ADDISON'S DISEASE

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Addison's disease has been a well known entity since its original description by Thomas Addison in 1855. He hypothesized that the syndrome was the result of bilateral destruction of the adrenal glands. Indeed the currently accepted usage of the term "Addison's disease" refers to a disease process where the common denominator is adrenocortical insufficiency. The clinical features of adrenocortical insufficiency were described with remarkable accuracy by Addison in his original manuscript and have remained unchanged throughout the years, Table I.

TABLE I

CLINICAL FEATURES OF CHRONIC PRIMARY ADRENOCORTICAL INSUFFICIENCY

	Percent
Weakness and fatigue	100
Weight loss	100
Anorexia	100
Hyperpigmentation	92
Hypotension	88
Gastrointestinal symptoms	56
Salt craving	19
Postural symptoms	12

from Baxter and Tyrrell

TERMINOLOGY

The adrenal cortex synthesizes over 50 different steroids. Many of these are hormones which have specific target tissues. As early as 1937 Hans Selye separated the adrenal hormones into two main classes: glucocorticoids and mineralocorticoids. It now is well appreciated that various sex hormones are also produced by the adrenal cortex. Definitions of some of the common terms used in the discussion of Addison's disease are given below.

Hormone--an organic compound which is secreted by one type of tissue that has a specific physiologic effect in another tissue (target tissue).

Target Tissue--a tissue which has a specific physiologic response to a hormone secreted elsewhere. I prefer to exclude a "biochemical response" to a hormone from this definition since many biochemical events may not be of physiological importance. An example of the latter would be the rise in cAMP in the thin ascending limb of Henle in response to antidiuretic hormone, but ADH neither stimulates salt nor water transport across this nephron segment. Thus the thin ascending limb of Henle does not fit the definition of "target tissue" for ADH.

Adrenocorticoid--a collective term used to define those steroid hormones which are produced by the adrenal cortex. The two main classes of adrenocorticoids are the glucocorticoids and mineralocorticoids.

Glucocorticoid--it now is quite clear that glucocorticoids have additional effects not related to glucose metabolism and, therefore, the definition should be broadened to those adrenocorticoids which mediate their effects through glucocorticoid receptors.

Mineralocorticoid--a group of adrenocorticoids which mediate their physiologic response through binding and subsequent physiologic response to mineralocorticoid receptors. These effects are largely expressed as effects on ion transport.

Receptor--a protein which binds a ligand (specific molecule) at a high enough affinity that at its physiologic concentrations enough receptors are occupied to affect a biological response.

Primary Adrenocortical Insufficiency--clinical disease which is the result of bilateral ablation of the adrenal glands.

Secondary Adrenocortical Insufficiency--disease state which is the result of deficient messages to the adrenal.

ETIOLOGY

The development of symptomatic Addison's disease requires destruction of 90 to 95% of both adrenal cortices. In the past, tuberculosis was the most common etiology of adrenocortical insufficiency; however, presently the most common etiology is thought to be secondary to auto-

immune mechanisms, Table II. Many authorities list "idiopathic" as the most common etiology of Addison's disease, but it appears that a large percentage of Addison's disease which were thought to be "idiopathic" are most likely the consequence of immune mechanisms.

TABLE II

ETIOLOGY OF PRIMARY ADRENOCORTICAL INSUFFICIENCY

1. Idiopathic/autoimmune (~80%)
2. Tuberculosis (~20%)
3. Miscellaneous (~1%)
   a. Vascular
      (1) Hemorrhage: sepsis, anticoagulants, coagulopathy, trauma, surgery, pregnancy, neonatal
      (2) Infarction: thrombosis, embolism, arteritis
   b. Fungal infection: histoplasmosis, coccidiomycosis, blastomycosis, moniliasis, torulosis
   c. Metastatic
   d. Lymphoma
   e. Amyloidosis
   f. Sarcoidosis
   g. Hemochromatosis
   h. Irradiation
   i. Surgery: bilateral adrenalectomy
   j. Enzyme inhibitors: metyrapone, aminoglutethimide, trilostane
   k. Cytotoxic agents: o,p'-DDD
   l. Congenital: adrenal hyperplasia, hypoplasia, familial glucocorticoid deficiency

Schmidt initially described the association of Addison's disease and chronic lymphocytic thyroiditis in two patients. Since this description, numerous reports have appeared where an association of Addison's disease with a number of other conditions have been documented. Most often these clinical disorders have been with various

endocrine abnormalities (polyglandular failure) but other non-endocrine associations have also been reported. Figure 1 schematically calls attention to the high frequency of endocrine disorders associated with idiopathic adrenocortical insufficiency. However, of note is that primary cases of ovarian failure, hypothyroidism, diabetes mellitus and hypoparathyroidism are not associated with a similarly high incidence of Addison's disease. Other non-endocrine associations with Addison's disease include increased frequency of vitiligo and pernicious anemia.

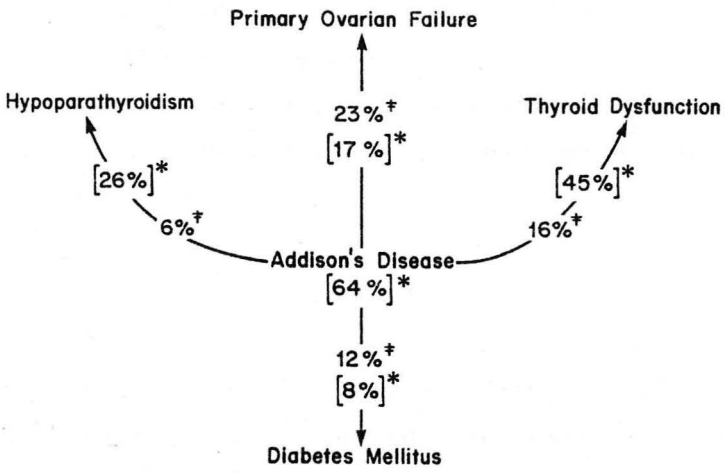

FIGURE 1. Polyendocrine† and circulating antibody* association in idiopathic adrenocortical insufficiency.

