hyper-reactivity to vitamin d*

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"It is significant that the high incidence of 'idiopathic' hypercalcemia of infancy in England in the years 1953-57 was correlated with the excessive fortification with Vitamin D_2 of National Dried Milk for infant formulas (and other foods) during that period."

PRECIS

The author claims that selection of the approved prophylactic dosage of vitamin D, and of the vehicle in which it should be administered, was based on findings in infants with relatively high requirements of vitamin D. More recent recognition of the similarity of several pediatric diseases to syndromes caused by hypervitaminosis D, calls for a re-evaluation of the safety of a uniform high prophylactic dosage of this nutrient.

Whether toxicity will develop when vitamin D is administered, constitutes a peculiarly medical problem. The physical status of the patient, and the degree of his responsiveness to vitamin D, establishes a set of conditions which determines whether he will react adversely or respond adequately to prophylactic doses of vitamin D. Patients at one extreme react adversely to doses below recommended requirements. At the other extreme, administration of doses more than 50 times the advised therapeutic dose may be necessary for amelioration of some of the physical signs of vitamin deficiency, or even to prevent rickets. Fanconi[1] has presented an analysis of pathological conditions in childhood, which can be differentiated by their completely different reactions to vitamin D: vitamin D-resistant rickets at one extreme, and idiopathic hypercalcemia at the other (Figure 1, see next page). Infants with rickets, characterized not only by deficient intestinal absorption of calcium and phosphorus, but also by diminished renal tubular reabsorption of phosphorus,[2] have long been known to require and to tolerate much larger doses of vitamin D than normal infants.[3,4] Avioli et al.[5] have reported that familial vitamin D-resistant rickets is caused by a genetic abnormality in the metabolism of vitamin D, with increased formation and excretion of its water-soluble, inert degradation products.

A disease associated with elevated serum calcium and/or phosphorus may increase susceptibility to vitamin D toxicity. Hypercalcemia and/or hyperphosphatemia can result from primary or secondary failure of renal excretion. Increased mobilization of calcium from body stores may be caused by hyperparathyroidism, immobilization with atrophy of disuse, or primary or metabolic neoplasms of bone. Disturbances of calcium metabolism in sarcoidosis, and in idiopathic hypercalciuria has been attributed to hyper-reactivity to vitamin D,[6] as has

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*Vitamin D_2 = irradiated ergosterol or calciferol
Vitamin D_3 = natural fish oil vitamin D

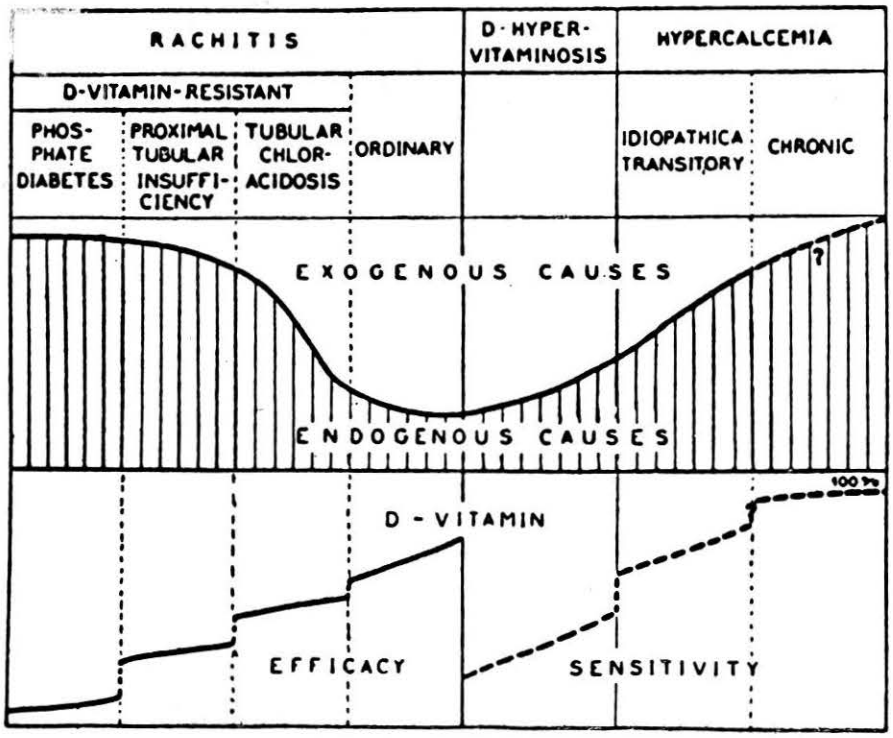


Figure 1. Spectrum of varying reactions to vitamin D. (G. Fanconi) Bone Structure and Metabolism. Ed. by G. E. W. Walstenholme and C. M. O'Connor (Little Brown & Company, Boston, Massachusetts, 1956)

infantile hypercalcemia and its sequellae[7] *(infra vide)*. Taussig[8] has proposed that there may be a genetic trait that, because it allows for better than average utilization of vitamin D, results in greater resistance to rickets and greater susceptibility to vitamin D toxicity.

Norman[9] has presented a thought-provoking postulate that vitamin D does not act as a vitamin or as a co-factor for enzymes, but as a steroid hormone. As such, vitamin D or one of its metabolites may interact on either gene activation or regression, or on one of the other steps in the regulation of calcium metabolism. Norman has concluded that vitamin D probably plays a crucial role, with parathyroid hormone and calcium, in a DNA, gene-dependent, homeostatic control mechanism for calcium metabolism. Since only slight alterations in the chemical structure of vitamin D may increase or abolish its activity, it is possible that differences in its metabolic handling in the body may explain the differences in reactivity to administered vitamin D in the clinic. For example, De Luca et al.[10,11] have recently identified a metabolic product of vitamin D (25-hydroxycholecalciferol, or 25-HCC), formed in the liver from vitamin D, that has 1.5 times the antirachitic potency of vitamin D, and that is probably the physiologically active form of vitamin D. Possibly hyper-reactive infants more effectively produce 25-HCC from vitamin D or the precursors. Hypo-reactive infants may produce less 25-HCC or may more effectively degrade vitamin D to inert metabolic products.[5]

Relative Hypo-reactivity to Vitamin D; Rickets Prophylaxis

The early investigators into the susceptibility to rickets of children, who had not received exogenous vitamin D, found differences in amounts of vitamin D required, depending on the population groups studied. Drake[12] reported from Toronto that only 13% of 244 infants (of British or Northern European stock) had detectable rickets, although none had received vitamin D supplementation. After five months observation, during which no vitamin D was added to their diets, only an additional 8% had active advancing rickets. As little as 300 units of vitamin D_2, administered as irradiated ergosterol, was therapeutic in rickets of moderate or marked degree.[12] The lowest amount tested: 95 units vitamin D_2 daily in irradiated milk, or 150 units of vitamin D_3, as cod liver oil, was fully prophylactic, as determined by roentgenographic examination.

