The Genetic and Acquired Syndromes of Metabolic Alkalosis

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Biography of Donald W. Seldin, M.D.

I received a B.A. degree from New York University in 1939 and an M.D. degree from Yale University in 1943. Shortly after graduation, I joined the University of Texas Southwestern Medical Center where I served as Chairman of the Department of Medicine from 1952 to 1988. Since that time, I have been the William Buchanan Chair of Internal Medicine and University of Texas System Professor of Internal Medicine. My primary focus has been in Renal Physiology, particularly the mechanisms of regulating salt and water homeostasis. Currently, my major research activities are centered on the regulation of potassium transport in the distil nephron principal cell with Gerhard Giebisch at Yale and Shigeaki Muto at Jichi Medical School in Japan, as collaborators.

Purpose and Overview:

To develop the physiologic basis underlying the pathogenesis of metabolic alkalosis and the implications for diagnosis and treatment.

Educational Objectives:

1) To identify and elucidate the physiologic factors generating and maintaining metabolic alkalosis.
2) To emphasize the critical role of the coupling of inappropriate salt intake with persistent mineralaocorticoid excess in the pathogenesis of hypokalemic alkalosis.
3) To examine the role of volume expansion and chloride administration in the treatment of volume-contraction metabolic alkalosis.

Under normal circumstances, the kidneys maintain the concentration of serum bicarbonate within a normal range of about 25-28 mEq/L. This is accomplished in the face of acid invasion which would serve to lower its serum concentration or alkali addition which would operate to raise it. Essentially, two mechanisms are deployed by the kidneys to stabilize the serum bicarbonate: *bicarbonate reclamation*, a process mainly in the proximal tubule and *bicarbonate regeneration*, principally located in the distal nephron.

PRESERVATION OF THE NORMAL SERUM BICARBONATE CONCENTRATION

Bicarbonate reclamation represents the process by which the kidney returns the filtered bicarbonate to the blood. (Fig. 1) Almost all the filtered bicarbonate is reabsorbed in the proximal tubule; a small amount that escapes is reabsorbed in the distal nephron, so that the final urine is virtually bicarbonate-free. The process operates in such a manner that all of the filtered bicarbonate is reabsorbed below a serum concentration of about 25 mEq/L, *the bicarbonate threshold*; an increase in serum bicarbonate results in further bicarbonate reabsorption, but not in proportion to the increased filtered load: bicarbonate excretion commences. Elevation of the serum bicarbonate above 28 mEq/L elicits no further increase in bicarbonate reabsorption: *an apparent Tm* or maximum reabsorptive capacity has been attained. (1)

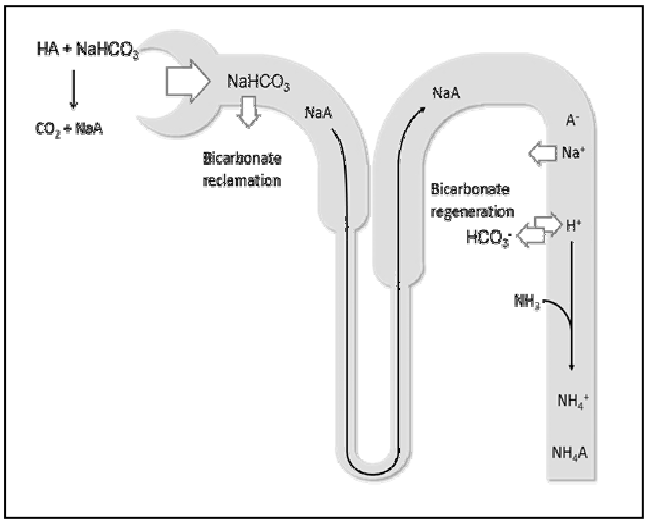


Figure 1

Even if all the filtered bicarbonate were reclaimed, metabolic acidosis would still eventuate if bicarbonate, decomposed by the accession of fixed acids to the blood, were not *regenerated*. About 50 to 100 mm of acid per day (H_3PO_4, H_2SO_4, organic acids, HCL) gain access to the extracellular fluid and are derived from three sources: 1) the production of organic acids in excess of organic bases by metabolic activity; 2) acid load generated by alkali stool loss; 3) acid-ash content of the diet.

Bicarbonate regeneration, (Fig. 2, right side) is the process, located principally in the distal nephron, where decomposed bicarbonate (NaA) is reconverted to$NaHCO_3$. Several processes are involved:

Sodium is reabsorbed under the influence of aldosterone in the principal cell through the ENaC, leaving a negative charge behind. This increases the transtubular potential difference, thereby serving to trap positive charges (H^+ and K^+) in the lumen. The reabsorbed Na^+ is returned to the serum as $NaHCO_3$, thereby regenerating decomposed serum HCO_3. Hydrogen is secreted into the lumen by the aldosterone-sensitive proton ATPase, located in the intercalated cell. The secreted H^+ reacts with NH_3 (diffusing down to the distal nephron from the proximal tubule), forming NH_4^+, and thereby preventing a drastic fall in luminal pH. NH_4^+ is excreted into the urine with A^- as NH_4A. Potassium enters the blood side of the principal cell through the Na, KATPase which is stimulated by high intracellular sodium concentrations and then diffuses through a channel into the tubular urine where it is trapped by the high negative potential difference and is excreted into the urine.

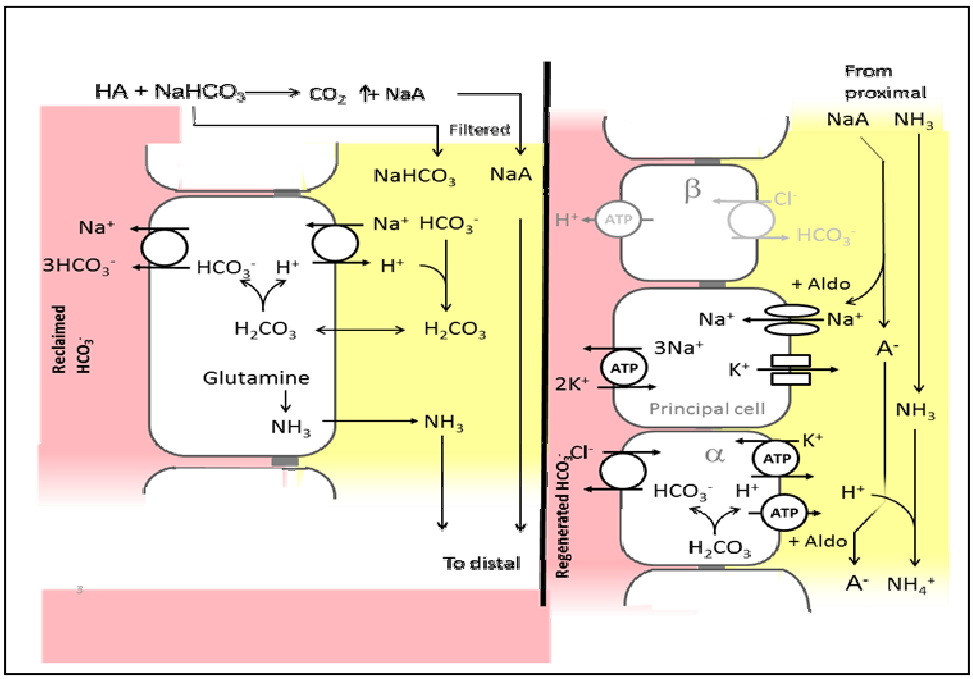


Figure 2

Assuming normal rates of acid production, a fall in net acid excretion indicates a defect in bicarbonate reclamation (e.g., Fanconi syndrome or diamox administration) or bicarbonate regeneration (various renal diseases). Metabolic acidosis results. On the other hand, a rise in net acid excretion (e.g., primary aldosteronism) will result in metabolic alkalosis.

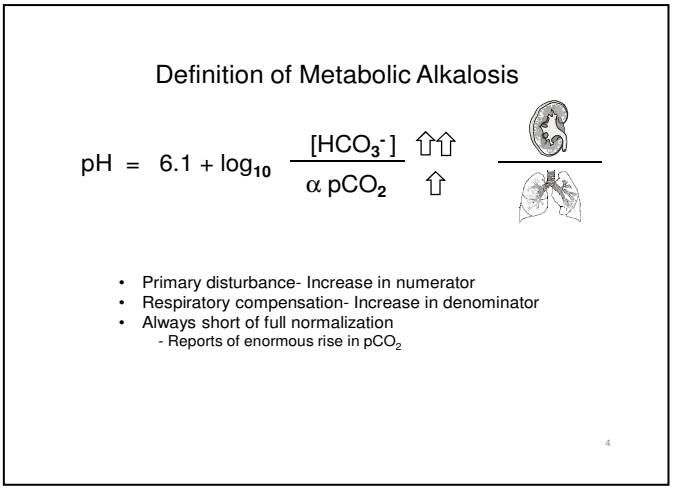
DEFINITION OF METABOLIC ALKALOSIS

Metabolic Alkalosis may be defined as a primary increase in the numerator of the Henderson-Hasselbalch equation, as indicated in (Fig. 3). The rise in serum bicarbonate alkalinizes the blood, leading to reduction in ventilation and a small rise in pCO_2. Within seconds after HCO_3^- is added to the blood, the pCO_2 rises further, owing to titration of added HCO_3 by non-bicarbonate buffers: $NaHCO_3$ +H buffer → Na buffer +H_2CO_3 → CO_2 + H_2O. This further rise in pCO_2 stimulates ventilation, thereby returning pCO_2 toward normal. This acute response is followed in about an hour by a more sustained rise in pCO_2, probably due to alkaline blood pH.

In several hours, a steady state is attained where the pCO_2 is elevated, but not sufficiently to return the pH to normal. The pCO_2 increases about 0.74 mm Hg for every 1 mEq/L increase in serum HCO_3.

Several recent reports have described occasional patients with metabolic alkalosis and profound hypercapnia which could not be attributed to neuromuscular weakness or pulmonary disease. The elevated pCO_2, in some instances in excess of 75 mm Hg, was the consequence of profound alveolar hypoventilation resulting from extreme compensatory depression of the respiratory center (5,6,7).

Figure 3



The processes regulating the degree of respiratory compensation are obscure. Cerebral interstitial fluid alkalosis has been proposed as the major regulator (4). The fact that severe hypercapnia tends to occur in metabolic alkalosis only in the absence of hypokalemia suggests that the intracellular pH of the respiratory center may play a critical role(8). Presumably, potassium deficiency, by promoting intracellular acidosis, might lead to respiratory stimulation, and thereby mitigate hypercapnia. It should be recognized therefore that severe hypercapnia in primary metabolic alkalosis need not be attributed to CNS or pulmonary disease, particularly if hypokalemia is absent.

PATHOGENESIS OF METABOLIC ALKALOSIS

The kidney has an enormous capacity to excrete $NaHCO_3$. Sanderson and his associates could produce only a mild elevation of serum HCO_3 despite the administration of massive $NaHCO_3$ loads (up to 140gm/day) given continuously through a gastric tube for periods up to three weeks (9). Two distinct physiologic derangements are required for the production of sustained metabolic alkalosis (Fig 4): 1. Generation; and 2. Maintenance. (1)

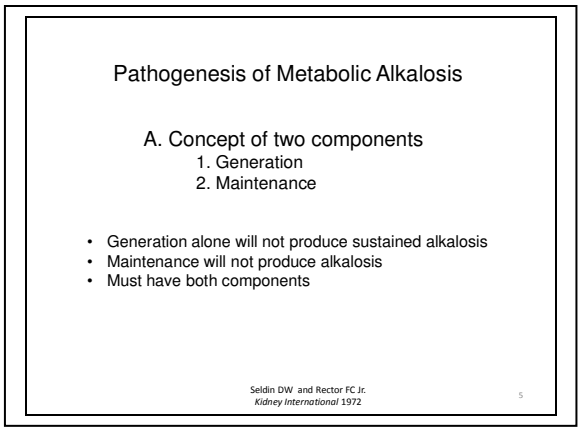


Figure 4

Generation

Bicarbonate generation may result from either a loss of acid or a gain of alkali. Either renal or extra-renal mechanism may be operative. If renal mechanisms are responsible, net acid excretion must exceed at least transiently, the acid load resulting from dietary and metabolic acid production and alkaline fecal losses. The excess represents renal bicarbonate generation.

