A Discussion of the Forms of Blood Calcium

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DIETARY INTAKE

PHOSPHORUS
IN FOOD AS LECITHINS, PHOSPHATIDES, INORGANIC PHOSPHATES, ABSORBED IN SMALL INTESTINE.

VITAMIN F (UNSATURATED FATTY ACIDS) AIDS DIETARY ABSORPTION OF PHOSPHORUS (6)(7)

CALCIUM
SOLUBLE & DIFFUSIBLE SALT NECESSARY. COMPLEX Ca SALTS ARE ABSORBED ONLY WHEN ENOUGH HCl OR OTHER ACIDS ARE PRESENT TO CONVERT THEM INTO SIMPLER FORMS. (2)(3)

PARATHYROIDS INCREASE DIETARY ASSIMILATION (2)

RESORPTION OF Ca & P FROM BONE (SEE #2 UNDER NOTES ON METHOD OF BONE CALCIFICATION)

BONES & TEETH
INSOLUBLE $NCa_3(PO_4)_2CaX$

N VARYING BETWEEN 2 & 3

X MAY BE CO_3, OH, OR FLUORINE

ADULT BONE; $Ca_3(PO_4)_2$ - 88%

(10)(1) $CaCO_3$ - 12%

PHOSPHORUS EXCRETED IN RICKETS. (2)
ALSO EXCRETED BY PARATHYROID EFFECT. (21)

SERUM PHOSPHORUS
SOME DIFFUSIBLE (2) ABOUT 30% TOTAL SERUM P, INORGANIC, FREE LECITHINS, ETC. (5)

NON-FILTRABLE CALCIUM-PHOSHORUS COMPLEX
NON-DIFFUSIBLE
ABOUT 10% SERUM Ca (2)

PHYSIO-CHEMICAL BALANCE

ULTRAFILTRABLE CALCIUM-PHOSPHORUS COMPLEX
COLLOIDAL BONE PRECURSOR ALWAYS LOW IN RICKETS NON-DIFFUSIBLE. (2) ABOUT 30% SERUM Ca & 70% SERUM P

VITAMIN D CATALYZES THIS FORMATION OF Ca:P BONE PRECURSOR FROM IONIC SERUM Ca & SERUM P (2) ALL ANTIRACHITIC SUBSTANCES LIKEWISE (2)

ACTION OF ENZYME PHOSPHATASE PRODUCED BY OSTEOBLASTS. (33) (SEE NOTE ON METHOD OF BONE CALCIFICATION)

TISSUE FLUID CALCIUM
THE PERICELLULAR FLUID CONTAINS A CONCENTRATION OF IONIC DIFFUSIBLE CALCIUM WHICH IS NECESSARY FOR PROPER MUSCLE & NERVE TONE. (11)

BALANCE OF IONIZED Ca IN SERUM & IN PERICELLULAR FLUIDS A PHYSIO-CHEMICAL ONE.

DIFFUSIBLE IONIZED CALCIUM (2)
PRINCIPALLY Ca $(HCO_3)_2$ (8)
ABOUT 20% SERUM Ca AMOUNT DEPENDS UPON pH OF THE SERUM. PART OF THE BUFFER MECHANISM. (8)

THE EFFECT OF VITAMIN F OR PARATHYROID IS TO BREAK DOWN Ca:P BONE PRECURSOR INTO IONIZED Ca & SERUM PHOSPHORUS. (13)(2)(3)

TYPES OF CALCIUM & PHOSPHORUS PRESENT IN BLOOD SERUM

PHYSIO-CHEMICAL BALANCE

PHYSIO-CHEMICAL BALANCE

NON-IONIZED DIFFUSIBLE CALCIUM
ABOUT 5% SERUM Ca (10)

