CHAPTER 17 - FLUID AND ELECTROLYTES - PART II
POTASSIUM

Introduction

Hypokalaemia (plasma K+ < 3.3 mmol/l), and Hyperkalaemia (plasma K+ > 5.5 mmol/l) are both common and potentially lethal, particularly if acute.

POTASSIUM HOMEOSTASIS

Dietary intake varies from 20-200 mmol/d. Absorption is passive in the gut so that the luminal concentration approaches that of plasma. Total body potassium is about. 4500 mmols, of which approx. 80 mmols are in the ECF and 4400 mmols in the ICF. Potassium is the major intracellular cation. The corollary of this is that the major factors causing changes in plasma K+ concentration are shifts from the intracellular to the extracellular fluid compartment. Urinary excretion represents the major source of potassium output (50-100 mmol/d) but losses also occur from other bodily fluids, especially the gut (faecal loss 10-20 mmols/d). Since potassium is mainly an intracellular cation, total body depletion of potassium is hard to judge from measurement of plasma potassium alone. Nonetheless, plasma potassium levels are important in their own right, especially in their cardiac effects.

CONTROL OF PLASMA POTASSIUM

Depends on intake, ECF-ICF distribution and renal potassium excretion.

1. ECF/ICF distribution. Normally, cell membrane sodium pump (Na-K-ATPase) keeps intracellular sodium low (approx. 10 mmol/l) and the intracellular potassium high (approx. 140 mmol/l).

(a) Acid base status

This is an important cause of variation in plasma potassium, due to redistribution across the cell membrane. In acidosis due to administration of mineral or inorganic acids such as HCl or NH4Cl, there is cellular uptake of H+ as a buffering mechanism and this leaves electrostatically negative ions behind in the ECF. (There is a strong barrier to inorganic ions like Cl- entering the cell) As a consequence, K+ leaves the cell (passively) in exchange for the H+ uptake, to maintain electrical neutralty. In this situation:

Clinical Point. A decrease in plasma pH of 0.1 units results in an increase in plasma potassium of approx. 0.6 mmol/l

Another factor tending to increase plasma K+ in inorganic acidosis is a decrease in renal potassium excretion, due to a lower amount of K+ in the renal tubular cells as in other cells, and therefore a reduced availability of distal tubular K+ for exchange in Na+ reabsorption. (By contrast, there is an increased amount of intracelluar H+, so helping to correct the acidosis.) In alkalosis, e.g. due to sodium bicarbonate infusion, the opposite holds i.e., H+ tends to move out of the cell in exchange for K+, again as a buffering mechanism maintaining plasma pH, and this may result in hypokalaemia.

A different situation arises in acidosis associated with organic acids such as lactic acid, acetoacetic acid etc. Here, in contradistinction to the above, most organic ions are freely permeable across the cell membrane and can therefore follow H+, so the whole organic acid is taken up into the cell, leaving no electrostatic imbalance to drive potassium out.

This leads us into the important but rather confusing situation of diabetic ketoacidosis. There, the acidosis is due to the accumulation of organic acids such as acetoacetic acid, hydroxybuturic acid, etc. as by-products of severly deranged carbohydrate metabolism. And being an organic acidosis we would therefore not expect much increase in plasma K+. Yet in practice this is one of the important situations where plasma K+ can beclome dangerously high. The major reason is that **lack of insulin prevents the normal glucose-facilitated cellular uptake of potassium**. Incidentially, this situation also serves to illustrate how misleadinding the plasma K+ level can be as a reflection of total body K +, because here not only is cell entry of K+ reduced but there is a high urinary excretion of K+ secondary to both increased filtered load of K+ and glucose-induced osmotic diuresis. Thus, despite the high plasma K+, total body K+ is markedly depleted.

Clinical Point. This becomes very important **in treatment of diabetic coma states**, because **giving insulin to correct the situation will rapidly lower plasma K+ to even dangerously low levels, unless careful and appropriate K+ supplementation is given at the same time.**

Lactic acidosis is an example of an organic acidosis where plasma K+ does not rise much at all, because of the free permeability of lactic acid across the cell membrane. Again, in this situation there is little or no exchange of intracellular K+ for extracellular H+ ; the pH is buffered by direct uptake of lactic acid into the cell. Lactic acidosis usually arises when aerobic metabolism is impaired, where lactic acid is the end-product of the glycolytic cycle in the cytoplasm. This is most characteristically seen where there is gross shutdown of organ perfusion as in haemorrhagic shock. There, in the interests of maintaining cerebral and coronary blood flow, flow to other organs may virtually be shut off, so resulting in their metabolising anaerobically. Because haemorrhage is common, this is an important clinical condition. Superior mesenteric artery thrombosis and secondary gut ischaemia(therefore anaerobic metabolism) is also a subtle and important cause of lactic acidosis.

(b) Insulin in the presence of normal or increased blood glucose is another powerful stimulant to cellular potassium uptake, especially in muscle and liver cells.

(c) Beta-receptor agonists such as adrenaline, salbutamol etc. also increase cellular potassium uptake and may cause hypokalaemia.

2. Renal Potassium Excretion. Potassium excretion by the kidney is influenced by three major factors, viz. aldosterone, distal renal tubular flow rates, and acid-base balance.

(a) Aldosterone. This acts by promoting sodium reabsorption in exchange for potassium (and H+) excretion in the late distal tubule and early collecting ducts. The major controllers of aldosterone release are the renin-angiotensin system, plasma potassium levels (via a direct action on the adrenal glomerulosa), and to a lesser degree ACTH.

(b) Distal Tubular Renal Flow Rates. Increased rates result in increase in clearance of potassium by a 'washout' effect. This is because the ability to maintain the normal cell:lumen potassium gradient is unaffected by high tubular flow rates. Thus, in states such as osmotic diuresis (Ch 16), significant urinary potassium losses occur.