Extrarenal factors may be responsible for HCO_3 generation. Acid loss, as in vomiting, or alkali gain, as in the milk-alkali syndrome, may be the source of the new HCO_3 added to the blood.

Chronic metabolic alkalosis sometimes persists when new bicarbonate is no longer generated. This may be termed *transient bicarbonate generation*. Extra renal factors, such as vomiting, may stop. Or chronic metabolic alkalosis resulting from renal losses of acid may persist despite a return of net acid excretion to the level of the net acid load: diuretics may be discontinued; hydrocortisone administration may be stopped. Alkalosis nevertheless persists despite the cessation of new bicarbonate generation if it is produced in a setting of persistent high bicarbonate reclamation.

Persistent bicarbonate generation is present when new bicarbonate is continually added to the blood, through either extrarenal or renal routes: vomiting may be unrelenting; diuretics may be continually administered. Chronic metabolic alkalosis of this type is an expression of both persistent HCO_3 generation and enhanced HCO_3 reclamation.

Transient HCO_3 generation may be particularly deceptive, since chronic alkalosis may be present long after the factors causing its generation have disappeared. Moreover, some patients shuttle between a non-steady and steady state, as in patients who vomit intermittently and surreptitiously, so that varied patterns of urinary acid excretion may be detected, depending on when the urine is examined.

Maintenance

Ordinarily, the addition of new bicarbonate to the blood, even when massive, will not produce a sustained metabolic alkalosis. Associated hypercapnia and hypokalemia doubtless contribute to increased bicarbonate reclamation, especially if coupled with a reduction in GFR. However, the major factor correcting the alkalosis is connected with an expansion of extracellular volume.

Expansion of extracellular volume must be capable of increasing effective arterial blood volume. In edematous states, for example, saline infusions only increase edema.

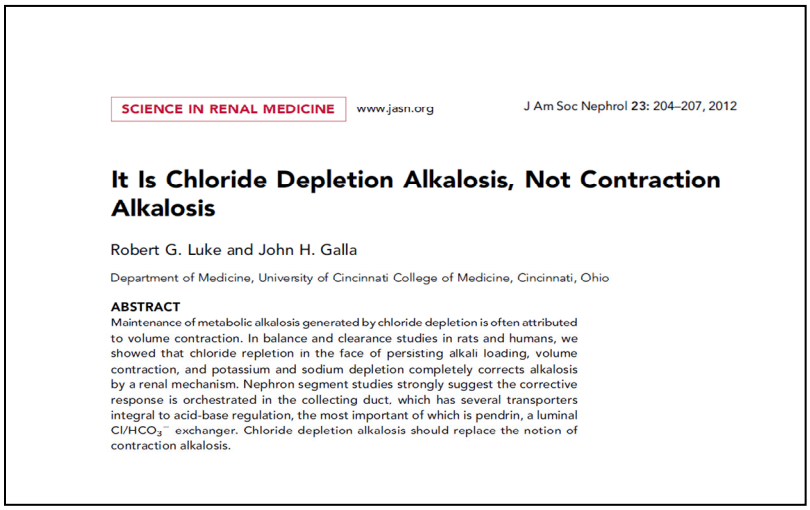
The mechanism by which volume contraction sustains alkalosis and volume expansion corrects it is the subject of considerable debate. Some have contended that hypochloremia per se is responsible for the maintenance of alkalosis. The studies of Cohen militate sharply against this proposal. In diuretic-induced metabolic alkalosis, dogs were infused with a solution containing [Na] and [Cl] at the same concentrations as existed in dog's plasma. This isometric solution expanded extracellular volume, corrected metabolic alkalosis, but did not alter serum [Cl]. (10)

Moreover, by reducing GFR with an aortic clamp, isometric volume expansion corrected metabolic alkalosis even though the total filtered load of chloride was reduced (11). These studies clearly established that neither the normalization of [Cl] nor increased filtered load was the mechanism by which volume expansion corrected metabolic alkalosis.

Nevertheless, other data point to a pivotal role of chloride in the correction of metabolic alkalosis. Intravenous infusion of a mixture of 20 mM KCl, 20 mM LiCl, 10 mM $CaCl_2$ and 10 mM $MgCl_2$ does not expand volume but does correct metabolic alkalosis; infusion of albumin expands volume but does not correct alkalosis (12). Oral administration of choline chloride corrects metabolic alkalosis without expanding volume (13).

Recently, Luke and Galla (14) have marshaled all the evidence for "chloride depletion" as the key factor in the maintenance of volume contraction metabolic alkalosis. (Fig. 5) Some of their arguments are summarized above.

Figure 5



SCIENCE IN RENAL MEDICINE www.jasn.org J Am Soc Nephrol 23: 204–207, 2012

It Is Chloride Depletion Alkalosis, Not Contraction Alkalosis

Robert G. Luke and John H. Galla

Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

ABSTRACT

Maintenance of metabolic alkalosis generated by chloride depletion is often attributed to volume contraction. In balance and clearance studies in rats and humans, we showed that chloride repletion in the face of persisting alkali loading, volume contraction, and potassium and sodium depletion completely corrects alkalosis by a renal mechanism. Nephron segment studies strongly suggest the corrective response is orchestrated in the collecting duct, which has several transporters integral to acid-base regulation, the most important of which is pendrin, a luminal Cl/HCO_3^- exchanger. Chloride depletion alkalosis should replace the notion of contraction alkalosis.

It is important to question what the meaning of the term "chloride depletion" is. In Fig. 6, various interpretations are summarized. Clearly, as the evidence listed above indicates, the usual interpretation refers to a deficit of total body chloride, a plasma volume deficit, a reduction in serum Cl concentration or a low filtered Cl. The evidence is against any of those playing a role in the maintenance of volume contraction alkalosis. However, they are on sound grounds in attributing the maintenance of volume contraction alkalosis to a sharp reduction in the delivery

of Cl to the distal nephron, where two Cl/HCO_3 exchangers are present (pendrin Cl/HCO_3 exchanger and the recently described Na-dependent aldosterone sensitive Cl/HCO_3 exchangers(15)).

Figure 6

Meaning of chloride depletion

1. Total body Cl^- deficit? No
2. Plasma volume Cl^- deficit? No
3. Low serum Cl^- concentration? No
4. Low filtered Cl^- deficit? No

Chloride deficit in this context means
Diminished Cl^- distal delivery

Role of volume expansion
Suppress proximal ion reabsorption increasing distal delivery

Mechanism of reduced proximal absorption
Increased back-leak of filtrate in proximal tubule

Effect of suppressed proximal reabsorption
Increased distal $NaHCO_3$ delivery and excretion (minor)
Enhanced distal NaCl delivery causing augmented Cl^-/HCO_3 exchange
mediated by:
1. Na-dependent aldosterone sensitive Cl^-/HCO_3^- exchanger
2. Pendrin Cl^-/HCO_3^- exchanger

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Presumably, volume expansion suppresses proximal reabsorption, thereby increasing the distal delivery of NaCl, where Cl can be exchanged for HCO_3. (Fig. 6)
Since neither [Cl] nor filtered Cl is necessarily increased, it is possible that volume expansion, by increasing the back-leak of filtrate in the proximal tubule, thereby diminishes net proximal reabsorption and increases distal delivery (Fig 6 & 7). Volume expansion thus becomes a means of increasing distal Cl delivery, and the supposed opposition of volume expansion vs. chloride load is merely different aspects of the same process. Under normal circumstances, the distal delivery of chloride would reflect chloride intake. The key point, as Galla and Luke long insisted, is a sufficient supply of Cl to the distal Cl/HCO_3 exchangers.

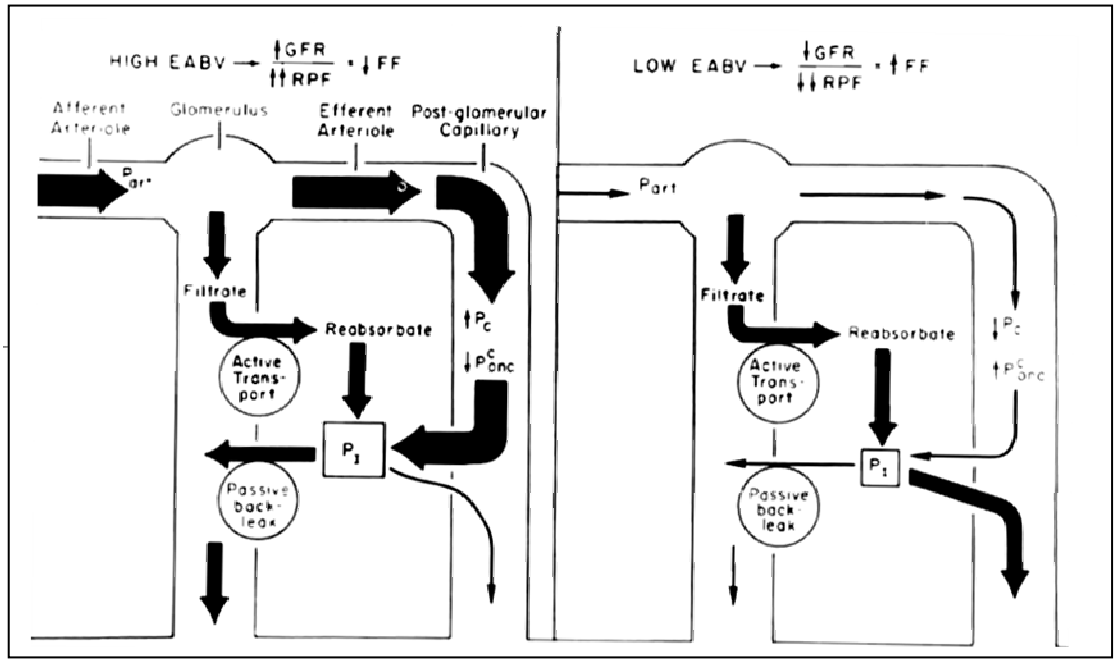


Figure 7

MINERALOCORTICOID ACTION AND SALT RESTRICTION

The administration of a salt-free diet results in a contraction of effective arterial blood volume and consequently enhanced secretion of renin, angiotensin, and aldosterone. However, neither hypertension on the one hand nor potassium deficiency or alkalosis on the other hand ensue. Hypertension does not develop because the pressor effect of high levels of renin-angiotensin is counterbalanced by the contraction of effective arterial blood volume; in consequence the blood pressure remains constant. In the kidneys high levels of aldosterone do not accelerate potassium or hydrogen loss because the distal delivery of sodium is sharply reduced owing to augmented reabsorption more proximally; in consequence neither alkalosis nor potassium deficiency develop. When salt is furnished in abundance to normal subjects, effective arterial blood volume is expanded and renin-angiotensin-aldosterone secretion is suppressed. Hypotension does not occur because the reduced pressor action caused by low levels of angiotensin is counterbalanced by expanded effective arterial blood volume. Hyperkalemia and acidosis do not eventuate because reduced levels of aldosterone occur in a setting where distal sodium delivery is plentiful. The normal feedback system, therefore, between renin-angiotensin and aldosterone ensures that stable levels of blood pressure, serum potassium and acid-base balance are maintained in the face of wide fluctuations of effective arterial blood volume.

Under special circumstances, however, this feedback system is disrupted. Inappropriately high distal sodium delivery occurs in a setting of persistent mineralocorticoid excess. The mineralocorticoid action may result from high rates of aldosterone secretion which has escaped feedback regulation. On the other hand, a variety of non-aldosterone mineralocorticoid substances may be responsible for the persistent mineralocorticoid action. (2,3)

The disorder generated by persistent mineralocorticoid action in the presence of plentiful distal sodium delivery may be divided into two categories: (1) volume expansion with mineralocorticoid excess; and, (2) volume contraction with mineralocorticoid excess.

