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CALCIUM AND PHOSPHORUS METABOLISM*

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The bones contain more than 99% of the entire calcium of the body (1,200 g. in the adult). The intracellular fluid is completely free of calcium and there is only 0·9 g. in the extracellular fluid. Approximately 6 mg. of the 10 mg. per 100 ml. of total serum calcium are ionized and highly active; 3 - 4 mg. are protein-bound and about 0·5 mg. is found as a complex-salt, bound to citric acid and other organic acids.

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The effect of the 6 mg. per 100 ml. of calcium ions in the serum as electrolyte is completely negligible (3 mEq./l.Ca^{++}), whereas Na^{+} represents 140 mEq./l., but this small quantity of calcium is most important in the maintenance of several biological functions. These include neuromuscular excitability, autonomic balance, cardiac function (Ca - K antagonism), blood coagulation, cellular and capillary permeability, antigen-antibody reactions, complement-fixation, and phagocytosis by leucocytes.

The optimum range of calcium concentration for these biological reactions is extremely narrow and must be kept at a very constant level. In childhood it varies between 9·4 and 10·2 mg. per 100 ml. (after Elkington and Danowski), in the younger adult between 9·4 and 10·2 mg. per 100 ml. and in the older adult between 9·6 and 11·0 mg. per 100 ml. This constancy is astonishing when we consider that the total calcium which is absorbed, stored and excreted, has to pass the 'bottle neck' of serum calcium of about 10 mg. per 100 ml. The activity of calcium metabolism varies according to the body's requirements; in spite of this the organism succeeds in keeping the serum-calcium level constant. For instance, radioactive calcium-45 injected intravenously disappears from the blood in less than 1 minute (Hansard, Comar and Davis).

The phosphate concentration in the serum fluctuates much more. It varies between 7·0 mg. per 100 ml. in the newborn and less than 4 mg. per 100 ml. in the adult. It varies also with the season; in spring it is higher than in winter. The inorganic phosphorus determined in the serum by the method of Bell and Doisy exists entirely in the ionized form. Whereas even minor variations in the calcium level cause severe symptoms (hypocalcaemic tetany and hypercalcaemic intoxication), the phosphate level can range from 1·0 to 15 mg. per 100 ml. without causing any symptoms. The control of the phosphate level is done by the kidneys; when the glomeruli are inefficient, hyperphosphataemia will occur; when the tubules are not able to reabsorb phosphates hypophosphataemia will result.

The bones are not only a frame tissue, they also have a very important exchange function. In the iso-ionic exchange calcium and phosphate ions are precipitated in or withdrawn from the bone; in the hetero-ionic exchange other ions like sodium, carbonate, citrate, etc. are exchanged against calcium and phosphate. We know that one-third of the body sodium is bound in an inactive state (dry retention) in the skeleton; in acute cases of sodium-depletion so many calcium ions may be bound in the bones to permit the release of sodium that a hypocalcaemic tetany may occur (personal observation).

Citrate, too, plays an important rôle in the iso-ionic exchange; variations in the concentration of citrate ions in the intracellular fluid of the bones are probably the cause of calcification or decalcification of the matrix.

CONTROL OF SERUM CALCIUM

Considering the severity of the disturbances caused by variations in the level of serum calcium, we must conclude that very accurate mechanisms of control exist. The first, and most rapid one, is in the serum itself; it is the exchange between calcium ions and protein-bound calcium, which follows the mass law. The second mechanism is the iso-ionic exchange between serum and bone. It can only raise the calcium level to 6 mg. per 100 ml.

To increase the serum calcium to the normal level of 10 mg. per 100 ml., a third and more powerful but slowly-acting mechanism, the action of the parathyroids, is necessary. The parathormone has a double function; it stimulates the osteoclasts, so that calcium and phosphate ions are mobilized; furthermore it inhibits the reabsorption of phosphate in the renal tubules. The final result of this double function is the transfer of calcium from the bones into the serum and of phosphate from the bones into the urine. The fourth mechanism of control is the intestinal absorption of calcium; it is increased by vitamin D and decreased by cortisone. In this respect cortisone is an antagonist to vitamin D. The fifth mechanism is the renal excretion probably depending on the level of complexed calcium.

