CHAPTER 18 - CALCIUM CALCIUM HOMEOSTASIS

CALCIUM BALANCE

Normal total plasma Ca++ (bound and free) = 2.1-2.5 mmol/l.

Calcium Balance

Input

Normal diet contains 20-25 mmol calcium of which about half is absorbed in the upper small intestine mostly under the influence of vitamin D. Of this, approx. 7 mmols is secreted back into the gut in digestive juices so that approx. Thus, 15-20 mmols appears in the faeces daily. Normal net absorption is therefore 5-10 mmols/day, depending on diet and age. Calcium binders (e.g. phosphate, oxalate, insoluble alkali), decrease absorption.

Distribution

Once absorbed, blood calcium equilibrates with a large bone reservoir (approx 35,000 mmol calcium in the adult) but only approx. 1% of bone calcium is available for rapid exchange with ECF calcium.

Plasma Calcium

About half of the total plasma calcium is bound to circulating albumin. What matters physiologically though is the free, or more correctly, the "ionized calcium", which is maintained within narrow limits by the action of parathyroid hormone (PTH). Thus, we can only interpret total plasma calcium levels in the light of plasma albumin. The measured total plasma calcium concentration will be low when plasma albumin is low, so as to maintain ionized plasma calcium normal. A fall or rise in plasma albumin concentration of 10 g/l is normally associated with a change (in the same direction) in the total plasma calcium of about 0.25 mmol/l. Binding of calcium to albumin is also highly pH dependent - alkalosis increases binding and acidosis decreases it. (Hence the hypocalcaemic symptoms of parasthesiae/tetany of hyperventilation-induced respiratory alkalosis). None of the other normally circulating plasma proteins bind plasma significantly, but some of the abnormal ones do, such as myeloma proteins (IgG) and other paraproteins.

N.B. Laboratories now report calcium levels corrected for albumin. If requested, free ionized calcium can be measured independent of albumin binding by ion selective electrodes.

HORMONES IN IONIZED CALCIUM CONTROL

Tight control of plasma ionized calcium is achieved by parathyroid hormone (PTH), the active metabolite of Vitamin D (1,25-OHD), and calcitonin, each acting at one or more of three levels, namely calcium absorption (1,25-OHD), bone resorption (mostly PTH), and renal calcium retention (1, 25-OHD and PTH both). As an approximation, we can say that the (ionized) calcium x phosphate product is reasonably constant, i.e. that if the phosphate rises, then by the law of chemical mass action, calcium will tend to fall. But although this reciprocal relationship does generally exist in plasma, it is not really related to the law of mass action at all, but rather to the action of parathyroid hormone to alter plasma calcium and phosphate in opposite directions.

1. Parathyroid Hormone (PTH).

PTH release is stimulated by reduced plasma ionized calcium and its main action is to raise plasma calcium and lower plasma phosphate. Relevant direct actions in this respect are activation of bone osteoclasts to increase bone resorption (releasing both calcium and phosphate) and a renal action to increase calcium reabsorption and decrease renal phosphate (and bicarbonate) reabsorption. PTH also stimulates the conversion of vitamin D to its active 1,25-OHD metabolite in the renal tubules, and so has a further indirect effect on plasma calcium and phosphate through the action of the latter to increase calcium phosphate reabsorption from the gut.

The classic biochemical features of **excessive PTH** action are as follows:

Hypercalcaemia (increased bone resorption; increase renal calcium reabsorption; increased gut absorption via PTH stimulating increased 1, 25-OHD).

Hypophosphataemia - occurs via increased renal phosphate excretion, and despite tendency of plasma phosphate to be increased by direct PTH action on bone and indirect effect on gut. Because of these conflicting actions, plasma phosphate may rise in some circumstances, particularly where PTH is chronically high enough to cause hypercalcaemic damage to the kidney (phosphate retention), and massive bone resorption.

Increased plasma alkaline phosphatase activity (ALP) results from the increased bone osteoblastic activity occurring as a secondary or compensatory response to the primary bone resorption.

Excess PTH mostly arises from primary hyperparathyroidism. This is mostly secondary to an adenoma in one of the four parathyroid glands. Then, surgery is the treatment.

2. Vitamin D

This fat soluble vitamin is absorbed from the gut, converted first to 25-OHD in the liver, and then to its final metabolically active form, 1,25-OHD, in the renal tubules (some conversion also occurs in bone, placenta, and even pulmonary alveolar macrophages - see relevance below).

Renal 1,25 OHD synthesis is stimulated by increased levels of PTH, decreased circulating 1,25-OHD (negative feed-back), and by decreased dietary calcium and/or phosphate; synthesis is decreased when PTH levels are low, and in renal tubular disease.

The primary action of physiological doses of 1,25-OHD is on the gut, where it increases the absorption of calcium (and phosphate) thereby maintaining plasma calcium levels. Its most important overall effect on bone is to ensure that newly formed bone matrix or osteoid is calcified. Physiological levels of Vit D promote bone formation, but large doses increase bone resorption. 1,25-OHD also has some effect to increase calcium reabsorption in the renal tubules.

The overall effect of 1,25-OHD is therefore to raise both calcium and phosphate levels in the plasma, whereas PTH classically leads to an increase in calcium and a reduction in plasma phosphate. 1,25-OHD is really a hormone.