CATEGORIES OF METABOLIC ALKALOSIS

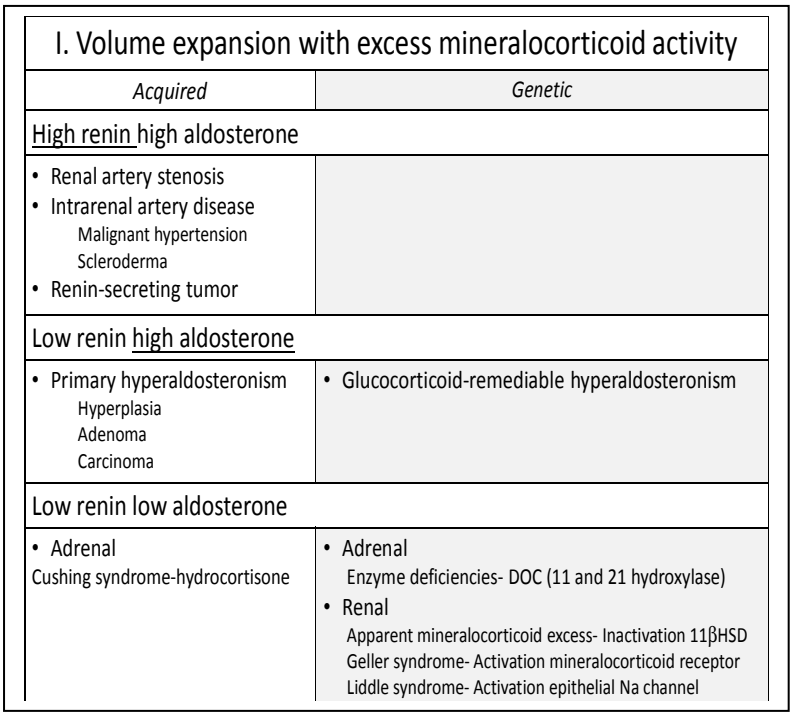
From a clinical point of view, it is helpful to classify metabolic alkalosis into three categories, all dependent of the mechanism by which the alkalosis is generated (Fig. 5)
1. Volume expansion metabolic alkalosis, 2. Volume contraction metabolic alkalosis; 3. Excess alkali loads.

1. VOLUME EXPANSION WITH MINERALOCORTICOID EXCESS

The disorders in this category have a number of features in common, listed in Fig 8:
Different humoral agents may be responsible for excess mineralocorticoid activity.

Persistent high renin secretion may result from renal artery stenosis (16), accelerated or malignant hypertension (17), and intrarenal vascular disease as in scleroderma are well-recognized causes of non-suppressible aldosteronism. Rarely, a renin-secreting tumor may be the responsible stimulus (18). These states are all characterized by both elevated renin and aldosterone.

Figure 8



I. Volume expansion with excess mineralocorticoid activity	
Acquired	*Genetic*
High renin high aldosterone	
• Renal artery stenosis • Intrarenal artery disease Malignant hypertension Scleroderma • Renin-secreting tumor	
Low renin high aldosterone	
• Primary hyperaldosteronism Hyperplasia Adenoma Carcinoma	• Glucocorticoid-remediable hyperaldosteronism
Low renin low aldosterone	
• Adrenal Cushing syndrome-hydrocortisone	• Adrenal Enzyme deficiencies- DOC (11 and 21 hydroxylase) • Renal Apparent mineralocorticoid excess- Inactivation 11βHSD Geller syndrome- Activation mineralocorticoid receptor Liddle syndrome- Activation epithelial Na channel

Hypersecretion of aldosterone, with suppressed plasma rennin secretion, may be due to an adrenal tumor (19), adrenal carcinoma (20), or bilateral adrenal hyperplasia, (a syndrome identical to Conn's syndrome, differing only in the absence of any neoplasm and in the failure of the bilateral adrenalectomy to relieve the hypertension (21-24).

Mineralocorticoid hormones other than renin-angiotensin-aldosterone may be responsible for excess mineralocorticord activity. High levels of hydrocortisone exert mineralocorticoid effects, and by expanding volume, suppress renin and aldosterone plasma levels: Cushing's syndrome, due to exogenous administration of hydrocortisone or ACTH, or such endogenous disorders as adrenal adenoma and especially extra-adrenal tumors producing ACTH-like hormones.

In addition to these acquired forms, primary mineralocorticoid excess may be attributable to genetic disorders, as indicated in the right side column of Fig 8. These disorders may be in the adrenal cortex or the renal tubule.

Glucocorticoid-remediable hyperaldosteronism (Laidlaw's syndrome) is a genetic defect in the adrenal cortex characterized by high levels of aldosterone, which are suppressed by glucocorticoid administration (25). Lifton and his associates demonstrated the genetic defect as a cross-over of aldo synthase from the adrenal glomerulosa to the fasciculata, where it stimulates 11-B hydroxylase, coming under the influence of ACTH (Fig. 9,10,11), and enhancing aldosterone secretion.

Figure 9

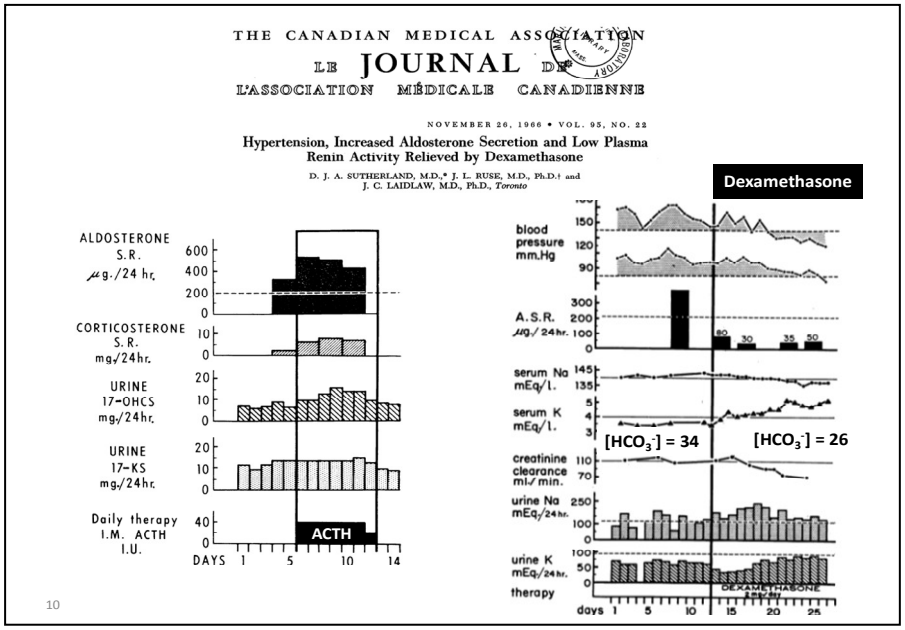


Figure 10

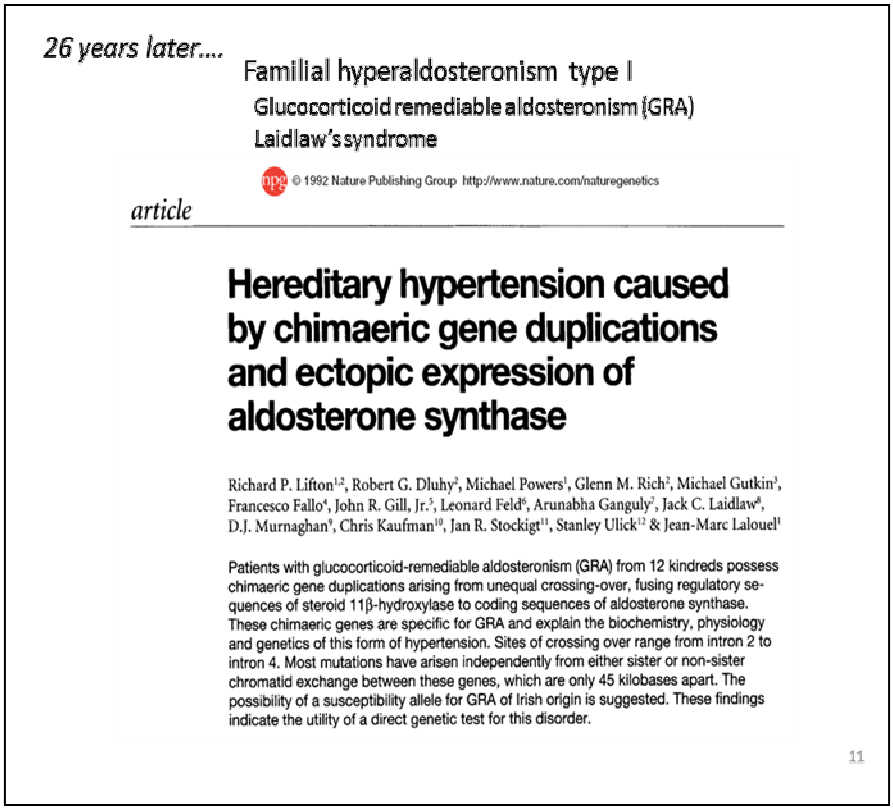
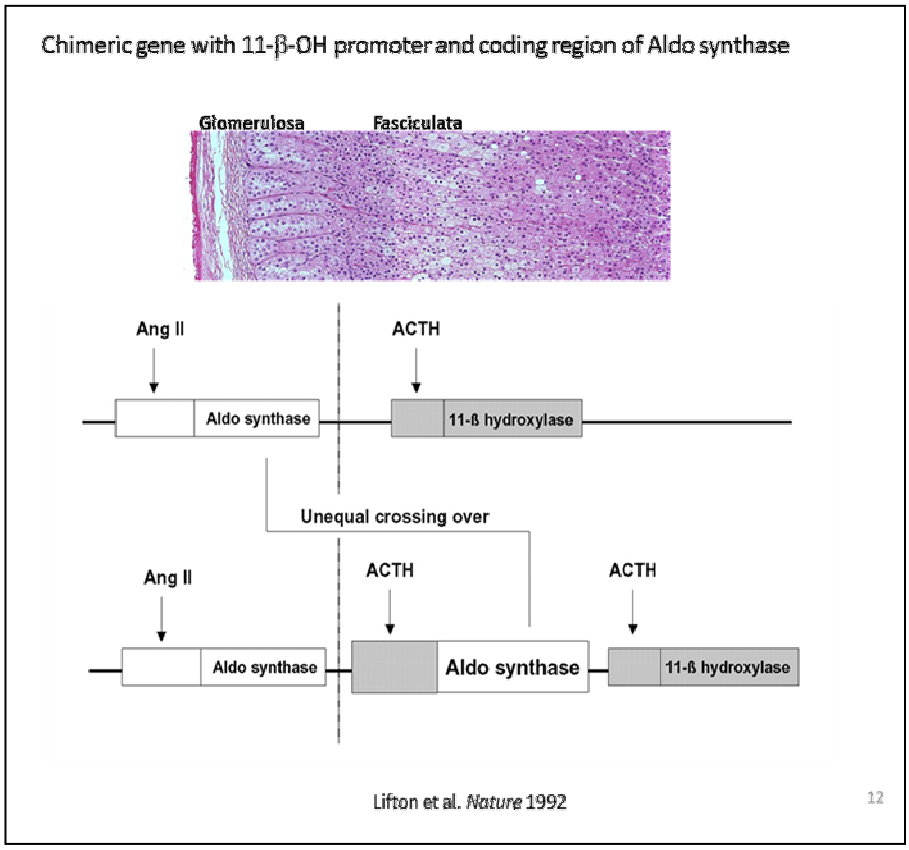
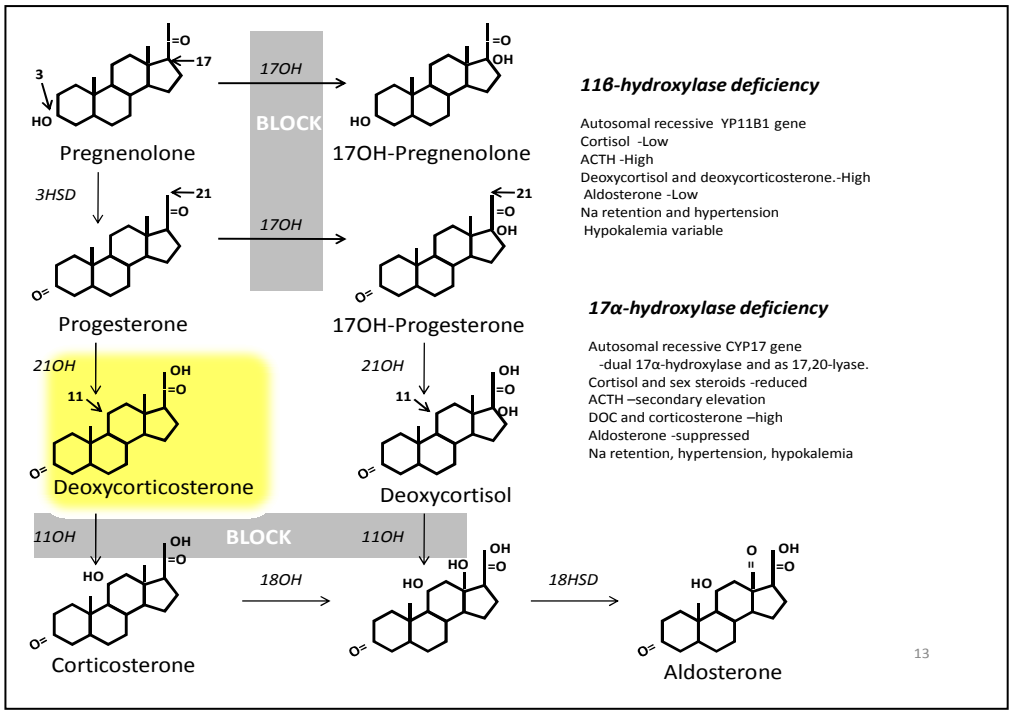