NON-DIFFUSIBLE CALCIUM RESERVE
PROTEIN BOUND VARIES WIDELY WITH SERUM PROTEIN CONCENTRATION (2)
ABOUT 38% SERUM Ca

SEMI-PERMEABLE VASCULAR WALL

EXCRETION
DIFFUSIBLE IONIC Ca PRESENT IN SERUM & PERICELLULAR FLUIDS IS IN PHYSIO-CHEMICAL BALANCE WITH KIDNEY THRESHOLD & SALIVA CONCENTRATIONS. IT IS ALSO EXCRETED THROUGH THE SKIN UNDER CERTAIN CONDITIONS. (15)

HIGH SERUM K OR Mg WILL CAUSE Ca ION EXCRETION BECAUSE THEIR HIGHER COMBINING POWER REPLACES Ca IONS IN BODY SALTS RESULTING IN Ca ION EXCRETION. (6)

INSTRUCTIONS
1. ALL INFORMATION PRINTED IN RED INDICATES CALCIUM CHANGES OR RESERVES, WHICH ARE A PART OF THE METABOLISM OF BONE & TOOTH FORMATION.
2. ALL INFORMATION PRINTED IN BLUE INDICATES CALCIUM CHANGES OR RESERVES, WHICH ARE A PART OF THE METABOLISM OF IONIC CALCIUM BALANCE IN THE TISSUES & EXCRETION.
3. ALL INFORMATION PRINTED IN BLUE & RED INDICATES CALCIUM CHANGES OR RESERVES, WHICH ARE A PART OF BOTH OF THESE FUNCTIONS.
4. THE CIRCLE IN THE CENTER REPRESENTS THE TYPES OF CALCIUM & PHOSPHORUS PRESENT IN THE BLOOD SERUM. IF THE TYPE EXTENDS OUTSIDE THE CIRCLE IT IS DIFFUSIBLE, IF NOT, IT IS NON-DIFFUSIBLE.

PATHOLOGICAL DEPOSITS
CALCIFICATION OF TISSUE, ARTHRITIS, ARTERIOSCLEROSIS, RENAL CALCULI, ETC.

POSSIBLE ETIOLOGY OF RENAL CALCULI:
THE URINE MUST REMAIN ACID FOR EXCRETED CALCIUM TO REMAIN IN SOLUTION. ALKALINE URINE CAUSES ITS PRECIPITATION, PRINCIPALLY AS $Ca_3(PO_4)_2$. ORDINARILY THE KIDNEY SYNTHESIZES NH_3 TO REPLACE ALKALINE SALTS (Na, K, ETC.) WHICH CAUSE ALKALINITY. (17) IN VITAMIN A DEFICIENCY THIS NH_3 SYNTHESIS FAILS, WITH CONSEQUENT CALCIUM PRECIPITATION. IN HYPERPARATHYROIDISM THERE IS AN INCREASED EXCRETION OF ALKALINE SALTS (14)(19) WITH THE SAME RESULTS. (18)

POSSIBLE ETIOLOGIES OF DENTAL CALCULI:
TOO HIGH K OR Mg IN SALIVA OR LOWERED ACIDITY CAUSES Ca PRECIPITATION. (6)
VITAMIN C DEFICIENCY INTENSIFIES THIS LOSS OF CALCIUM INTO THE SALIVA.
HIGH P INTAKE CAUSES DENTAL CALCULI. (6)

TETANY
IN TETANY, THE Ca IONS IN TISSUE FLUIDS ARE TOO LOW. THIS INTERFERES WITH ELECTRICAL BALANCE & HYPEREXCITABILITY & TWITCHING RESULTS. (2)
TOO HIGH SERUM P WILL CAUSE THIS BY COMBINING WITH IONIC CALCIUM TO FORM Ca:P BONE PRECURSOR.
PARATHYROID EXCRETES P PREVENTING HIGH P RATIO, (21) & EXCRETES ALKALINE SALTS OF HIGHER COMBINING POWER PREVENTING THEM FROM REPLACING & CAUSING EXCRETION OF Ca IONS. (14)
BY PREVENTING THE COMBINATION OF Ca AS Ca:P BONE PRECURSOR BOTH PARATHYROID & VITAMIN F INSURE ADEQUATE IONIC Ca CONCENTRATION. (2)(13)(3)

