic effects of epinephrine and nor-epinephrine, both of which occur in the adrenal medula, have been reported by Goldenberg *et al.* [35,36]

Next let us recall that 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. For example, rats with experimental renal hypertension show significant degrees of polydipsia and polyuria[37] and tend to reduce their sodium intake when allowed freedom of choice.[38] Tissue studies in hypertensive dogs imply that muscle sodium may be elevated at the expense of intracellular potassium.[39] Furthermore, rats with an elevated blood pressure induced by renal manipulation

have an increased ratio of serum sodium to chloride.[40] Grollman and Harrison[41] found that a rice diet exerted a pronounced blood pressure-lowering effect (blocked by the addition of sodium chloride) and an extension of the percentage survival in hypertensive rats. It was even claimed that the adrenals of rats on a restricted sodium intake were smaller and different in color.[42] In contrast to these studies, the addition of salt to the diet has been accompanied, except in chickens,[43,44] by slight or no increases in the blood pressure of normal animals.[45]

Elevation of blood pressure following the *administration of various sterols* has been reported by some workers and denied by others.[46-51] The complexities of accurate blood pressure measurement, the need for more adequate controls and problems of dosage make it difficult to evaluate some of these studies. Nevertheless, they lead us to the final chapter to date in the story of animal experimentation, which deals with the pressor properties of specific steroids of probable adrenal derivation.

Toxic effects of *desoxycorticosterone esters* in dogs were noted in 1939 by Kuhlmann, Ragan, Ferrebee, Atchley and Loeb.[52] In two animals, receiving 20 mgs. of desoxycorticosterone acetate daily for 70 days, a small rise in systolic blood pressure was recorded. Since that time many experimenters have observed a rise in arterial tension often to abnormal levels following the sustained administration of this steroid.[48,53-60] Even nephrectomy did not halt the appearance of hypertension, according to one report, suggesting that it is not dependent upon a renal mechanism for its maintenance.[61] Elevation of blood pressure occurred no matter whether the hormone was injected in the acetate form or given as subcutaneous pellets; however, Green[62] reported no hypertension if intrasplenic pellets were implanted and suggested inactivation by the liver. There is only one study, that of Summers,[63] in which the results were contrary to those generally obtained.

Morphological changes caused by massive doses of desoxycorticosterone acetate and salt were first described by Selye and his co-workers.[55,64] These included the development, in several animal species, of a decrease in adrenal size, and in later studies of cardiac hypertrophy and widespread vascular lesions—similar to those seen in human nephrosclerosis and in the accelerated phases of essential hypertension. Subsequent studies by Knowlton and her associates,[65] employing much lower dosages in rats, revealed no significant vascular lesions but some degree of cardiac and renal enlargement (even in the absence of hypertension).

In addition, a change in renal histology was produced by the desoxycorticosterone acetate, consisting of distention of cortical and medullary tubules, swelling and vacuolization, and sometimes atrophic changes in the convoluted tubules. With these smaller doses, striking hypertension appeared within a matter of a few weeks only in nephritic rats given the steroid (the nephritis having been induced by a cytotoxic serum), but it was not evident in controls. Incidentally, in the dosages employed, adrenal cortical extract did not produce hypertension in normal or nephritic rats,[48, 65]

Selye[66] noted that the degree of pathological response to desoxycorticosterone acetate was intensified by an increase in the sodium chloride supplement in the diet or by preliminary excision of one kidney; similarly, the group working with Knowlton[67] found that the action of the steroid was potentiated by salt. Still other workers reported that desoxycorticosterone, particularly in the presence of added sodium salts, resulted in an impaired renal function as measured by clearance techniques.[59, 68] The adrenal cortex of rats injected with this compound presented atrophic changes in the subcapsular zone but only when the animals were maintained on a liberal intake of salt;[67] and under similar conditions a decrease in adrenal size was confirmed by Carnes and his associates.[69] "Whatever may be the mechanism responsible for the various changes induced by desoxycorticosterone acetate, it is obvious that they are dependent upon a liberal supply of the sodium ion in the diet."[67]