3. Calcitonin

Secreted by the C-cells of the thyroid. It does not lower plasma Ca++ in normal adults, but often has a significant effect to do so in situations of increased calcium turnover, e.g. in children, Paget's disease and malignant hypercalcaemia. Its major actions are to inhibit osteoclastic activity (and decrease renal reabsorption of calcium and phosphate).

4. A number of **other hormones** can affect calcium homeostasis, including glucocorticoids (increased osteoid catabolism) thyroxine (increased bone turnover), growth hormone (decreased renal calcium reabsorption, increased plasma phosphate), androgens (increased bone growth and calcium deposition), oestrogens (increased osteoblastic activity and therefore increased bone deposition) and glucagon (suppressed bone resorption).

HYPOCALCAEMIC STATES

Clinical Features.
Acute hypocalcaemia is manifest by cramps (and even tetany), and paraesthesiae of the extremities and circum-oral areas, reflecting increased neuromuscular excitability. If severe, Trousseau's and Chvostek's signs may be positive. Hypotension is not uncommon. Chronic hypocalcaemia (especially in the young) may cause significant further changes in a number organs, and give rise to a number of problems, e.g. mental retardation, extrapyramidal symptoms, skeletal malformations (including short stature, poor formation of teeth), dermatitis and hyper-pigmentation.

ECG abnormalities include prolonged Q-T interval and ventricular conduction abnormalities.

Hypocalcaemia can come about in a number of different ways, and the following will give a background to set the stage for our hierarchic approach to diagnostic-problem solving, particularly of the anatomical site of the condition involved in the individual patient.

CAUSES OF HYPOCALCAEMIA.

1. **Hypoalbuminaemia**.(pseudohypocalcaemia).

2. **Hypoparathyroidism**. This is the classic form of hypocalcaemia. It usually results from reduced PTH secretion by the parathyroids due to either disease or surgical damage. But there are a number of steps along the pathway from PTH production to its end-organ effect, and failure of PTH action can therefore occur (rarely) by an abnormality at any of these various levels including:

(a) Inability of the parathyroid to secrete the PTH molecule (normal parathyroid glands demonstrable, circulating PTH absent, normal response to exogenous PTH).

(b) Inability to cleave the PTH molecule to its active form (hypoparathyroidism with normal parathyroid glands demonstrable, high radioimmunoassay levels of PTH in the plasma (but biologically inactive), normal response to exogenous PTH).

(c) Failure of end-organ receptor interaction with circulating PTH. (Hypoparathyroidism with normal parathyroid glands, high circulating levels of PTH, no second messenger (C-AMP) or other evidence of biochemical response to exogenous PTH).

(d) Lack of response to the C-AMP released from normal PTH-receptor interaction. ("hypoparathyroidism" with normal parathyroids, high levels of circulating PTH (no feed-back), normal adenylate cyclase response to exogenous PTH, but no biochemical response of the cell).

Of course, when it comes to diagnostic problem-solving, our first task is to separate ANY form of impaired PTH action from other causes of hypocalcaemia. In this respect, we must bear in mind that the classic biochemical features of failure of PTH action are a low plasma ionized calcium, high plasma phosphate and a normal to low alkaline phosphatase.

Treatment: Hypoparathyroidism is usually treated by giving 1,25-OHD (and/or calcium supplements), to maintain plasma calcium at normal (preferably low-normal) levels. However, this needs close monitoring of plasma Ca++ to avoid inducing the more dangerous hypercalcaemia long-term.

3. Vitamin D deficiency

This causes **rickets** in children and **osteomalacia** in adults. Clinically symptoms may be vague, but more specific ones include bone pain/deformity and (proximal) myopathy. Biochemically, the classic picture is hypocalcaemia (often mild), reduced plasma phosphate, and increased plasma alkaline phosphatase (ALP), although these changes can be subtle. The reason for the variable biochemical picture, particularly for the plasma calcium often being in the normal range, is the variable degree of secondary hyperparathyroidism invoked by the hypocalcaemia.

Vitamin D deficiency from poor intake is rare in Australia, not only because diets are usually adequate, but also because of abundant sunlight. However, nutritional vitamin D deficiency may occur in elderly immobile institutionalised patients (especially in the context of previous gastrectomy predisposing to malabsorption), and in dark-skinned migrants, especially covered women. Vitamin D is a fat soluble vitamin, so deficiency may occur in any of the malabsorption syndromes, especially those associated with chronic biliary obstruction. Other liver disease is a theoretical cause of osteomalacia (reduced 25 hydroxylation of absorbed vitamin D) but this is rarely seen in practice. However, the anticonvulsant phenytoin can act via the liver to produce osteomalacia by inducing hepatic microsomal enzyme systems to markedly increase the metabolism of 1,25-OHD, thereby lowering its circulating plasma level. Osteomalacia may also arise because of decreased renal 1-hydroxylation of 25-0HD to reduce production of the active 1,25-OHD (rickets resistant to standard vitamin D therapy, but responsive to 1,25-OHD). Rickets may rarely be due to a decreased receptor responsiveness to 1,25-OHD (resistant to both vitamin D and 1,25-OHD).

The classic symptoms of osteomalacia include muscle weakness and bone pain. The latter is characteristically associated with a reduction of bone density on X-ray, radio-translucency and "Looser's zones" or pseudofractures around the pelvic and upper limb girdles. In severe cases there may be symptoms of hypocalcaemia including paraesthesiae, cramps and tetany, and even hypotension. However again, subtle (secondary) hyperparathyroidism often maintains plasma calcium relatively normal, so in some cases all we may have to go on are (i) clinically: vague bone pain, lethargy, and (proximal) muscular weakness; (ii) biochemically: a low-normal calcium and phosphate, and a slight elevation of plasma alkaline phosphatase; and (iii) radiologically: a generalised loss of bone density (osteopenia) without pseudo-fractures. Bone biopsy then becomes important for definitive diagnosis.