Figure 1 also summarizes the high incidence of circulating antibodies that Addisonian patients have against various other endocrine glands. This increased incidence of antibodies often occurs in absence of clinical symptoms. It, therefore, is prudent to follow closely all patients with "idiopathic" Addison's disease for development of other endocrinopathies. It is not clear why patients with autoantibodies to adrenal cortex have such a high probability of making antibodies to other endocrine glands. It has been postulated that perhaps these glands have some common antigen but this view is not likely since patients with autoantibodies to other endocrine glands have a low chance of developing antibodies to the adrenal cortex. An outstanding synthesis of probable autoimmune pathogenic mechanism of polyglandular failure syndrome is contained in the November, 1979 SWMS Endocrine Grand Rounds protocol prepared by Mark Leshin.

DIAGNOSIS

The diagnosis of Addison's disease is straightforward once the index of suspicion has been raised. Unfortunately many of the symptoms of adrenocorticoid insufficiency, Table I, are non-specific enough that the possibility of Addison's disease often is overlooked in the differential diagnosis.

There are "routine" laboratory findings which also are suggestive of Addison's disease--hyponatremia, hyperkalemia, mild metabolic acidosis and hypoglycemia. The pathophysiology and incidence of these will be described in detail later but if these combined laboratory findings

occur in association with the clinical manifestations as outlined in Table I then it is imperative that the diagnosis of adrenocortical insufficiency is ruled out.

Plasma cortisol levels can be measured by the PMH clinical pathology laboratories. They require that 10 cc of blood is drawn in a serum separation tube (tiger top). PMH uses radioimmunoassay techniques with normal levels being 10 to 25 µg/dl. However, there exists significant variation in this value which is related to multiple factors (values are higher in a.m., trauma, surgery, acute illness). Thus to rule out Addison's disease one should determine the response of cortisol to ACTH.

One recommended protocol would be the following:

1. Draw control 10 cc of blood in serum separation tube (SST) for cortisol

2. Start an IV of NS and give 0.25 mg cosyntropin. Cosyntropin is a synthetic ACTH. PMH pharmacy has Cortrosyn® which comes in 0.25 mg ampules and is equivalent to 25 units of ACTH. Draw second and third 10 cc SST tubes for cortisol at 30 and 60 minutes after injection of cosyntropin.

Figure 2 represents typical responses of patients with normal adrenals as compared to those with primary and secondary adrenal insufficiency.

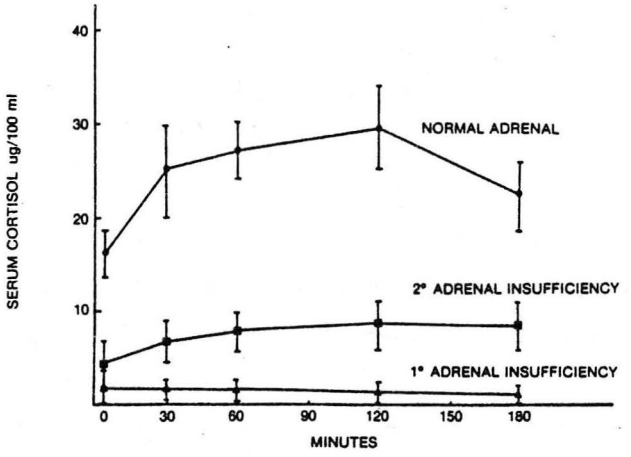

FIGURE 2. Serum cortisol response to 0.25 mg cosyntropin in nine normal individuals (normal adrenal), eight patients with hypopituitarism (secondary adrenal insufficiency), and seven patients with Addison's disease (primary adrenal insufficiency). Source: Speckart et al.

Prior to development of nonallergenic synthetic ACTH there existed two modifications of the rapid ACTH infusion test of adrenal reserve. These were to give insulin to produce hypoglycemic induced increase in ACTH secretion or to administer ADH which also stimulates ACTH release. These tests are not as easily standardized, and furthermore, they require the physician to be present. Thus these tests no longer are performed frequently since the rapid infusion of synthetic ACTH has proved to be quite accurate and easy to perform. However, the ACTH infusion test does not distinguish accurately between primary and secondary adrenocorticoid insufficiency, and therefore patients with low basal values of cortisol which respond to cosyntropin warrant further testing.

Metyrapone testing can be used to test for both primary and secondary adrenocortical insufficiency and should be the next test after

cosyntropin infusion. Metyrapone blocks cortisol synthesis by inhibiting 11 β-hydroxylase. If the hypothalamic-pituitary axis is intact then serum levels of ACTH and 11-deoxycortisol should rise. In this test metyrapone (2.0 gm <70 kg; 2.5 gm 70-90 kg and 3.0 gm >90 kg patients) is given po as a single dose at midnight. Normal response is a rise of plasma 11-deoxycortisol to levels greater than 7 μg/dl. The 11-deoxycortisol is sent to an outside PMH laboratory and requires 10 cc of blood in a large green-top tube.