(c) Acid-Base Status. In metabolic alkalosis, most commonly due to an excess of the inorganic bicarbonate ion, K+ moves into cells in exchange for the effluxing H+ ions, which are moving out of the cell to buffer the bicarbonate ion and limit pH change. This in itself lowers plasma K+. In addition, because the DCT renal tubular cells take up K+ just as other cells do, this favours urinary K+ excretion (rather than H+) in exchange for Na+, under the influence of aldosterone, thus lowering plasma K+ further. Metabolic alkalosis is therefore an important cause of low plasm K+, particularly in more chronic states.

In metabolic acidosis, the situation is complex and renal potassium excretion varies with different causes, as discussed above.

HYPERKALAEMIA

Definition: Plasma potassium level greater than 5.5 mmol/l.

(Normal plasma K+ range = 3.5-5.0 m.mol/l.)

Clinical Features.

Not usually a problem until plasma K+ > 6.0

As with most fluid and electrolyte/acid base disorders, symptoms are vague and include (proximal) muscular weakness, usually beginning in the lower limbs. Increasing weakness may be associated with parasthesiae. However, these findings may be absent despite life threatening hyperkalaemia. Key points in history-taking should include diet, medications, history of renal disease and assessment of urinary output volume. The most important clinical consequence of hyperkalaemia iscardiac dysrhythmia. ECG changes are related to the level of hyperkalaemia in the following general way:

6-7 mmol/l: tall peaked T waves.

7-9 mmol/l: flattening of P waves; prolongation of PR interval; aberrant QRS complexes; fusion of QRS and T waves (sine waves).

9-11 mmol/l: ventricular fibrillation and eventual death.

Before embarking on our hierarchic dissection of hyperkalaemia we should consider broad aspects of its causes.

CAUSES OF HYPERKALAEMIA

In broad terms these may be due to alterations of input, redistribution, or output. Factitioushyperkalaemia should always be excluded first. Haemolysis of the blood sample due to poor collection technique is the commonest cause. Another is when blood samples are left (e.g. overnight) uncentrifuged (worse if refrigerated - inhibits ATP pump mechanism). If in doubt, collect a fresh sample without tourniquet and *without* exercise such as fist-clenching to help blood flow.

1. Increased Potassium Intake. Not normally important, but can become so, particularly in renal failure, also in patients on intravenous therapy in hospital. In the latter situation, any IV potassium should be restricted to 4 mmol/hr, and be monitored (including ECG).

2. Tissue Redistribution. Causes include:

(i). Severe insulin deficiency with hyperglycaemia (with or without ketoacidosis) - see above.

(ii). Acidosis. Already discussed. Includes diabetic ketoacidosis as well as the administrarion of inorganic acids.

(iii). Tissue damage. Because cells contain such high concentrations of K+, extensive tissue damage can cause enough release of K+ into the ECF to result in hyperkalaemia. In this respect, tissue necrosis is an important medical as well as surgical cause of hyperkalaemia.

(iv). Medical causes include tumour lysis (especially after the administration of cytotoxic drugs), large tissue blood clots (haematomas); intravascular haemolysis; extensive tissue damage associated with inflammation.

(v). Surgical causes include burns and surgery/trauma. Extensive skeletal muscle damage (rhabdomyolysis) is a particularly important cause of hyperkalaemia, doubly so since myoglobinuria can impair renal function to impede excretion of the released K+.

(vi). In hospital common cause of hyperkalaenmia is excessive IV. administration of exogenous potassium, especially - as often occurs in the elderlym where there is any associated impairment of renal function. Stored blood administration can also be important in this context; (potassium leaches out of stored cooled cells).

(vii). Strenuous exercise is occasionally a cause of hyperkalaemia.

(viii). Hyperkalaemic - periodic paralysis is a rare disorder characterised by acute episodes of muscular weakness lasting a few hours, and probably due to sudden alterations of K+ tissue distribution.

3. Output. Any cause of renal dysfunction may give rise to hyperkalaemia, including both acute and chronic renal impairment / failure. In the latter, hyperkalaemia only becomes significant at GFR values of less than about 40 ml/min (plasma creatinine above about 150 micromol/l). Aggravating factors include metabolic acidosis and failure to limit potassium intake. Any given level of potassium intake is better tolerated in chronic renal failure than acute, in part due to the adaptation of the few remaining relatively normal renal tubules to the increased potassium load.

Since potassium excretion is markedly diminished with reduced rates of presentation of fluid to the distal tubule, severe ECF volume depletion is also a potential cause of hyperkalaemia (even despite secondary hyperaldosteronism).

(i). Potassium-sparing diurectics may produce hyperkalaemia, particularly in the presence of renal dysfunction. Spironolactone is a direct aldosterone antagonist which causes sodium loss in exchange for potassium in the renal DCT, and therefore potassium retention. The drugs triamterine and amiloride act somewhat differently from spironolactone in the DCT but have a similar effect. Be particularly careful about using such K+ sparing diuretics (even in combination with a thiazide diuretic) in patients with renal impairment.

(ii). Angiotensin converting enzyme inhibitors and angiotensin receptor blockers, used in the treatment of hypertension and heart failure may also increase plasma K+ due to inhibition of the renin/aldosterone system. Concurrent NSAIDs may complicate the picture.

(iii). Addison's disease or mineralocorticoid deficiency. Lack of aldosterone here prevents the renal reabsorption of Na+ in exchange for K+ and H+; hence plasma K+ rises, and plasma pH and Na+ fall. In the elderly a picture similar to primary adrenal failure (Addison's disease) can be seen in patients with a primary impairment of renal renin secretion.

HIERARCHIC APPROACH TO THE DIAGNOSIS OF HYPERKALAEMIA.

If plasma potassium unexpectedly high, repeat the measurement, because the most common cause is factitious hyperkalaemia (haemolysis). Next, eliminate obvious conditions such as diabetic ketoacidosis, renal failure, and hyperkalaemia-inducing drugs such as ACEI, and ARBs, amiloride, spironolactone, NSAIDs. Bear in mind that the elderly are especially prone to hyperkalaemia because of the high incidence of impaired renal function.