4. Renal Disease

Renal tubular disease or dysfunction can cause osteomalacia directly via a failure to form 1,25-OHD from its precursor. However, there are several other important aspects of the kidney and calcium. First, renal disease can produce a variable effect on plasma biochemistry/calcium etc. as well as a rather complex bone response. So although most patients with renal failure have mild hypocalcaemia, in some cases plasma calcium can be quite low, partly because phosphate retention (high plasma phosphate) acts to functionally inhibit any remaining capacity of the kidney to convert 25-OHD into its active 1,25-OHD metabolite. Decreased renal reabsorption of calcium, as well as decreased intestinal calcium uptake may aggravate the situation.

Secondary hyperparathyroidism (parathyroid gland hyperplasia) as a physiological response to a low calcium in renal disease. This tends to compensate any low calcium levels toward normal, but it cannot always fully compensate because: (i) it cannot exert its full effect on the diseased renal tubules (increased calcium reabsorption); (ii) it cannot be fully effective in stimulating renal tubular conversion of 25-OHD to 1,25-OHD (and hence calcium uptake from the gut); and (iii) uraemia per se causes resistance to the action of PTH on bone. Despite this, many patients who clearly do mount an effective secondary parathyroid response to return plasma calcium levels back to at least low normal. Then, the pathological bony picture tends to become a mixed one i.e. one of osteitis fibrosa cystica (from hyperparathyroidism) and osteomalacia, giving rise to an overall picture of so-called renal osteodystrophy. In this situation, the price for maintaining calcium is one of bone disorganisation, and given the presence of a plasma phosphate, soft tissue calcification can occur as well. Because of this, dietary phosphate restriction and phosphate binders are prescribed early on. Calcium supplements and/or small doses of 1,25-OHD are sometimes also given early in patients with renal disease with a low ionised plasma calcium, so as to avoid these secondary hyperparathyroidism problems.

[In some patients with chronic renal disease the parathyroid glands may actually become autonomous, due to hyperplasia eventually going on to the development of micro-adenomata and even macro-adenomata, and then the plasma calcium may actually become elevated above the normal range to give a bone picture dominated by osteitis fibrosis cystica. This situation is sometimes referred to as "tertiary" hyperparathyroidism. One of its dangers then is that, with plasma calcium and phosphate both now being high, extensive soft tissue calcification can occur; and that, in the kidneys, may further aggravate renal damage so as to rapidly worsen the situation. Patchy bone calcification may even occur, giving rise to areas of bone sclerosis strangely super-imposed on a background of demineralisation (from osteomalacia and hyperparathyroidism). These problems may be minimised by giving such patients (early on) phosphate binders orally, to reduce gut phosphate absorption and therefore plasma phosphate, so reducing the high Ca x PO4 product, and therefore the tendency for precipitation of calcium phosphate in tissues. See also Section on Hypercalcaemia.]

5. Other Causes of Hypocalcaemia

(a) EDTA contamination of the sample. EDTA is used as an anticoagulant in the collection of some blood samples, because it strongly inhibits the clotting process by chelating (binding) calcium. Therefore, we occasionally find artefactual hypocalcaemia due to blood being taken into the wrong tube, i.e. one containing EDTA. A special tube is needed.

(b) Hypomagnesaemia. Low plasma magnesium is often associated with hypocalcaemia, and if severe may actually contribute to it. Mild hypomagnesaemia stimulates PTH in much the same way as hypocalcaemia, but severe hypomagnesaemia (which may be associated with chronic diarrhoea/ malabsorption, alcoholism, and total parenteral nutrition in hospital) impairs the secretion of PTH by the parathyroid gland and may lower target organ PTH sensitivity as well.

(c) Acute Pancreatitis. Hypocalcaemia can be seen in severe acute pancreatitis due partly to hypoalbuminaemia, partly to hypomagnesaemia, and partly to the formation of calcium soaps as a result of the action of lipase within the damaged gland.

(d) Hungry Bone Syndrome. Important to remember. Following parathyroidectomy, vitamin D therapy for osteomalacia, and in some osteoblastic malignancies, new bone formation may outstrip bone resorption and intestinal uptake of calcium. This characteristically results in a low plasma calcium and phosphate, in association with an increased plasma alkaline phosphatase.

HIERARCHIC ANATOMICO-FUNCTIONAL APPROACH TO THE DIAGNOSIS OF HYPOCALCAEMIA

As with so many of the metabolic and electrolyte disturbances, hypocalcaemia is often associated with vague symptoms, especially when the condition is mild, e.g. lethargy, proximal muscle weakness, vague bone pain, so you are often only alerted to its presence by investigating the plasma electrolytes. But having found a low plasma calcium, it is imperative to go back and re-examine the patient, not unlike the way we so frequently have to return to obtain more history after physical examination findings in making a final clinical Aetiological diagnosis. And since you have other plasma biochemistry as well, look carefully at the plasma albumin, phosphate, alkaline phosphatase, magnesium, urea and creatinine, because all of these can help build your diagnosis on a hierarchic basis. Thus, you should:

Dissecting the problem of a low plasma calcium:

First exclude artefacts such as EDTA contamination (blood taken into the wrong tube), and other obvious if unusual situations like the hungry bone syndrome. Next measure:

Plasma albumin.