Urinary values of cortisol are more cumbersome to obtain than plasma values. While 24 hr urinary-free cortisol levels are of benefit in evaluating adrenal disease under certain circumstances (PMH requires the urine to be collected without preservatives and sent down immediately after its collection) it is currently felt that plasma values give more precise evaluation of adrenal status.

PATHOPHYSIOLOGY OF SALT AND WATER ABNORMALITIES IN ADDISON'S DISEASE

The pathophysiology of salt and water metabolism can be discussed in some detail using a case presentation as the focal point.

CASE REPORT

Patient is a 46 y/o obese, previously well, white female who was admitted for treatment of deep thrombophlebitis. She was treated with bedrest and heparin anticoagulation. On the tenth day she complained of severe epigastric pain requiring narcotics. Physical examination revealed abdominal distension but with normal bowel sounds. Stool guaiac was 2+ positive. No other changes were noted. No additional diagnosis was made and she was discharged from the hospital one week later in spite of not feeling well nonspecifically. All laboratory determinations and x-rays were normal at the time of discharge.

She was readmitted ten days later with severe weakness, anorexia and nausea. BP 100/60 (previously 130/90 range) P 110. Rest of physical examination was normal except for subtle generalized pigmentation. Diagnosis of acute Addison's disease secondary to anticoagulant-induced bilateral adrenal hemorrhage was made.

Admission laboratories revealed a BUN 32 mg%, Cr 1.1 mg%, Na 120 mEq/L, K 5.9 mEq/L, CO_2 21 mEq/L. Arterial pH - 7.34. Urine electrolytes: Na 80 mEq/L, K 8 mEq/L and osmolality 645 (she had not eaten or drank water for 18 hours prior to admission). Urine pH - 5.0. Plasma cortisol was 1.0 µg% without rise in response to 25 units of ACTH administered IV.

She was treated acutely with IV Solucortef and saline. She now is asymptomatic taking maintenance cortisone acetate (37.5 mg/day) and 9 α-fluorohydrocortisone (0.1 mg/day). She is able to withstand all foods. Specifically, she can intermittently ingest diets with high K content without untoward effects.

Metabolic Acidosis

It has been appreciated for a long time that metabolic acidosis is a feature of untreated adrenocorticoid insufficiency. The issue of discussion, however, has been which group of adrenocorticoids are necessary for the maintenance of normal acid-base balance.

The role for mineralocorticoid in maintenance of acid-base balance appears established. Figure 3 defines relation between the change in plasma carbon dioxide content and the cummulative change in net acid excretion following the first five days of discontinuation or initiation of mineralocorticoid replacement therapy. Thus, in an otherwise normal human maintained on normal diet the aldosterone-dependent variation in plasma HCO_3 is roughly 5 mEg/L. Clearly these changes could be much more extreme if aldosterone deficiency occurs in a setting of increased endogenous acid production and/or under circumstances of pre-renal failure.

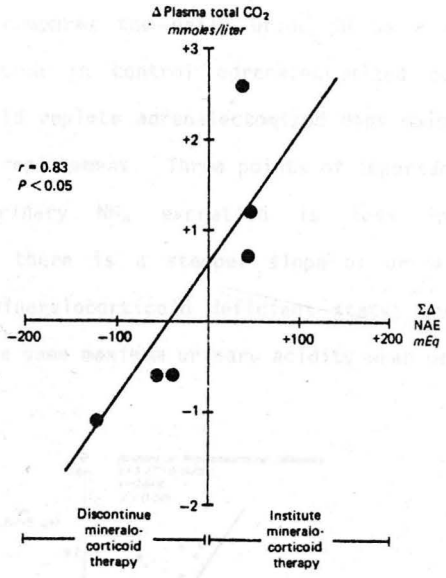

FIGURE 3. Relation between change in plasma carbon dioxide content and the cumulative change in urinary net acid excretion (ΣΔNAE, mEq) following the first 5 days of discontinuation or initiation of mineralocorticoid replacement therapy in six adrenalectomized patients without apparent intrinsic renal disease. In one patient (patient no. 3) the duration of study was only 3 days. Source: Sebastian et al.

The mechanisms by which mineralocorticoid modulates acid-base balance have not been examined in the human as well as in animals. In broad terms renal acidification defect can occur either as a consequence of decreased capacity to secrete H or as a result of decreased ability to secreate a maximal gradient for H.

Figure 4 compares the daily urine pH as a function of urinary ammonium excretion in control adrenalectomized dogs as compared to mineralocorticoid replete adrenalectomized dogs maintained on continual glucocorticoid replacement. Three points of importance evolve from this figure: 1) urinary NH_4 excretion is less in mineralocorticoid deficiency; 2) there is a steeper slope of urine pH to urinary NH_4 excretion in mineralocorticoid deficient state; and 3) each group of dogs reaches the same maximum urinary acidity when urinary NH_4 excretion is low.

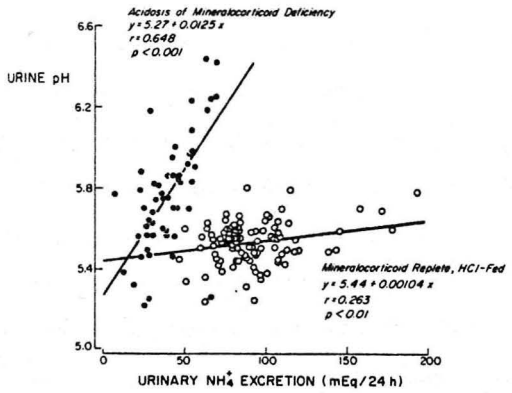

FIGURE 4. Daily urine pH as a function of daily urinary ammonium excretion in group I (acidosis of mineralocorticoid deficiency, n = 5) and group III (mineralocorticoid replete, HCl fed, n = 8) during steady-state metabolic acidosis. Source: Hulter et al.