If the diagnosis is not clinically obvious, we must take a more systematic approach, first by having a high index of clinical suspicion for certain conditions, given their clinical context, and next by adopting a broad hierachic approach so as to narrow down the diagnosis from the broad to the more defined. In this respect, we should consider which of the three above broad causes of hyperkalaemia may be involved, viz. increased intake, K+ redistribution, or K+ retention.

Having disposed of the more common causes, urinary potassium concentration measurement helps dissect the rest. Thus, urine K+ is often elevated in the disorders of potassium redistribution and low in situations of aldosterone deficiency.

In the the context of acidosis, measurement of plasma bicarbonate also helps. If increased, we are usually dealing with chronic respiratory acidosis. If decreased (metabolic acidosis), we should look at the anion gap which, if normal, suggests mineralocorticoid deficiency, altered tissue distribution or a renal tubular defect; if high, it suggests other causes of acidosis such as keto-acidosis or intake of exogenous acids like salicylic acid.

Renal potassium retention causes are best dissected by first measuring the:

(i). Plasma creatinine. If greater than approx. 250 micromoles/l, then renal failure failure is likely to be the major cause of the hyperkalaemia. If, on the other hand, plasma creatinine is less than 200 micromoles/l, then measure:

(ii). Plasma aldosterone and renin. If plasma aldosterone low (and renin high), then in the main you are dealing with Addison's or the more common situation of administration of angiotensin converting enzyme inhibitors. In hyporeninemic hypoaldosteromism, plasma renin and alsodterone are both low.

If plasma creatinine not greatly raised and plasma aldosterone normal or high, then you are dealing with some:

(iii). Renal tubular cause of hyperkalaemia.

This includes drugs which interfere in some way or another with the action of aldosterone (spironolactone, triamterine, amiloride); also NSAIDs. Renal tubular dysfunction ('interstitial nephritis') - as may occur as a reaction to drugs, and in diabetes and other diseases involving the renal tubules . This can cause hyperkalaemia, especially if the process involves the DCT excretion of K+ in exchange for Na+ reabsorption.

Treatment of hyperkalaemia.

Where K+ levels exceed 7.0 mmol/l or where there are bizarre QRS complexes on ECG, you must immediately act to lower the plasma K+. This can be done in several ways including the administration of 50 mls of 50% glucose together with 10 units of soluble insulin; the effect is rapid and lasts for several hours (it pushes potassium back into cells along with glucose). A useful immediate treatment is 10-20 mls of 10% calcium gluconate IV over 2-3 minutes; this immediately though temporarily protects the heart against the toxic effects of potassium, but must be followed by more the long lasting intervention above to maintain the lower plasma K+. Sodium bicarbonate, 50-150 mmol (8.4% sodium bicarbonate contains 100 mmol/100 ml) given slowly I.V. (over 30-60 minutes) shifts potassium intracellularly and reduces plasma K+ for some hours. But you must give this carefully, with close monitoring of both plasma K+ and blood volume, because sudden hypokalaemia and volume overload are real hazards, particularly in patients with renal failure, . Over the long term, you may need to give sodium/potassium ion exchange resins either orally or rectally to maintain plasma K+ normal. If hyperkalaemia is severe and/or recurrent, haemodialysis may be needed.

HYPOKALAEMIA

Definition: Plasma potassium concentration of less than 3.0 mmol/l.

Clinical Features. The most important are the cardiac dysrhythmias including ventricular tachycardia, and even ventricular fibrillation in severe cases. Patients on digitalis are particularly vunerable. Other important symptoms include proximal myopathy, paraesthesiae tetany, reduced contraction of gut smooth muscle (sometimes ileus after surgery), as well as effects on renal function, from reduced GFR and, most importantly, reduction in sensitivity of the collecting tubules to the action ADH with resultant polyuria, thirst and polydipsia ('nephrogenic diabetes insipidus'). Glucose tolerance is also impaired and may sometimes precipitate glycosuria/diabetes mellitus. ECG changes include flattened T waves, the presence of U waves, and ST segment depression.

CAUSES OF HYPOKALAEMIA

We first consider this before our hierarchic diagnosis of hypokalaemia. As with hyperkalaemia, hypokalaemia can be considered under the headings of reduced intake, altered redistribution and increased output. But first consider artefactual causes, e.g. leukaemia, where the high number of white cells in the blood can take up K+ from the plasma whilst it is standing. If in doubt, repeat venesection and separate plasma immediately.

1. Reduced K+ intake. Rare outside hospital, but not uncommon in fasting hospitalised patients on IV preparations lacking potassium, especially if over-transfused with isotonic sodium chloride, when there will be an increased delivery of fluid to the distal tubule and with it an increase in potassium excretion.

2. Tissue Redistribution.

(a) Metabolic alkalosis results in a shift of K+ into the cells in exchange for H+, as a buffering pH mechanism (see above).

(b) Insulin, in the presence of a glucose load, also shifts potassium intracellularly. Administration of insulin may cause profound hypokalaemia. This is especially true in diabetic ketoacidosis, because there, replacement of ECF volume also corrects the acidosis, so creating a second reason for potassium to move back into cells. So much is this true that potassium supplements are usually given when treating patients with this medical emergency by the administration of insulin and replacement fluids, even though the initial plasma K+ is usually high. This becomes especially important if ever acidosis correction is aided by the administration of sodium bicarbonate, and indeed this is not any longer recommended. Normally, in moderate ketoacidosis, one only needs to correct the ECF volume depletion (with I.V. NaCl), and the elevated plasma glucose level (with insulin), and the acidosis will eventually take care of itself. The point is that, in the treatment of any diabetic keto-acidosis, correction of the acidosis by whatever means will cause potassium to move rapidly back into cells, and potassium supplements must be given simultaneously, and ECG and plasma K+ closely monitored at the same time. The basic problem in diabetic ketoacidosis is that the initial pre-treatment plasma potassium is high in the face of a depletion of total body potassium, i.e. a low intracellular K+. Moreover, this potassium depletion can be aggravated by increased K+ losses in the urine under the influence of the elevated plasma K+, especially if there is associated sodium depletion with secondary hyperaldosteronism.