Figure 11



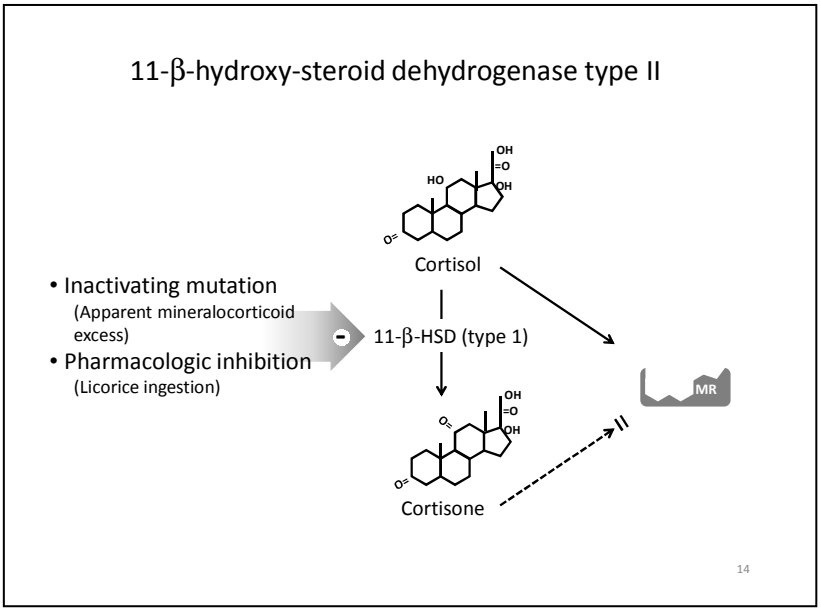
11 and 17 *Hydroxylase deficiencies* in the adrenal cortex both generate large amounts of desoxycorticosterone, as is illustrated in Fig 12. In 11 hydroxylase deficiency the block in hydrocortisone synthesis results in excessive secretion of androgens with virilization, in addition to a mineralocorticoid syndrome driven by high levels of desoxycorticosterone with suppression of aldosterone (26). In 17-hydroxylase deficiency, the block to hydrocortisone synthesis is associated with high levels of desoxycorticosterone as well as the absence of adrenal and gonadal androgens and estrogens. In addition to hypokalemic alkalosis and hypertension, these patients display evidence of a failure of secondary sexual development at puberty with amenorrhea and hypogonadism in girls and ambiguous genitalia in boys (27, 28). In both syndromes, exogenous glucocorticoids will inhibit ACTH secretion and thereby suppress mineralocorticoid production. Glucocorticoids will also reduce androgen production and virilization in children with 11-hydroxylase deficiency. With 17-hydroxylase deficiency, supplemental sex hormones are required for sexual development.

Figure 12



Apparent mineralocorticoid excess- Inactivation of 11- B-HSD is a mutation of the enzyme system which converts cortisol to cortisone (Fig 13). In consequence extremely high levels of cortisol activate the mineralocorticoid receptor and produce (in the presence of dietary salt) a full-blown picture of volume expansion mineralocorticoid excess (29, 30). Naturally occurring licorice (but not the synthetic variety) and some chewing tobaccos ("rat gut") contain glycyrrhizic acid which can also inhibit the enzyme and produce the same effect (31).

Figure 13



Gain of function of mineralocorticoid receptor (Geller's syndrome). This mutation alters the mineralocorticoid receptor specificity so that other steroids, lacking 21-hyddroxyl groups, especially progesterone, become potent agonists (fig 14 & 15). These mutations are responsible for the progesterone-induced hypertension in pregnancy. They do not tend to develop prominent mineralocorticoid excess features (32).

Figure 14

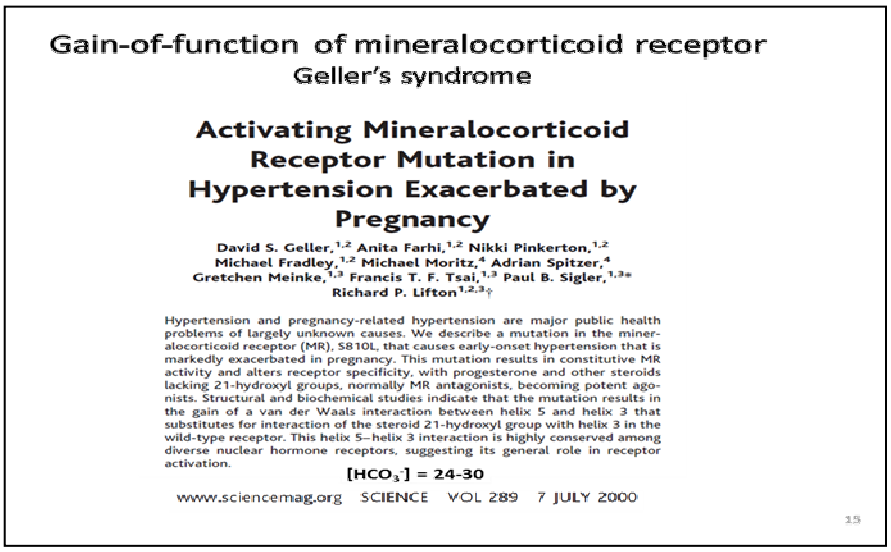
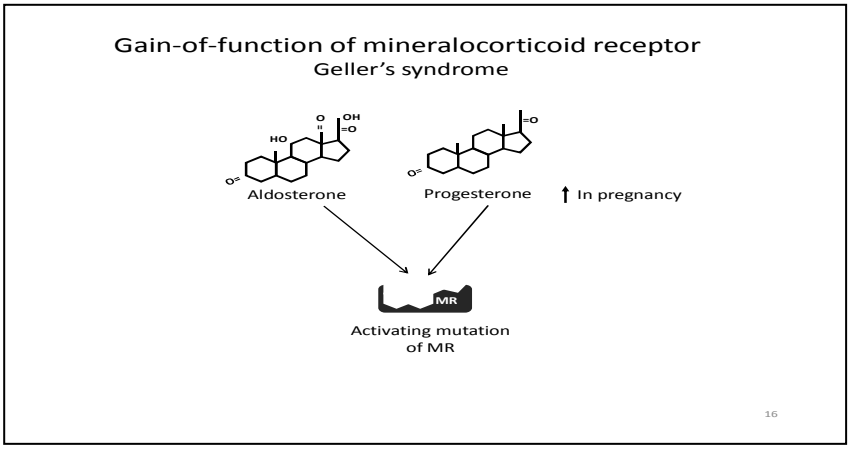


Figure 15



Activating epithelial Na channel (Liddle's syndrome). This rare autosomal dominant disorder is characterized by a complete volume expansion mineralocorticoid excess syndrome without any detectable mineralocorticoid (Fig. 16,17). Nor could the syndrome be blocked by aldosterone inhibitors as spironolactone (33). The syndrome can be inhibited by triamterene or amiloride. These are non-specific inhibitors of the ENaC channel, thereby blocking excessive Na reabsorption, volume expansion, a mineralocorticoid excess state, and a suppression of aldosterone secretion (34). Triamterene, amiloride, and K supplements are appropriate therapeutic measures. Kidney transplantation of Liddle's original patient was curative (Fig. 18). In Fig 19, the ENaC channel in the principal cell is the site of the lesion.

Figure 16

Grant W. Liddle, M.D.

Liddle's Syndrome

A Familial Renal Disorder Simulating Primary Aldosteronism But with Negligible Aldosterone Secretion

Grant W. Liddle, T. Blesdoe and W. S. Coppage
Trans Assoc Am Physicians, 76: 199-213, 1963.

Patients
G.S. 16 year old girl
C.S. Her younger brother

History:	Autosomal dominant, hypertension
Physical exam:	High BP
Laboratory:	Hypokalemia, urinary K wasting
	Metabolic alkalosis
	Suppressed aldosterone
Tests:	Aldosterone – no effect on urinary Na and K excretion
	Spironolactone – no effect on urinary Na and K excretion
	Triamterene- increase urinary Na and decrease urinary K excretion
	Kidney transplant of proband

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Figure 17

Liddle's Syndrome
(Liddle, G.W. Trans. Assoc. Am. Phys. *76*, 199-213, 1963))

Patients: G.S., 16 yr old girl and C.S., a younger brother

Findings: ↑ Bl pr.; hypokalemic alkalosis with plentiful urinary K; negligible aldosterone secretion

Workup:

1. Salt-free diet: urinary Na excretion reduced but still present
   No ↑ aldosterone secretion
2. Spironolactone administration: no increase in Na excretion or ↓ in K excretion
3. Triamterene administration: ↑ urinary Na excretion; decreased urinary K excretion. Serum K and HCO_3 returned to normal
4. Triamterene + low-salt diet: normal Bl pr.
5. Subsequent kidney transplant (Warnock, 1994) associated with normal Bl pr and serum K.

Figure 18

THE NEW ENGLAND JOURNAL OF MEDICINE

Jan. 20, 1994

BRIEF REPORT: LIDDLE'S SYNDROME REVISITED — A DISORDER OF SODIUM REABSORPTION IN THE DISTAL TUBULE

MAURICIO BOTERO-VELEZ, M.D., JOHN J. CURTIS, M.D., AND DAVID G. WARNOCK, M.D.

Index case of Liddle's syndrome

- Hypokalemic
- Metabolic alkalosis
- Hypertension

Kidney transplant from normal donor

Normalization
- Potassium
- Bicarbonate
- Blood pressure

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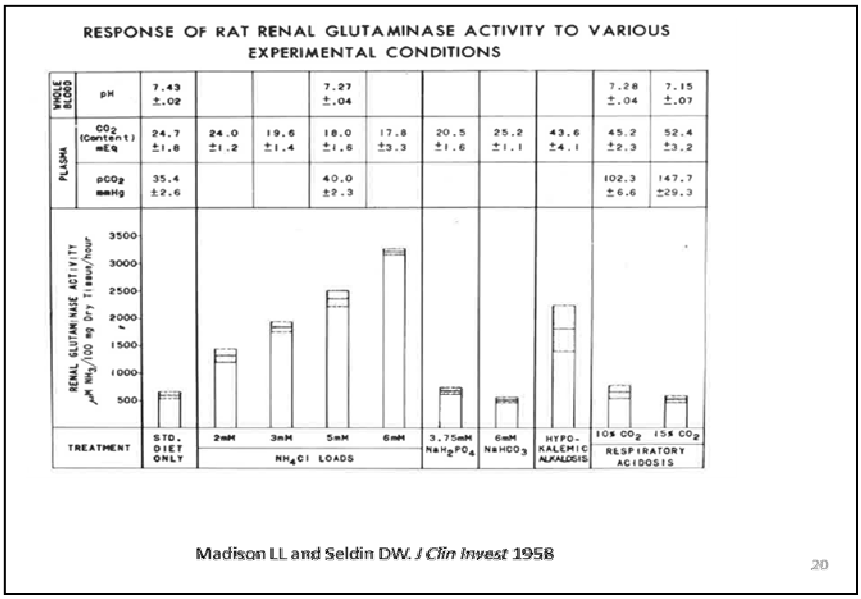
Figure 19



Madison LL and Seldin DW. *J Clin Invest* 1958

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The unrelenting character of mineralocorticoid excess is the second feature common to volume expansion syndromes. The syndromes are unrelenting in the sense that they persist in the face of activation of the control system normally responsible for its suppression, an expansion of effective extracellular volume. Causal factors include autonomous renin secretion or aldosterone secretion (tumors, genetic blocks, etc.) which do not respond to feed-back inhibition.