The water and electrolyte changes which follow the administration of desoxycorticosterone esters in small or large doses constitute a familiar but separate story. The apparent lack of relationship of salt and fluid retention to the appearance of hypertension will be brought out later. 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.[67] Green[60, 70] observed the increased voluntary fluid intake of rats receiving the steroid; merely because the intensity of the blood pressure rise could be related to fluid exchange, despite some evidence to the contrary, he suggested that hypertension might be a compensatory mechanism to fluid and electrolyte changes. Selye[66] has claimed that the concurrent administration of ammonium chloride tends to inhibit the development of vascular and renal

damage, but then it must be recalled that massive doses of desoxycorticosterone were generally employed in his studies. Raising the question of some action on peripheral vascular tone, it has been stated that desoxycorticosterone protects dogs against the depressor effect of intravenous hypertonic sodium chloride.[71] A final comment—no direct relationship of hypertension to the urinary output of antidiuretic factor, increased by desoxycorticosterone, was established.[72]

Observations in Man

As might be expected, the first attempts to relate the adrenal cortex to hypertensive vascular disease in man were morphological. The elevated blood pressure of some patients with hyperfunction of the adrenals, either cortical or medullary, has already received comment. The nodular hyperplasia of the medulla reported by Goldzieher,[73] and the "sympathogenic neurohormonal" emphasis of Raab,[74] need not be discussed here except to remind us that epinephrine-like compounds and sympathetic nerve activity may possibly modify steroid elaboration.

There are numerous references to *adenomatous or nodular hyperplasia* of the adrenal cortex in essential hypertension since the description in 1904 of adrenal enlargement and increased cortical lipoid in patients with contracted kidneys.[75] Many authors observed increased adrenal weight, hyperplasia, adenomata or nodules with increased frequency in hypertensive subjects.[76-84] Others, on the other hand, felt that these abnormalities were uncommon or existed with equal frequency in normotensives.[85-88] *Hypertrophy of the adrenal veins* was mentioned by several investigators,[89,90] but this finding could not be confirmed in subsequent studies.[85] If all these pathological reports were laid end to end, it would be apparent at best that anatomical changes occur with slightly greater frequency in patients with an elevated blood pressure, and that such changes are evident in only a small percentage. It is, therefore, highly doubtful that any significance can be attached to these morphological findings alone.

In 1939, Loeb and his associates[91] called attention to two patients whose arterial 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.[92-102] At the Presbyterian Hospital, together with Drs. Knowlton, Lowell and Loeb,[100] we observed the appearance of hypertension in a number of patients

with Addison's disease in the course of prolonged administration of desoxycorticosterone acetate in therapeutic doses. 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. It was not dependent apparently upon an abnormally labile peripheral vascular system as measured by the cold pressor test. In our clinic today, the majority of patients with adrenal-cortical insufficiency exhibit some elevation of arterial tension, providing they are receiving adequate therapy with this steroid given parenterally or in the form of subcutaneous pellets. One individual has developed transitory retinal hemorrhages; another has sustained, coincidentally or otherwise, a myocardial infarction after several years of drug-induced hypertension.

Desoxycorticosterone acetate, administered to three normotensive patients without adrenal disease, was associated with a gradual increase in blood pressure over a period of weeks without more than transient salt or water retention.[100] As in the Addisonian group, the blood pressure returned to normal values as soon as the drug was withdrawn. One of these patients, toward the close of the experimental period, complained of severe headaches, with the appearance of a subconjunctival hemorrhage and a rise in pressure to 160/108 during the final week.

The blood pressure *response of hypertensive individuals to desoxycorticosterone acetate* was next considered. In a study undertaken with Dr. David Blood,[103] utilizing "resting" blood pressure measurements in patients on a constant regimen, this steroid (10 mgs. daily for a week) caused no significant change in the arterial tension of 10 normotensive subjects, whereas definite increases in systolic and diastolic readings were obtained within a few days in 14 patients with uncomplicated hypertensive vascular disease. The prompt rise in blood pressure in those with hypertension could not be ascribed to changes in salt and water retention alone as there were comparable transitory changes in the normotensive group. Alterations in cardiac output were not responsible for this pressor effect.

Daily injections with this steroid for longer periods produced a transient or at times a sustained increase in the "resting" blood pressure of hypertensive patients.[104] The continued treatment was associated with a progressive drop in serum potassium concentration, an increase in carbon dioxide content, and a fall in chloride concentration. Salt and water retention, on the other hand, was observed only during the first

seven to ten days of treatment, with reversal to control levels thereafter. Although Goldman and Schroeder[105-106] recorded an immediate pressor effect after the intravenous injection of desoxycorticosterone acetate, we were unable to reproduce this action using the glucoside. In our clinical studies the fact that the pressor response occurred in a matter of days rather than of hours was testimony against a direct humoral mechanism.