The mode of action of vitamin D is not completely known. Its main functions are believed to be as follows:

Primary functions: Control of intestinal absorption of calcium and phosphorus; transfer of bone minerals from bone to serum and from serum to bone; control of citric-acid content of serum, intestinal wall, bone, and other

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organs; preparation of bone matrix for calcification, and control of renal tubular reabsorption of amino-acids.

Secondary functions: Calcification of bone matrix (*via* increased serum-calcium level); control of renal excretion of phosphate (dependent on the functional state of the parathyroid glands), and control of the serum level of alkaline phosphatase (*via* its action on osteoblasts and probably on osteoclasts and chondroblasts).

The most important effect is on the intestinal absorption of calcium and therefore also of phosphate. A second effect is the stimulation of the transfer of calcium and phosphate from the bones into the serum if the intestinal absorption is insufficient, and *vice versa* if sufficient calcium is available. The effect of vitamin D on the kidneys is negligible except in rickets (Harrison), where the tubular reabsorption of phosphate increases.

DISEASES WITH A TENDENCY TO HYPOCALCAEMIA

In vitamin D deficiency the normal serum-calcium level is maintained by hyperfunction of the parathyroids. But only in rare instances can signs of fibro-osteoclasia be observed. In a 7-year-old idiot suffering from severe vitamin-D deficiency for a long time we found not only the symptoms of rickets but also those of secondary hyperparathyroidism, i.e. subperiosteal bone resorption, disappearance of the lamina dura of the teeth at the gum margins, and alterations of the bone marrow with extensive replacement of the haematopoietic system by fibrous tissue with only a few blood cells but with numerous osteoblasts (47%) and osteoclasts (3%) remaining. After treatment with dihydrotachysterol all symptoms of rickets and of secondary hyperparathyroidism disappeared.

Amino-aciduria in rickets has been wellknown since the publications of Jonxis. In addition to this renal defect we have observed other signs of tubular dysfunction. In an 11-months-old child we saw not only amino-aciduria but also hypercalciuria in spite of a serum-calcium level of only 8·8 mg. per 100 ml. In our opinion, the hypercalciuria was probably caused by another tubular dysfunction leading to hyperchloraemic acidosis. Serum chlorides were high (113 mEq./l.), and the bicarbonate low (15·9 mEq./l.). After a total of 45 mg. of vitamin D, given in 3 doses within 6 weeks, all symptoms of rickets and of tubular dysfunction disappeared.

The cause of primary vitamin-D-resistant rickets is not a vitamin-D deficiency but a resistance to vitamin D. The most typical and most constant finding is hypophosphataemia. Fanconi and Girardet therefore proposed the name 'chronic phosphate diabetes'. The treatment of phosphate diabetes, as in chronic hypoparathyroidism, is to give high doses of vitamin D. We suggest a daily dose of 1·25 - 2·5 mg. of vitamin D corresponding to 50,000 - 100,000 i.u. The Sulkowitch test should always be strongly positive. It is advisable, therefore, to check the serum calcium at regular intervals in order to avoid hypercalcaemia.

This danger arises especially when immobilization is necessary. We saw a child suffering from typical phosphate diabetes in which immobilization after osteotomy was soon followed by a hypercalcaemic syndrome. Even under these circumstances the serum phosphate level remained very low. The main disturbance seems to be located in the renal tubules as is shown by the high phosphate clearance. The simultaneously-existing hypocalciuria could be caused either by a renal defect or by the decreased intestinal calcium absorption which is always present in phosphate diabetes.

This disease follows the dominant X chromosomal pattern of hereditary transmission, as was recently shown by Winters. In the X chromosomal dominant hereditary transmission all daughters of a sick father must be affected whereas his sons are expected to be healthy. In the case of an affected mother half of her sons and half of her daughters will present this disease. All our family trees are indeed of this type (Prader). In following them up the interesting discovery was made that several individuals had hypophosphataemia as well as a high phosphate clearance, though they presented no bone deformities.