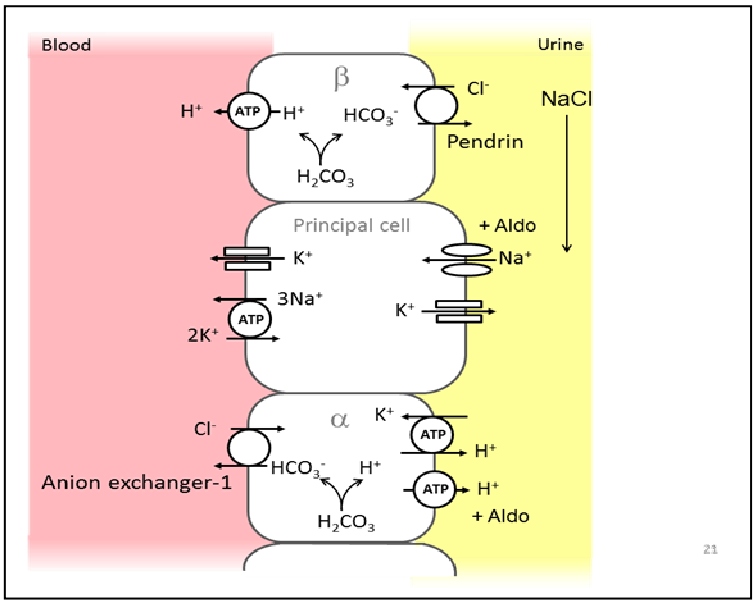
The continuous distal delivery of NaCl is a third distinctive feature. As long as dietary NaCl intake continues distal NaCl delivery will be plentiful. This differs from the pattern of Na retention in edematous states (such as heart failure or liver cirrhosis.) In these latter disorders, there is also mineralocorticoid excess that persists despite dietary salt intake, but owing to a Starling block in the circulation, the retained salt & water are sequestered in interstitial spaces, behind the failing left ventricle, or in the abdomen, and therefore does not expand effective arterial blood volume. Na re-absorption is avid in the more proximal nephron, and distal delivery is low. By contrast, in the syndrome here being considered there is no Starling block in the circulation, so that Na salts, reabsorbed in the distal nephron by mineralocorticoid action, can expand effective arterial blood volume, thereby suppressing more proximal reabsorption and ensuring continuous and ample distal delivery of Na salts.

The "escape" phenomenon is a fourth shared feature. Despite persistent mineralocorticoid secretion, extracellular volume stops expanding after an increase of about 2 or 3 liters. Although the results of micropuncture studies are somewhat conflicting, the data of Wright and his associates indicate that escape is due to increased delivery of filtrate out of the proximal tubule, owing to a reduction in absolute reabsorption, perhaps together with a rise in filtration rate (34). A new steady-state is reached after modest volume expansion where reduced proximal reabsorption offsets enhanced distal action, extracellular volume is modestly expanded, and urinary output of NaCl equals intake.

Increased urinary K and net acid loss is the fifth common factor of all these syndromes. Potassium deficiency accompanies almost all forms of volume excess metabolic alkalosis. The delivery of NaCl to the distal nephron in the presence of mineralocorticoid excess results in reabsorption of Na in the ENaC channel of the principal cell (Fig 19). The reabsorbed Na leaves an anion behind, increasing the negativity of the lumen potential. The reabsorbed Na is secreted into the blood in exchange for K through a Na-K ATPase, probably stimulated by high intracellular Na or a direct effect of the mineralocorticoid on the enzyme. In consequence of the sustained intracellular K concentration, K diffuses through a channel into the tubular urine and is trapped by the negative potential. Since this process is maintained because of continuous delivery of distal Na in the presence of a mineralocorticoid, urinary K losses accumulate. As K losses exceed dietary intake, K deficiency develops, with potassium leaving the intracellular compartment of body cells (including proximal and distal renal tubular cells) in exchange principally for H^+, leading to intracellular acidification. In K deficient alkalotic rats who were subsequently nephrectomized, infusion of KCl resulted in a striking correction of metabolic alkalosis (35). Clearly, part of the metabolic alkalosis associated with K deficiency is due to a loss of acid into cells.

The consequences of K deficiency on acid-base balance are several-fold. K deficiency directly inhibits adrenal aldosterone secretion (36). This would tend to mitigate hypokalemic alkalosis only in those mineralocorticoid excess states dependent on adrenal aldosterone secretion. On the other hand, in the treatment of hypokalemic alkalosis with K, part of the fall in serum bicarbonate is due to a cellular exchange of extracellular K for intracellular H. In the kidney, K deficiency enhances proximal (37) distal (38) tubular hydrogen secretion. Ammonia production is greatly enhanced through stimulation of the renal glutaminase enzyme system (39) (Fig 19). Finally, it should be pointed out that aldosterone activates not only Na reabsorption through the ENac channel but also stimulates directly H secretion through the H-ATPase in the intercalated cell (Fig 20). Finally, Stone and his associates identified an aldosterone sensitive Na independent proton ATPase in the collecting duct (40). These various mechanisms serve to enhance bicarbonate reabsorption during volume expansion hypokalemic alkalosis: both hypokalemia and mineralocorticoids promote hydrogen secretion and thus serve to generate and maintain metabolic alkalosis.

Figure 20



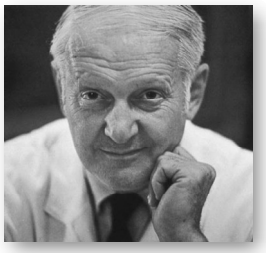
2. VOLUME CONTRACTION WITH MINERALOCORTICOID EXCESS

The disorders in this category of metabolic alkalosis are all associated with shrinkage of extracellular volume owing to either renal salt wasting or gastrointestinal salt loss. K deficiency is common. Fig 21 lists the acquired and genetic causes of these disorders.

Figure 21

II. Volume contraction with excess mineralocorticoid activity	
Acquired	*Genetic*
Renal H^+ loss	
Diuretics Na^+ salts with non-absorbable anions	Bartter's syndrome Gitelman's syndrome Pendred syndrome
Gastrointestinal H^+ loss	
Vomiting Villous adenoma	Congenital chloride diarrhea
Cellular H^+ loss	
K^+ deficiency	

Bartter's syndrome is an autosomal recessive disorder characterized by renal salt wasting with normal or low blood pressure, elevated renin and aldosterone levels, and hypokalemic alkalosis. Increased calcium excretion and nephrocalcinosis are frequent (Fig 22 & 23).



Frederic C. Bartter, M.D.

Bartter's Syndrome

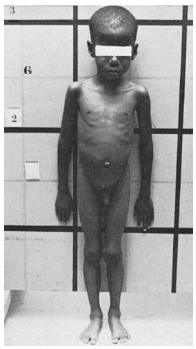
Clinical Studies

Hyperplasia of the Juxtaglomerular Complex with Hyperaldosteronism and Hypokalemic Alkalosis*

A New Syndrome

FREDERIC C. BARTTER, M.D., PACITA PRONOVE, M.D., JOHN R. GILL, JR., M.D. *and* ROSS C. MACCARDLE, PH.D., WITH THE TECHNICAL ASSISTANCE OF ESTHER DILLER
Bethesda, Maryland

Am J Med. 1962 Dec;33:811-28.

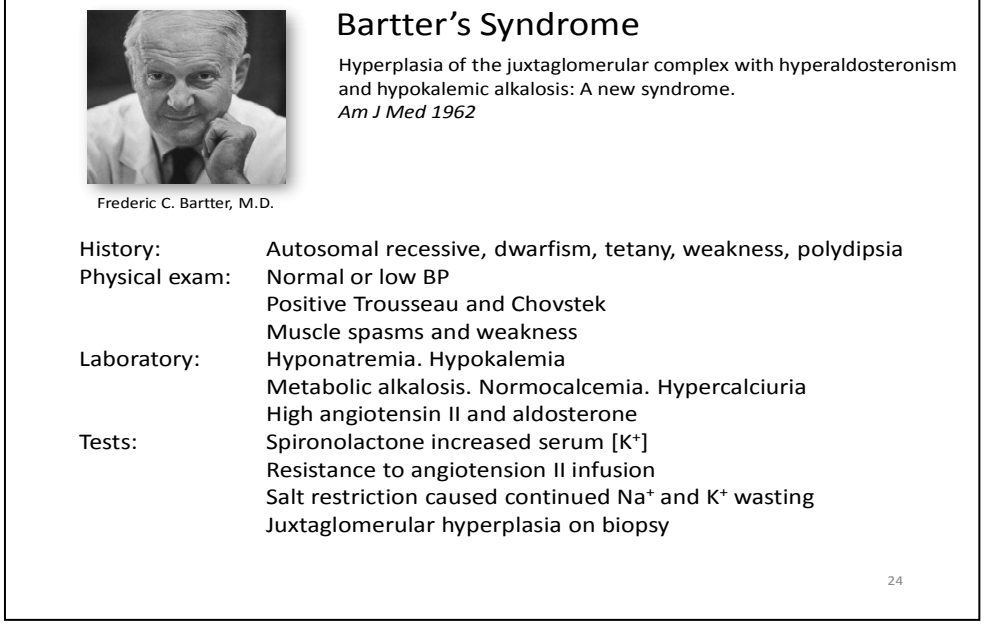


2 patients
C.J. 5 year old black boy
M.W. 25 year old black man

23

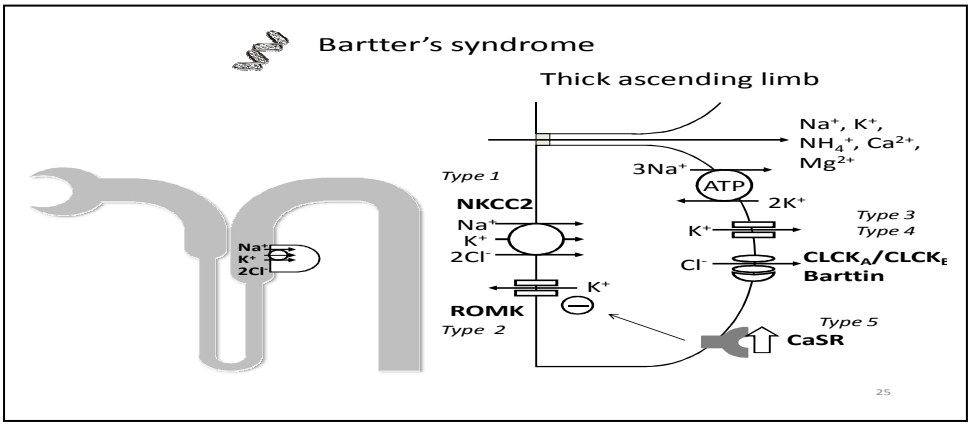
Figure 22

Figure 23



The defect has been localized to the NaK2Cl transporter in the thick ascending limb of Henle's loop (Fig 24). Lifton and his associates (ref 3) have identified 5 defects that impair the normal functioning of this transporter. Type 1 is a non-functioning transporter. Type 2 is a defect in the K channel on the luminal cell surface, secondarily impairing the transporter. Type 3 is a defective NaK ATPase on the basolateral surface: Na accumulates in the cell. Types 3 & 4 are defects in the basolateral K channel. Type 5 is an overactive calcium sensor on the basolateral membrane which inhibits K exit on the luminal surface from its cell.