In a New York City study of darker skinned children (Puerto Rican and Italian: 45%, and Negro 55%), Lewis[13] found that among 22 infants who had received no vitamin D during a five month observation period, eight, all of whom were black, developed rickets. This constituted 62% of the 13 Negro infants in this group. Eight percent, or 27 of 355 children given vitamin D_2 for five winter months, in doses ranging from 145 units in corn oil, propylene glycol or milk to 1,450 units in corn oil, developed rickets. Among the 155 Negro infants in this study, 21 or 14% developed rickets; among the 200 Puerto Rican and Italian infants, six or 3% developed rickets. None of the infants given vitamin D_2 in milk, even in doses as low as 145 units/28 ounces, developed moderate or advanced rickets; 3 developed mild rickets. However, one black child developed a mild

form of the disease, even on as much as 1,450 units of crystalline vitamin D_2 in corn oil.

Autopsy studies by Follis et al.,[14,15] of a series of 1,303 infants under two years of age, revealed that half of those who had received no vitamin D had rickets. The rachitic lesions were more prevalent and severe in Negro children than in white.

The failure to prevent rickets in one infant given 1,450 units vitamin D in oil suggested to Lewis[13] that 2,000-2,500 units might have been more fully protective. Three (5%) of the 58 infants given 145 units vitamin D_2 in milk having developed mild rickets, Lewis[13] recommended adding 332 units of vitamin D_2 to each quart of milk. A later paper by Glaser, et al.[16] presented evidence that all preparations of vitamin D in an oily vehicle in daily doses of 100 units were prophylactic against clinical rickets, even in premature and in Negro infants. However, because nine (5.6%) developed roetgenographic evidence or suspicion of rickets, among the 166 who were followed for the full observation period of eight months, the authors recommended the general use of 400-800 units (in oil) as a prophylactic dose. (For further data on effect of vehicle on potency, *infra vide.)*

Infantile Hypercalcemia: an Expression of Hyper-reactivity to Vitamin D

Infantile hypercalcemia has developed in children on doses of vitamin D considered prophylactic. Anorexia, vomiting, fretfulness, constipation, and weight loss or failure to gain are frequent during the first weeks or months. Renal and cardiac damage may be detectable next, and severe mental retardation, often associated with a peculiar "elfin" facies may become manifest later in the first year of life. Excessive absorption of calcium from the gut, in response to given doses of vitamin D, and/or abnormal metabolism of this vitamin or of related cholesterol derivatives have been demonstrated in this condition.[17-25] The similarity of the renal and cardiovascular findings in infantile hypercalcemia to those of experimental hyper-vitaminosis D, in the face of intakes that were not excessive has led many to suggest that the afflicted children are hyper-reactive to vitamin D.[1,7,8,17-54]

Lightwood[55] reported the first case of infantile hypercalcemia, that was probably caused by hyperreactivity to vitamin D. The infant had received only "physiological" amounts of vitamin D at a time (1932) when there was no vitamin D-supplementation of milk. She developed hypercalcemia, albuminuria, and mental retardation, was dwarfed, and died at 27 months of age. Her mother had taken no vitamin D during pregnancy.

In 1936, Thatcher[26] attributed the progressive failure in health of an infant who had thrived until six months of age, to idiosyncratic response to prophylactic administration of vitamin D. He had been given 100-400 units/day, and exposed to sunlight or ultraviolet irradiation from six months until he died of renal damage at almost a year of age. An infant who died at 15 weeks of age with hypercalcemia, and who had pathological signs of generalized arteriosclerosis of infancy at autopsy, had never received more than 500 units daily.[45] Infantile hypercalcemia, diagnosed in the first half year of life, has been reported to develop on vitamin D intakes of 130-1,000 units daily.[41,53] The condition of these children improved when the vitamin D and calcium intakes were restricted. Among the infants diagnosed as hypercalcemic at 6-20 months of age, the early vitamin D intakes were estimated at not over 2,000 units daily in over 50 cases.[17-21,23,28,29,33-36,44,45,51] Among five children diagnosed in late childhood, as presenting late stigmata of infantile hypercalcemia, reported by Black and Bonham-Carter,[54] two had had "usual" supplementation, and three had been breast-fed for one and a half to six months before receiving "usual" supplements. Seven such patients had histories of irregular vitamin supplementation,[56] no more than "usual" prophylactic doses,[38,57] 1,000-1,500 units daily for 5 years,[38] and less than 1,000 units daily.[50] In no instance, in which the vitamin intake of the mother had been recorded, had pre-natal vitamin D intake been over 1,000 units daily.[23-50,52,55]

The responses to the administration of vitamin D to infants with hypercalcemia have been found to differ from case to case. In one of the early studies, Bonham-Carter et al.,[18] in an attempt to identify a pathogenic factor, found that loading a hypercalcemic baby in remission with high doses of vitamin D_2 caused an increase in plasma calcium and a deterioration of his condition. His intake of vitamin D and calcium was then reduced with subsequent improvement. However, the hypercalcemic response to vitamin D and to its removal, seems to differ from case to case. Spontaneous fluctuations in serum calcium, as great as 2-3 mg/100 ml, have been reported by Fraser et al.[51] during the acute phase of the disease. Forfar[22] administered large doses of vitamin D_2 (50,000-100,000 units) for about a week

to three infants with hypercalcemia. In two instances, after a few days, the serum calcium rose significantly. It took about three weeks for the serum calcium to fall to dosage load levels. In one case, the serum calcium level fell following the administration of calciferol, and rose again to the pre-calciferol load level within a day of stopping treatment. Girardet[58] has stated that in certain individuals, even large doses of vitamin D may produce signs of renal toxicity without significant hypercalcemia.

Either hyper-reactivity to administered vitamin D,[18,31] or its defective inactivation,[40] is suggested by metabolic balance studies that show the high percentage of dietary calcium that is absorbed (60%) after administration of vitamin D to hypercalcemic infants. Measurements of vitamin D activity in the plasma of hypercalcemic infants have shown both insignificant differences from normal values in one series,[59] and markedly higher than normal values in others.[19,37,44] Garcia et al.[44] reported a serum value of 1,540 units in an infant who had hypercalcemia and supravalvular aortic stenosis, and whose daily vitamin D intake was 400 units from milk and 1,000 units from a supplement. (The normal range of serum vitamin D in this institution was 60-400 units.) Fellers and Schwartz,[19] reported that three patients with hypercalcemia had serum vitamin D activity that was 20 to 30 times that seen in normal infants, although all exogenous vitamin D had been removed from their diets. Two additional hypercalcemic infants were reported by Manios and Antener[49] to respond to vitamin D (700 units in oil for four days) by a twofold rise in serum vitamin D levels from pretreatment values of 520 and 580 (as compared with the normal mean in this laboratory of 133 units: range = 50 to 200 units).