At this point it might be appropriate to tell the story of a patient with documented essential hypertension who subsequently developed hypoadrenalism.[107] After it was established that he had Addison's disease, this man showed a persistent elevation of blood pressure while under treatment with desoxycorticosterone for a matter of years. Thereafter, replacement therapy with salt alone, even though the patient was maintained in water and electrolyte balance, resulted in a drop in blood pressure to normal limits. One could not help but conclude that the adrenal cortex or appropriate steroid substitution therapy was important for the development or maintenance of this man's essential hypertension.

As in the animal studies, *sodium metabolism* also enters the human story. The effect of rigid sodium chloride restriction in hypertensive vascular disease has been reviewed elsewhere.[108] In our opinion there is convincing evidence that the disorder is associated with a disturbance of salt and water metabolism, and that some modification of the "resting" blood pressure (of still doubtful therapeutic application) may result from extremes of sodium withdrawal or supplementation. It is claimed that serum sodium-to-chloride ratios are elevated in proportion to the height of the diastolic pressure in hypertensives.[109] Furthermore, despite an otherwise constant regimen, sodium restriction is generally followed by immediate significant weight loss and increased urine output in control subjects which are not evident in hypertensive patients.[110] And lastly, in our clinic, Dr. Kermit Pines has noted that treatment with thiocyanates increases the excretion of sodium in some cases; perhaps its occasional depressor action operates through the same channels as salt restriction. These observations are consistent with, but certainly not proof of the view that the adrenal cortex may be implicated. Of perhaps greater pertinence is the fact that rigid restriction of sodium chloride masks the pressor response of hypertensives to desoxycorticosterone.[111, 112]

Preliminary trials with *other adrenal steroid preparations* have been undertaken with the view that depression of existing adrenal cortical function or counteraction of some desoxycorticosterone-like pressor hormone might alter the blood pressure. Although adrenal cortical extracts exerted no immediate blood pressure effects,[106] we were able to demonstrate a small decrease in "resting" values in three of four uncomplicated hypertensive subjects following the continued administration of such an extract for one month.[113] The changes in arterial tension could not be ascribed to alterations in serum volume, fluid or electrolytes, or apparent change in cardiac action. Furthermore, the simultaneous use of adrenal cortical extract appeared to block the pressor effect of desoxycorticosterone acetate.[114] Finally, and all of these studies were carried out in association with Dr. Pines and others, opportunity was given us to employ *cortisone* in the acetate form prepared synthetically (Merck).[115] Administered in doses of 80 mgs. daily, small but definite decreases in "resting" blood pressures have now been recorded in four hypertensive patients. The decline usually occurred immediately after the discontinuance of therapy in these short-term studies. In another hypertensive patient, treated for a month with 200 mgs. of cortisone, a preliminary rise in arterial tension was followed by a more pronounced and sustained fall. In contrast, and similar to Guadino's adrenalectomized animals,[17] the blood pressure rose in a patient with Addison's disease more than would be expected on the basis of salt and water retention alone. This suggests that this steroid requires the presence of an intact adrenal for its depressor action and may be pressor in the absence of the adrenals. Cortisone, in our experience, exerts little effect on the blood pressure of normotensive man.

We have confirmed the report of Hench and his associates[116a] that *adrenocorticotropic hormone* (Armour) may raise the blood pressure of non-hypertensive patients. In addition, a marked increase in arterial tension and signs and symptoms of hypertensive encephalopathy followed its use in one of several hypertensives.[116b] Dosage and plasma volume changes played little part in this effect and it was not due to an increase in circulating epinephrine or nor-epinephrine. Cardiac output changes occurred but were variable. Further hemodynamic study of this drug is needed. At any rate, the adrenocorticotropic hormone—known to produce adrenal cortical hypertrophy—does not lower the blood pressure.

A 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*,[117-120] *denervation or subtotal bilateral adrenalectomy*.[121-126] It would be of interest to repeat these inconclusive studies in light of modern concepts of adequate baselines and consideration of psychotherapeutic factors in evaluating results. Dramatic effects following *complete bilateral adrenalectomy*, in a woman with severe hypertension and diabetes, have recently been reported by Green and his associates.[127] The final results of this and comparable studies must be awaited with interest.

