NUTRITIONAL IMBALANCES IN INFANT AND ADULT DISEASE

Mineral, Vitamin D, and Cholesterol

Edited by

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Introductory Comments

Nutritional and Metabolic Factors in Early and Later Life, Contributing to Acute and Chronic Disease

The failure of hypolipidemic regimens to lower the incidence of ischemic heart disease (IHD) in patients with high blood cholesterol levels has focussed attention on the arterial lesions detected in early childhood, which may be the initiating pathologic change of the cardiovascular diseases that are manifest in adult life. As a result, institution of hypolipidemic regimens in infancy has been suggested and disputed.

The program of the Sixteenth Annual Meeting of the American College of Nutrition, the proceedings of which are printed in this volume, was organized to consider additional nutritional or metabolic factors in early and later life which may contribute not only to ischemic heart disease, but also to other chronic disorders, and which often coexist with cardiovascular disease. Because the arterial and myocardial lesions of experimental vitamin D excess and of magnesium deficiency resemble those of cardiovascular damage of infancy

and childhood (seen in infantile hypercalcemia, supravalvular aortic stenosis, infantile generalized arteriosclerosis, and even in routine autopsies), invitations to participate in the meeting were extended to investigators working in related areas. It was anticipated that correlation of their findings might provide further insight into some nutritional factors that are usually not considered contributory to several of the chronic diseases accounting for much of the morbidity and mortality in the industrialized world.

The epidemiologic papers pertain to the hard/soft water data (as they relate both to ischemic heart disease and to urinary tract calculi) and to Vitamin D (slight to moderately increased intakes of which are correlated with hypercholesterolemia, myocardial infarction, and renal calcinosis). Dr. Harman considers the possibly protective effects of magnesium and calcium in hard water and emphasizes the potentially damaging effects of copper excess that may result from the use of copper pipes in soft water areas (soft water being more acid than hard water) as contributory to the greater incidence of sudden death due to ischemic heart disease in soft than hard water areas. It should be noted that other trace metals such as lead and zinc can also be leached out of pipes. Also to be kept in mind is the exchange of sodium for magnesium and calcium in artifically softened water. Thus, the epidemiologic evidence that death rates from IHD have increased in some areas after the general water supply has been softened cannot be attributed to a single factor. Such epidemiologic studies have limitations, particularly when they are based on studies of populations in large geographic areas, since localities often differ in the hardness of drinking water where the water may be obtained from wells or be artifically softened in individual households. Dr. Linden's paper is predominantly devoted to his own studies which suggest that even slight excesses of vitamin D may increase the risk of cardiovascular and calcifying renal disease and hyperlipidemia, particularly in subjects hypersensitive to solar irradiation. However, he notes the parallels between the "water story" and his hypervitaminosis

D theory and comments on the magnesium loss caused by vitamin D excess. Dr. Landes and his coworkers provide statistically significant evidence that the incidence of urinary calculi is inversely related to the hardness of drinking water. It is provocative that where the problem of encrusted plumbing is less (naturally soft water) or lessened (artifically softened water), the risk of calcium deposits in arteries and urinary tract is greater.

Dr. Clark has reviewed evidence from animal studies that shows that the absorption and blood levels of magnesium, calcium, and phosphate are interrelated and considers the ion-hormonal interplay among the minerals and hormones—parathyroid, calcitonin, and vitamin D. He shows that alterations in the dietary levels of calcium, magnesium, and phosphate influence one another and emphasizes the risk of high phosphate intake. Dr. Norman and his coworkers present the evidence that the structure and mode of action of vitamin D and its active metabolite(s) are those of a steroid hormone. They review the evidence that the synthesis of the biologically active metabolite, 1,25-$(OH)_2$-D_3, by the mitochondria of the renal cortex is determined by the ionic environment, that high calcium levels decrease its synthesis, and that low levels increase it. Thus, the hormones (parathyroid [PTH] and calcitonin [CT]) and dietary factors that influence calcium homeostasis affect the synthesis of the active metabolite of vitamin D. This step is mediated by the enzyme, 1-hydroxylase, the ionic cofactor for which is magnesium. Calcium, phosphate, strontium and manganese inhibit the enzymes; as the calcium concentration rises, the enzyme activity, and thus the synthesis of 1,25-$(OH)_2$-D_3 falls. They put forth a thought-provoking evaluation of the calcium/enzyme/hormone interrelationships in the regulation of synthesis of this active vitamin D metabolite, the biologic responses to which are stimulation of intestinal absorption of calcium and of its mobilization from bone. In conclusion, they present an inclusive diagram of the diseases and drugs associated with abnormal vitamin D metabolism.

In the clinical metabolic section of these proceedings, the paper by Drs. Rosen and Finberg provide data on some of the conditions associated with defective utilization of vitamin D. They review the major theories explaining hypocalcemia and present their clinical experience with vitamin D metabolites. Neonatal hypocalcemia has been attributed to hypomagnesemia, "functional" hypoparathyroidism, and impaired transformation of vitamin D to its active metabolites. In hepatobiliary disorders, the block is at the hepatic conversion of vitamin D_3 to 25-OH-D_3, and treatment with this metabolite has proven useful. Since the metabolic error in vitamin D-dependent rickets is at the next step (renal conversion to the 1,25-$(OH)_2$-D_3), and since PTH stimulates that reaction, treatment with the dihydroxy-D_3 metabolite holds promise for the long-term management of idiopathic hypoparathyroidism and renal rickets.