Why urinary NH_4 excretion is diminished in mineralocorticoid deficiency has not been established, nor is there general agreement as to the qualitative significance of this observation. However, it is agreed that the associated hyperkalemia of mineralocorticoid deficiency will

diminish excretion of NH_4. However, at least in the dog, when hyperkalemia is prevented, urinary NH_4 excretion is still less than normal. There may be a direct effect of mineralocorticoid on NH_4 production but this has not been established.

However, it is evident from Figure 4 that for any given NH_4 excretion rate the urinary pH is greater in mineralocorticoid deficient states. Thus mineralocorticoid deficient states have a hydrogen secretory capacity defect. On the other hand, with decreased NH_4 excretion there does not appear to be a major gradient defect as evidenced by maximum urine acidity.

We have recently demonstrated that the medullary collecting duct (in contrast to the distal convoluted tubule or cortical collecting duct) is the site which has the highest distal capacity to secrete H (or reabsorb HCO_3). Furthermore, the recent studies of Stone et al have demonstrated that the proton secretory process is not dependent on Na and that aldosterone, by a primary Na-independent mechanism stimulates H secretion across the medullary collecting duct. These findings are consistent with those clearance studies which show that hydrogen ion secretion is reduced in the mineralocorticoid deficient dog despite total body sodium repletion. However, the degree of acidosis appears more severe during volume depleted states where limited quantities of Na are delivered to the distal tubule.

The role of glucocorticoids in the maintenance of normal acid-base balance is more controversial. The problem in interpretation of previously published data has been the extra-renal effect of glucocorticoids and often the use of such large doses of glucocorticoids that crossover

effects through mineralcorticoid receptors has been likely. A further complication of previous studies has been to give glucocorticoids to normal subjects. It is quite probable that glucocorticoid effects from zero to normal levels are not linear (or even directionally the same) when compared to glucocorticoid effects from normal levels to high concentrations.

Hulter and coworkers have administered low doses of triamcinolone (relatively pure glucocorticoid) to dogs which resulted in reduction of urinary pH and an increase in net acid excretion. Unfortunately their control and experimental dogs were non-adrenalectomized so it is not certain whether directionally same results would have been obtained if compared to adrenalectomized dogs. At higher doses of triamcinolone the dogs actually became acidotic due to increase in pre-renal production of acid. These results emphasize the importance of glucocorticoid dose on acid-base balance when given on a chronic basis.

At the present time there is only one study which has administered physiologic doses of glucocorticoid to adrenalectomized animals. Wilcox and coworkers found that dexamethasone given to adrenalectomized rats failed to reduce urinary pH but did increase net acid excretion, Figure 5. Thus these studies would suggest an important role for glucocorticoid in augmenting renal acid excretion. However, these studies were acute studies and do not necessarily reflect on the effect of glucocorticoid on chronic acid-base balance. Such studies have not been conducted. Glucocorticoids do not affect H secretion across the isolated perfused medullary collecting duct.

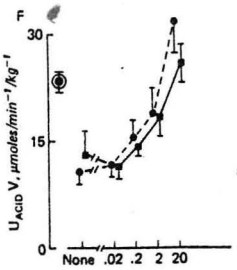

FIGURE 5. Responses of ADX rats to dexamethasone. Values shown are mean ± SEM. In the panel are shown first values from SHAM rats (double circles); next are results from ADX rats given no dexamethasone and thereafter, results (solid circles) with increasing doses of dexamethasone (0.02, 0.2, 2 and 20 μg/100g of body wt^{-1}). Other rats received aldosterone, 1 μg/100g of body wt^{-1} in addition to dexamethasone (solid squares). Source: Wilcox et al.

Sodium Balance

One of the cardinal features of adrenocortical insufficiency is that the patient is in negative sodium balance. It has been well established that normal subjects who receive aldosterone on a prolonged basis initially decrease their urinary sodium excretion and have an associated increase in weight gain, Figure 6.

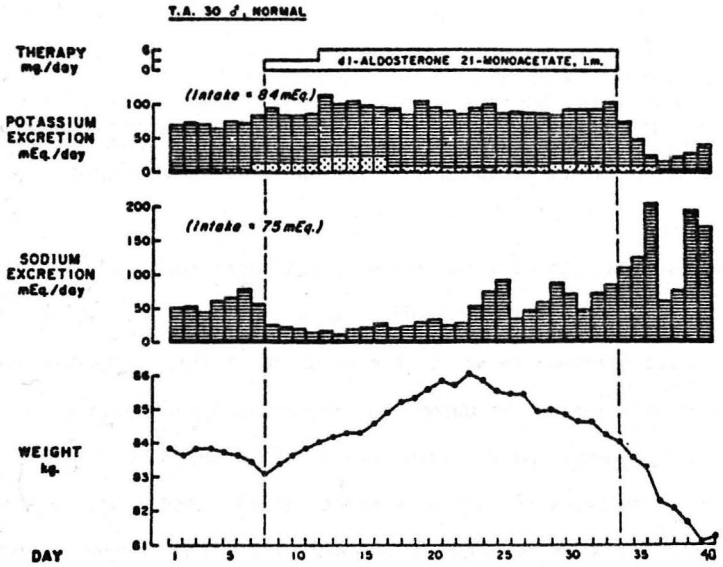

FIGURE 6. The effect of aldosterone on weight and sodium and potassium excretion in a normal subject. Source: August et al.