RICKETS
IN RICKETS, THE ULTRAFILTRABLE CALCIUM-PHOSPHORUS COMPLEX IS LOW. (2) LOW P PREVENTS THE FORMATION OF THIS COMPLEX AND ALWAYS PREDISPOSES TO RICKETS. (2) THE SPECIFIC ACTION OF VITAMIN D IS TO CATALYZE THE FORMATION OF THIS COMPLEX Ca:P BONE PRECURSOR FROM IONIC CALCIUM & SERUM PHOSPHORUS. EITHER PHOSPHORUS DEFICIENCY (2)(32) OR VITAMIN D DEFICIENCY MAY BE AN ETIOLOGICAL FACTOR IN RICKETS.

METHOD OF BONE CALCIFICATION
1. THE OSTEOBLASTS OR BONE-FORMING CELLS SECRETE A LOCAL ENZYME, PHOSPHATASE, WHICH HYDROLYZES THE PHOSPHORUS ESTER COMPONENT OF ULTRAFILTRABLE CALCIUM-PHOSPHORUS BONE PRECURSOR, GIVING RISE TO PHOSPHATE IONS (33) & APPARENTLY CALCIUM IONS, WHICH ARE PRECIPITATED AS CALCIUM PHOSPHATE BONE SALT. (20)(33)(22)
2. APPARENTLY PHOSPHATASE IS A REVERSIBLE ENZYME, & UNDER CERTAIN CIRCUMSTANCES, CAUSES A RESORPTION OF BONE SALTS BACK INTO THE BLOOD SERUM. THIS MAY BE THE RESULT OF AN INCREASED CONCENTRATION OF ENZYME ACTIVATORS SUCH AS HYPERVITAMINOSIS D (26)(25), HYPERPARATHYROIDISM (12)(22), HYPERTHYROID (28), OR A RESULT OF CHANGE OF SUBSTRATE SUCH AS LOWERED SERUM IONIC Ca CAUSED BY DIETARY INSUFFICIENCY OR INCREASED DEMAND AS IN PREGNANCY.
3. PHOSPHATASE IS ONLY PRESENT LOCALLY NEAR THE OSTEOBLASTS. (21) VITAMIN D TENDS TO KEEP IT IN THIS LOCAL CONCENTRATION. (20) IN RICKETS, (27) HYPERPARATHYROIDISM (27), & HYPERVITAMINOSIS D (21), PHOSPHATASE IS ABNORMALLY FOUND IN THE BLOOD STREAM & TISSUES. BLOOD PHOSPHATASE IS DEPRESSED BY ADRENAL CORTEX. (23)
4. IN VITAMIN C DEFICIENCY THE OSTEOBLASTS DEGENERATE RESULTING IN A CONDITION CALLED OSTEOPOROSIS, ASSOCIATED WITH LOWERED PHOSPHATASE PRODUCTION & CONSEQUENT DEFICIENT CALCIFICATION. (10) VITAMIN C ALSO CATALYTICALLY ACTIVATES PHOSPHATASE. (24) OSTEOPOROSIS ALSO RESULTS FROM INANITION OF BONE WITH CONSEQUENT ATROPHY OF OSTEOBLASTS. (29)
5. PHYSIOLOGICALLY, PARATHYROID STIMULATES OSTEOBLASTIC ACTIVITY. (21)

PARATHYROID ACTION
ANTI-TETANY
1. EXCRETES P, RAISING Ca:P RATIO THUS INSURING ADEQUATE TISSUE IONIC Ca CONCENTRATION.
2. PROMOTES BREAKDOWN OF Ca:P BONE PRECURSOR INTO IONIC Ca & SERUM P
3. INCREASE EXCRETION OF ALKALINE SALTS THUS SPARING Ca IONS.