(c) Initiation of Vitamin B12 therapy in severe pernicious anaemia can suddenly result in greatly increased red cell production, and with it increased utilisation of potassium. In this situation, clinically significant hypokalaemia can occur.

(d) Beta-adrenergic agonists (e.g. salbutamol, adrenalin etc.) may produce (mild) hypokalaemia, again by increasing cellular uptake of potassium.

(e) Hypokalaemic familial periodic paralysis is a rare autosomal dominant condition, predominantly affecting males. Episodic attacks of flaccid paralysis occur in association with marked hypokalaemia and last for 6-24 hours. The condition is almost certainly due to a shift of potassium into cells, for obscure reasons. Sometimes associated with hyperthyroidism

3. Output

Potassium may be lost from the body in a number of ways.

(a) **Nonrenal**

(i) Skin. Sweat ordinarily contains mostly sodium but as hyperaldosteronism occurs secondary to ECF volume depletion in severe sweating, the amount of potassium lost in both sweat and urine will increase so that substantial potassium loss may occur.

(ii) Gastrointestinal. Chronic diarrhoea (e.g. ulcerative colitis, laxative abuse) leads to potassium loss either from a decreased small intestinal potassium reabsorption or secretion of potassium into the colon. Na+ reabsorption in the colon is responsive to aldosterone, so that as time goes by sodium loss from diarrhoea will be associated with ECF volume depletion which will stimulate aldosterone and increase potassium loss not only in the stool but also the urine.

A special condition of lower gastrointestinal loss is villous adenoma of the rectum where the adenoma secretes a fluid relatively high in potassium content. Bowel fistulas of various sorts, and pancreatic fistulas, can also result in potassium depletion.

Prolonged vomiting is often associated with hypokalaemia, partly from potassium loss in the vomitus per se, and partly from the associated metabolic alkalosis (from H+ loss) and ECF volume contraction (from NaCl loss) - both of the latter increase the amount of K+ exchanged with Na+ in the distal tubule.

(b) **Renal Potassium Loss**

(i) Diuretics.

Any inhibition of renal DCT or loop of Henle sodium reabsorption by diuretics (thiazides, frusemide) will result in increased fluid delivery to the distal tubule, and this increased flow rate causes kaliuresis. Secondary hyperaldosteronism from ECF volume depletion aggravates this further.

(ii) Mineralocortoid Excess.

Suspect where patient is hypertensive. The classic condition is Conn syndrome or primary hyperaldosteronism where sodium is retained in the DCT in exchange for potassium, and the latter is lost in the urine (urinary Na:K ratio therefore normally becomes less than 1.0). Hypertension occurs as a consequence of the sodium retention. Other endogenous or exogenous mineralocorticoids or mineralocorticoid-like substances (e.g. liquorice) can have the same effect.

(iii) Renal tubular acidosis.

Two types, type 1 or distal renal tubular acidosis (DTA), and type 2 or proximal tubular acidosis.

a) Type 1 (DTA) is associated with a defect in the excretion of H+ in the distal tubule. This results in metabolic acidosis with neglible ammonium excretion and low titratable urinary acidity. The hypokalaemia results from increased urinary potassium secondary to a failure of H+ competition with potassium into the distal tubule in exchange for excreted sodium.

b) Type 2 or proximal renal tubular acidosis is associated with a defect in the ability of the PCT to secrete H+ and so facilitate the normal PCT reabsorption mechanism of bicarbonate. This results in massive amounts (15-20% of filtered load) of the relatively impermeant bicarbonate anion being delivered to distal tubular sites and swamping its reabsorption mechanisms. The combination of sodium (bicarbonate) loss causing ECF volume contraction and aldosterone stimulation, together with increased (volume) delivery of sodium bicarbonate to the distal tubule, produces urinary potassium depletion.

(iv) Bartter's syndrome

Is a condition of normotensive renal potassium loss associated with hyperaldosteronism, probably resulting from a subtle primary defect in (sodium) chloride reabsorption. Care should be taken to exclude furtive diuretic abuse before making this diagnosis.

(v) Magnesium depletion

Can increase K+ excretion to cause secondary potassium depletion. Consider in undernourished, alcoholics, and those on Mg++ free parenteral feeding.

Other renal tubular disease or dysfunction can cause renal K+ loss, but we now have enough background to consider an approach to the hierarchic diagnosis of hypokalaemia, based on urinary K + excretion.

HIERARCHIC APPROACH TO THE DIAGNOSIS OF HYPOKALAEMIA.

Assessment should begin with a careful history and physical examination, concentrating particularly on drug and psychosocial history, and assessment of the patient's volume status, particularly ECF/ blood volume. Measurements of blood pressure and urinary as well as blood electrolytes are of central importance. Serum magnesium and arterial blood gases may provide critical information, Additional important investigations include plasma renin, aldosterone and cortisol.

1. First determine whether hypokalaemia is artifactual, the result of redistribution of K+, or a reflection of true K+ depletion.

Artifactual values may be seen in leukaemic patients with a WBC of 100-250,000. To avoid spuriously low values of plasma K, separate plasma in leukaemic patients immediately after venesection.

2. Redistribution (intracellular shift). Discussed above, and should always be borne in mind. Includes metabolic alkalosis and insulin administration.

3. Potassium depletion.

A. A Hierarchic Approach Based on Urinary Potassium Measurement

A helpful early investigative step is to measure 24 hour urinary potassium excretion, particulartly in the normotensive patient.

1. **If urinary potassium is low**,

(< 20mmol/day), then we are not dealing with a renal cause of hypokalaemia, and the problem becomes one of dissecting whether it is due to a reduced potassium intake (rare), a redistribution of potassium associated with alkalosis, or potassium losses from elsewhere. Vomiting and diarrhoea are usually obvious, but both may be furtive (e.g. laxatives; vomiting related to so-called 'bulimia nervosa'). Check to see whether the patient is on any relevent drugs such as salbutamol.