The reciprocal set of findings are common with sudden withdrawal of mineralocorticoids in patients with Addison's disease, Table III.

TABLE III

STUDY OF SALT BALANCE IN AN ADDISONIAN PATIENT* (Source: Welt)

Day	Wt	Conc. in Serum and Whole Blood				Intake		Urine	
		Na	K	T.P.	NPN	H_2O	Na	H_2O	Na
	kg	mEq/L		gm%	mg%	cc	mEq	cc	mEq
6/26-27	88.8	136.8	4.5	7.45	30	1750	95.5	1860	131
6/27-28	88.0					2650	95.5	2800	154
6/28-29	87.25	135.8	4.8	7.65	31	3550	95.5	3040	117
6/29-30	87.1					3350	95.5	3120	99
6/30	87.4	134.8	4.9	7.90	36				

*The beginning of the balance period was the morning of June 26, and his diet contained 10 mM of NaCl. In addition, he used 85.5 mM of dry salt (5 Gm) to season his food. Each 24-hour period begins and ends at 8 A.M. The chemical analyses of the serum and whole blood, and the body weight, refer to 8 A.M. of the first of the two dates listed under "Day." The patient was not taking cortisone, and the last DOCA pellets had been implanted about 12 months prior to this examination.

However, as is illustrated, characteristically in the patient summarized in Table III, changes in serum sodium concentration may or may not become apparent. This tends to be a function of completeness of adrenocortical insufficiency and intake of sodium and water. The body weight may remain unperceptually decreased initially but does decrease as the crisis is approached. It is common also for serum sodium concentration to remain normal until times when adrenocortical crisis is approached. As adrenocortical crisis is approached then hypovolemia and hyponatremia may become life threatening.

While non-renal losses of sodium may contribute to the overall clinical state, the renal losses of sodium are quantitatively most important. The mechanism by which aldosterone regulates renal sodium reabsorption has been the subject of intense investigation in recent years by our and other laboratories.

The technique whereby isolated segments of renal tubules are perfused in vitro has allowed precise definition of the renal site of action of aldosterone. These studies have shown that the cortical collecting tubule is the principle site where both acute and chronic mineralocorticoid exposure lead to an increase in net transport of Na across this nephron segment.

The cellular mechanism by which aldosterone increases Na transport is schematically summarized in Figure 7. This model is based on the recent work of Kevin Petty (M.D., Ph.D. student at SWMS) and coworkers. The figure is obtained from his Ph.D. dissertation. In this model aldosterone gains access to cytoplasmic receptors where it initiates a series of biochemical steps culminating in synthesis of a protein (permease) which increases the luminal membrane entry of Na. The increased intracellular entry of Na, in turn, secondarily increases Na-K ATPase activity. Studies are also consistent with the view that aldosterone also stimulates energy production by the mitochondria by increasing the production of ATP, Figure 7. The increased entry of Na and the increased activity of the Na pump (Na-K ATPase) will lead to increased net transport of Na from the collecting duct lumen into blood.

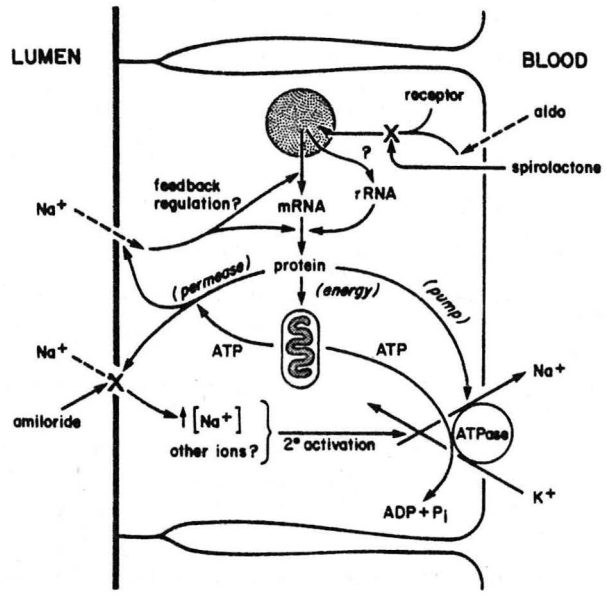

FIGURE 7. Schematics to illustrate the cellular mechanism by which aldosterone stimulates Na transport across the cortical collecting tubule. Source: Kevin Petty, SWMS Ph.D. thesis.

Potassium Balance

Hyperkalemia is a well published laboratory finding of Addison's disease. However, the review of literature indicates that hyperkalemia is an unusual association of adrenocortical insufficiency, and when present, is an indication of incipient adrenocortical crisis. Earliest workers originally thought that mineralocorticoids affected directly renal K excretion but this view has not been substantiated by the majority of more recent data.

The initial conviction that mineralocorticoids affect directly renal K excretion was first challenged by the studies of Seldin, Welt and Cort. In 1951 they reported, and subsequently published in 1956, studies in rats and humans which showed that the administration of DOCA had no effect on potassium excretion if the study subjects were on restricted sodium diets, Figure 8. These findings were consistent and not dependent on the level of K intake. However, if these similar studies were conducted in the presence of dietary Na then they demonstrated augmented excretion of K in response to DOCA administration. Their studies thus suggested that DOCA had no direct effect on K excretion but that the kaliuretic effect of DOCA was the result of coupling to DOCA induced increased reabsorption of Na. These studies were subsequently extended by Burnett, Seldin and Walser where it was shown that increased ingestion of Na did not increase K excretion in an Addisonian man, Figure 9.