Can hypertension be maintained or can it appear in man in the absence of intact adrenals? Apparently the answer is yes. We have repeatedly observed the persistence of an elevated blood pressure in some hypertensive patients who developed chromophobe adenomata of the pituitary with laboratory evidence of secondary hypoadrenalism. Loeb[96] has commented on the Addisonian subject whose blood pressure rose to 160/100 when salt was given in doses of 15 gms. daily without any cortical hormone; at autopsy this patient was found to have marked renal arteriolosclerosis and both adrenal glands were replaced by tuberculous masses. In addition, there is a case report including pathological findings of another individual with Addison's disease, hypertension becoming apparent even in crisis in association with bilateral cortical infarction of the kidneys.[128] Furthermore, toxemia of pregnancy and hypertension have developed in women with Addison's disease, the blood pressure elevation continuing even after the withdrawal of steroid therapy.[129] The mechanism of these forms of hypertension would seem to exclude a primary role of the adrenal gland, but these observations do not apply necessarily to the situation in essential hypertension.

Even though the behavior or reactivity to certain steroids is apparently different, the final question may be asked: *is there any evidence of adrenocortical dysfunction* in hypertensive vascular disease? Increased sensitivity of hypertensives to small doses of methacholine has been reported,[130] a situation encountered also in Addison's disease.[131] A small decrease in the excretion of urinary 17-ketosteroids has been noted by some observers.[88, 109] Fisher and Hewer[83] have recorded an increased adrenal content of sudanophil and anisotropic lipids. Dobriner's group[132] isolated a steroid, found in the urine of some hypertensives, but only rarely in other conditions.

On the other hand, determinations of the formaldehydogenic steroid content of hypertensive urine have been within the normal range.[133, 134] and Tobian and Joseph[134] have disclosed no differences in plasma corticoids. These latter workers reported a slightly lower fasting blood eosinophil concentration, and in this connection the few observations of Laragh and Almy[135] should be mentioned—an exaggerated drop in circulating eosinophils following epinephrine or insulin injection in hypertensive subjects.

At the present time, therefore, evidence of adrenal dysfunction in essential hypertension remains to be established; but then, it is possible that blood pressure regulation, perhaps in some way concerned with salt and water metabolism, represents a fairly discrete function independent of other known actions of the adrenal cortex.

Comment

A conspicuous feature of this review is the large number of references that have already accumulated which bear on an adrenal cortical relationship in hypertensive states. It is equally conspicuous that the adrenal seems to be connected in some fashion with many forms of experimental hypertension as well as the various approaches being made in different etiological directions. It is most conspicuous, however, that we remain completely in the dark as far as possible mechanisms are concerned.

The weight of evidence would indicate that the adrenal cortex and the sodium ion are definitely related in some way to the regulation of blood pressure and that a possible relationship to essential hypertension cannot as yet be excluded. Whether primary or secondary mechanisms are involved remains completely obscure, but no data have been presented thus far which establish the adrenal cortex as playing a primary causative role in hypertensive disease in man. In fact, the delays and lags in steroidal response are good testimony pointing toward complex mediation as opposed to some primary humoral action.

Is the adrenal merely the "guardian of the glomerular filtrate?"[83] Should attention be paid to Heinbecker's speculation[136] referring to a humoral mechanism operating through the hypothalamic nuclei and the neurohypophysis, or to Selye's "diseases of adaptation?"[66] Do the steroids achieve their effects through modification of the pituitary release of adrenocorticotropic hormone?[137] Do products of the adrenal

serve to alter the reactivity of vessels or the sensitivity of smooth muscle to other pressor and depressor agents?[12] Is it remotely conceivable that an excess of a pressor hormone or a deficiency of a depressor hormone exists in the hypertensive state, that the adrenal cortex may possess a homeostatic group of substances concerned with blood pressure regulation?[113, 138] There is at present no definitive answer to these questions.

We really know very little about the peripheral action of the steroid hormones. The problem would be greatly simplified if there were readily-available methods for measuring desoxycorticosterone-like substances in the circulation. The long-range therapeutic effectiveness of complete ablation of the adrenals remains to be determined. Only through such information can the answers to these and other questions be provided.

It is doubtful that the solution to the problem of hypertensive vascular disease lies within the adrenal. On the other hand, one should hesitate to discard this possibility as completely unprofitable, for it is quite conceivable that an understanding of adrenal mechanisms may cast light on some fundamental mechanisms of hypertensive disorders. Meanwhile, to quote Dr. Joseph Jailer, the adrenal cortex may be the "stockpile of the steroids," but it remains to be seen whether these structures represent the "seat of the soul."

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