Figure 24



All these disturbances serve to impair the NaK2Cl transporter and therefore result in salt-wasting. Shrinkage of volume leads to vascular instability and activation of the renin-angiotensin-aldosterone system. Distal Na delivery coupled with increased aldosterone causes K

loss. Moreover, owing to the failure of Na and K reabsorption, the voltage across the paracellular pathway falls, permitting the passive reabsorption of positively charged ions, especially Ca and Mg. This leads to hypercalciuria with nephrocalcinosis and often Mg deficiency as well. Elevated levels of cyclooxygenase accumulate in the thick ascending limb: elevated prostaglandin E_1 and E_2 lead to salt and water loss, perhaps by inhibiting the stimulation of salt and water transport by vasopressin. Cyclooxygenase inhibitors such as indomethacin reduce the levels of prostaglandin E_1 and E_2, and thereby alleviate the salt-wasting and other features of Bartter's syndrome (41). However, although prostaglandin inhibition is helpful, it only partially ameleorates many features of the disorder. Moreover, the improvement is often temporary.

The finding that persistent vomiting and diuretic abuse, perhaps because they are associated with K deficiency, also increase renal prostaglandin production (42,43) suggests that K wasting is responsible for the high prostaglandin levels. Massive amounts of potassium may be required to replenish K stores, even when indomethacin is used. Correction of Mg deficiency, if present, will lessen the electrolyte abnormalities.

The differential diagnosis of Bartter's syndrome may be difficult. Renal tubular Mg wastage may produce the identical electrolyte syndrome. Surreptitious vomiting may be difficult to distinguish from Bartter's syndrome. In the steady state of vomiting, urine Na is usually high, but urine Cl is very low by contrast. Bartter's patients waste both Na and Cl. Diuretic abuse, if suspected, may require urine analysis for thiazides or furosemide.

Gitelman's Syndrome is an autosomal recessive disorder, often confused with Bartter's syndrome (44). The electrolyte abnormalities consist of hypocalcemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. The syndrome is caused by a genetic abnormality in the Na and Cl co-transporter in the distal tubule (Fig. 25 & 26).

Figure 25

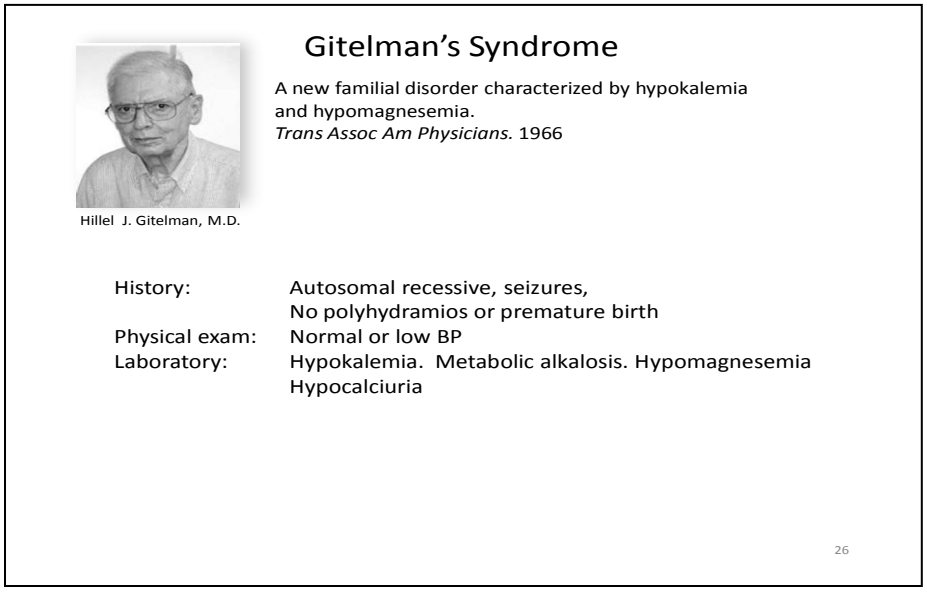
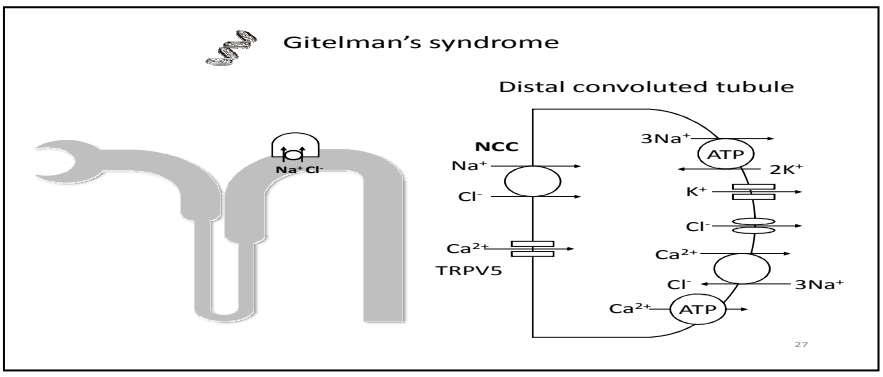


Figure 26



As a result there is NaCl wasting, volume contraction, activation of renin-angiotensin-aldosterone, metabolic alkalosis, hypokalemia. Unlike Bartter's syndrome, hypocalciuria is present; the mechanism has been elucidated by Friedman (45), and is outlined in Fig. 27.

Figure 27

The Mechanisms of Hypocalciuria in Gitelman's Syndrome

Inhibition of Na-Cl cotransport decreases cell Na^+ and Cl^-. Ca absorption increases because:

1. $\downarrow[Na]_C$ activates the basolateral Na/Ca countertransport, thereby increasing basolateral Ca exit.
2. $\downarrow[Cl]_C$, owing to large basolateral Cl conductance, hyperpolarizes apical membrane, activating apical Ca channel, thereby stimulating Ca absorption.

Friedman, P.A. Annu. Rev. Physiol. *60*:179-197, 1998

The contrast between Gitelman's and Bartter's syndrome is drawn in Fig. 28 & 29. Since the defect in Gitelman's syndrome is in the distal tubule, well beyond the counter-system there is no urinary concentrating defect. Invariable hypocalciuria and hypomagnesemia are also characteristic of Gitelman's.

Figure 28

Gitelman's Syndrome

(Gitelman, H.J. et al Trans. Assoc. Am. Phys. 79: 221-235, 1966)

Familial disorder: hypokalemic alkalosis, **mild** volume deficit, **no urinary concentrating defect, invariable hypomagnesemia, hypocalciuria, clinical onset apparent after age 6, no polyhydramios, and no premature delivery, convulsions and tetanic seizures** (Mg deficiency).

Figure 29

Bartter's vs. Gitelman

	Bartter's (n=18)	Gitelman's (n=16)
$[K^+]$ mM	2.5	2.7
$[HCO_3^-]$ mM	33.5	29.2
$[Na^+]$ mM	130	138
Hypomagnesemia	7/18	16/16
Urinary Ca^{2+} /Creatinine	1.41 (all >0.4)	0.06 (all <0.1)
Urine osmolality mOsm	406	885
Polyhydramnios	8/18	0/16
Premature delivery	7/18	0/16
Age at diagnosis <1 year of age <6 years of age	 12/18 18/18	 0/16 2/16
Polydipsia, polyuria, volume contraction	16/18	16/18
Febrile seizures or tetanic episodes	0/18	12/16

30

Mg Depletion: Hereditary urinary Mg wasting has been documented in several families as well as in Gitelman's syndrome. Severe hypokalemic alkalosis develops, giving a clinical picture suggestive of Bartter's. Mg administration corrects the entire disorder. Experimental Mg depletion in human subjects produces K wasting and hypokalemia (46). Since spironolactone corrects renal K wasting, an elevation of some component of the renin-angiotensin-aldosterone system is suggested (47). Apart from genetic lesions, cisplatin and aminoglycoside can produce renal Mg wasting with K deficiency and less commonly metabolic alkalosis.

Pendred Syndrome: A Cl/HCO_3 exchanger is located in the distal tubule, and mediates the reabsorption of tubular chloride in exchange for HCO_3. It is therefore a critical transporter for the correction of volume-contracted metabolic alkalosis (Fig. 30). As would be expected, loss of this transporter would lead to NaCl wastage, metabolic alkalosis, and hypokalemia. Fig. 31 documents a rare Pendred syndrome in which extreme hpyokalemic alkalosis supervene.

Figure 30

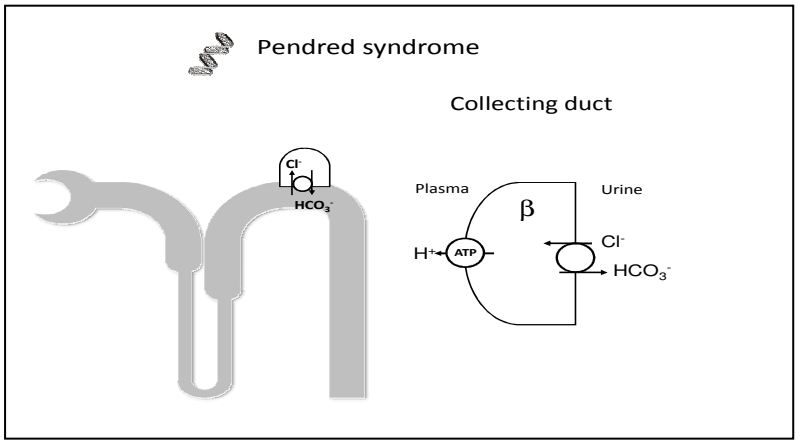
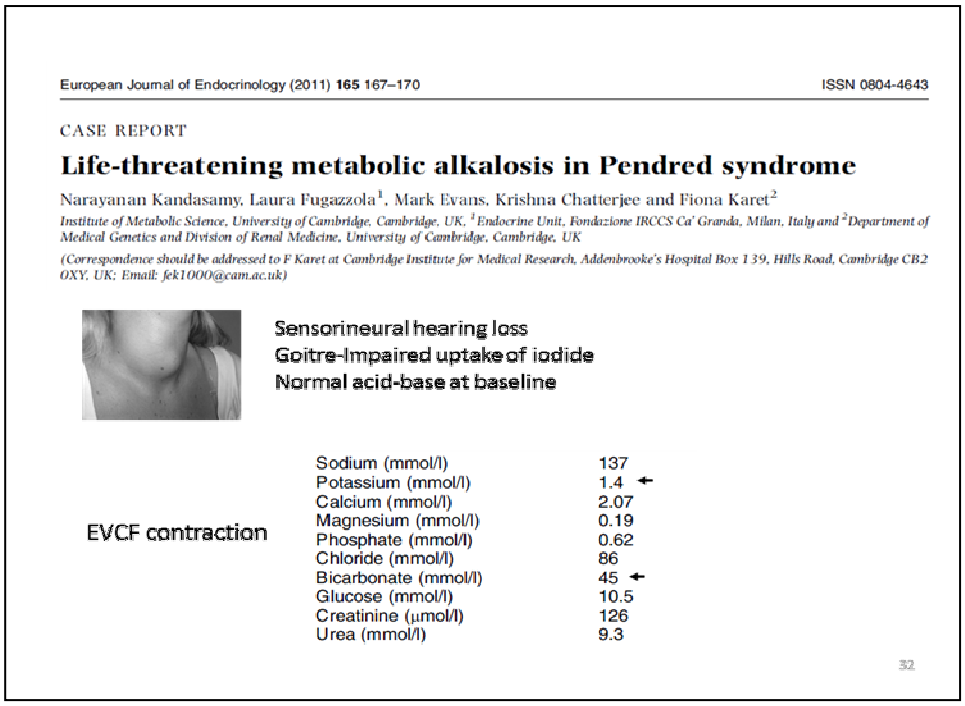