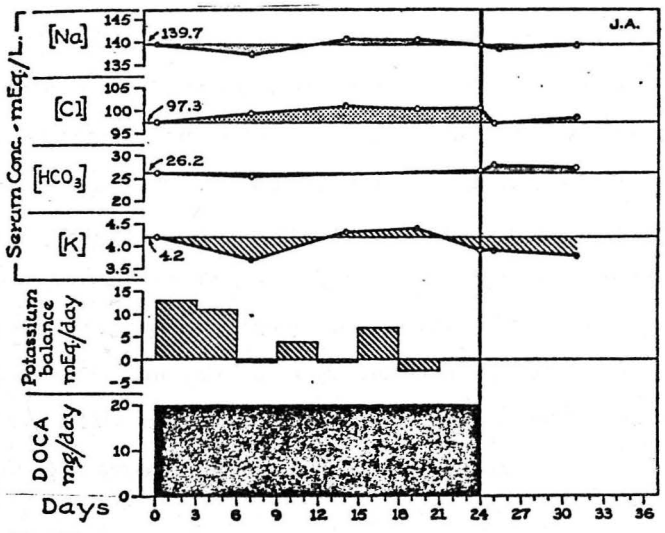

FIGURE 8. The effect of DOCA on serum composition and potassium balance during salt restriction. Source: Seldin, Welt and Cort.

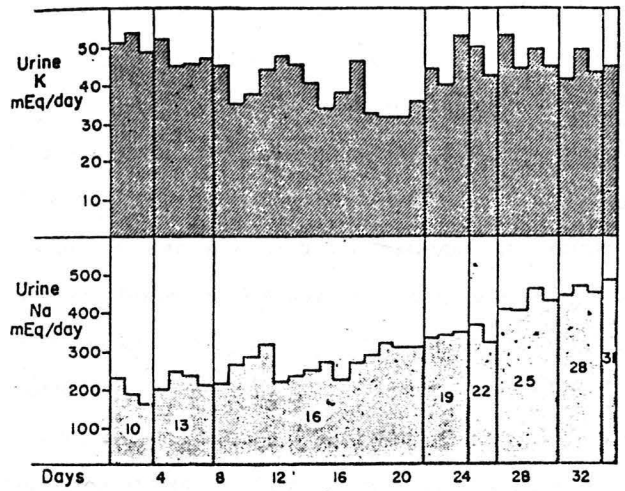

FIGURE 9. Effect of oral salt on K excretion in an adult male with established Addison's disease. Source: Burnett, Seldin and Walser.

It is not at all clear why the concept that the adrenal cortical hormones have a specific primary effect on K excretion was continued to receive support. Rabinowitz has recently reviewed exhaustively the evidence either in favor of or against the role of aldosterone regulating renal K excretion. He concludes that within physiologic secretory ranges of mineralocorticoids the overwhelming evidence suggested that mineralocorticoids do not increase K excretion even when an antinatriuretic response to mineralocorticoids is documented. Our own clearance studies in rabbits conducted by Wingo, et al also failed to show a kaliuretic response after an acute administration of aldosterone at a time when antinatriuretic response was clear.

The studies at the isolated tubule level are interesting. When tubules are harvested from rabbits which have received chronic doses of DOCA, these tubules have a higher secretory rate of K than tubules from rabbits not receiving DOCA. Indeed there seems to be a nice correlation between plasma levels of aldosterone and K secretory capacity of the cortical collecting tubule, Figure 10. Initially it would appear that these studies are at variance with the clinical and animal clearance studies. However, these results may represent some nonspecific effect of chronic and supraphysiologic doses of mineralocorticoids and may be counterinfluenced by other regulatory factors in in vivo studies. In studies by Wingo, et al there was no effect of acute aldosterone exposure on K secretion across the cortical collecting tubule at a time when Na reabsorption was stimulated.

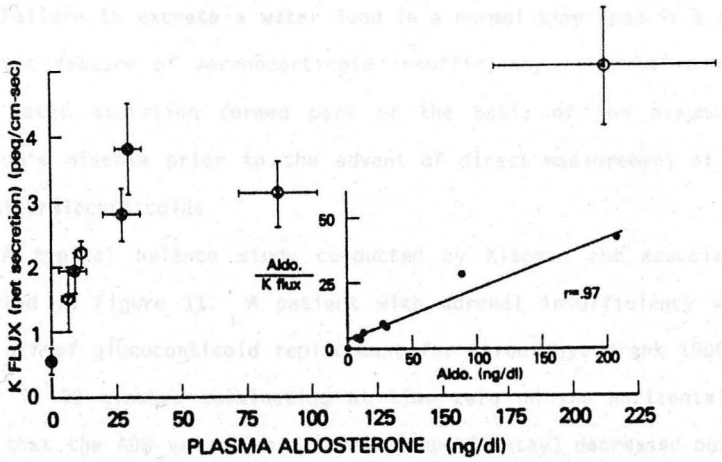

FIGURE 10. In vitro flux of K across the cortical collecting tubule as a function of plasma aldosterone of rabbit from which the nephron was dissected from. The endogenous aldosterone was varied by various dietary means. Inset shows a Hames plot from which $K_{1/2}$ = 16 ng/dl and V_{max} = 5.0 peq/cm/sec. Source: Schwartz and Burg.