If this is abnormal, correct the plasma calcium for any change in it (see above), to ensure that you are indeed dealing with true hypocalcaemia. Measure ionized Ca++ if in any doubt. Next measure:

Plasma phosphate level.

If increased, you are either dealing with either hypoparathyroidism (check plasma PTH) or renal failure (check creatinine, urea).

If the plasma phosphate is normal or decreased:

First exclude drugs (e.g. mithramicin, frusemide, citrate) and then further dissect on the basis of plasma alkaline phosphatase.

Plasma alkaline phosphatase.

If normal, you may well be dealing with pancreatitis, or more subtly, hypomagnesaemia. If plasma alkaline phosphatase elevated, probably osteomalacia. Then, you should again go back to the history and ask about diet, bowel habit (malabsorption), cramps, parasthesiae tetany, bone pain; and radiologically look for the signs of pseudo-fractures, loss of bone density etc., to confirm the diagnosis.

Vitamin D and Intact PTH levels.

Once you have established, in this hierarchic way, whether you are dealing broadly with hypoparathyroidism or vitamin D deficiency etc. you can then dissect each to further Anatomico-Functional levels. Thus, you can determine whether any defective vitamin D metabolism is due to a lack of vitamin D intake, lack of absorption, decreased 25-hydroxylation in liver disease (uncommon), decreased 1-hydroxylation in renal disease (elevated creatinine), decreased response to the active 1,25-OHD metabolite in the more specific vitamin D-resistant rickets, or an increased clearance of the active 1,25-OHD metabolite either by the induction of microsomal enzymes by drugs such as phenytoin, alcohol etc., or in the nephrotic syndrome where there may be increased clearance from loss of albumin-bound 1,25-OHD via the renal route.

In the same way, we have seen how we can dissect the level of any failure of PTH action in terms of parathyroid abnormalities including an inability to secrete the PTH molecule, inability to cleave the PTH molecule to its active form once released, failure of renal receptor interaction with circulating PTH, and failure of adenylate kinase response to PTH receptor interaction.

Plasma ionized calcium (not total) also falls with alkalosis, especially acute respiratory alkalosis. This is important not only in diagnosis, but when correcting metabolic acidosis. This is a further reason for avoiding IV. bicarbonate in the correction of metabolic acidosis.

HYPERCALCAEMIA - FEATURES

Hypercalcaemia also usually presents with vague symptoms. Clinical features of hypercalcaemia depend on the level of plasma calcium, with many patients being asymptomatic even up to levels of 3.0 mmol/l. Nonspecific complaints include nausea, anorexia, vomiting, fatigue and generalised weakness. Hypercalcaemia also alters nerve/muscle function, so that muscular weakness may arise either directly as a proximal myopathy or secondary to impaired neuronal transmission. Other neurological features include irritability, confusion, headaches, and even seizures and coma if plasma calcium level exceeds 3.5 mmol/l. More general symptoms include cardiac dysrhythmias,

hypertension, and constipation (from alteration of cardiac/smooth muscle function). Polyuria, polydipsia and thirst may arise from functional alteration of the renal concentrating mechanism.

Deposition of calcium in various tissues can be seen in band keratrophy (deposition of calcium near the corneoscleral junction of the eye), and pancreatic and renal calcification. If there is increased renal excretion of calcium salts, renal calculi may form. If hypercalcaemia is associated with removal of mineral from bone, e.g. in hyperparathyroidism, then there will often be associated bone pain, sometimes due to actual pathological fractures. Hypercalcaemia also predisposes to other disorders including pancreatitis and duodenal ulcer.

ECG characteristically shows shortened conduction intervals.

CAUSES OF HYPERCALCAEMIA

1. **Factitious** - a mild hypercalcaemia can result from concentration of the blood during collection by use of a tourniquet. Therefore avoid this when collecting blood for calcium estimation.

2. Hyperparathyroidism. Hypercalcaemia may result from primary or "tertiary" hyperparathyroidism.

Primary hyperparathyroidism is usually due to a benign adenoma of one of the parathyroid glands (may be associated with multiple endocrine adenomas - MEN 1). Prior to the wide availability of biochemical tests, most of these patients suffered from massive resorption of calcium from bone, due to excessive PTH, resulting not only in severe bony changes (bone cysts and sub-periosteal erosions along the borders of the phalanges and metacarpal bones), but often renal disease as well (nephrocalcinosis, renal stone formation) secondary to the increased urinary excretion of calcium. Nowadays, th condition is picked up earlier with the characteristic biochemical picture of a high plasma calcium, low plasma phosphate (reduced renal phosphate reabsorption), reduced plasma bicarbonate (reduced renal PCT reabsorption of bicarbonate), and a slightly raised plasma alkaline phosphatase. The low phosphate typically differentiates the condition from hypervitaminosis D, where the plasma phosphate is characteristically high. But difficulties arise where the hypercalcaemia of primary hyperparathyroidism leads to secondary impairment of renal function, because this will increase plasma phosphate in its own right. However, with a good history and physical examination, there should be no trouble differentiating these two conditions in practice. Note, too, that although some patients with primary hyperparathyroidism present as renal stone formers (ureteric colic) without much in the way of bony involvement, this is not common, presumably because PTH normally acts to increase calcium reabsorption from the kidney, so that high urinary calcium levels do not tend to occur until the condition is quite advanced, when the plasma calcium itself becomes so high that the filtered load of calcium exceeds the renal calcium reabsorptive capacity.