These observations suggest that this condition is associated with abnormal metabolism of vitamin D. Forfar and his co-workers[20-22] found that hypercalcemic infants also have a marked increase in free serum cholesterol, a finding reported also by Lefebvre.[25] In view of the vitamin D-like effect of some cholesterol derivatives, Forfar and his coworkers have suggested that this disease may be related primarily to a disorder of cholesterol metabolism. They postulated that even a small amount of calciferol may act as a chemical mediator in this disease, by activating endogenous vitamin D precursors that may be present in excess in susceptible infants.[21,22]

Williams' Syndrome or Supravalvular Aortic Stenosis — (SAS) Syndrome: Late Expression of Infantile Hypercalcemia

It is possible that the SAS or Williams' Syndrome, an abnormality characterized by supravalvular aortic stenosis, a peculiar facies, and severe mental retardation[60] (Figure 2) is a late expression of hyper-reactivity to vitamin D during infancy.[7] Black and Bonham-Carter[54] first observed the similarity in the stigmata of children who survived infantile hypercalcemia, to those seen in children with supravalvular aortic stenosis (Figure 3). Both conditions have been associated with cardiac damage, often with renal impairment, "hypercalcemic facies" and mental retardation.[7,8,48,51,52,60-74] One of the children, reported by Black and Bonham-Carter,[54] later died at 16 years of age with renal failure, hypertension, and left ventricular failure[61] (Figure 4). Garcia et al.[44] reported the Williams' syndrome in an infant with biochemically diagnosed hypercalcemia and a markedly elevated vitamin D blood level (Figure 5). Bauman and Bauman[62] reported two children with hypercalcemia and cardiac damage, in one of whom all symptoms, signs and abnormal laboratory findings disappeared five years later (Figure 6). The only significant treatment had been curtailment of vitamin D intake. Beuren et al.[64-66] reported supravalvular aortic stenosis with mental retardation and "hypercalcemic facies" in German children with definite histories of hypercalcemia. Many of these children had received excessive vitamin D parenterally during infancy. In some instances, the mothers had also been given "usual" prophylactic doses of vitamin D pre-natally (in multivitamin preparations.)

The possibility that pre-natal insult (caused by excess vitamin D during pregnancy) is the most important contributing factor to this disease has been proposed by several authorities.[51,75-77] They suggest that the excessive response of the infant to vitamin D may be caused by metabolic and anatomic damage to the fetus. Support for this concept was obtained largely from the experimental work of Friedman et al.,[78,79] who had earlier shown aortic lesions in some of the young rabbits, and in all of their mothers, given toxic doses of vitamin D during pregnancy.[80] However, there is no evidence that excessive vitamin D had been taken during pregnancy by any of the mothers of children with hypercalcemia or the SAS syndrome.[7,67A] The mother of the child with infantile hypercalcemia, who had been reported by Smith et al.[37] was later found to

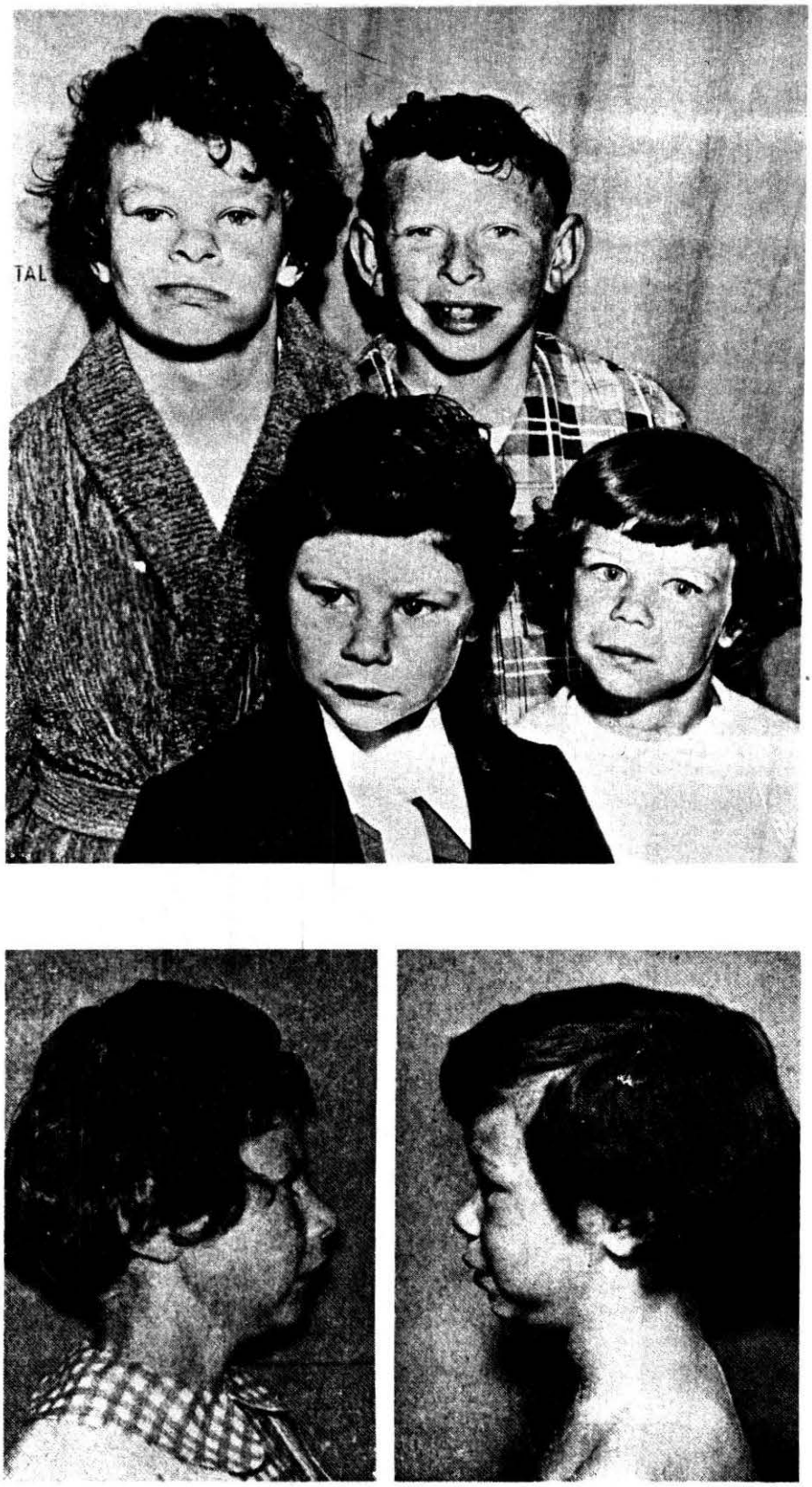


Figure 2 (Top): Four patients with supravalvular aortic stenosis (courtesy of J. C. P. Williams. **(Bottom):** Profiles of children in front row (reproduced by permission of J. C. P. Williams, B. G. Barratt-Boyes, and J. B. Lowe, and Circulation, 24:1311-1318, 1961).