The complex interrelationships of calcium and magnesium with PTH and CT have been explored in depth and elucidated by Dr. Anast. In his long-term study of a young woman with an isolated intestinal defect in magnesium absorption and convulsive seizures associated with hypomagnesemia and hypocalcemia, he showed that she had subnormal response to vitamin D and calcium therapy. Administration of magnesium salts raised her serum magnesium to the low limit of normal or slightly below, and raised her serum calcium to normal. Her responses to PTH and to calcium, phosphate, and magnesium are in accord with the evidence that magnesium deficiency interferes with PTH release rather than its synthesis. Because of the difficulty in measuring CT, it has been necessary to study the influence of magnesium on CT in patients with abnormally high CT levels (patients with medullary carcinoma of the thyroid). In contrast to animal studies which indicate that magnesium's effect is similar to that of calcium in stimulating CT release, Anast's clinical studies demonstrate a rapid and striking fall in the imtially high CT levels and, usually, a detectable fall in the serum calcium in response to intravenous

infusions of magnesium. He suggests that the calcium lowering effect of magnesium in patients with thyroid medullary carcinoma may be the result of redistribution of body calcium mediated by neither PTH nor CT.

Neonatal hypocalcemia has been reviewed by Drs. Tsang and Brown, who consider the contributory maternal and neonatal factors. It is prevalent among prematures, infants who are small for gestational age (SGA), and those with birth asphyxia or who are born to insulin-dependent diabetic mothers or to very young or toxemic mothers. They correlate the condition with low calcium intake in the first few days, a low calcium/phosphate ratio, hypomagnesemia, and hypoparathyrodism. Premature infants have subnormal 25-OH-D_3 levels; neonates may also have increased CT function. They point out that correction of acidosis with alkali and the use of citrate in exchange transfusions can intensify the condition. They comment that maternal hypomagnesemia (such as is seen in diabetic mothers) can contribute to neonatal hypomagnesemia. which leads to hypocalcemia, and that the condition resolves with improved intakes of calcium and magnesium, increased phosphate excretion, and establishment of normal parathyroid function. Dr. Caddell summarizes the basis of her hypothesis that maternal magnesium deficit may contribute to a poor initial magnesium endowment of infants and that this may play a role in the sudden infant death syndrome (SIDS), the cause of which remains unknown. She is investigatigating the possibility that subnormal magnesium may predispose an infant to increased histamine release (such as has been reported in magnesium-deficient animals) and that this may be a key to the premonitory signs and to the pulmonary findings at autopsy.

Dr. Lennon's contributions to the understanding of the effect of glucose loads on renal tubular function in man, including the demonstration of resultant, sharply augmented excretion of calcium and magnesium, may help explain the hypomagnesemia of diabetic mothers, as well as the prevalence of hypomagnesmia and hypocalcemia in their newborn

infants. Perhaps it also relates to the hypomagnesemia of uncontrolled diabetes which has been reported elsewhere.

The paper by Dr. Glueck and his coworkers on the pediatric genesis of atherosclerosis was placed last in this volume because it brings us back to the still unresolved problem of how to prevent cardiovascular disease which increasing evidence suggests begins very early in life. They recommend screening of children, particularly of parents with premature ischemic heart disease or hyperlipidemia, for familial hypercholesterolemia. They suggest that lowering the blood cholesterol to normal in such children by providing diets low in cholesterol in the first two years of life, may prevent atherosclerosis. They also introduce their current investigations into possible problems associated with the greater intake of plant sterols present in the vegetable oils that are substituted for animal fats.

This conference was planned and the papers arranged to focus on a few of the manifold problems that must be considered in attempting to determine how nutritional imbalances in infancy and childhood can contribute to chronic diseases of later life. In addition to the commonly considered contribution of saturated fat to the pathogenesis of atherosclerosis, papers were given that provide evidence of magnesium deficiency in infancy. There is experimental and epidemiologic evidence that magnesium inadequacy not only contributes to cardiovascular disease, but also to urinary tract calculi. Animal and clinical studies that demonstrate the interrelationships of Mg/Ca/PO_4/ PTH/CT and vitamin D provide justification for considering how imbalances in the nutrients in the complex (Ca/Mg/PO_4/ vitamin D) may affect PTH, CT, and the synthesis of the vitamin D metabolites. During the neonatal period among infants with hypocalcemia and hypomagnesemia, and with hypoparathyroidism levels of vitamin D metabolites are often low; they rise on correction of both deficits. The possibility that the synthesis of the active metabolites may be subnormal in hypomagnesemic patients (as suggested by the impaired response to vitamin D by Anast's hypomagnesemic

patient) should be considered. On the other hand, hyperreactivity to vitamin D and experimental vitamin D toxicity causes cardiovascular and renal lesions like those of magnesium deficiency. Magnesium is protective; excess calcium and phosphate each intensifies the lesions. Bone wasting may be caused by hypervitaminosis D, particularly in the presence of a low Ca/PO_4 ratio, as a result of mobilization of bone minerals. The evidence that it also contributes to hyperlipidemia and magnesium loss suggests that a combination of high intakes of vitamin D and phosphate with marginal intakes of magnesium, common in America, may contribute to several common chronic diseases.

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