As we have seen, secondary physiological hyperparathyroidism may arise in chronic renal disease from hypocalcaemia secondary to lack of renal conversion of 25OH Vitamin D to its metabolically active form, 1, 25. OH Vit. D. This latter leads to secondary stimulation of the parathyroid in attempted compensation. The parathyroid glands become hyperplastic as a consequence, butcalcium levels remain somewhat below normal at this physiological stage.

Tertiary hyperparathyroidism sometimes follows the above, due to the hyperplastic parathyroid glands developing adenomatous change and becoming autonomous with chronic stimulation, hence consequent uncontrolled release of PTH. Hypercalcaemia ensues. The latter can be especially dramatic after renal transplantation for chronic kidney disease.

3. Hypervitimanosis D. Already partly discussed in our differential diagnosis. Causes include over-enthusiastic treatment of hypoparathyroidism with 1,25-OHD (regularly monitor plasma calcium); also increased vitamin D sensitivity and/or conversion of 25-OHD to 1,25-OHD as may occur in pulmonary sarcoidosis (probably related to the capacity of pulmonary macrophages to 1-hydroxylate 25-OHD). Note that although 25-OHD has only about 1,000th the activity of the active vitamin D metabolite, 1,25-OHD, it is normally present in plasma in much greater concentrations. Hence, 25 OHD can have effects on calcium homeostasis if significant amounts of Vitamin D are ingested.

4. Malignancy. Hypercalcaemia is not uncommon in patients with malignant disease, particularly in the latter stages. Carcinomas which have a particular propensity to metastasise to bone (e.g. breast, lung, kidney and prostate) are especially likely to cause hypercalcaemia. However, sometimes hypercalcaemia is associated with the primary tumour (e.g. ectopic PTH-like production from tumours such as squamous cell carcinomas of the lung). Hypercalcaemia may also occur in multiple myeloma (partly from the increased level of calcium-binding globulin - check ionized calcium), lymphoma and leukaemia. Actually, the causes of hypercalcaemia in malignancy are complex and often multiple, and include direct invasion of bone, tumour secretion of PTH-like material and/or other factors including prostaglandin E, "osteoclastic activating factor" (OAF), cytokines and vitamin D-like sterols, all of which can increase bone resorption.

5. Other Conditions producing Hypercalcaemia include:

(i) Patients with bone disease, particularly Paget's disease, after immobilisation in bed;

(ii) So-called milk -(soluble)alkali syndrome where the milk supplies the calcium and the soluble alkali increases its absorption - rarely seen nowadays with the use of nonabsorbable alkalis in the treatment of peptic ulcer.

(iii) Occasional endocrine causes including thyrotoxicosis (increased bone turnover), acromegaly (increased gut absorption of calcium) and Addison's disease (mild hypercalcaemia partly due to haemoconcentration from ECF volume depletion);

(iv) Drugs, including lithium (stimulates PTH release), thiazide diuretics (ECF volume depletion from thiazides can lead to decreased PCT renal tubular flow rates and this causes an increased proximal tubular reabsorption of calcium as well as sodium).

(v) Acute renal failure, particularly the late polyuric phase, may be associated with acute hypercalcaemia, perhaps due to a persistently increased PTH secretion following the initial stimulus of hypocalcaemia during the oliguric phase.

HIERARCHIC APPROACH TO THE DIAGNOSIS OF HYPERCALCAEMIA

First exclude artefactual hypercalcaemia by making sure that the specimen is taken without a tourniquet (if in doubt repeat), and corrected for any change in plasma albumin and pH.

From the history and physical examination, it is usually relatively simple to rule out thyrotoxicosis, renal failure, advanced malignancy, sarcoidosis, Addison's disease, the milk-alkali syndrome and drugs including thiazides and excessive vitamin D.

If doubt remains, measure:

Plasma phosphate concentration.

Decreased or low-normal in patients with primary hyperparathyroidism. This also occurs in some patients with malignancy and others on thiazide diuretic therapy. If you suspect the patient may be taking thiazide diuretics furtively, next measure:

Urinary calcium and sodium in the sub-group of patients with decreased or low-normal phosphate. Urinary Ca++ is decreased in patients on chronic thiazide therapy and urinary Na+ increased.

If the urinary calcium is increased, you are probably dealing with primary hyperparathyroidism, and a useful next step is to measure the **plasma** bicarbonate. This tends to be low in primary hyperparathyroidism (PTH inhibits renal PCT reabsorption of bicarbonate) and normal in malignancy. If still in doubt measure:

Plasma Intact PTH

In some patients with malignancy, hypercalcaemia is due to "ectopic" secretion of PTH-like substances by the tumour, which cross-react on the immuno-assay.

If the plasma phosphate is raised, measure:

Plasma alkaline phosphatase (ALP).

If this is normal you are probably dealing with an increased vitamin D effect, occasionally with malignancy and the milk-alkali syndrome.

If the plasma alkaline phosphatase is increased, think of malignancy, hyperparathyroidism as well as the endocrine causes.