respond to test with a large dose of vitamin D by development of hypercalcemia, and by symptoms of mental agitation.[63] It is of interest that her second daughter, who had been reported earlier by Kenny et al.[41] to have had symptomless hypercalcemia that was diagnosed at three and a half months because of the history of the older sister with the infantile hypercalcemia syndrome, improved on a low vitamin D regimen, and developed normally. Another mother of a child with infantile hypercalcemia became pregnant shortly after being given large dosage vitamin D to see if she was hyper-reactive. She was immediately taken off all vitamin D, and after a normal gestation, gave birth to a normal infant.[81]

Friedman[73] has stated that the SAS syndrome is not uncommon, and that its association with infantile hypercalcemia may be missed. He has commented on the fact that not all of the infants who developed hypercalcemia had received large doses of vitamin D, and reviewed the evidence that an inborn error of metabolism of vitamin D — possibly with production of a cholesterol derivative with anti-rachitic activity (Forfar[20]) — might be responsible.[78] Taussig[48] has suggested that the two types of supravalvular stenosis syndrome — that associated with, and that without the characteristic facies and severe mental retardation — may represent different responses to the same underlying condition. She has suggested that the inborn variation in man's ability to metabolize vitamin D may be responsible for the injury to the cardiovascular system seen both in infantile hypercalcemia and in supravalvular aortic stenosis.[8] The increase in blood cholesterol, often seen in hyper-vitaminosis D, further sug-

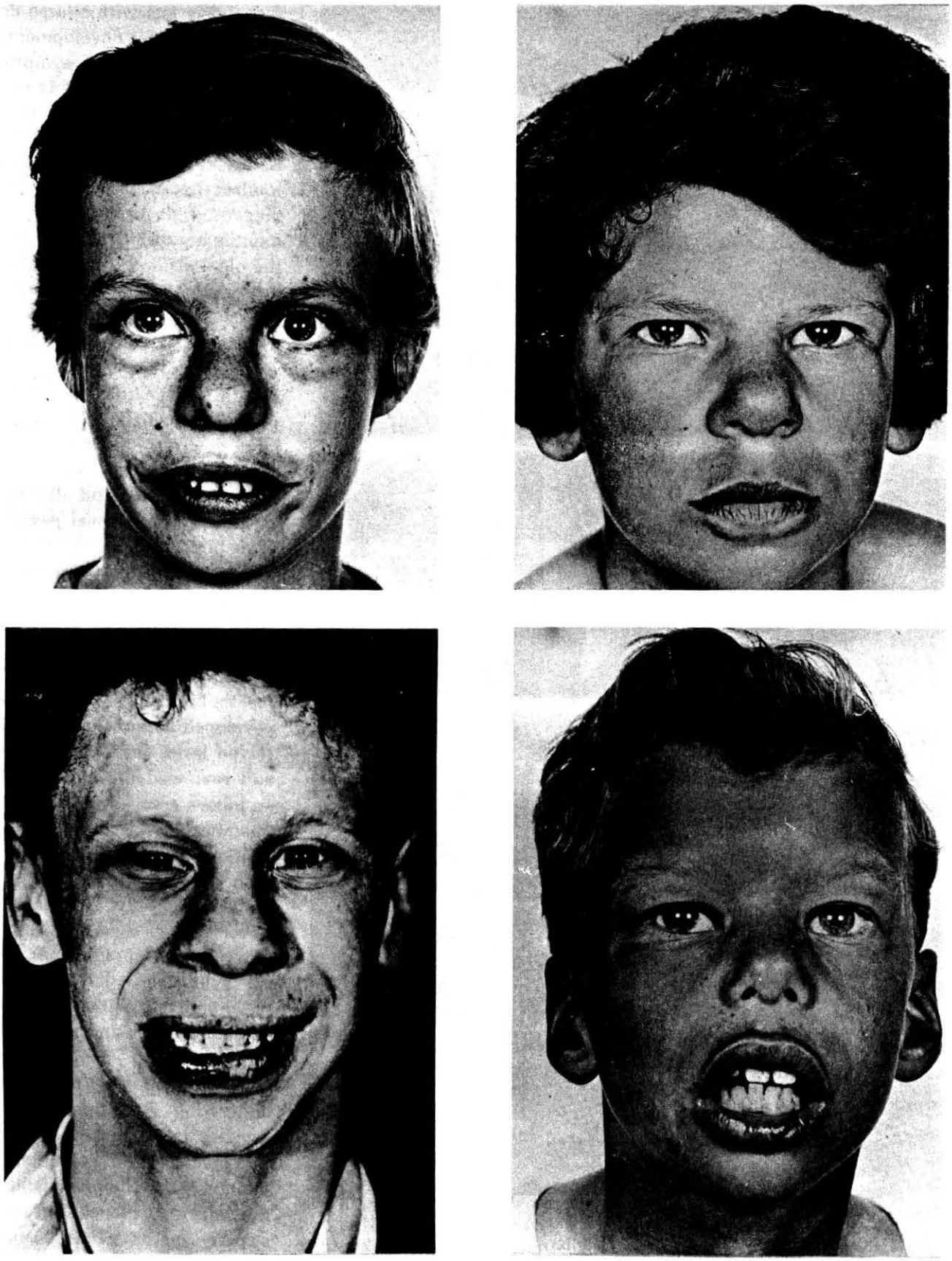
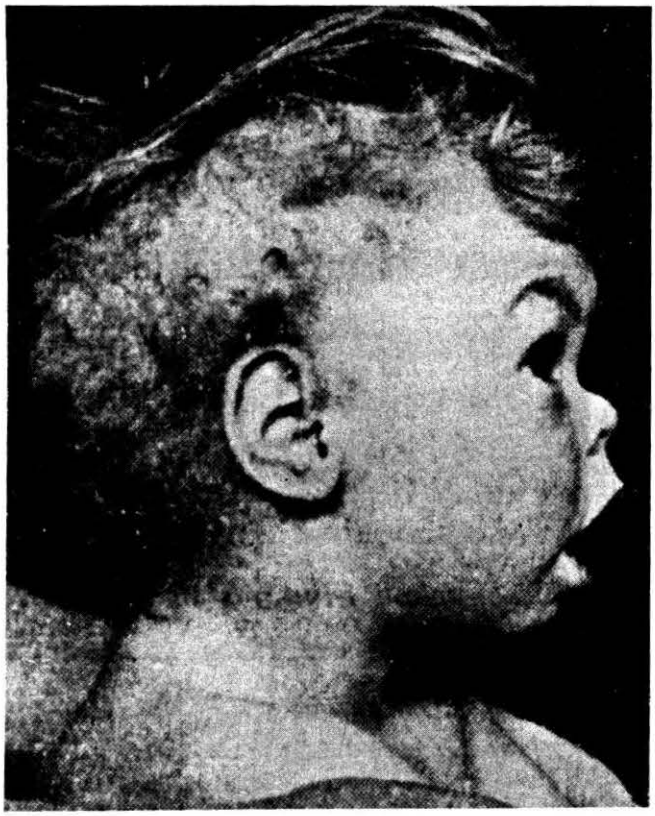