2. **If urinary potassium is high**,

(> 20 mmol/day), the diagnosis can be more difficult because hyperaldosteronism secondary to ECF volume depletion from sodium loss may occur to complicate matters in situations such as diarrhoea by causing secondary renal potassium loss.

(a) In the assessment of any hypokalaemia, it therefore becomes important to

Estimate the ECF volume.

(i) If ECF vol. low,

In this situation, any elevation of urinary potassium does not necessarily indicate a primary renal source of potassium loss, and you should look hard for vomiting or laxative abuse (especially furtive). If you suspect furtive vomiting, measure plasma bicarbonate as an index of metabolic alkalosis (confirm with blood pH). Differentiate from furtive diuretic abuse by measuring urinary Na+ : low in vomiting, laxative abuse and prior diuretic use/abuse (<10 mmol/day), high (>10 mmol/day) in current diuretic usage.

Prolonged vomiting is a situation where there are two quite potent causes of potassium loss in the urine (alkalosis and ECF volume depletion) in addition to an effectively reduced potassium intake.

(ii) If ECF vol. normal,

Think of magnesium deficiency; also the rarer tubular acidoses and Bartter's syndrome; villous adenoma of the rectum.

(iii) If expanded ECF volume,

Look first at whether this expansion falls right across the whole plasma volume and interstitial fluid volume compartment, or mostly on the interstitial compartment in the form of oedema. Hypokalaemia in the latter situation is usually due to one or other of the hypoalbuminaemic states already discussed in Ch. 16, and is caused by secondary hyperaldosteronism.

Where the expanded ECF volume falls on both the plasma volume and interstitial fluid volume compartments, then we are dealing with some form of primary sodium retention associated with renal potassium loss, i.e. an increase in mineralocorticoid or mineralocorticoid-like activity. These patients are usually hypertensive, and this leads us to a second hierearchic approach to the diagnosis of hypokalaemia.

B. A second level to the hierarchic diagnosis of hypokalaemia.

Having eliminated non-renal (primary) causes of potassium (or sodium) loss, and conditions of potassium redistribution (e.g. insulin administration, alkalosis), a high urinary potassium can be taken to mean hypokalaemia brought about by primary renal potassium wasting. The physiologic mechanisms involved in this form the basis of developing a further practical clinical approach that divides renal potassium wasters into normotensive and hypertensive groups, and then further subdivides the hypertension groups on the basis of the secretion of renin and aldosterone and cortisol - but always taking into account our first hierarchic level of diagnosis based on ECF volume status.

1. Renal Potassium Wasting in the Normotensive Patient.

This includes patients with renal tubular disease or dysfunction. The commonest cause is the administration of diuretics. All diuretics inhibiting sodium reabsorption proximal to the site of potassium excretion would be expected to increase sodium and fluid volume delivery to the DCT, and so facilitate potassium excretion. Thus, diuretics acting on the PCT, loop of Henle, and DCT will all induce increased potassium excretion. Such diuretics include carbonic anhydrase inhibitors, frusemide and the thiazides. All diuretics have the potential to produce ECF volume contraction, and with it secondary hyperaldosteronism to accentuate renal potassium loss.

2. Renal potassium wasting in the hypertensive patient.

Nearly all such patients have excess mineralocorticoid activity, be it due to adrenal or other mineralocorticoid-like activity. As a consequence they have an elevated blood pressure and a decreased Na+/K+ ratio in the urine. They can be further subdivided on the basis of whether their plasma renin, alsosterone, cortisol and ECF volumes are high or low.

(i). High renin activity.

Characteristically occurs in patients with renal artery stenosis; and in patients with malignant hypertension (where the hyperaldosteronism is secondary to 'pressure natriuresis' and resulting low ECF volume). Almost any condition producing renal cortical ischaemia can produce hypertension associated with high renin and high aldosterone plasma levels. Rare patients have primary renal renin-secreting tumours. Of course, patients with essential hypertension on diuretics, particularly thiazides, may be hypokalaemic.

(ii). Hypertensive patients with low renin activity usually have primary excess of mineralocorticoid effect.

These can be further subdivided into those where the increased mineralocorticoid effect is due to aldosterone (Conn syndrome), and those where it is due to other mineralocorticoid or mineralocorticoid-like effect.

Primary elevations of aldosterone can be further subdivided on the basis of whether they are caused by adrenal adenomas or by diffuse adrenal hyperplasia.

Patients with excessive other mineralocorticoid activity on the other hand, can be subdivided into:

(a) Increased endogenous mineralocorticoid activity, as in the ectopic ACTH syndrome (diagnose by increased plasma cortisol),

(ii) Increased exogenous substances with mineralocorticoid-like activity (e.g. furtive **liquorice**ingestion), and

(iii) In rare cases, called syndromes of 'apparent mineralocorticoid excess', reduced plasma levels of aldosterone and other mineralocorticoids. In one such condition, there is stimulation of an aldosterone-independent renal potassium-sodium exchange (Liddle's syndrome). In another, an enzyme (11-beta-hydroxysteroid dehydrogenase) which normally degrades cortisol in the renal DCT is deficient, thus allowing this adrenal steroid to both access and stimulate the renal tubule aldosterone receptor.

SUMMARY

In assessing patients with hypokalaemia, we need to have a complete history and physical examination. Aspects of special importance in the history are drug and psychosocial history - particularly relevant in furtive laxative or diuretic abuse, and furtive vomiting. In the examination we need to make a thorough assessment of the ECF volume, including the circulating blood volume, and blood pressure. In difficult cases, where the clinical signs and symptoms do not point strongly in any particular direction, we need biochemistry to help but again we must use this in a hierarchic way, approaching broad questions first. The two most important of these are whether the patient is hypertensive or not, and whether or not we are dealing with a primary renal leak of potassium.

In non-hypertensives, if urinary potassium is low, then the primary problem is certainly not renal potassium loss.