The above approach of using clinical features together with the plasma phosphate, alkaline phosphatase and urinary calcium usually sorts out most problems. However, in practice difficulties can still arise. First, as we have seen, hypercalcaemia itself may eventually induce renal damage (e.g. by nephrocalcinosis), and with it, phosphate retention, to make differential diagnosis difficult, e.g. between primary and so-called "tertiary" hyperparathyroidism. Moreover, in any situation of renal impairment, plasma PTH tends to be high because of failure of the normal renal excretion of PTH and its metabolites (which can cross-react in the immunoassay for PTH). Nevertheless, the clinical situation, and particularly the mode of onset and progression of the hypercalcaemia in relation to the renal disease, taken together with the different bony pictures of primary versus "tertiary" hyperparathyroidism will usually allow differentiation between the two. Also, we can now measure intact PTH to separate the PTH fragments which accumulate in renal failure.

Comment.

Most cases are characteristic, and diagnosis is much aided by going back into the history. Try at the first broad level to different hyperparathyroidism from hypervitaminosis D and malignancy; then, if the former, further dissect clinically and biochemically whether there is over-production of intact PTH, and if so, whether this is parathyroid PTH over-production (primary or "tertiary" hyperparathyroidism), or ectopic PTH-like production by a tumour (e.g. squamous cell Ca lung). If the clinical and biochemical features point in directions other than PTH, and if malignancy, drugs, artefacts etc. have been excluded, you should determine whether you are dealing with hypervitaminosis D; and if so, whether this is due to excessive administration of vitamin D (e.g. in hypo-parathyroidism treatment) or to increased conversion of 1,25-OHD to the active metabolite as in sarcoidosis. Follow a hierarchic approach to diagnosis, and keep going back for further clinical information no matter how far down the biochemical line you have travelled.

PATH, FUNCT, AND AETIOL DIAGNOSES, and TREATMENT

Pathological, Functional, and Aetiological diagnoses- as before.

Treatment of hypercalcaemia

Removal of the cause.

Primary hyperparathyroidism is usually due to a solitary autonomous hyperparathyroid adenoma, which can be cured by surgery.

In tertiary hyperparathyroidism, it is sometimes possible to control the calcium levels with cinacalcet, a synthetic agent which increases the sensitivity of the parathyroid calcium-sensing receptor to calcium feedback, so inhibiting PTH release.

Other treatments

In severe cases, intravenous sodium chloride together with frusemide can be useful, because frusemide causes both calcium and sodium chloride loss and the sodium chloride infusion replaces the sodium losses. Measure urinary K+ and Mg++ losses, and replace these if diuresis continued longer than 24 hrs. IV phosphate administration might seem rational, and was used in the past, but is potentially dangerous. IV calcitonin can be effective, by inhibiting bone resorption to cause increased urinary calcium excretion.

Glucocorticoids improve most forms of hypercalcaemia except those related to primary hyperparathyroidism - useful diagnostically as well as in treatment.

In more chronic cases, reduction of dietary calcium intake, together with calcium binding agents (e.g. oral phosphate in the form of 'buffered' phosphate) are often very effective (they inhibit gut uptake of calcium). (The use of oral phosphate therapy is contra-indicated in cases of renal impairment, where plasma phosphate is high and there is risk of increasing it still further; that, together with hypercalcaemia can lead to dangerous soft tissue calcification including nephrocalcinosis and further renal damage.) The bisphosphonates (which inhibit osteoclastic bone resorption) are emerging as important treatments, especially in ongoing hypercalcaemia.

MCQs & PROBLEM SOLVING

A. Mechanisms in Disease

1. A patient is admitted with a diagnosis of chronic renal failure and secondary osteomalacia without hyperparathyroidism.

Which of the following would be typical.

1. Plasma calcium elevated above the normal range.

2. An elevated plasma albumin.

3. Metabolic alkalosis.

4. Histological picture of 'osteitis fibrosis cystica' on bone biopsy.

5. A low level of circulating of 1-25 dihydroxy vitamin D.

6. A reduction in the plasma phosphate level.

7. Elevated plasma alkaline phosphatase.

Mechanisms in Disease 2.

You had been seeing a 45 year old (1) patient for ten years (2) with chronic stable renal failure (3) up until four years ago (4). At that stage he had a plasma creatinine 5 times the normal level (6), an elevated plasma phosphate (7), and a persistently low plasma calcium (8) in the presence of a normal plasma albumin (9). You elected at that stage to observe rather than treat (10). After leaving the district for some four years, he now returns and investigations show little change in the plasma creatinine (11), but his plasma calcium is now above the normal range (12). He complains of some bone pain (13) and when you X-ray his hands there are sub-periosteal erosions along the borders of the phalanges and metacarpal bones (14) as well as a generalised decrease in bone density and some bone cysts (15).

Which of the following statements is/are likely to be correct:

1. This man has recently developed secondary osteomalacia.

2. It is likely that his plasma phosphate will have risen from its previous level.

3. Bone biopsy will show the classic changes of osteoporosis.

4. He is liable to soft tissue calcification.

5. He should now be given therapeutic doses of 1,25-OHD.

6. In retrospect it may well have been best to treat this man with a small dose of 1,25-OHD when he first developed hypocalcaemia.