Figure 3. Survivors of infantile hypercalcemia. (Reproduced by permission of J. A. Black and P. E. B. Bonham-Carter and Lancet. 2:745-748, 1963.)



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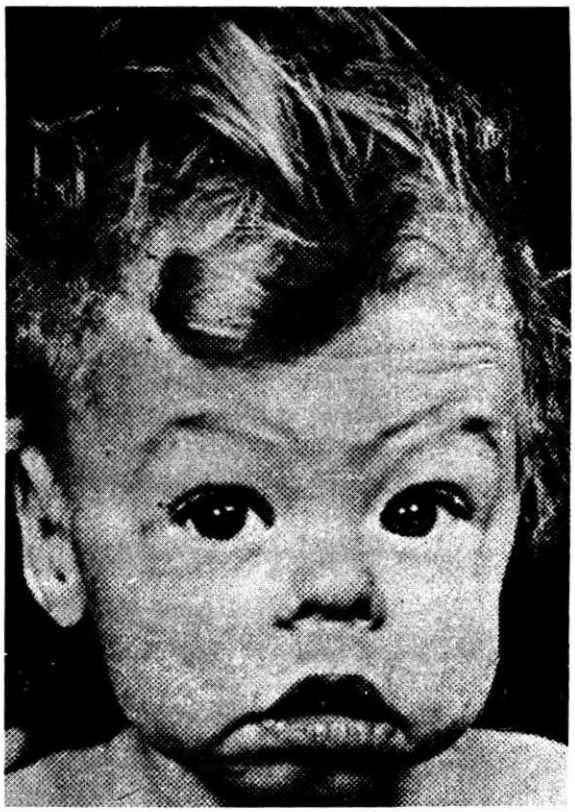

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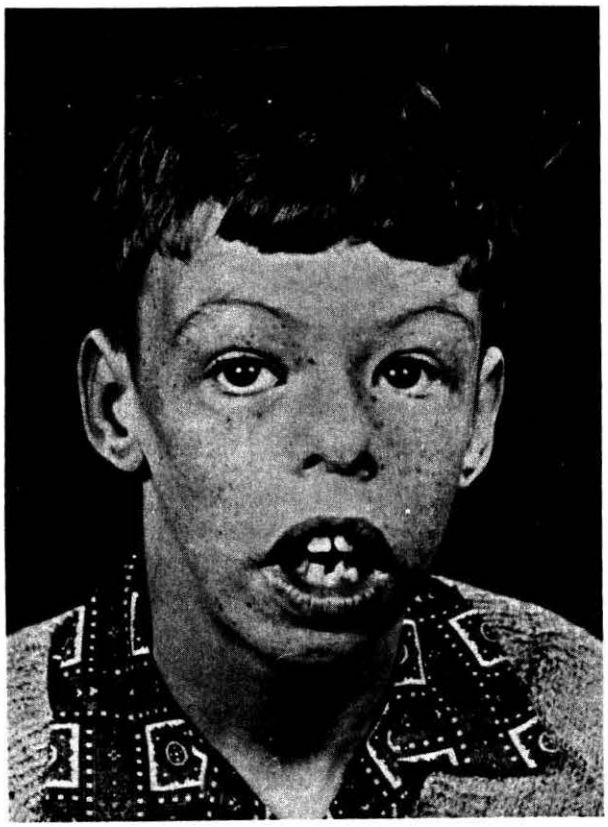

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Figure 4 (A, B). Patient with hypercalcemia at 21 months of age. (Reproduced by permission of B. E. Schlesinger, N. R. Butler, and J. A. Black and Brit. Med. J. 1:127-134, 1956). **(C).** Same child at 11 years of age (reproduced by permission of J. A. Black and R. E. B. Bonham-Carter and Lancet 2:745-748, 1963).

