THE RELATIONSHIP OF THE ADRENAL GLANDS TO DISEASES OF ADAPTATION

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Four principal lines of evidence support an interest in the hypothesis that hormones of the adrenal cortex play a primary role in the aetiology of renal-cardiovascular diseases and other diseases of growth and metabolism. First, corticotrophin, cortisone, cortisol, and certain synthetic derivatives of cortisol can suppress the symptoms of a large number of human diseases, most of which are classified as inflammatory diseases. The growth of some cancers can be retarded by these hormones. There is no satisfactory evidence that the hormones cure these diseases or that these diseases represent any form of adrenocortical insufficiency. Second, removal of the adrenal glands may be followed by amelioration of diabetes, hypertension, and certain cancers in experimental animals and in patients. Third, overdosing of experimental animals with one or another corticoid can cause a great deal of interesting pathology, including steroid diabetes, hypertension, arteriosclerosis, gastrointestinal ulcers, nephritis, nephrosclerosis, periarteritis nodosa, and so on. Resistance to infectious agents is dramatically decreased in animals and patients with severe hypercorticalism. Fourth, as discovered by *Skelton* (1959), enucleation of the adrenal glands of the sensitized rat (unilateral nephrectomy, high sodium load) is followed by hypertension and renal and cardiovascular lesions. These lines of evidence can be interpreted as supporting the *Selye* (1956) concept of the role of the adrenal cortices in the aetiology of the "adaptation disease" when linked with the information that many stressful situations cause at least a temporary increase in the secretory activity of the adrenal cortices.

The first weakness of the Selye concept is that most of the supporting evidence is derived from conditions which do not occur naturally. The second weakness is the absence of any convincing experimental evidence that naturally occurring stressors can cause "adaptation diseases" under naturally
occurring conditions. Even if such evidence were available, it would remain to be shown that the adrenal glands must be present in order for the disease to be produced.

Some of the artificial steroids have greater pathogenic potency than do naturally occurring hormones. Deoxycorticosterone, 2α-methyl-9α-chlorocortisol, and other sodium retaining steroids are damaging, especially if given to an animal (usually the rat) whose renal system is crippled by uninephrectomy and which is receiving an abnormally high load of sodium chloride. These animals may develop severe hypertension and sclerosis of vessels in the heart and kidney. Large doses of these steroids can cause some hypertension and some pathology when given for several weeks to normal rats on a commercial diet which contains approximately 1 per cent salt. If the sodium intake is reduced to the smallest amount of salt needed by the animal, hypertension and renal-cardiovascular pathology no longer occur. Cortisone, corticosterone and whole adrenal cortex extract are each pathogenic when given in large doses to uninephrectomized salt-loaded rats but the pattern and nature of pathology changes somewhat from one steroid to another. Very large doses of corticotrophin cause some hypertension with renal-cardiovascular pathology in uninephrectomized, salt-loaded rats; the lesions are similar to those caused by overdosing similar rats with cortisone. We cannot confirm the claim that physiological doses of corticotrophin cause renal-cardiovascular damage in adult rats used for breeding.

When uninephrectomized salt-loaded rats are exposed to cold for several weeks, they develop nephrosclerosis and hypertensive vascular disease. Some animals develop cerebral haemorrhages. These changes are associated with a voluntary increase in the intake of the high salt diet. When the intake of diet is restricted to that normally eaten at room temperature and the animal is allowed to drink a solution of sucrose to meet its increased need for energy, there is only a small amount of damage to the renal-cardiovascular systems. When uninephrectomized rats are tube-fed amounts of the high salt diet comparable to those eaten ad libitum by cold-exposed rats, the extent of damage at room temperature is almost as great as that occurring in the cold-exposed rats.

No other stressor has been shown to cause nephrosclerosis and hypertensive vascular disease in the uninephrectomized salt-loaded animal (Crane & Ingle 1958) or in the normal animal. There is a small rise in blood pressure and some increase in inflammatory changes in kidneys and hearts of uninephrectomized salt-loaded rats subjected to laparotomy once per week or a burn per week or limb ligation shock once per week for 8 weeks. We have exposed aging rats to severe neuromuscular stress twice each week for 8 weeks. These unoperated animals were maintained on a commercial diet without added salt. Some of these animals have spontaneously occurring hypertension, renal-cardiovascular
diseases, and other inflammatory and degenerative lesions. The incidence and severity of the damage was not increased above that of control animals of similar age.

We have confirmed Meneely (1953) by showing that high dietary loads of sodium chloride can cause severe hypertension and renal-cardiovascular damage in uninephrectomized rats and somewhat milder changes in intact rats. The pathology found at the end of an experimental period of two months is much less severe in the untreated adrenalectomized salt-loaded rat than in similar rats either having the adrenal glands intact or adrenalectomized and given adrenal cortex extract. The amelioration of damage is not complete. Adrenally insufficient rats show some positive correlation between salt-load and blood pressure and we have now shown that full-blown hypertensive vascular disease can be caused by salt-loading in the absence of adrenal cortical hormones, but the onset of hypertension and renal-cardiovascular pathology is retarded; it now requires 6 months to a year to cause changes that can be brought about within 8 weeks in the presence of cortical hormones.

By what means does removal of adrenal cortical hormones retard the pathogenic effects of salt-loading? It seems improbable that salt-loading causes an increase in the secretion of adrenal steroids. Most of the available evidence indicates that a high salt load causes a significant decrease in the secretion of aldosterone, the most potent known sodium-retaining compound among the natural steroids. But salt-loading does not suppress the secretion of sodium-retaining steroids to zero and the basal secretion of the adrenal cortices may have some obligatory sodium-retaining action. The untreated adrenalectomized rat drinks less water than does the nonadrenalectomized rat given a dietary load of salt. We suppose that the animal without steroid can rid itself of sodium chloride more easily than can an animal in a state of eucorticalism and that for this reason the pathogenic effects of a salt-load are less.

If a severe stress causes increased secretion of corticoids, should not hypercorticalism ensue? We do not understand why increased titer of steroid in the body fluids of the stressed individual are needed to maintain homeostasis; we do not know why hypercorticalism is not a consequence of prolonged exposure to stress. This is the way things are. When stress is severe, the animal or patient needs more corticoids in order to survive the stress. Cushing’s disease is not an outcome.

Recent and current studies in our laboratories show that both pancreatic and steroid diabetes are dramatically suppressed by a growing tumour (Walker carcinoma) in the rat. When tube-fed diabetic rats are subjected to other stressors such as the excision of skin, injection of dilute solutions of formalin and neuromuscular stress, there is moderate suppression of glycosuria. Fractures of bone in sensitized rats fail to aggravate hypertension and renal-cardiovascular damage. Repeated fractures of bone cause some sup-
pression of blood pressure in sensitized rats overdosed with cortisone but does not prevent damage to the kidney and heart; there is no aggravation of pathology by stress. The growth of the Walker carcinoma is significantly retarded by neuromuscular stress in tube-fed rats.

Suppression of some but not all symptoms of hypercorticalism by stressors may be related to the well known fact that the need of the organism for cortical hormones is greatly increased by severe stress. Our current research is guided by the hypothesis that the effect of severe stress in suppressing the symptoms of some abnormal processes may be related to the suppression of these same processes (certain tumours, glycosuria, and hypertension) by adrenalectomy.

REFERENCES