VITAMIN F ACTION
SYNERGIST OF BOTH
1. CATALYZES FORMATION OF IONIC Ca & SERUM P FROM Ca:P BONE PRECURSOR, & INSURES ADEQUATE IONIC TISSUE Ca CONCENTRATION.
2. AIDS DIETARY ABSORPTION OF PHOSPHORUS FOR FORMATION BY VITAMIN D OF Ca:P BONE PRECURSOR.

VITAMIN D ACTION
ANTI-RACHITIC
1. CATALYZES FORMATION OF Ca:P COMPLEX BONE PRECURSOR FROM IONIC Ca & SERUM P.
2. LOCALIZES ENZYME PHOSPHATASE NEAR THE OSTEOBLASTS.

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A DISCUSSION OF THE FORMS OF BLOOD CALCIUM★

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Calcium has numerous functions in human metabolism. It comprises (as tri-calcium phosphate and calcium carbonate) about 98% of the mineral component of bone and tooth structure (1). It forms an important blood buffer (as ionized calcium bicarbonate). It is a necessary constituent of tissue fluids in maintaining proper electrical potential balance in muscle and nerve.

The accompanying chart* attempts to illustrate the various phases and controlling factors of calcium metabolism as far as it has been followed in medical literature to date.

The calcium and phosphorus forms in the bloodstream are represented by the paragraphs within the circle in the center of the chart. The bloodstream functions principally to carry these forms to the various parts of the body where they are needed. We are primarily interested in how the calcium is put into this bloodstream, how it is kept there, and how it is deposited in various tissues where and when it is needed. Inasmuch as phosphorus is intimately connected with calcium in its deposition as bone, we have included phosphorus in this treatment.

DIETARY ABSORPTION OF CALCIUM AND PHOSPHORUS

First, calcium and phosphorus are absorbed into the blood from the food in the small intestine. In order for the blood to pick up calcium from the small intestine the calcium must be in the form of simple, soluble and diffusible salts (2). More complex calcium salts are utilized only if there is enough hydrochloric acid present in the stomach to break them down into simpler salts (3). The parathyroid hormone aids this absorption (2), and large doses of vitamin D likewise (4), probably by increasing the osmotic demand through the conversion of diffusible to non-diffusible calcium.

Phosphorus is obtained from foods in the form of inorganic phosphates, lecithins, phosphatides, etc. (5), and unsaturated fatty acids aid in its absorption (6), probably activated by vitamin F (7). This phosphorus goes into a blood reserve consisting of lecithins, and inorganic phosphates some of which are diffusible (6) (5) this reserve comprising about 30% of the serum phosphorus (2). (The other 70% is combined with Ca as seen later.)

CALCIUM FORMS IN SERUM

Various investigators have stressed the important fact that study of the blood concentration of the inorganic salts gives no indication of the rate of direction of their flow into the excretory channels or into the tissues (3).

**The chart inside the back cover presents the picture of blood calcium forms and their functions, which is difficult to present in an orderly text form.*

The assimilated calcium salts become diffusible ionic calcium mainly as bicarbonate, $(Ca(HCO_3)_2)$ on reaching the bloodstream (8) comprising roughly about 20% of the serum calcium* (2).

This ionized calcium depends for its concentration upon physio-chemical relationships with free floating proteins, tissue fluids, and an amount of blood alkaline salts of higher periodic activity, such as potassium or magnesium, which tend to replace it (6). It thus acts in part as a blood buffer (8).

The concentration of diffusible ionized calcium in the blood serum increases to an extent with a lowered pH of the blood serum (8) (2). This may be due to the fact that lowered pH results in the fixation of more potassium and magnesium buffer salts. When these salts are lowered they are replaced by calcium ions and the total calcium in blood will increase, resulting in more elimination (3).

Depending upon the amount of free floating serum proteins, this type of ionic calcium will combine with these proteins into a non-diffusible calcium proteinate, which is a blood calcium reserve (2). This calcium proteinate will split and give back ionic calcium if the serum protein concentration is reduced. This calcium proteinate reserve comprises about 38% of serum calcium (2).

Vitamin C is a catalyst for protein synthesis and thus it would follow that it is necessary to the retention of this reserve (9). The integrity of this reserve thus is probably dependent upon vitamin C and is lowered in scurvy.