In conclusion, it appears that the majority of studies have failed to support the notion that aldosterone has a direct regulatory role on renal potassium excretion. The results of the minority studies which are at variance with these conclusions probably are the result of some unknown metabolic factors.

Water Balance

Addisonian patients have two distinct and separate derangements in the regulation of water excretion: 1) the inability to excrete normally a free water load; and 2) a decreased ability to generate a maximally concentrated urine. The overall clinical effect of these defects is a tendency towards hyponatremia at a time when maximally concentrated urine cannot be generated. Different pathophysiological mechanisms exist for these two findings.

Failure to excrete a water load in a normal time span is a characteristic feature of adrenocorticoid insufficiency. Indeed, a test of free water excretion formed part of the basis of the diagnosis of Addison's disease prior to the advent of direct measurement of gluco- and mineralocorticoids.

A typical balance study conducted by Kleeman and associates is depicted in Figure 11. A patient with adrenal insufficiency who had been off of glucocorticoid replacement for three days drank 1500 cc of water in 30 minutes culminating at time zero on the horizontal axis. Note that the ADH value (as determined by bioassay) decreased but there was no increase in free water clearance until 100 mg Solucortef was given I.V. Within one hour there was a significant improvement of his free water clearance which is a typical finding of others with Addison's disease.

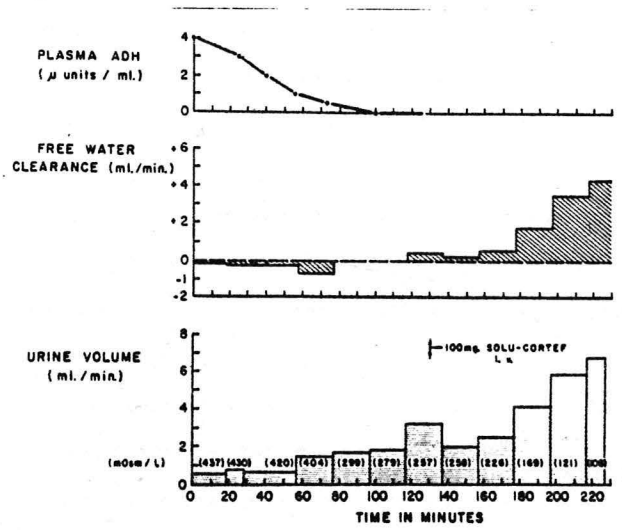

FIGURE 11. Relationship between the impaired water diuresis after an IV water load and the level of ADH in the plasma of a patient with secondary adrenal insufficiency. Source: Kleeman, et al.

The mechanism of impaired free water excretion has been the subject of intense investigation and no definite consensus exists at the present time. Initially it was suggested that there is an increase in back diffusion of free water across the collecting duct system. Both increased secretion of ADH or inherent increase in water permeability were postulated as possible etiologies. However, neither of these reasons seem tenable. First, the collecting ducts from adrenalectomized rabbits do not respond normally to ADH even if ADH levels are high (see next section on concentrating defects) and second, our studies have shown that collecting ducts obtained from adrenalectomized rabbits are impermeable to osmotic flow of water. Thus this does not appear to be an intrarenal defect.

Failure to excrete a free water load may also be the consequence of pre-renal effects, i.e. incompetent hemodynamic machinery would not respond normally to deliver the increased water loads to the kidney. A significant body of evidence is evolving to support this postulate. First it is well known that Addisonian patients tend to have small hearts, be hypotensive and have secondary increases in blood urea nitrogens. It has been well documented that glucocorticoids increase cardiac output, not only in patients with varying etiologies of shock but also in normal subjects.

The cellular mechanism by which glucocorticoids support blood pressure and cardiac output has not been ellucidated completely but a significant amount of exciting new information is evolving. While not all studies have documented an increase in intra-arterial blood pressure following glucocorticoids it is well accepted that the hemodynamic status of Addisonian patients is fragile and improves after glucocorticoids. Part of this improvement may be secondary to changes in the renin-angiotensin system. Most studies have shown that renin secretion increases in adrenal failure. This may be a secondary consequence of compromized renal perfusion. The resultant increase in angiotensin would promote aldosterone secretion and also act as an important pressor hormone which would prevent the development of hypotension. Recent studies on humans with adrenal insufficiency have shown that there is a nice correlation between plasma cortisol and renin substrate, Figure 12. Furthermore these studies showed that severe adrenocortical failure reduced renin substrate levels to less than ten percent of normal. While it is attractive to suggest that depletion of renin substrate may

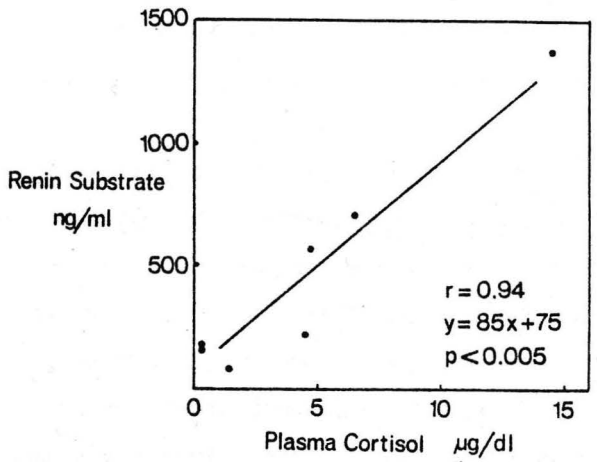

FIGURE 12. Relationship between plasma renin substrate and plasma cortisol, before treatment in seven patients with primary adrenal insufficiency. Source: Stockigt et al.

be a factor which contributes to circulatory failure in Addisonian crisis, the quantitative significance of this observation is not known. Recent studies which have also demonstrated the existence of high affinity corticosteroid binding sites in both smooth muscle and fibroblasts cultured from aortic explants of rats are of interest. This finding also awaits the experimental evidence to link receptor binding to physiologic response.

