THE ENDOCRINE ASPECTS OF HYPERTENSION

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It is generally accepted that an increase in blood pressure is merely a symptom and not a disease. The use of the diagnostic term, essential hypertension, is simply a compromise with our ignorance of the etiology of the condition, the outstanding symptom being used for its designation.

A number of clinical conditions have been shown to be associated with an increased intravascular tension. One group of cases of hypertension owe their genesis to primary parenchymatous, nonsuppurative renal changes, the group commonly designated as Bright's disease. The exact manner in which hypertension develops from renal change is still a matter of debate. Recent researches by Goldblatt[1] would suggest that some interference with renal circulation produces a pressor substance which circulates in the blood stream and produces directly a contraction of the arterial musculature. Amyloid disease of the kidneys and suppurative diseases such as pyelonephritis, even apparently unilateral, may result in a marked increase in the blood pressure. The renal degeneration associated with the toxemia of late pregnancy may result in sudden and marked elevation of blood pressure. Hypertension may also be found in congenital polycystic disease and it often accompanies obstructions to the outflow of urine in such conditions as hypertrophy of the prostate gland. In these latter mechanical conditions, the onset of increased pressure may be sudden and, on relief of obstruction, it may subside as quickly as it occurred.

In the hypertension due to cardiovascular conditions, the increased pressure can apparently be explained on a purely mechanical basis. Here it represents an effort on the part of the organism to preserve circulation, especially cerebral circulation, under the pressure of circumstances which tend to lower it dangerously. In this group, the systolic blood pressure usually shows the elevation, the diastolic frequently being below normal. Thus an increased systolic pressure is common in aortic insufficiency, coarctation of the aorta, arteriovenous aneurism, and heart block.

Elevated blood pressure associated with increased intracranial pressure is well known and is seen in any space-filling lesion of the cranium as well as in asphyxia and in certain psychic states.

The increased amount of study and interest which, in recent years, has been given endocrinology has revealed a number of instances where obvious endocrinological dysfunction has been found to be associated with disturbances of blood pressure, and it seems to be a well-established fact that the physical status of the blood pressure can be varied

greatly by the endocrine mechanism. The purpose of this paper is to review briefly the evidence which has been advanced in regard to this relationship. It must be acknowledged that the data to be presented are fragmentary and proceed to no definite conclusions. Apart from the groups which have been cited, there still remains a great number of cases of so-called idiopathic hypertension in which no obvious etiological factor can be demonstrated and in which the genesis of the symptom is still a matter of controversy and conjecture. The question as to whether these have some, so far unrecognized, endocrine basis must remain unanswered at present.

The time-honored theory of the etiology of essential hypertension is that of an increased peripheral resistance attendant upon vasoconstriction, chiefly of the arterioles, thus presenting some degree of obstruction in the path of the circulation of the blood. Vasoconstriction has been shown to be dependent upon the integrity of certain fibers of the sympathetic nervous system, the stimulation proceeding from a center in the medulla. These vasoconstrictor nerves exert a tonic action on the vessels; this may increase or decrease under various circumstances and is abolished by section of the nerves. In addition, it is stated that there are vasodilator nerves which also are of sympathetic origin according to some authorities, while others state that these are of parasympathetic origin. Less is known of these and they have not as yet acquired any practical importance. Stimulation of the sympathetic nerves results in the production of sympathin in the muscle cells. This material has an action similar to adrenalin; it is absorbed into the blood stream and may produce effects in other parts of the body, its effect on the vascular musculature being to produce powerful tonic contractions. Parasympathetic stimulation, on the other hand, has been shown to produce acetylcholine or parasympathin which is depressant in its action. It has not been shown, however, that the blood, spinal fluid, or urine of human beings with hypertension invariably contains a pressor substance. Recent work by Goldblatt[1] and Prinzmetal and Wilson[2] minimizes vasomotor activity as a factor in hypertension and ascribes the increased peripheral resistance to an intrinsic vascular hypertonus, presumably of humoral origin from the kidney.

Concerning centers above the medulla which may exert a control over this mechanism, Sir Humphrey Rolleston[3] suggests that the nuclei of the posterior part of the hypothalamus control the sympathetic division of the autonomic nervous system, whereas those in the anterior portion are the seat of the parasympathetics. Lesions of the hypothalamus are known to be associated with polyuria, glycosuria, and probably obesity, but no evidence has apparently been produced to show that they have

any effect on blood pressure. Physiologically, at least, this regulation of circulation by the vasomotor nerves is supplemented by the action of substances circulating in the blood, the most certain instance of this being when the internal secretion of the adrenal gland is released in circumstances of general vasoconstriction. The influence of the nerves and the chemical substance exercise a joint control over vascular tone.