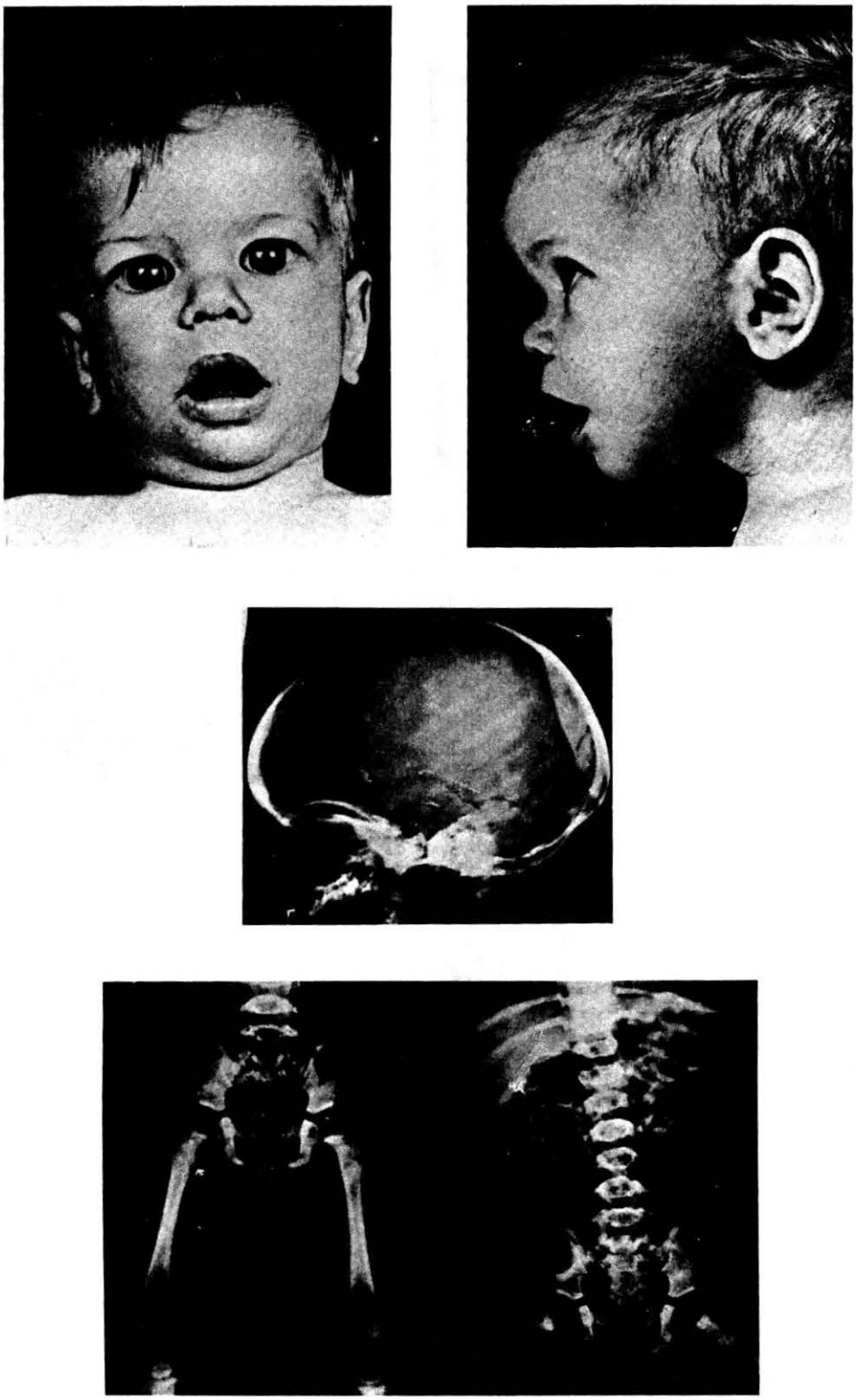

Figure 5. Hypercalcemic infant with supravalvular aortic stenosis. **(Top)** Note the high, prominent forehead, epicanthal folds, underdeveloped bridge of the nose and mandible and overhanging upper lip. **(Center and Bottom)** Roentgenograms of the skull, pelvis and long bones and spine, showing appreciable sclerosis of the calvaria and base of the skull, as well as diffuse osteosclerosis, with bands of increased density at the metaphysical ends of the long bones and the epiphyseal margins of the vertebras. (Reproduced by the permission of R. E. Garcia, W. F. Friedman, and R. D. Rowe and New Eng. J. Med., 271:117-120, 1964.)

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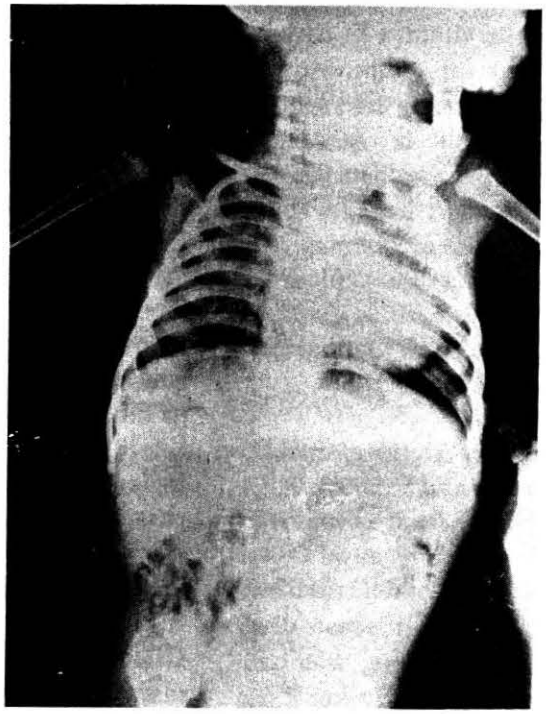

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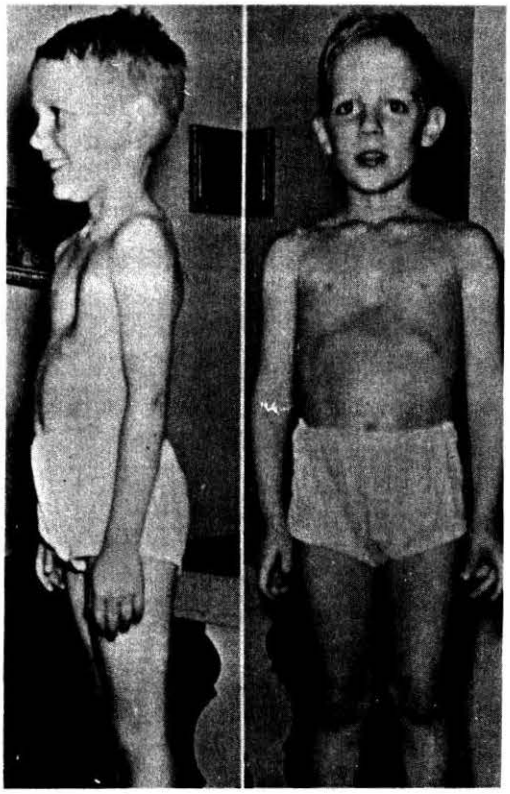

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Figure 6. Hypercalcemic patient, who recovered on curtailment of vitamin D. **A.** Hypercalcemic infant: Note malnutrition, poor development, low position of pinnas. **B.** Roentgenogram, showing cardiac enlargement; "coeur en sabot" configuration. **C.** Patient, five years later: Note alert appearance, good muscular development. (Reproduced by permission of A. Bauman and C. G. Bauman and N. Y. State J. Med., 65:1910-1917, 1955.)

gests that such variation in susceptibility to vitamin D may be related to the far commoner vascular lesions such as arteriosclerosis, which is associated with abnormal cholesterol metabolism. Black[24] has reviewed this and additional theories that have been proposed to explain the metabolic abnormalities that may be responsible for hyper-reactivity to vitamin D.