The ionic calcium bicarbonate is also in physio-chemical relationship with a non-ionized form of calcium bicarbonate comprising about 5% of total serum calcium, but having no known physiological significance (10).

CALCIUM IN TISSUE FLUIDS — TETANY

The ionic calcium, being diffusible, is an important constitutent of tissue fluids, serving to maintain muscle tone, and being essential to normal action of the sympathetic nervous system (11). Both parathyroid hormone (2) (12), and vitamin F (13) are necessary to maintain a proper concentration of ionic calcium in tissue fluids.

One of the ways in which parathyroid hormone insures this calcium concentration is by its promotion of the excretion of the higher periodic alkaline salts (K and Mg) having a calcium sparing action (14). Other means will be mentioned further in this discussion. If (as a result of parathyroidectomy) the calcium ions in tissue fluids drop below a necessary concentration there is an electrical potential disturbance resulting in hyperexcitability and spontaneous contractions of muscle, called tetany (2). Since ionic calcium is the only diffusible blood serum form of calcium, and this is low in tetany, the total blood calcium will also be lowered in this condition. As we shall see, this does not happen in rickets.

EXCRETION OF CALCIUM

If more ionic calcium than is necessary is present, and there is not free floating serum protein to take it up as a blood reserve, it will be excreted. Normal muscular activity causes an increase in sweat gland excretion with

**Most Biochemists consider the ionized calcium to be mainly bicarbonate, however when tissue fluid calcium is precipitated as dental calculi or eliminated by perspiration the major percentage is in the form of phosphate (33) (34) (16).*

a temporary sharp drop in ionic calcium (15). This may explain why tremors may be associated with hard exercise. When calcium is lowered no more is excreted after the urinary threshold of 8.5 mg. per 100 cc. is reached (16).

In order for calcium bicarbonate to remain in solution its media must be acid or contain an excess of CO_2 (8). Urinary excreted calcium will therefore only be soluble in acid urine because of the absence of CO_2. An alkaline urine will result if basic salts (Na, K, Mg, etc.) are excreted. Normally these basic elements are replaced with ammonia (synthesized in the kidney) (17) and retained in the blood. In hyperparathyroidism (14) (18) and vitamin A deficiency (19), basic salts are excreted. The resulting alkaline urine precipitates the ionic calcium with the pathological deposition of renal calculi.

Some calcium bicarbonate is in the saliva. The same holds true here. It has been shown clinically that a high phosphorus intake will result in dental calculi (6).

RICKETS AND TETANY

Bones and cement of teeth (1) are composed about 88% of calcium phosphate and 12% calcium carbonate hydroxide and fluoride in varying proportions (10). The calcium and phosphate are deposited together by the enzyme phosphatase (20).

The only calcium and phosphorus in the bloodstream that forms bone structure is a special form of ultra-filtrable, non-diffusible calcium phosphorus (2). This calcium-phosphorus complex is colloidal and answers best to the description of calcium-phosphorus bone precursor. Apparently, it is a loosely held combination of phosphorus esters and calcium. The specific action of any anti-rachitic substance or vitamin D is the formation of this calcium-phosphorus compound in the blood from ionic calcium and inorganic phosphates. In rickets this colloidal complex is always lowered, although total serum calcium is usually normal (2). The breakdown of this calcium-phosphorus complex gives rise to corresponding amounts of ionic calcium and diffusible phosphorus resulting in phosphorus excretion (2).

That is the essential difference between rickets and tetany. In tetany the diffusible ionic calcium is low. But in rickets, it is the special ultra-filtrable, non-diffusible calcium-phosphorus complex that is low with a correspondingly high diffusible calcium and consequently normal total serum calcium (2).