TABLE I. FORMS OF RENAL RICKETS, SECONDARY TO DISTURBANCE OF PARTIAL FUNCTIONS

	Proximal tubule				*Distal tubule*	
Disease	*Glomeruli*	*acidogenesis*	*amino-acids*	*dextrose*	*acidogenesis*	*NH_3^+ production*
Glomerular hyperphosphataemic rickets	+	n	n	n	n	n
de Toni-Fanconi-Debré syndrome with and without cystinosis	n later +	+	+	+	+	?
Phosphate diabetes	n	+	n	n	n	n
Lightwood-Albright tubular acidosis with and without nephrocalcinosis	n later also +	?	n	n	+	n or +

n = normal, + = disturbed

Another form of renal rickets (Table I) is seen in the so-called de Toni-Fanconi-Debré syndrome: besides phosphate diabetes we found an amino-aciduria, a glycosuria and frequently also an anacidogenesis.

In the renal tubular hyperchloraemic acidosis, especially in the chronic form (Albright), calcium is eliminated in increased quantities into the urine to neutralize the acid metabolites. Sodium and potassium are not available in sufficient amounts because their storage in the body is limited whereas calcium can be released from the bones. The consequence is a nephrocalcinosis and/or a nephrolithiasis, and an osteoporosis and rickets.

Recently we saw a case of rickets of hitherto unknown aetiology. Even though the X-rays and laboratory findings were thought to be typical, the history failed to reveal any known cause for the development of rickets. On admission, however, a reparative giant-cell granuloma of a rib was discovered. After its surgical removal complete recovery from rickets took place within a few weeks, without any vitamin-D treatment. Obviously there was a pathogenic relation between rickets and the tumour. We believe that the tumour produced a substance which caused rickets. Two hypotheses are proposed for its possible action:

1. The substance has a vitamin-D inactivating effect.
2. It is a parathormone-like substance with selective effect on tubular phosphate reabsorption.

A hypocalcaemia of about 6 mg. per 100 ml. combined with a hyperphosphataemia of 10 mg. per 100 ml. and

more are the typical findings of chronic hypoparathyroidism. The serum chemistry can be brought to normal levels, and the other symptoms, for instance epileptiform fits, can be improved, by the administration of high doses of vitamin D (1·25 mg. daily). The danger of hypercalcaemia arising from this treatment is the same as in chronic phosphate diabetes.

DISEASES WITH HYPERCALCAEMIA

The importance of hypercalcaemic intoxication in infancy and childhood has been known only for about a decade. There are several more or less clear-cut syndromes in which the hypercalcaemic intoxication prevails. These are as follows:

1. Those of known aetiology: Primary hyperparathyroidism; overdosage of vitamin D or dihydrotachysterol; lack of cortisone in Addison's disease and after adrenalectomy; increased bone catabolism (bone tumours and leukaemia); decreased bone anabolism (immobilization); sarcoidosis; milk-alkali syndrome; and hyperthyroidism(?).

2. Those of unknown aetiology: Tumours without bone involvement, and idiopathic hypercalcaemia.

Primary hyperparathyroidism is extremely rare in childhood. Secondary hyperparathyroidism is much more frequent; in these cases overproduction of parathormone is just sufficient to maintain the serum calcium at a normal level, so that no hypercalcaemic symptoms occur.

We followed a case of severe hypercalcaemic intoxication in a 13-year-old boy with Addison's disease. All symptoms disappeared when the boy was treated with prednisone. We saw a hypercalcaemia of 15·5 mg. per 100 ml. in a case of acute lymphatic leukaemia with severe bone destruction. Cortisone stopped the proliferative leukaemic process and possibly also the absorption of calcium from the intestine. In a few days the serum-calcium level was back to normal.

In severe cases of tetraplegia in poliomyelitis, hypercalcaemia is a frequent complication. It is caused by decreased bone anabolism following immobilization. A 15-year-old girl showed nephrocalcinosis of the tips of the renal pyramids during the period of maximal renal excretion of calcium. This was apparently reversible, but some months later a nephrolithiasis occurred in spite of a completely calcium-free diet.

In the case of sarcoidosis (Besnier-Boeck disease) starting from a chronic post-traumatic ulceration on the right wrist, and treated with high doses of vitamin D, all the symptoms of a severe hypercalcaemic intoxication appeared. Treatment with prednisone stopped all hypercalcaemic symptoms quickly and improved the signs of sarcoidosis. Without prednisone the serum-calcium level remained in the range of 11 - 12 mg. per 100 ml., but anorexia, apathy, constipation, polyuria and other hypercalcaemic symptoms reappeared. The Sulkowitch reaction in the urine became strongly positive, although no vitamin D was given and the diet was poor in calcium. This case demonstrates that symptoms of hypercalcaemic intoxication may be present even with a normal or only slightly increased calcium level.