Generalized Arteriosclerosis of Infancy and Vitamin D

The possibility that hypervitaminosis D may be a causal factor in generalized arterial calcification of infancy, a disease diagnosed only at autopsy, was considered in 1947 by Stryker.[82] He recorded the available information as to vitamin D intake in his series of five cases, as well as in 15 cases tabulated from literature. One stillborn infant had coronary and aortic calcification as well as myocardial necrosis and calcification. Four who died between two and seven months of age also had coronary calcification; two had myocardial infarctions. In the case of an infant who died at three months, the family physician had suspected hypervitaminosis D, but could elicit no history of unusual vitamin intake by either the mother or the infant. Menten and Fetterman[83] reported an infant who died of generalized arteriosclerosis and myocardial infarction, born to a mother who had taken no vitamin D during pregnancy, but who had taken two capsules of dicalcium phosphate daily. He had received five drops of Oleum Percomorph daily from two weeks of age. In his second month of life he began to show symptoms (i.e. vomiting and fretfulness) that are commonly seen early in infants with infantile hypercalcemia. At autopsy, all of the superficial coronary branches were found to be thickened, sclerotic and calcified, and the aorta was diffusely thickened. Wilkerson's[45] hypercalcemic infant, who had never received more than 500 units vitamin D/day, had severe calcinosis of arteries, kidneys, and soft tissues on autopsy at 17 weeks.

Infants who died early in the course of hypercalcemia, as well as those with generalized arteriosclerosis of infancy, had histologic aortic, myocardial, and renal changes that resemble markedly the lesions of experimental hypervitaminosis D in rats reported by Gillman and Gilbert[84] and by others reviewed elsewhere.[7] Intimal and sub-endothelial thickening with fragmentation, degeneration and calcification of the elastica, as well as medial and myocardial degenerative changes have been found on autopsy of infants and children reported here[7,23,27,31,43,45,55,72,74] as well as in the laboratory models of vitamin D toxicity.[7,84]

The renal damage seen in the picture of generalized arteriosclerosis of infancy has been emphasized by Stryker.[82] Moran and Becker,[85] who reviewed the published cases to date in 1959, suggested that renal damage might have predisposed to the metastatic arterial calcification seen in this condition.

Renal Acidosis and Vitamin D

Another disease of infancy with which vitamin D has been associated, and that may be related to hypercalcemia of infancy, is renal tubular acidosis. Lightwood[86] observed that there was a steady increase in the incidence of this disease in Great Britain from 1950 (the first date in his tabulation) through 1953, after which there was a sharp drop in incidence (See Figure 7). Since infants with this syndrome often exhibit elevated serum calcium levels, he proposed that there was clearly a biochemical overlap between infantile hypercalcemia and infantile renal tubular aci-

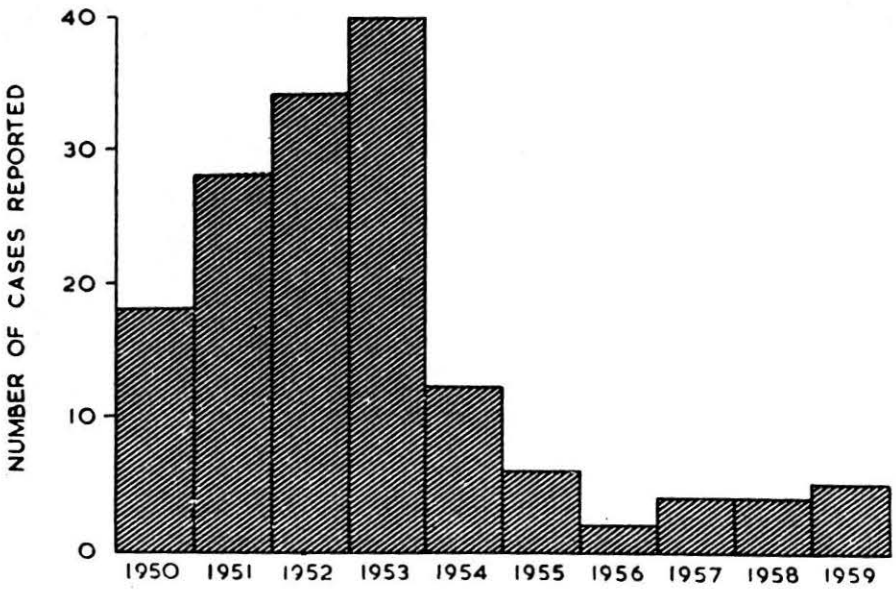

Figure 7. Infantile renal tubular acidosis: 153 cases by years of occurrence (14 centres). Information is lacking for 1950 for Liverpool. (Reproduced by permission of R. Lightwood and N. Butler and Brit. Med. J. 1:855-857, 1963.)

doses. However, the drop in incidence occurred in 1954, three years before the excessive fortification with vitamin D_2 of Dried Milk Formula in England was corrected.[7,87] The reduced incidence of infantile renal acidosis coincided with the sharp rise in incidence of hypercalcemia of infancy that occurred the year after the Ministry of Food recommended increasing the vitamin D content of dried milk from 280 to 500 I.U. per ounce.[7,88] It is possible that infants who developed the full blown syndrome of hypercalcemia of infancy, which includes renal impairment and calcinosis, might have developed only renal tubular acidosis on half the amount of vitamin D.

Graham[53] reported the association of renal acidosis with infantile hypercalcemia in his series of 47 infants with hypercalcemia. Except for the low plasma CO_2 in those with renal acidosis, the findings of all the affected infants were essentially the same. Renal calcinosis is common to both diseases. The author commented that he rarely saw renal acidosis uncomplicated by hypercalcemia.

In a study of 60 cases of nephrocalcinosis infantum, detected only at autopsy, Shanks and MacDonald[89] observed that only 12 had been diagnosed ante-mortem as having had "renal acidosis." Prolonged administration of fortified milk and/or vitamin supplements had been reported in the histories of 52. The authors postulated that symptomless hypercalcemia is a more widespread condition than has been appreciated and that the renal lesions may be detected only in children that died of some other condition.

Risk of Mass Medication with High Dose Vitamin D in Milk

Mass uniform prophylactic therapy, intended to prevent one disease, is justified only when the practice does not, at the same time, cause another. Evidence has accrued that the amount of vitamin D added to milk (which is enough to prevent, or even to cure, rickets in children who require very large amounts) is sufficient to cause renal, cardiovascular, and brain damage in those who are hyperreactive. Such children are now subject to diseases caused by hypervitaminosis D. Vitamin D is not only added to milk, but is commonly added to many other foods, as well as taken as specific supplements, so that apparent vitamin D intakes of as much as 2000 units/day may be reached.[90]

Since vitamin D is much more active in milk than it is in oil, and since there is evidence that vitamin D_2 is more toxic than vitamin D_3, the addition of 400 units of vitamin D_2 to a quart of milk may provide far more than a safe intake for susceptible infants. For children with a high intake of milk, the daily intake of vitamin D is undoubtedly higher.