It has been demonstrated that parathyroid hormone promotes the excretion of serum phosphorus (21). By lowering the phosphorus the chances of formation of calcium-phosphorus compound is lessened, and ionic calcium will remain as it is. Thus parathyroid accelerates rachitic lesions (3) (2). Vitamin F raises blood phosphorus (13), promotes the diffusion of ionic calcium into the tissue fluids (13), probably by breaking up the calcium-phosphorus colloidal complex, to form ionic calcium. Thyroid has a similar effect in raising ionic calcium and has been called a calcium eliminator for this reason. In presence of vitamin D, vitamin F cooperates in mobilizing phosphorus for vitamin D to form into calcium-phosphorus complex.

In accounting for all known forms of serum calcium it is of interest to note that the ultra-filtrable calcium phosphorus bone precursor has a

non-colloidal counterpart with which it is in physio-chemical balance (2). The ultra-filtrable calcium-phosphorus complex accounts for about 30% of total serum calcium and about 70% of the total serum phosphorus (2), while its physio-chemical partner comprises about 10% of total serum calcium and about 5% total serum phosphorus (2).

BONE AND TOOTH FORMATION

The osteoblasts or bone forming cells secrete a local enzyme, phosphatase, which hydrolyzes the phosphorus ester component of ultra-filtrable calcium-phosphorus bone precursor, giving rise to phosphate ions (33) and apparently calcium ions which are precipitated as calcium-phosphate bone salt (22) (20) (33).

Normal physiological amounts of parathyroid hormone tend to stimulate osteoblastic formation (21) and thus the formation of phosphatase; however, as mentioned later, hyperparathyroidism reverses to some extent the activity of this enzyme (22). Normal amounts of vitamin D tend to keep this enzyme locally concentrated and out of the bloodstream (20). Adrenal cortex acts similarly (23). In vitamin C deficiency the osteoblasts degenerate, preventing phosphatase formation and thus prevent calcification of bone (10). Vitamin C also catalytically activates the action of this enzyme phosphatase (24). This accounts for the deficient bone and tooth development in scurvy or pyorrhea.

The bones form a vast storehouse of calcium reserves which are drawn upon to supply calcium in dietary lack or in pregnancy. In early pregnancy it is interesting to note that estrogen increases the density and thickness of the mother's bones thus augmenting the calcium reserve (22). In these conditions, it is probable that phosphatase reverses its activity and redissolves bone so that the calcium is resorbed into the blood as ionic calcium bicarbonate and phosphate. (Most enzymes are known to be reversible depending upon hormonic and substrate controls or conditions (33).) Hypervitaminosis D (25) (26), hyperparathyroidism (12) (25) (22), and thyroid (28) supply ionic calcium by bone resorption in emergency, apparently through this enzyme reversibility.

Resorption of bone, resulting from reversing of phosphatase enzyme as described above, is called osteitis fibrosa generalisata. If there are not enough calcium salts precipitated into the organic matrix due to deficiency of calcium-phosphorus bone precursor, as in rickets, the condition is called osteomalacia. If there is an underactivity or degenertion of the osteoblasts, (phosphatase formers) with resulting phosphatase deficiency and consequent incomplete calcification, the condition is called osteoporosis (29).

The underactivity or degeneration of osteoblasts may be caused by atrophy from disuse (29) or from vitamin C deficiency (10). In osteoporosis there may arise an increase in serum ionic calcium since bone resorption is taking place faster than calcification, with resultant overloading of kidney calcium excretion capacity and consequent kidney damage (29). An erroneous diagnosis of hyperparathyroidism (bone resorption from phosphatase activity) may be made in this condition which may be due to inanition of skeleton (29) or from vitamin C deficiency (10).

Silberberg and Silberberg divide the formation of mammalian bone into three distinct periods, the extent of metabolism being predetermined. Various hormones accelerate or retard the rate of metabolism in each

period but do not change the total extent of metabolic activity which is predetermined by heredity. The physiological effect of various hormones in accelerating or retarding the rate of activity in each period is shown in the following chart (22).