Figure 31



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CASE REPORT

Life-threatening metabolic alkalosis in Pendred syndrome

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Sensorineural hearing loss
Goitre-Impaired uptake of iodide
Normal acid-base at baseline

EVCF contraction

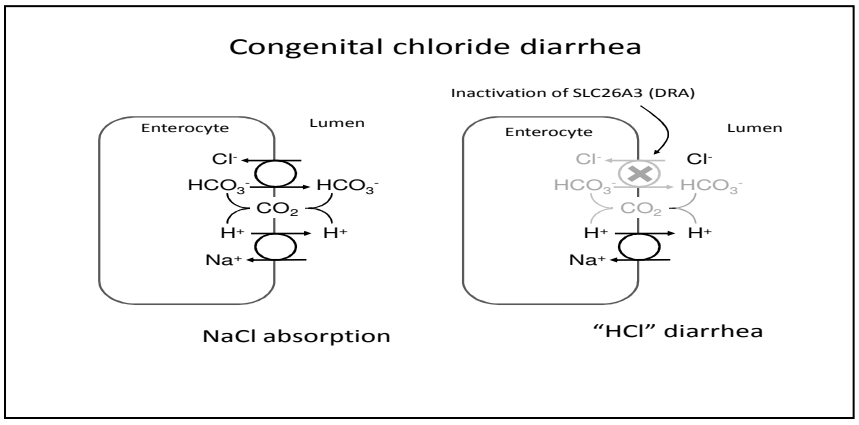
Sodium (mmol/l)	137
Potassium (mmol/l)	1.4 ←
Calcium (mmol/l)	2.07
Magnesium (mmol/l)	0.19
Phosphate (mmol/l)	0.62
Chloride (mmol/l)	86
Bicarbonate (mmol/l)	45 ←
Glucose (mmol/l)	10.5
Creatinine (μmol/l)	126
Urea (mmol/l)	9.3

32

Congenital Chloride Diarrhea: Darrow (48) and Gamble (49) described a syndrome of watery diarrhea, beginning at birth, in which stool Cl is higher than stool Na+K, and in which an acid stool, metabolic alkalosis, and a chloride-free urine are present. This disorder has been identified as a defect in active chloride reabsorption in the ileum (50).

In Fig. 32, a normal coupled exchanger Cl/HCO_3-Na/H is portrayed on the left side. The disorder illustrated on the right side is a defect in active Cl reabsorption, in which the failure of active Cl for HCO_3 exchange results in a loss of NaCl and K Cl into the stool. Na is reabsorbed into the cell in exchange for hydrogen secreted into the ileum lumen in normal fashion: the secreted hydrogen reacts with luminal HCO_3 to form Co_2 and water, thereby accomplishing net $NaHCO_3$ reabsorption. The alkalosis generated in this fashion is maintained by reduced extracellular volume and K deficiency.

Figure 32

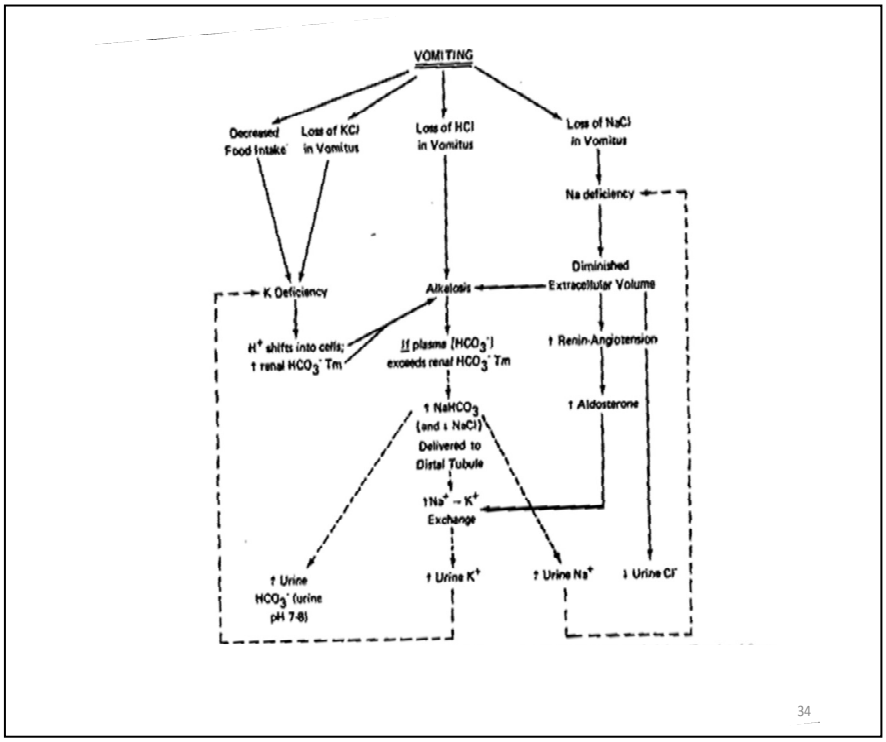


Vomiting and gastric drainage involve the loss of NaCl, K Cl, and H Cl. In consequence, extracellular volume shrinks, the renin-angiotensin-aldosterone system is activated, and K deficiency and metabolic alkalosis supervene. Two different urinary electrolyte patterns have been observed.

In some instances (51, 52) the urine is extremely alkaline (pH as high as 8.25) and contains large amounts of K, Na, and HCO_3 but almost no Cl; systemic alkalosis is very severe, GFR reduced, and plasma renin high. In other instances (53), urine pH is normal and contains very little Na, K, or Cl; systemic alkalosis is present but somewhat less severe than in the former group; GFR is reduced, and plasma renin and aldosterone are high.

The generation of alkalosis is principally a result of the loss of HCl. Even with profound alkalosis and hypochloremia of the order of 65 mEq/L, HCl secretion by the stomach continues at a normal rate (56). Contraction of extracellular volume results from loss of NaCl in vomitus and $NaHCO_3$ in the urine as well as in movement of Na into cells in exchange for K. The K deficiency, so prominent a feature of vomiting is in part the consequence of starvation and loss of K in gastric juice. However, the K content of gastric juice is low, and severe K deficiency develops even when K lost in gastric drainage is entirely replaced (54). The principal cause of the K deficit is urinary losses as Burnett, et. al. originally pointed out (55), a finding confirmed by several subsequent studies (52, 54). In all likelihood, the urinary K losses result from activation of the renin-angiotensin-aldosterone system in the presence of distal delivery of Na (as $NaHCO_3$).
This sequence of events (Fig 33) does not explain why the urine in some patients is extremely alkaline and contains large amounts of HCO_3, K, and Na, but little Cl, while in other patients the urine pH is normal and contains little HCO_3, K Na and Cl.

Figure 33



The most reasonable hypothesis would attribute the different urinary patterns to the varied capacity of the kidney to reabsorb the increased filtered HCO_3. A disequilibrium state exists if serum HCO_3 increases more than reabsorptive capacity; a steady state exists when the HCO_3 reabsorptive capacity can reclaim the filtered load. In Fig 33, the disequilibrium state is indicated by the interrupted lines. If vomiting is continuous and severe the concentration of serum HCO_3 may rise faster than the reabsorptive capacity. A contraction of effective extracellular volume will stimulate proximal tubular reabsorption, so that distal NaCl delivery will be markedly reduced. However, reabsorptive capacity for HCO_3 may be exceeded by the high concentration in the glomerular filtrate. In consequence, the distal nephron will be presented with excessive $NaHCO_3$ and diminished NaCl. Some of the $NaHCO_3$ (in the presence of secondary hyperaldosteronism) will be reabsorbed in exchange for K; the remainder of the $NaHCO_3$ will be excreted into the urine, raising urine pH and increasing urinary Na excretion. However, urinary Cl excretion remains very low, furnishing evidence of reduced extracellular volume. In the balance studies of Schwartz (54), it is during the period of active gastric drainage that the urine is alkaline and contains increased Na and K. The salt depletion of vomiting during the disequilibrium phase is characterized by increased Na (i.e. $NaHCO_3$) excretion. The depletion of extracellular volume is indicated by the low urinary Cl.

When vomiting stops or is mild, a steady state supervenes where contraction of extracellular volume and K deficiency augment HCO_3 reabsorptive capacity commensurate with the elevated serum HCO_3. Distal delivery of Na salts is greatly reduced. Although the stimulus for distal Na reabsorption is still intense, owing of secondary hyperaldosteronism, the reduced delivery of Na salts sharply decreases K excretion. As a result of more complete proximal $NaHCO_3$ reabsorption, urine pH is now normal and urine Na, K, and Cl very low.
The administration of NaCl, by expanding volume, reduces proximal reabsorption and suppresses the renin-angiotensin-aldosterone system. Copious excretion of $NaHCO_3$ now corrects the alkalosis. The reduction of aldosterone removes the stimulus for K excretion and a normal electrolyte pattern returns.

Glucose refeeding after fasting. Starvation causes a mild ketoacidosis. Initially, ketones are produced faster than they are metabolized, resulting in ketonemia and ketonuria.

As ketonemia increases, ketones are excreted into the urine with Na or K, or as an undissociated ketoacid. After 3-4 days of persistent ketonemia, NH_3 production rises and NH_4 ketone is the principal urinary form. Starvation ketosis is usually quite mild, because ketones stimulate the secretion of small amounts of insulin from intact pancreatic beta cells (59). With refeeding, ketoacid production promptly stops, and Na ketone is regenerated to $NaHCO_3$. Following the resumption of food intake, patients develop a metabolic alkalosis and edema. These effects of refeeding are greatest with glucose, less so with protein and absent with fat (57). The careful balance studies of Stinebaugh and associates (58) could disclose no mechanism for either the generation of new bicarbonate or its maintenance. Nor was the cause of the Na Cl retention responsible for edema elucidated. Refeeding alkalosis and edema persists for several days and then spontaneously resolves.

Diuretics. A common cause of metabolic alkalosis is diuretic administration to edematous patients. Heart failure and cirrhosis with ascites and edema are instances of enormous expansion of extracellular volume in a setting where effective arterial blood volume is reduced, resulting in activation of the renin-angiotensin-aldosterone system. Thiazides and frusemide, by inhibiting Na reabsorption in the more proximal portions of the nephron, increase the distal delivery of Na in a setting of high aldosterone. The consequence is K and H loss into the urine with hypokalemic alkalosis frequently following. The supplementation with K Cl mitigates this process. In some patients, nevertheless, spironolactone or amiloride may be necessary to block the ENaC channel so that aldosterone-stimulated distal Na reabsorption can be mitigated.

Perhaps the most frequent cause of alkalosis is the administration of diuretics to hypertensive patients with instructions to limit salt intake. If the patient actually adheres to a rigid salt-free regimen, he or she may be increasing vulnerable to hypokalemic alkalosis. This is because the diuretic may induce activation of the renin-angiotensin-aldosterone system by shrinking effective arterial blood volume at the same time that increased Na is delivered to its distal nephron as a result of more proximal inhibition.

The studies of Laragh and his associates (Fig. 34) indicate that in normal subjects given increasing amounts of dietary salt, renin and aldosterone levels fall in hockey-stick fashion from very high levels during salt restriction to low levels with high salt intake (61). If the subject is on a salt-restricted diet, renin-aldosterone may be very high. Normally, such high levels are associated with very little distal Na delivery. However, with pharmacologic block of Na reabsorption, large amounts may be inappropriately delivered to the distal nephron where high aldosterone will promote Na reabsorption and hypokalemic alkalosis. In this connection the studies of Wilcox are revealing (Fig. 35). On a low salt diet, frusemide produced marked K losses. On a high salt diet, K excretion was in balance. Administration of captopril, by inhibiting angiotensin-aldosterone mitigated the negative K balance.

Modest salt restriction to hypertensive patients given diuretics may be well-tolerated, but rigid salt-restriction may lead to hypokalemic alkalosis. Careful monitoring may be necessary to forestall complications if aggressive diuretic therapy is necessary.