With respect to cardiac output, studies have just been published that have shown that adrenal steroids potentiate β-adrenergic actions of the heart. This inotropic potentiation appears to result not from an increase in β-adrenergic receptors but rather the ability of the β-

adrenergic receptors to form a high affinity "coupled" state by modulating the interaction of the receptor with nucleotide regulatory proteins. Whether this observation is of physiological significance awaits demonstration but it is well known that the administration of glucocorticoids to Addisonian patients increases their cardiac output. However, taken together, the evolving literature does seem to support the contention that failure to excrete a free water load in Addison's disease is predominantly the result of pre-renal hemodynamic factors.

The mechanism by which Addisonian patients are unable to form maximally concentrated urine has been recently elucidated. On theoretical grounds the concentration defect could be the result of either a decreased medullary osmotic force, decreased circulating ADH or a failure of the collecting duct to respond to ADH. Critical studies have not been conducted which have examined the effect of adrenocorticoids on salt transport across the thick ascending limb of Henle. Thus it is not known whether the primary force for generating hypertonic medullary interstitium is deranged or not. With respect to ADH levels, there are no convincing studies to suggest that ADH levels are low. Studies actually are most consistent with somewhat higher than normal values of ADH. On the other hand, recent in vitro studies from our laboratory have demonstrated that collecting tubules harvested from adrenalectomized rabbits have a markedly blunted hydroosmotic response to ADH. Furthermore, it was shown that the decreased response to ADH was corrected by physiologic doses of glucocorticoids, mineralocorticoids and cyclic AMP. These results therefore suggest that the concentration defect seen in adrenal insufficiency is at least partly the result of

the absence of the permissive effect that adrenal steroids exert on the ADH-induced reabsorption of water across the collecting duct.

TREATMENT

Treatment of adrenocortical insufficiency should be considered under three headings: 1) management of acute Addisonian crisis; 2) maintenance therapy of Addison's disease; and 3) management of stable Addisonian patient during surgical procedures.

Acute Addisonian Crisis

Acute Addisonian crisis is a medical emergency requiring immediate attention. These patients usually present with severe hypotension and may have severe hyponatremia, hyperkalemia and acidosis. Occasionally hypoglycemia may be severe but this is unusual.

The life-threatening aspect of Addisonian crisis is shock. The initial approach, therefore, is to give normal saline. It is not at all unusual that the patient requires three liters of normal saline over the initial 1 to 2 hours of crisis. While getting the IV started one also must get access to glucocorticoids as soon as possible. Patient should be administered 100 mg hydrocortisone or 4 mg dexamethasone IV stat and follow with 50 mg hydrocortisone q6h until the crisis is over. Mineralocorticoid replacement does not require the same emergency approach as do the glucocorticoids. In the initial phases of the crisis the patient requires a close work-up for possible precipitating factors. Most uncomplicated Addisonian crisis are of short duration and

maintenance therapy can be begun usually within several days of acute crisis. The hydrocortisone doses should be tapered by about 50% per day until maintenance levels are reached.

Maintenance Therapy

Oral cortisone acetate is a rapidly absorbed and well tolerated glucocorticoid. Approximaely 37.5 mg has proven to be an acceptable dose in the majority of patients. This should be given as 25 mg (one tablet) in the morning and 12.5 mg (1/2 tablet) in the evening. This approach roughly approximates the normal circadian variation in glucocorticoid secretion.

Mineralocorticoids are often also required in primary Addison's disease. The majority of patients have been managed with 0.05 to 0.1 mg 9 α-fluorocortisol (Florinef®) each morning.

Routine clinical findings are indices of the adequacy of therapy. Subjective feelings are used to guide glucocorticoid administration while blood pressure, serum sodium and potassium concentration are indices of the adequacy of mineralocorticoid replacement.

Management During Stress

The aim of treating an Addisonian patient during stress is to administer a dose of glucocorticoid which a normal person would secrete in response to stress. This value has been difficult to determine. Dr. Leshin points out in his October 15, 1980 Endocrine rounds that some normal patients do not have a measurable increase in plasma cortisol in response to minor surgery while others have variable responses. Essentially the same type of response patterns have been observed in glucocorticoid treated patients. However, a number of patients require

increased glucocorticoids during surgery and it thus appears prudent to administer extra glucocorticoid to all patients who are Addisonian or who have been maintained on glucocorticoids. In view of the variable cortisol secretory rates in response to surgery, it is not surprising that different treatment protocols have been suggested. In general it is advisable to err on the high side on a temporary basis. A reasonable approach in elective surgery in these patients is to increase their glucocorticoid dose to 50 mg IM hydrocortisone succinate (Solu-Cortef®) q8h 24 hours prior to surgery and 50 mg at the time of anesthesia. Throughout the day of surgery the patient then should be treated with Solu-Cortef 50 mg IV or IM q6h with rapid tapering as clinically indicated. The rate of tapering will be a function of degree post-operative stress.

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