1st PERIOD Proliferation of the epiphyseal cartilage	2nd PERIOD Cessation of lengthwise growth with increase in density and thickness of the bony shaft	3rd PERIOD Ossification progresses with predominating resorption of bone
rate accelerated by thyroid	rate accelerated by thyroid	rate accelerated by thyroid
rate accelerated by anterior pituitary growth hormone		
	rate accelerated by parathyroid	rate accelerated by parathyroid
	rate accelerated by calcium administrations	rate inhibited by calcium administrations
rate inhibited by estrin	rate accelerated by estrin	rate accelerated by estrin
rate inhibited by testosterone	rate accelerated by testosterone	rate inhibited by testosterone
rate accelerated by gonadectomy	rate delayed by progesterone delayed by gonadectomy	accelerated by gonadectomy

Ordinarily the enzyme phosphatase is only found locally near the osteoblasts (21). In some pathological conditions it "leaks" into the blood stream which could explain pathological calcium deposition in the blood vessels (arteriosclerosis), in tissues, and in joints (arthritis). Rickets (27), hyperparathyroidism (27), and tremendous dosages of vitamin D (21) cause a rise of phosphatase in the blood stream. Adrenal cortex prevents this rise (23). Vitamin D normally keeps phosphatase localized (20).

PATHOLOGICAL CALCIUM METABOLISM

Much clinical experience has demonstrated the toxic calcification of tissue, especially in pregnancy, resulting from high dosages of synthetic vitamin D (21). Tremendous dosages of vitamin D are used in the treatment of arthritis with some success. This dosage would create considerable demand for ionic calcium, and pathological joint deposits can give this calcium to the blood. It is possible that this may account for the success of vitamin D in these conditions, although there is insufficient experimental evidence to warrant a positive conclusion. Single high dosages or tremendous dosages of vitamin D would seem to be contra-indicated by reason of its promotion of phosphatase in the bloodstream, which can cause pathological calcium deposits in blood vessels as arteriosclerosis. Arteriosclerosis from hypervitaminosis D is a common clinical picture (30).

In view of the presence of arteriosclerosis resulting from hypervitaminosis D in the absence of its synergist vitamin F, we might assume that vitamin F would tend to prevent arteriosclerosis in this respect. The fact that arteriosclerosis is a rare disease in China (36), where the diet contains foods high in F, such as soybean products, deserves careful investigation.

Arthritis is also apparently not a common disease in China, there being no reference to it in Dr. Snappers' review of cases he encountered in the Peiping Union Medical College Hospital (36).

It has been noticed that cod liver oil does not have the pathological calcifying effects of viosterol or synthetic vitamin D. Recent work has shown that cod liver oil contains vitamin F (31). It might be remembered that vitamin F increases ionized calcium at the expense of calcium-phosphorus complex.

A lack of phosphorus will cause a poor production of colloidal calcium-phosphorus bone precursor. Phosphorus deficiency has been claimed to be a primary cause of rickets (2) (32). The action of vitamin F in promoting phosphorus absorption (6) should not be overlooked in this sense.

In such a phosphorus deficiency the serum content of ionic calcium may become super-saturated and deposit pathological calcium carbonate in the joints and tissues (35).

The etiological factors in disorders of calcium metabolism, other than endocrine abnormalities, may be dietary deficiencies of vitamin D, vitamin F, vitamin C, calcium, or phosphorus, or more likely a combination of these.

In children, this absence of calcium deposition means that bone and tooth structure will fail to keep pace with the growing body, and rickets, deformities, and dental malformations are a result. In adults, the resorption of bony structure may mean a tendency to fracture easily, dental caries, pyorrhea, and resorption of the alvelolar ridge with loose teeth. These deficiencies may also cause a disturbed balance of serum ionic calcium bicarbonate and serum phosphorus that will precipitate insoluble calcium forms aggravating arteriosclerosis or arthritis.

Calcium metabolism is a field of biochemistry which probably has more extensive ramifications than the study of any other nutritional element. In view of the importance of this subject, it is surprising how incomplete our knowledge is and what few attempts have been made to put what knowledge we have on a systematic basis. A proper review of the subject would touch upon almost every phase of biochemistry.

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