The control of the nervous mechanism of circulation by the hypothalamus is very closely allied to the function of the adjoining pituitary gland. Heretofore greater etiologic significance in hypertension has been ascribed to pituitary disturbances than to the effect of these disturbances on the hypothalamus. Recently, however, the conception seems to have changed somewhat. Now it is considered that changes in the pituitary may influence the nuclei of the hypothalamus either directly or mechanically through pressure or the effect of irritation or secondarily through transfer of pituitary secretion by the hypo-physio-portal system of vessels in the case of secretion of the anterior lobe, or through the tissue spaces of the pars nervosa to enter the third ventricle through its wall in the case of the secretion of the pars intermedia. In addition to the influence of the pituitary secretions upon the hypothalamic vegetative centers, there seems good evidence that the centers themselves exert an influence upon the pituitary as well as other endocrine glands, the so-called central neuro-humoral mechanism of Roussy and Mosinger[4].

Anterior lobe of the pituitary gland: In considering the anterior lobe of the pituitary from the physiological point of view, it has not been suggested, so far as the writer is aware, that any vasopressor hormone exists, although enough function has been ascribed to that particular organ to give it an undisputed title as the body's busiest bit of tissue. Yet, only thirty years ago such eminent physiologists as Schäfer and Herring[5] referred to the anterior lobe of the pituitary as having no physiological effect and in the same year Salmon[6] suggested that the secretion of the pituitary gland caused sleep. It seems possible that increased pressure might be expected from excessive administration of the adrenotropic hormone.

Posterior lobe of the pituitary gland: It was shown as early as 1895 by Oliver and Schäfer[7] that the intravenous injection of an aqueous emulsion of whole pituitary produced a rise of blood pressure, arterial constriction, and increased force of heart beat, and in 1898 Howell[8] proved this pressor effect to be due to the secretion of the posterior lobe. Schäfer and Swale Vincent[9] confirmed Howell's results but noticed that a second injection produced a fall in blood pressure. These workers then described a depressor substance in the posterior lobe which differed from the pressor substance in that it was soluble in absolute alcohol and

ether. Generally, it is assumed that the intramuscular injection of pituitrin into the human subject is followed by an increase in blood pressure, but numerous investigators have observed that there are no constant or striking results. In 1928 Kamm[10] and others isolated from the posterior lobe two fractions, pitressin, the pressor fraction and oxytocin which has a specific action on unstriated muscle tissue. In addition to the pressor effect, the pitressin fraction also exerts a diuretic-antidiuretic effect, and it has been suggested that an excess of antidiuretic hormone may be responsible for water retention, edema, and increased blood pressure associated with diminished urinary excretion, instances of which have been recognized clinically.

Cushing's[11] idea is, or was in 1933, that it is inconceivable that the neural core of the posterior lobe could independently elaborate a hormone. He felt that it must arise from the epithelial investment and that the active principal must come from the infiltrating basophilic cells of the investing pars intermedia which become transformed into hyaline bodies and migrate in the loose neural spaces of the posterior lobe.

Hyperpituitarism: Certain clinical conditions in which hypertension is associated with definite pituitary disease or dysfunction are of considerable interest. Acromegaly, which is usually due to an adenoma of the acidophilic cells and is, therefore, to be regarded as hyperpituitarism, frequently is accompanied by hypertension although this is exceedingly variable. Increase in intracranial pressure must, of course, be thought of as a mechanical factor in the case of a tumor of any size. Cushing's syndrome or pituitary basophilism was originally associated by Cushing with the presence of a basophilic adenoma, but later it was shown to be associated with basophilic hyperplasia without a demonstrable adenoma. Hypertension is a constant finding in this condition and may be of the malignant type. A similar clinical picture has been recorded from carcinoma, adenoma, and hyperplasia of the adrenal cortex, and in some instances somewhat similar clinical manifestations have been associated with malignant tumors of the thymus and possibly arrhenoblastomas of the ovary. Whether the basis be adrenal or pituitary, these patients present the common findings of a marked elevation of both systolic and diastolic pressures along with the painful obesity, hypertrichosis, diabetes, muscular weakness, and skeletal and sexual changes which are characteristic. Cushing ascribes this to an excessive secretion of vasopressin by the basophilic cells of the pars intermedia which have invaded the pars nervosa. Kraus[12] and Berblinger[13] described an increase in the number of basophilic cells in all cases of persistent hypertension and Russell, Evans, and Crooke[14] found a close correlation between basophilic adenoma, obesity, and

hypertension without basophilic invasion of the posterior hypophysis. Fishberg[15] points out that the symptoms of Cushing's syndrome are rare in essential hypertension and refuses to accept any suggestion that essential hypertension is of pituitary origin.