However,the reverse is not always true: Renal K+ losses can be high even where this is not primary. Thus, non-renal potassium loss can be associated with sodium loss (eg. diarrhoea), causing secondary hyperaldosteronism to complicate the interpretation of the urinary potassium (which becomes high because of exchange foe Na+). A simple check on whether there is hyperaldosteronism is to measure the urinary Na:K ratio - less than 1.0 if there is hyperaldosteronism. A low urinary sodium is also a good indicator of non-renal sodium loss, and a high urinary sodium may be the only clue to furtive diuretic abuse.

If there is ECF volume expansion, hypertension, and renal potassium wasting, you will need to identify the various excess mineralocorticoid activity subgroups as discussed.

These guidelines will help formulate an ANATOMICAL DIAGNOSIS.

PATHOLOGICAL DIAGNOSIS is based on our usual guidelines.

FUNCTIONAL DIAGNOSIS is the way we have already made our Anatomical diagnosis. But it is also useful in treatment, e.g. hyperaldosteronism may be overcome with spironolactone in appropriate cases.

AETIOLOGICAL DIAGNOSIS. Much of this has been discussed above. In any case where diagnosis of hypokalaemia is difficult, be particularly careful to look out for furtive abuse with laxatives, furtive vomiting, drugs and particularly diuretics.

MCQs and Problem for Solving No.1.

A**. Mechanisms in Disease**

1. A patient in a surgical ward has acute pancreatic disease with a pancreatic fistula, is sweating and has associated pain.

Which of the following statement is/are likely to be correct?

1. The fluid being lost from the fistula will be relatively alkaline.

2. Any isotonic Na+ loss would normally be expected to lead initially to a reduction in plasma volume and interstitial fluid volume, but not to intra-cellular volume.

3. ECF volume depletion in such a patient might eventually produce secondary hyperaldosteronism.

4. Plasma K+ might eventually become elevated despite any secondary hyperaldosteronism because of the development of secondary acidosis from bicarbonate loss.

5. A significant reduction in plasma Na+ concentration is recognised to occur in severe cases due to stimulation of ADH secretion by ECF hypovolaemia.

6. Any reduction of plasma Na+ concentration could be contributed to by a decrease in both fluid volume and chloride concentration delivered to the thick ascending limb of the loop of Henle.

2. Mechanisms in Disease

A patient is admitted with a marked reduction in plasma albumin (22 g/l) related to chronic alcoholic liver disease. Which of the following would be likely?

1.Oedema.

2. High effective plasma volume.

3. Secondary hyperaldosteronism.

4. A high plasma potassium.

5. A high plasma sodium.

3. Mechanisms in Disease

A 22 year old patient is admitted with a diagnosis of Addison's disease (adrenal cortical atrophy). Which of the following would be characteristic?

1. Hypokalaemia.

2. Hypernatraemia.

3. Difficulty in excreting a standard water load.

4. A relatively low blood urea.

5. A high plasma creatinine.

6. A high urinary Na+.

7. A low urinary K+.

8. A reduced glomerular filtration rate with corresponding elevation in the level of plasma creatinine.

9. Postural hypotension.

10. ECF volume contraction.

11. A low urinary pH.

12. A brisk rise in plasma cortisol after the administration of ACTH.

B. Problem-Solving

A 25 year old woman (1) complains of a 12 months history (2) of increasing lethargy, tiredness and general malaise (3), and a 3 months history of progressive thirst together with an increased intake of

water (4), muscular weakness, noticed particularly on climbing stairs (5) and "pins and needles" in her fingers (6). She has lost approx. 2.5 kg over the 12 month period but has been deliberately dieting (7). She has occasionally noticed excess sweating but her temperature has been normal (8). Appetite normal; some constipation (9). Nocturia increasing to up to five times per night over the last three to four months (10). No headaches, visual disturbance or other CNS symptoms, no dyspepsia or abdominal pain, and no shortness of breath or chest pain. No history of ankle swelling (11) or palpitation. Family history: all are well except her father who, at aged 65, suffered a severe heart attack 18 months ago and now has 'cardiac failure' requiring digoxin, an ACEI and diuretic treatment (12). Four older normal siblings; mother well, aged 62. The patient has been dieting for the past two years to try and lose weight (13) but otherwise her past history is negative. Social history: lives at home with her parents, works as a nursing sister, smokes 20 cigarettes per day (14) and drinks "occasional" alcohol. No stable male relationships; no particular emotional domestic or financial stress. Not under under medical treatment with any drugs (15).

On examination you find a somewhat tense and not overweight young woman (16) with cool clammy hands and feet and a pulse of 108/min (17). General appearance is fairly normal except that the skin appears dry and tissue turgor over the cheekbones and forehead is diminished (18). BP 100/60 mm Hg lying and 90/50 mm Hg standing (19). On standing the pulse rate also rises from 108 to 120 beats per minute (20). JVP is not visible even with the patient lying flat (21), but is eventually seen after pressure is exerted by the examining finger over the lower aspect of the supraclavicular fossa (22). Lymph node areas clear. Heart NAD except for tachycardia. No bruits heard in the neck, heart or epigastrium. Peripheral pulses all normal. No radio-femoral delay. Chest normal. Abdomen normal. CNS: slight difficulty in standing unaided from squatting position (23); Trousseau's sign negative (24). Temperature normal (25). Urine examination SG 1.005 (26). 24 hour urine volume 3.5 litres (27). Urine microscopy: NAD.

Investigations: Plasma electrolytes: Na+ 130 mmol/l (28), K+ 2.6 mmol/l (29), bicarbonate 34 mmol/l (30). Plasma creatinine 140 micromol/l (normal < 115) (31). Blood urea 4 mmol/l (normal 4-8) (32). Plasma calcium, magnesium, phosphate normal; liver function tests normal, plasma albumin normal. Urine 24 hour protein excretion normal; K+ excretion 50 mmol/day (33), Na+ excretion 60 mmol/day (34). No amino-aciduria, phosphaturia or glycosuria (35).

Draw up a columned solution to this problem, then answer the following questions.

Which of the following questions is/are likely to be correct?