7. His urinary creatinine excretion (mg per day) will be unchanged from four years ago, and normal.

Problem-Solving MCQ

2. A 42 year old housewife (1) presented with a four months history (2) of nausea (3), general malaise, increasing tiredness, lethargy (4), vague headache (5), constipation (6), irritability and vague aches and pains (7), as well as increasing thirst and nocturia (8). There had been no recent weight loss or change in appetite (9), but on direct questioning she did admit to some difficulty in climbing stairs (10), seemingly related to weakness of the lower limbs (11). There had been no shivers or sweats (12) and no respiratory or cardiac symptoms (13). In the past she was known to be normotensive 12 months beforehand (14) and had not had any previous renal disease (15), peptic ulcer (16), or carcinoma of the breast or elsewhere (17). No past history of tuberculosis (18). Social history: non-smoker, non-drinker (19). Happily married, two children (20). Family history: nil relevant. Drug history: no history of drug intake, in particular no spironolactone or related potassium-sparing diuretics such as amiloride (21); no past history of any excessive vitamin B6 consumption (22). Not taking any antacids (23) or potassium supplements (24).

On examination: general NAD. Skin normal. BP 180/100 mm Hg (25). Pulse 82/min. JVP normal (26). Intermittent ventricular extra systolic beats (27). Heart otherwise NAD. No bruits in heart, neck or epigastrium (28). No delay of radio-femoral pulses (29). Foot pulses normal (30). No ankle oedema (31). Chest NAD. Abdomen NAD. Bone/joints: mild tenderness to percussion over the dorsal and lumbar spines (32). CNS: hyper-reflexia, bilaterally symmetrical; plantar reflexes downgoing (33). Some difficulty in standing unaided from the sitting position (34), otherwise only minimal generalised weakness (35); no sensory signs or symptoms (36). Mentation, cranial nerves, optic fundi, all NAD (37).

The patient was investigated and subsequently had an operation (21/9). The biochemical findings prior to operation (20/9), and on the day after(22/9), were as follows:

Solve problem using the four column approach and answer the following questions before viewing the graphic solution at end of the chapter.

Which of the following statements is/are correct?

1. The symptoms of thirst and nocturia are probably related to the plasma potassium level.

2. The pre-op. plasma ionised calcium was probably normal when corrected for plasma albumin and pH.

3. Given the initial biochemistry, the first step would have been to repeat it, making sure that blood was taken without a tourniquet.

4. An initial normal urinary calcium would exclude a diagnosis of a primary hyperparathyroidism.

5. The low plasma phosphate before operation is explained by the relatively low plasma creatinine.

6. There was clinical and biochemical evidence of ECF volume contraction prior to operation.

7. The raised plasma alkaline phosphatase (ALP) in this situation indicates secondary osteomalacia.

8. The low plasma bicarbonate is more in favour of a diagnosis of hypervitaminosis D than other causes of hypercalcaemia.

9. The pre-op. aches and pains this patient complained of may well have been related to the hypercalcaemia.

10. There is pre-op. evidence to suggest "tertiary" hyperparathyroidism.

11. The anion gap before surgery was higher than normal.

12. The high plasma Cl- pre-operatively suggested isotonic ECF volume depletion.

13. Vitamin B6 was the important vitamin to ask about in the history.

14. It would have been more relevant, in the drug history, to ask about possible intake of thiazide diuretics than the potassium-sparing diuretic group.

15. The sudden fall in plasma calcium post-operatively is well recognised in such cases.

16. Typically, patients with hypercalcaemia of malignancy present with such a biochemical picture.

17. The operation performed on 20/9 was probably a removal of the four parathyroid glands in the neck.

A graphic solution is available now for this problem. But try to solve yourself first.

PROBLEM SOLUTION-Part1

CHAPTER 18 PROBLEM.

WHERE?	WHAT?	HOW?	WHY?
	4/12. = subacute. 9. No recent wt. loss, or appetite change. i.e. No evid. of neoplasia 12. No shivers or sweats = No evid. of inflamm^{n}.	3. Nausea - rel. non-specific symptom. 4. Malaise, lethargy - non-specific. 5. Vague headache - also non-specific. 6. Constipation - non-specific. (?dehydr^{n}.) 7. Irritability - ? anxiety, but don't prejudge. 8. Thirst/nocturia (prob. polyuria) ?1° inc. in water intake. ? 1° (renal) water loss ? osmotic e.g. diab. mellitis ?ADH. lack i.e. diab. insipidus. ?DCT/coll tubule dysfunction. 10, 11. Difficulty climbing stairs - prob. prox. muscle weakness (hip extensors; knee extensors also). 13. No CVS or resp symptoms.	1. 42 yrs 2. Female housewife. 14.Past history . No prev. H/T. 15. No renal dis. 16. No peptic ulcer. 17. No prev. cancer. 18. No past TB. 19. Social history Nil relevent - presume no FH of H/T. Drug history . 21. -24. - nil.
INTERIM	CONCLUSION. - 1.		
?	Subacute.	A. Generalised symptoms, but with prox. myopathy (lower limbs). Thus, ?Some Metabolic Disorder. Polyuria would fit with this e.g. Low pl. K^{+} or high Ca^{++}. B. Irritability - ?anxiety, but could be 2°to metab. /electrolite prob.	A. ? B. ?
O/E			
	14. BP. rise is recent	Skin normal. - prob. no decr in I.F.Vol. 25. BP. high 26. JVP. Normal. = no evid. of ECF vol. ↑ (e.g. 2° to renal or cardiac dysfunct^{n}). 27. VEB's. -? normal, - ? 2° to ↑ cardiac muscle irrit. (28) Heart NAD. Presume no LVH. - consistent with recent H/T. 28. No bruits in epig. i.e. no evid. of renal art stenosis 29. No radio-fem. delay - no evid. of coarctation. No evid. of 2° cause for H/T, but keep looking in view of lack of neg. FH. (30) Normal foot pulses i.e. No evid of any vasc. damage from H/T 31. No ankle oedema. consistent with 26. No evid. of ↑ ECF Vol. Chest, abdo - NAD. 32. Tender over spine - ?bony involvement . 33. CNS. - hyperreflexia ? altered nerve conduction. ? incr. sympathetic activity. Planter reflexes normal. 34. Difficulty standing from chair. = weakness of hip (& ? knee) extensors . 35. Minimal gen. weakness. 36. No sensory signs. 37. Higher CNS function & cranial nerves normal. Retinal vessels normal. i.e. No evid. of 2° effects of (recent) H/T	? Cause FH. 'nil relevent'