Figure 34

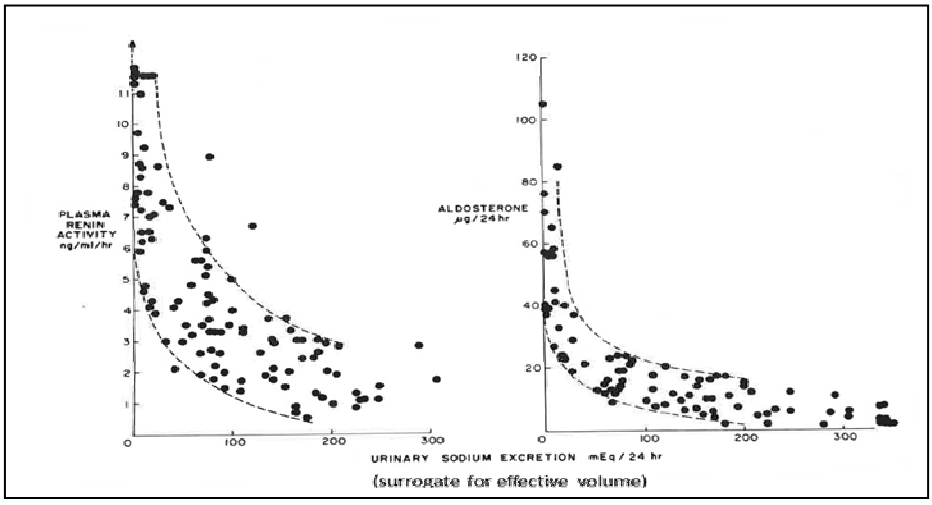
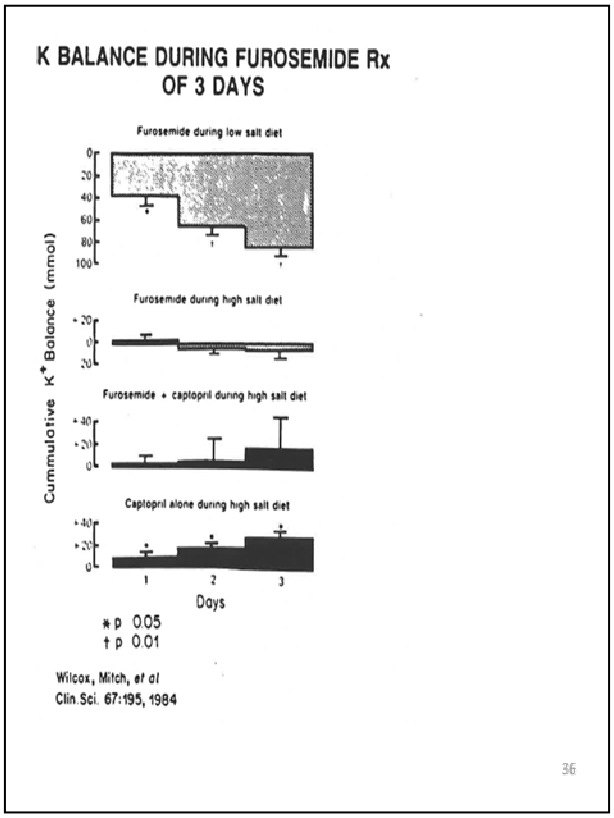


Figure 35



TREATMENT OF METABOLIC ALKALKOSIS

1. Treat the underlying cause both generating and maintaining the alkalosis.
   a. Saline as an agent to correct volume contraction metabolic alkalosis
   b. Replenish K deficits. Evaluate and correct Mg & P
   c. Stop mineralocorticoid action: spironolactone, triamterene, amiloride
2. In refractory patients, especially those with pulmonary insufficiency ischemic heart disease, or cerebral ischemia, special consideration should be given to therapeutic approaches.
   a. Acetazolamide administration may be dangerous in patients with advanced lung disease, since they may not be able to increase ventilation to lower the pCO_2.
   b. If nasogastric suction must be maintained, an H_2 receptor blocker may reduce tendency to generate metabolic alkalosis.
   c. NH_4Cl can be given by mouth, but is dangerous in the presence of advanced liver disease.
   d. HCl infusions as a 0.15 – 0.25 N solution in saline or 5% glucose through a central line in the superior vena cava, verified by chest x-ray prior to infusion.
   e. Dialysis, peritoneal or hemodialysis, with high Cl low HCO_3 dialysis solution, in patients with renal failure.

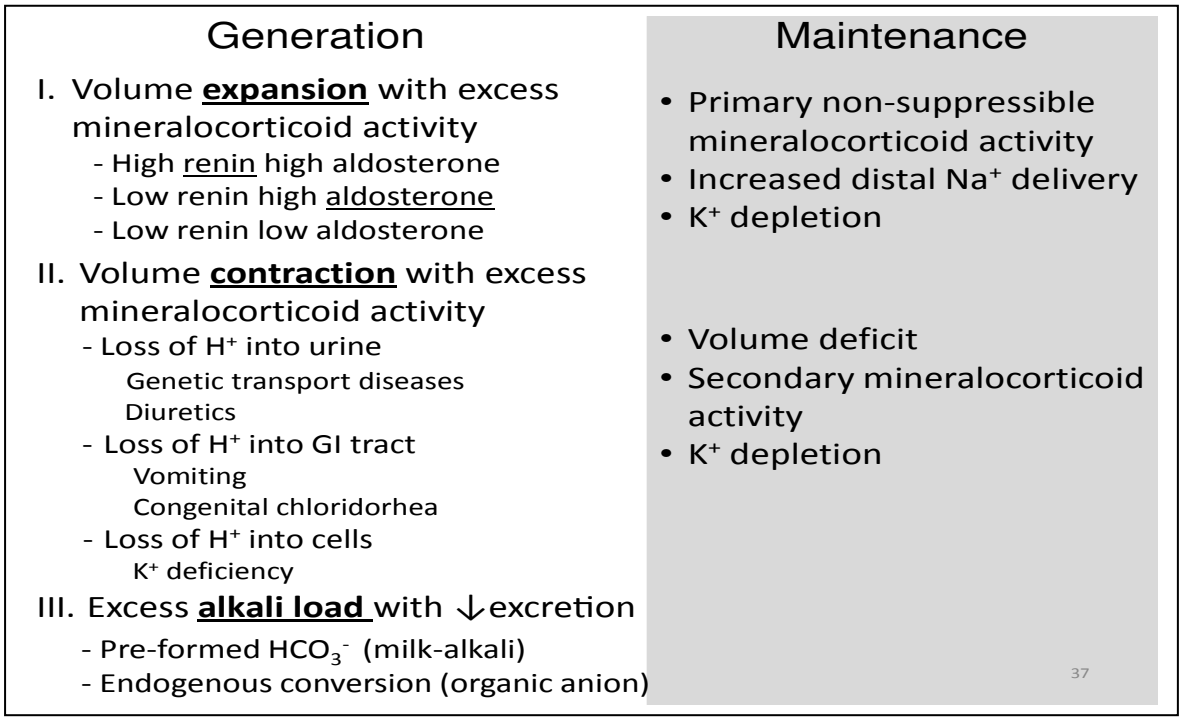


Figure 36

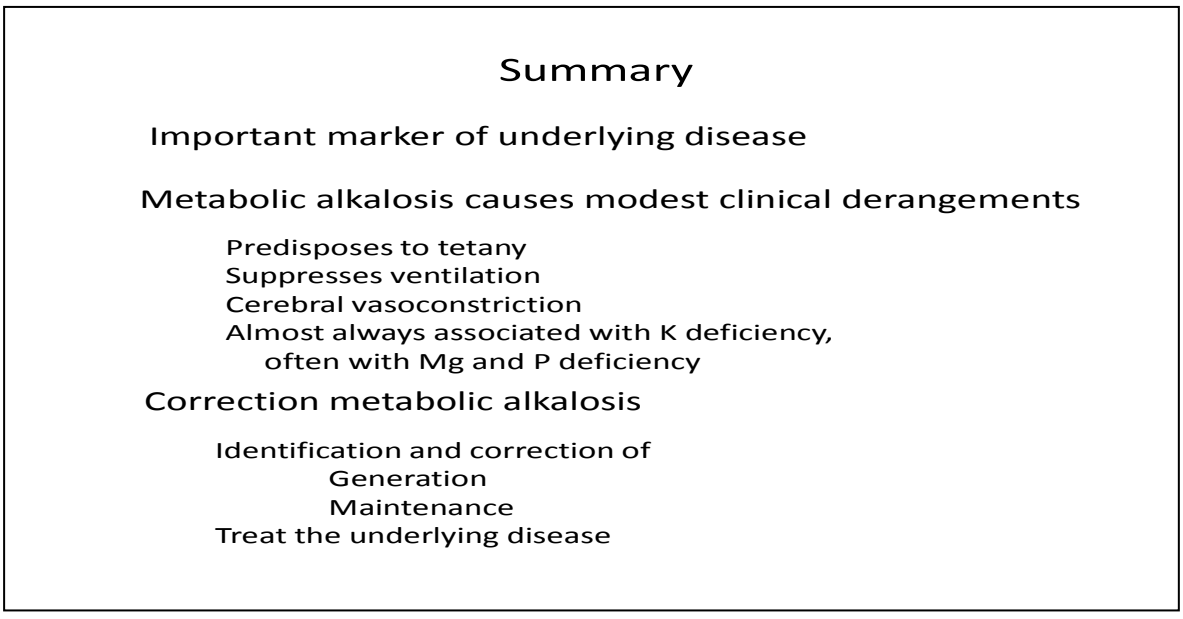


Figure 37

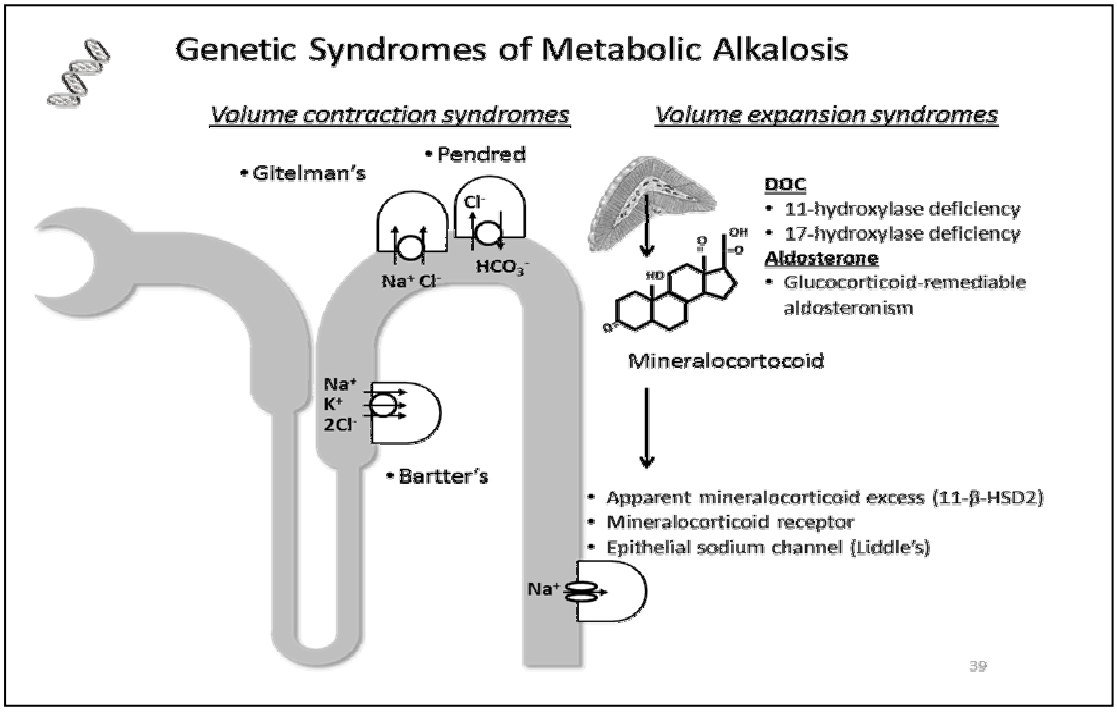


Figure 38

References

General reviews containing detailed description of the clinical syndromes as well as extensive bibliographies are included in references 1,2,3.

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