1. This patient has evidence that renal K+ loss is contributing to the hypokalaemia.

2. There may be a component to the renal K+ loss which is secondary.

3. The most likely diagnosis is primary hyperaldosteronism.

4. It would be important to question her closely about licorice intake.

5. The relatively normal Na+ excretion is evidence against ECF volume depletion in this case.

6. The chronic history of weight loss in this particular patient is suggestive of an underlying neoplastic process.

7. A renin-secreting tumour is a rare but real diagnostic possibililty.

8. This problem is characteristic of hyperaldosteronism secondary to hypoproteinaemia.

9. The whole picture is classical of laxative abuse.

10. Her father's condition and treatment may well be relevant to her problem.

11. The elevated plasma bicarbonate could be secondary to the hypokalaemia.

12. The low urine specific gravity and high urine volume are likely to be secondary to the low plasma sodium concentration in this patient.

13. She probably has proximal renal tubular acidosis.

Problem 1 Solution Part 1

WHERE?	WHAT?	HOW?	WHY?
	3. 12 months ,with symptoms increasing = chronic progressive condition. 7. Wt. loss of 2.5 kg. , but on diet; thus hard to interpret.	3. lethargy, malaise. = non-specific symptoms.	1. 25 yrs. 2. Female 7. Dieting.
INTERIM	CONCLUSION		
?	Chronic,progressive	Non-specific symptoms	Young female.
	4. 3/12. = Subacute 5. 3/12. subacute 8. Afebrile = no evid. of inflamm^{n}. 9. Appetite unchanged &wt. loss assoc. with dieting. Thus, nothing to suggest malignancy. 10. 3/12 - subacute. 24. Temp. N. i.e. No evid of inflamm^{n}.	4. Thirst, polydypsia. ? Diabetes mellitis, insipidus ? struct. or funct. renal tubular prob. ?primary polysypsia. 5. Weak climbing stairs = prox. lower limb girdle weakness, espec hip extensors. 6. Paraesthesia in fingers abnormality of sens. nerve conduction. 8. Excessive sweating, but afebrile, thus ?adrenergic i.e. ? anxiety. 9. Constipation. Non-specific symptom, but ? 2° to dehydration. 10. Nocturia/polyuria. Conclusions similar to 4. above. 11. No CNS, GI., RESP. or CVS symptoms. No ankle swelling = no overt RHF, renal failure. 16. Tense/anxious. Not overweight.- ? why dieting. 17. Cool clammy hands; pulse 108/min consistant with anxiety. 18. Skin dry; poor tissue turgor = ? ECF vol. depletion. 19. BP low, espec on standing = ? ECF vol. depletion. 20. Pulse rate rise on standing = Art. baroreflex intact. 21. JVP ↓ 22. JVP.also fills slowly = ECF VOL. DEPLETION. Lymph nodes, CVS, chest, abdo., CNS., all normal. 23. Trousseau's sign neg = no overt Ca^{++} ↓. 25. Urine SG. low = dilute urine. 26. High 24 hr. urine vol. prob. 2° to dilute urine, but is this due to polydypsia or to renal dysfunction. Micro. N.A.D.	12. FH. Father, aet.65 yrs., has"CCF", following a "heart attack". Now on Rx..incl. dig. vasodilators, & diuretics. No other signif family history. 13. Dieting for 2 yrs in an attempt to lose weight. No other past illnesses. 14. Social history. Lives at home. Nursing sister. Smokes 20/day. "Occass" EtOH No evid stress. 15. no prescribed medications.

Problem 1 Solution -Part 2

WHERE?	WHAT?	HOW?	WHY?
INTERIM	CONCLUSION		
1.	Chronic(12/12).	Lethargy; wt.loss despite N. appetite. Dieting despite rel. normal wt. ? Why.	Father on Rx for "CCF", incl. diuretics.
2.	Subacute (3/12).	Prox. muscle weakness prob. of neurol. origin in view of paraesthesia. ? metabolic cause. ECF. vol. depletion.(salt & H_2O). Therefore, thirst & polyuria not likely due to 1°polydypsia. ↑ vol of dilute urine, despite ECF vol. depletion = Not 1° polydypsia.Thus, prob. renal dysfunction causing polyuria. Tense, cool hands = evid. of Anxiety	Patient's occupation. = Nursing sister.
Investiations			
		27. Plasma Na^+ low 28. Plasma K^+ low. 29. Plasma HCO_3 high, = prob. metab. alkalosis, 2° to low K^+ 30. Plasma creatinine sl. high. 31. Plasma urea rel. low c.f. creat. prob. 2° to high urine flow, reflecting polydypsia / renal tubular dysfunction. Plasma Ca^{++}, Mg^{++}., phos., LFT's, alb. all normal. No proteinuria. 32., 33. Urinary Na^+ & K^+ both high rel. to plasma levels. = ? 1° renal leak of Na^+, K^+. 34. No aminoacids, phosphates, or glucose in urine = no PCT.dysfunction.	