PROBLEM SOLUTION-Part 2

CHAPTER 18 PROBLEM. (contd.).

WHERE?	WHAT?	HOW?	WHY?
INTERIM	CONCLUSION - 2.		
A. B.	Recent SUBACUTE	Hypertension without obvious 2° cause. - no renal art stenosis, coarct.or ECF incr. - but keep looking in view of apparentlynegative family history. Prox myopathy & polyuria . ? metabolic disorder - no evid. of Cushing's disease - no evid. of thyrotoxicosis. low K^+ (e.g. Conn's syndrome) or high Ca^{++} (e.g. from ↑ PTH) could explain both. Low K^+ / high Ca^{++} can also be assoc. with H/T.	FH. 'nil relevent' Presume no FH of H/T.
INVESTIGAT.	(PRE-OP).		
		38. Pl. Sodium - N. 39. Pl. K^+ low Normal. -not enough to cause symptoms above. 40. Cl^- sl. ↑, consistent with 41. HCO_3 sl. ↓. - not really explained by low normal K^+ (pH N or sl. low in any case - see 47.) 42. Pl. Ca^{++} very high. (rpt. - no torniquet). 43. Pl. phosphate low - 42, 43, both consistant with ↑ PTH.plasma level. ↓ HCO_3 (41.) also consistent with this. 44. Pl. albumin Normal. i.e. No ↑.Pl. alb. to explain ↑ Ca^{++}. 45. Pl. ALP (alkaline phosphatase) ↑ - consistent with PTH action on bone (from compensatory incr. in osteoblastic activity). 46. Pl. creatinine low N. i.e. - no renal impairment to explain ↑ PTH. - consistent with sl. ↑GFR for age ?? 2° to efferent art. constriction assoc. with H/T. 47. Pl. pH. low N. - consistent with renal HCO_3 leak from PTH effect on renal tubules. - certainly not low enough to explain ↑Pl. ionised Ca^{++}.	↑ Ca^{++} not due to - 'milk-alkali' syndrome.(16). (no peptic ulcer) - metaststic cancer.(9, 17). - renal dis. (15,46), prod. either 2° or 3° hyperparathyroid overactivity. - TB. bone dis.(18). - Vit D excess (Pl. phos. ↓ - 43)

PRE-OP. CONCLUSION.

Anatomic Diagnosis	Pathological Diagnosis	Functional Diagnosis	Aetiological Diagnosis
PARA - THYROID	CLINICALLY **SUBACUTE** **? ADENOMA** ? HYPERPLASIA.	**HYPERCALCAEMIA** from ↑ **PTH** (secretion) with 2° irritability, hyper-reflexia,irritability constipation, **prox. myopathy** , mild pH ↓ **bony involvement** **&hypertension** .	? 1°, not 2° or 3°. Basic cause **Unknown**

PROBLEM SOLUTION-Part 3

Ch 18. Problem (contd). — Post-op. Course.

WHERE?	WHAT?	HOW?	WHY?
POST-OP.	INVESTIGATIONS		
	2 day change of electrolyte pattern, i.e. ACUTE	38. Pl. Na^+ - Normal. 39. Pl. K^+ - Normal. 40. Pl. Cl^- - now normal. 41. Pl. HCO_3 - now normal. 42. Pl. Ca^{++} now below normal!! 43. Pl. phos. also now lower than pre-op. 44. Pl. Alb. remains N. i.e. doesn't explain sudden Ca^{++} fall. 45. ALP. remains high (reflects incr. osteoblastic activity). 46. Pl. creatinine rel. unchanged i.e. GFR., & prob. ECF vol stable. 47. pH now N. i.e. mild acidosis reversed (by reversal of HCO_3 leak).	45. Continuing high ALP. in the face of removal of PTH. stimulus to bone breakdown is now causing rapid return of Ca^{++} and phos. back to bone, so lowering both Pl. Ca^{++} & phos.

POST-OPERATIVE DIAGNOSIS

Anatomic Diagnosis	Pathological Diagnosis	Functional Diagnosis	Aetiological Diagnosis
BONE	ACUTE	INCREASED (CONTINUING) OSTEOBLASTIC ACTICITY	REFORMING BONE AFTER REMOVAL OF THE (PTH.) CAUSE OF PREVIOUS OSTEOCLASTIC BREAKDOWN.

POST-OP DIAGNOSIS — CONCLUSION.

ACUTE POST-OP. 'HUNGRY BONE SYNDROME'.

MCQ ANSWERS

A. Mechanisms in disease.
No.1. 5 & 7 correct. All other false.

No.2. Only 4, 6, 7, correct.

B. Problem Solving Case.
3, 9, 14, 15, correct. All others false