Hypopituitarism: The negative evidence derived from the study of cases of hypopituitarism is of some interest. In pituitary infantilism or dwarfism, low blood pressure is the common finding as might probably be expected from the infantile state of these patients. In Simmond's disease, which is generally regarded as being due to primary destruction of the anterior lobe or to the loss of the anterior lobe and adjacent tubercinereum, low blood pressure is the invariable rule and this is associated with the extreme wasting, low metabolism, muscular weakness, and precocious senility which these patients present. In Fröhlich's syndrome there appears to be primarily a deficiency of the gonadotropic hormone. No characteristic changes in the blood pressure are found.

In summary, there seems no reasonable evidence that the pituitary is associated with essential hypertension as it exists clinically. Hoyle[16] in 1933 found no excess of pituitrin in the cerebrospinal fluid in 189 cases of essential hypertension which he examined. However, in certain pathological states of hyperpituitarism, notably Cushing's syndrome, there appears to be a hypertension indistinguishable in its essential features from idiopathic essential hypertension, and in corresponding states characterized by lack of pituitary substance, notably Simmond's disease, low blood pressure is the rule.

Thyroid: There appears to be an amazing variation of opinion regarding the effect of hyperthyroidism on the arterial blood pressure. The usual opinion is that there is a moderate rise in systolic blood presture with a diastolic pressure either normal or more commonly below normal so that increased pulse pressure results. Goodall and Rogers[17] in 1920 expressed the opinion that there were three phases of hyperthyroidism as far as the question of blood pressure is concerned: first, a short, primary hypertension due to the vasoconstriction caused by an output of adrenalin following emotion; second, the stage of low blood pressure lasting for years due to dilatation caused by thyroid secretion; third, a late stage of hypertension due to secondary changes in the cardiovascular system and reduction in thyroid activity. These observers regarded the systolic pressure as usually less than normal, the pulse pressure smaller, and the diurnal variation exaggerated. Alvarez and Zimmermann[18] found the systolic pressure raised in hyper- and hypothyroidism and believed that it was due to the primary disturbances which damage the thyroid rather than to the quantity of thyroxin.

Essential hypertension has at times been regarded as the sequel of

thyrotoxicosis, and Fishberg[15] believes that it is more common in middle-aged patients who suffer or have suffered from toxic goiter than in the remainder of the population, but he feels that this is due more to a constitutional proneness to hypertension than to the thyrotoxicosis directly. Parkinson and Hoyle[19] in 1934 described thyrotoxic hypertension as being common in women over 40 years of age, frequently when a small adenomatous goiter was present, usually associated with a low diastolic pressure, and often complicated by paroxysmal auricular fibrillation; certainly, numerous cases which would fit this description have been seen clinically.

Adrenal gland: The presence of a pressor hormone in the adrenal medulla was demonstrated in 1894 by Oliver and Schäfer[7] and the presence of adrenalin in the adrenal veins was established. It has been regarded that constant secretion of adrenalin has been responsible for a vascular tonus which has had to do with the maintenance of normal pressure. Cannon[20] in 1914 propounded the view of intermittent or emergency function of the adrenal medulla in response to various types of stimulation but he has since admitted that there may well be a continuous secretion as well. Stewart and Rogoff[21] have minimized the physiological effects of the adrenal, even denying any pressor action, rather regarding it as of no importance in the maintenance of normal blood pressure.

The adrenal cortex has been the subject of much theorizing but little is definitely known regarding its function. Its association and interrelationship with other glands, particularly the pituitary, thyroid, and gonads, has been apparent. Swingle and Pfiffner[22] believe that the cortex maintains the volume of the circulating blood and that, in adrenalectomized animals, death is due to shock. Reduction of sodium, and to a lesser extent of chloride in the blood, has been regularly noticed in cortical deficiency and may play some part in the hypotension noted in adrenal failure. In Addison's disease the initial lesion is in the medulla but the syndrome is no longer regarded as due solely to a lack of adrenalin; opinion now has swung around to the idea that cortical damage is chiefly responsible for the symptoms. This change of opinion is due partially to the knowledge that physiologically the cortex is essential for life, whereas the medulla can be destroyed without causing death. The benefits derived clinically from the administration of cortical extracts supports the belief that Addison's disease is hypocortical adrenalism. However, the cortical extract, despite its clinical benefit and production of increase in muscular power, does not raise the blood pressure. It has been shown that, in adrenal cortical deficiency, there is a scarcity of basophil cells in the anterior lobe of the pituitary and

Crooke and Russell[14] believe that the hypotension in Addison's disease is primarily due to cortical deficiency and directly due to the diminution of basophil cells. At any rate, Addison's disease is characterized by a persistent hypotension together with constitutional weakness, gastro-intestinal symptoms, and pigmentation.