In paediatrics the most frequent form of symptomatic hypercalcaemia is vitamin-D intoxication. We have had the opportunity of observing 23 cases in the last decade. The therapy consists of the withdrawal of all drugs containing vitamin D and reduction of calcium intake (decalcified cows' milk after the method of Dent). Prednisone, which in many respects is an antagonist of vitamin D, is necessary in severe cases only.

Since our first description (1952), in collaboration with Schlesinger, Butler, Black and Girardet, of severe chronic idiopathic hypercalcaemia, a similar case was observed in Zurich. The diagnosis was established at the age of 6 months. The first symptoms of the disease appeared at the age of 2 months. The child presented all the main features (Fig. 1) of the disease with the exception of craniostenosis; the mental retardation was not severe.

Fig. 1. Idiopathic hypercalcaemia. Typical face with hypertelorism, long upper lip, receding mandible, low-set ears, and ill-tempered appearance.

Transient improvement was achieved with prednisone as well as with decalcified cows' milk, but the child finally died at the age of 14 months in a state of hyperpyrexia. Postmortem examination showed severe nephrocalcinosis and osteosclerosis.

The usual symptoms and signs of hypercalcaemia are: anorexia, apathy, vomiting, constipation, loss of weight, polyuria, polydipsia, dehydration, osteosclerosis of metaphyses, and soft-tissue calcification.

In the serum, calcium is increased, phosphorus is variable, alkaline phosphatase is decreased, non-protein-nitrogen is increased, and cholesterol is increased.

In the urine, Sulkowitch's test is positive (+++), and

there is albuminuria, pyuria, cylindruria, and hypo- or isosthenuria.

Lightwood (1952) described the transient mild form of idiopathic hypercalcaemia. We saw only 4 cases of this disease in our hospital, while in England the incidence of this disease seems to be much higher. This fact could be explained by the difference in vitamin-D prophylaxis. In England rather high doses of vitamin D are given, usually as an addition to cows' milk or to baby foods. In our country vitamin D is seldom added to any kind of food.

The familial incidence of idiopathic hypercalcaemia became evident with the following observation. Binovular twins failed to thrive and presented all the typical symptoms and laboratory findings of the mild form of idiopathic hypercalcaemia. An investigation of the family revealed a high serum-calcium level in a 5-year-old sister not showing any other pathological signs. Both children responded well to decalcified cows' milk. One of them had to be hospitalized for a second time because of a relapse, although no vitamin D had been given. The twins continued to show a tendency to hypercalcaemia and hypercalciuria. This observation can be regarded neither as a mild nor as a severe form of idiopathic hypercalcaemia; it might be classified as an intermediate form.

A practitioner prescribing vitamin D must know whether he is facing a hypo- or hypersensitivity to vitamin D. He will think of a reduced sensitivity to vitamin D in cases with a familial disposition to rickets, with familial aminoaciduria and with accelerated growth, as for instance in premature infants.

He will have to watch for an increased sensitivity to vitamin D in cases of retarded growth, especially in endocrine disorders. Among our four cases of this group there was one child suffering from hypothyroidism and a second one presenting as a Turner's syndrome. Retarded growth with increased density of metaphyseal margins should make one cautious in using vitamin D. Children showing a premature closure of the fontanelles and the cranial sutures are also predisposed to hypersensitivity. Immobilization of a normal child may lead to symptoms of hypersensitivity if a normal dose of vitamin D is administered. We observed this in a 4-year-old boy suffering from Perthe's disease.

It is evident from this short review that some children require extremely large doses of vitamin D while others show a severe hypercalcaemia without ever having received any vitamin D. In our opinion the various intermediate syndromes represent a gradual transition between the two extremes of hypo- and hypersensitivity to vitamin D.

SUMMARY

The normal physiology of calcium and phosphorus is discussed. The various factors responsible for the control of serum calcium within narrow limits are evaluated.

Diseases with a tendency to hypocalcaemia and those with a tendency to hypercalcaemia are discussed and differentiated.