CONCLUSIONS

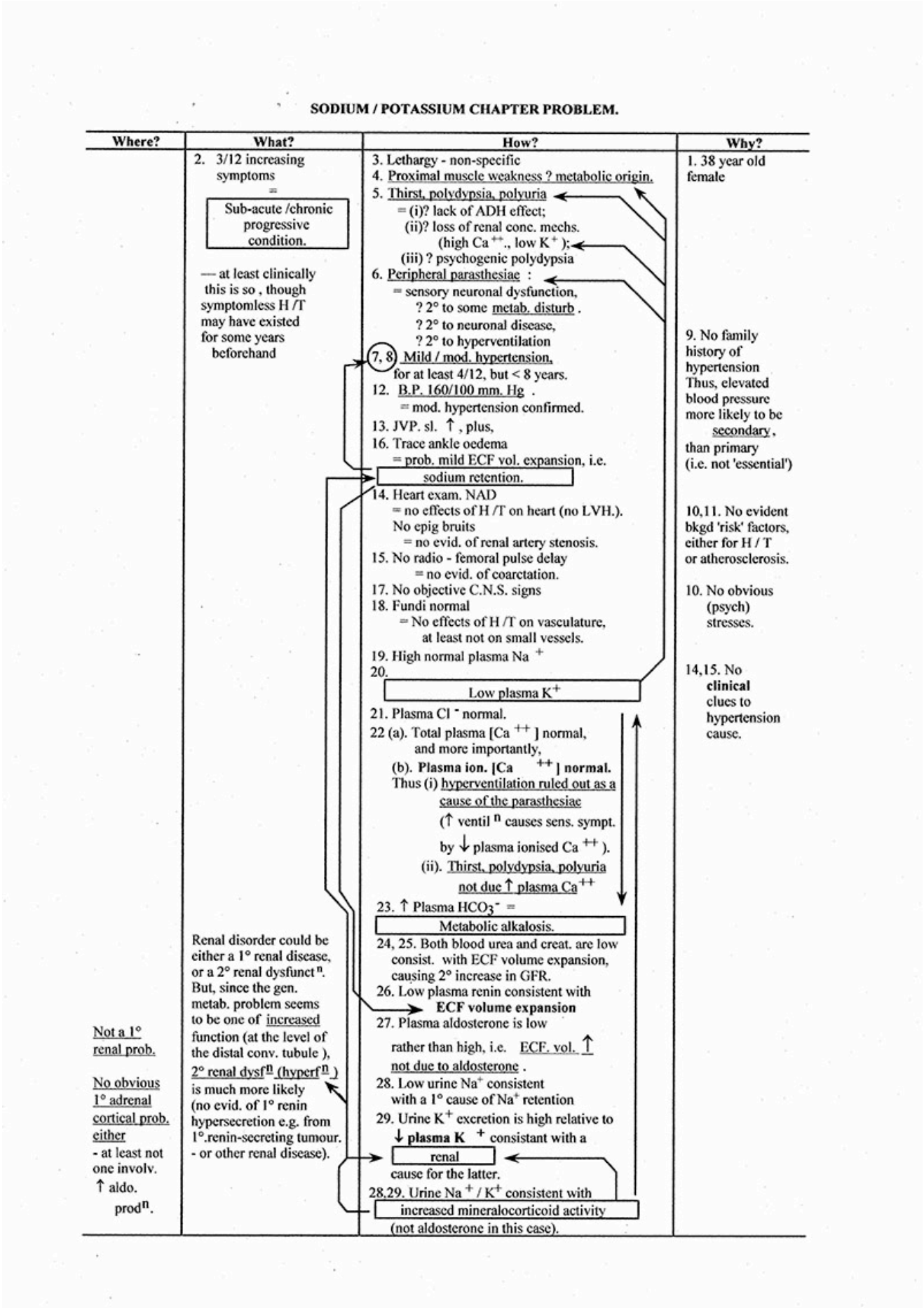
ANATOM. DIAGNOSIS	PATHOLOGICAL DIAGNOSIS.	FUNATIONAL DIAGNOSIS	AETIOL. DIAGNOSIS.

Problem 2. for Solving

2. A 38 year old female (1) presents with a three months history (2) of increasing lethargy (3) proximal muscle weakness (4), increased thirst, polydipsia, and polyuria (5) together with some bilaterally symmetrical parasthaesiae of the hands and feet (6). No other specific symptoms. In the past, her doctor noted her blood pressure to be "slightly elevated" some four months ago (7); no hypertension with pregnancies 14, 10 and 8 years ago (8). Family history - nil relevant, in particular no family history of hypertension (9). Social history: happily married, nonsmoker; "occasional" alcohol; no particular stresses (10). Medications: nil (11).
On examination: General inspection NAD. CVS - BP 160/100 mm Hg (12); JVP 4 cm (13); heart NAD, no bruits in heart or epigastrium (14); no delay in femoral pulse (15); minimal ankle oedema (16). Chest NAD. Abdomen NAD. CNS: subjective parasthesiae over the fingers and toes of both limbs, but no objective signs (17). Fundi NAD (18).

Note: After studying the following investigations, draw up the usual four column table to solve this problem, giving your final diagnosis in each of the diagnostic categories at the end. Do this before viewing the columned solution to the problem set out in the next section.

Problem 2 Solution Part 1



Problem 2 Solution Part 2

SODIUM / POTASSIUM CHAPTER — CONCLUSIONS

Anatomic Diagnosis	Pathological Diagnosis	Functional Diagnosis	Aetiological Diagnosis
Nil obvious.	2. (3/12) = Sub-acute / chronic, at least clinically.	ECF volume expansion (Na^+ retention - 13, 16, 19, 24, 26). Low plasma K^+ (20) causing (i) prox. myopathy (4). (ii) polyuria, polydypsia (5). 2° to impairment of renal conc. mechs. (iii) sensory neuronal dysf^n (6). (iv) 2° alkalosis (by H^+ moving into K^+ depleted cells). Hypertension , mod. severity (7, 12), — Cause - 2° to Na^+ retention — Effects - no 2° effects of H / T on CVS. (i) No LVH. (ii) No retinal vasc. change. Renal Na^+ retention (28) & K^+ loss (29), (via. distal convoluted tubule, at site of Na^+ / K^+ exchange).	Hypertension, secondary to Na^+ retention, caused by ↑ mineralcorticod activity, either (i) endogenous (e.g. some non-aldosterone mineralo-corticoid, such as DOCA., secreted by an adrenal tumour (benign in view of time - course) ** or - (ii) exogenous

CONCLUSION

Increased mineralocorticoid not due to aldostetrone.

**Comment: Assays for other endogenous mineralocorticoids also turned out to be normal. Further close questioning revealed that the patient had been eating large quantities of licorice for the past 6 - 9 months. (Licorice contains the mineralocorticoid-mimiking compound glycyrrhetinic acid, which causes the syndrome of 'apparent mineralocorticoid excess' by inhibiting renal DCT 11-ß-hydroxysteroid dehydrogenase -see text; also ref. 3.).