Tumors of the adrenal medulla—those composed of chromaffin tissue, adrenalin-secreting tissue, the so-called paragangliomas, or pheochromocytomas—have been shown to be associated with paroxysmal elevations of systolic pressure, the diastolic pressure usually remaining normal. The absence of a raised diastolic pressure differentiates this from the considerable fluctuations which may occur in essential hypertension. In this connection one must remember the crises of paroxysmal hypertension which may accompany lead poisoning with colic, eclampsia, or in irritation of the fifth cranial nerve, the vagus, and the splanchnic. The intermittent hypertension has been explained on a basis of a pathological equivalent of Cannon's emergency hypothesis. A transient hyperadrenalinemia has been the usual explanation although pressure exerted by the tumor on the abdominal sympathetics has been suggested. Crises of hypertension may, of course, occur in the ordinary patient with permanent high blood pressure and it is possible that these paroxysmal attacks are merely the forerunner of a later permanent condition.

Adrenal-cortical tumors have frequently been associated with a persistent arterial hypertension as well as with hirsutism, obesity, amenorrhea in women, and diabetes, the so-called diabetes of bearded women. It is associated also with hyperplasia of the adrenal cortex and in the cases reported from the Mayo Clinic,[23] with proliferation, adenoma or carcinoma of the adrenal cortex. The relationship of this adrenal-cortical syndrome to Cushing's syndrome discussed above is not clear. By some observers the two conditions are held to be identical, whereas others suggest that the absence of genital hypertrophy in Cushing's syndrome differentiates it. Removal of the adrenal tumor has been shown to relieve the condition. As stated previously, Cushing believes that both the hyperplasia of the adrenal cortex and the arterial hypertension may be due to an increase of basophil cells in the pituitary, either hyperplasia or adenoma. Cushing's argument in regard to this question seems somewhat less valid in view of the finding of pituitary basophilic adenoma in from 7 to 8 per cent of routine autopsies at the Mayo Clinic, many of such patients having had absolutely no symptoms during life. Whatever the relationship between these two conditions, there are certainly clinical instances of persistent hypertension associated with primary cortical tumor of the adrenal.

Ovary: The frequent association of hypertension with post-meno-

pausal symptoms suggests the possibility that ovarian atrophy may have some etiological significance. Certainly, the proportion of patients with hypertension at the time of the menopause seems greater than one would expect if there were no such causal relationship. It may be related to the obesity characteristic of the period, or in some way, with the apparent irritability of the vasomotor system. The hypertension has been little affected by sufficient estrin to relieve all symptoms of the menopause. It has been shown that so-called castration cells appear in the anterior lobe of the pituitary following the menopause; whether these are acidophilic or basophilic seems controversial, but if they are the latter, following the argument of Cushing, one might ascribe menopausal hypertension to a pituitary basis. Mention might be made of the rare masculinizing tumors of the ovaries, the so-called arrhenoblastomas, which produce a clinical picture strongly suggestive of adrenal-cortical syndrome but apparently without hypertension.

It is interesting to note that in the experimental hypertension produced by partial occlusion of the renal arteries, as reported by Goldblatt[1], it has been demonstrated by Page[24] that total hypophysectomy does not prevent the development of such ischemic hypertension although it does reduce the blood pressure in animals suffering from this condition. This is suggestive, at least, that in this type of hypertension, the pituitary is not necessary as an etiological factor. However, it has been shown that even the persistence of small amounts of the adrenal cortex or the use of adequate supportive and substitution therapy in cases of bilateral adrenalectomized animals is necessary before hypertension can be produced by renal ischemia. This suggests that the adrenal-cortical hormone plays a part in conjunction with the hypothetical substance produced in the kidney in the pathogenesis of this type of hypertension.

In summary, therefore, it seems apparent that the endocrine mechanism plays a part in the physiological control of blood pressure and that certain obvious states of endocrine dysfunction are related to variations of pressure of pathological degree.

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