Effect of Vehicle on Potency of Milk

Increases in potency, 3-10 fold, have been reported when vitamin D is added to milk, as compared with its potency in oil.[12,13,91-93] Stearns et al.[91] calibrated the effect of different doses of vitamin D_3 against the growth of infants. Their work suggested that infants given 300-400 units of vitamin D_3 in cod liver oil grew at faster than average rates, whereas infants getting all of their vitamin D_3 from cod liver oil emulsified in milk required only 135 units per quart for the same rate of growth. Lewis[92] has demonstrated that 90 units of vitamin D_2 in milk healed all nine rachitic infants in his study, whereas of the nine infants who received 90 units in oil, three showed no healing at six weeks and the rachitic process became worse at the end of the eight weeks in two. On the basis of his studies with vitamin D_2 in both vehicles in the treatment of rickets (see Table I, following page) he observed that the therapeutic results obtained from 90 units in milk were superior to those obtained with 900 units in oil.

Supplee et al.[93] explored the factors in milk that might have accounted for this enhancement effect. Using the rachitic rat "line test," they found marked differences in the anti-rachitic response, depending on the vehicle in which the vitamin D had been delivered. Milk, or even an isolated milk constituent, lactalbumin, was shown to enhance the potency of vitamin D.

It should be noted here that Black[24] and Thomas et al.[94] have cautioned that this assay does not detect every substance in the serum that is capable of raising the serum calcium (i.e., to pathogenic levels). For example, dihydrotachysterol has 10 times the activity of vitamin D in causing calcifying cardiomyopathy (in rats),[95] but has only 1/400 the anti-rachitic activity of vitamin D by the rat "line test," and has hypercalcemic activity approximately equal to that of vitamin D_2 in man.[94]

The decision as to the amount of vitamin D_2 to be added to milk was based largely on the early work done by Lewis,[13] Drake,[12] and Glaser.[16] These investigators found that 100 to 290 units of vitamin D_2 in oil were sufficient to prevent rickets in over 90% of the children on test. To assure adequate prophylaxis in all children, Glaser[16] recommended 400-

Table I

COMPARISON OF HEALING, AMONG 36 RACHITIC INFANTS, BROUGHT ABOUT BY CRYSTALLINE VITAMIN D INCORPORATED IN MILK OR IN CORN OIL

CASE	AGE (MO.)	DATE BEGUN	MENSTRUUM IN WHICH CRYSTALLINE VITAMIN D WAS INCORPORATED	NO. OF RAT UNITS (STEENBOCK) GIVEN	ROENTGENOLOGIC RICKETS					COMMENT
					AT ONSET	HEALING AFTER 4 WK.	HEALING AFTER 6 WK.	HEALING AFTER 8 WK.	HEALING AFTER 10 WK.	
C. M.	8	1/23	Milk†	45	Moderate	+	++	+++	++++	Porto Rican
B. G.	6	1/25			Moderate	+	+±	++	++±	Porto Rican
F. S.	13	1/26			Moderate	0	0			Negro
E. D.	6	2/ 7			Slight	+	++	+++±		Italian
C. N.	8	2/18			Moderate	+	+±	++	+++	Porto Rican
C. W.	22	2/17			Marked	+±	++	++±		Negro
G. B.	8	2/21			Moderate	+±	++±	+++±		Negro
J. N.	6	2/24			Mild	0	0	0 (worse)		Negro
V. L.	6	1/13	Milk‡	90	Slight	++	+++	Normal		Italian
S. Q.	4	1/13			Moderate	+±	++±	+++±	++++	Porto Rican
J. A.	5	1/13			Slight	+++	++++	Normal		Negro
R. L.	5	1/19			Moderate	+++	Normal	Normal	Normal*	Negro
C. H.	20	1/25			Marked	+++	+++±	++++	Normal	Negro—1/25: calcium, 9.8 mg.; phosphorus, 3 mg. 2/23: calcium, 10.6 mg.; phosphorus, 5 mg.
K. S.	4	2/22			Slight	++	+++	Normal		Negro
B. C.	7	3/ 2			Moderate	+				Porto Rican
F. S.	15	3/17			Moderate	+	+±			Negro
B. R.	6	3/17			Moderate	+±	+++			This infant had received 90 units of crystalline vitamin D in oil for one month, and no healing resulted
T. R.	5	2/ 4	Oil§	90	Moderate	+±	++±	+++	++++	Porto Rican
S. L.	7	2/12			Slight	?	+	+±		
B. M.	4	2/14			Slight	+	++		++	Negro
B. R.	5	2/16			Slight	0 (worse)				Negro
V. B.	14	2/16			Marked	+	+±	++	+++	Negro
D. R.	7	2/21			Moderate	0	0	0 (worse)	0	Negro
C. Q.	5	2/23			Slight	?	+	+±	++±	Porto Rican
C. B.	8	2/28			Moderate	0	0	0 (worse)		Negro
T. B.	8	3/19			Moderate	0	0			Negro
J. B.	3	2/16	Oil‖	900	Slight	++		Normal	Normal	Negro
P. G.	6	2/ 9			Slight	++	++++			Italian
J. B.	6	2/16			Slight	++	++±	+++	+++±	Negro
T. B.	6	2/16			Slight	++	++++	Normal		Negro
C. M.	6	2/16			Moderate	++				Negro
R. P.	17	2/17			Marked	+				Negro
H. B.	4	2/17			Slight	++	+++	+++±	Normal	Negro
J. D.	7	2/17			Moderate	+±	+±±	+++	+++±	Negro
N. E.	3	2/17			Slight	+	++	++±		2/15: calcium, 7.2 mg.; phosphorus, 5.3 mg. 3/13: calcium, 10.3 mg.; phosphorus, 6.1 mg.
J. D.	24	1/30			Marked	+	+	+	+±	Negro; at 12 weeks healing ++

§One drop contained 15 units.
‖One drop contained 150 units.

+Denotes slight healing; ++, moderate healing; +++, marked healing; ++++, healed rickets.
* X-ray picture taken at 13 weeks.
†One liter contained 60 units.
‡One liter contained 120 units.

From LEWIS, J.M.: Clinical Experience With Crystalline Vitamin D: The Influence of the Menstruum on the Effectiveness of the Antirachitic Factor. J. of Pediatrics 6: 362-373 (1935)

800 units in oil; Lewis,[13] who had found vitamin D_2 in milk to be far more potent than vitamin D_2 in oil, suggested adding 332 units to milk, in order to protect even infants with very high vitamin D requirements.

Quite apart from the effect of the vehicle on the potency of vitamin D, is the type of vitamin D provided. Forfar and his co-workers[21,22] have suggested that the vitamin D_2 provided in milk, to a greater extent than natural fish oil vitamin D_3, might activate chemical precursors of anti-rachitic sterols in sensitive infants. Furthermore, direct evidence was provided over thirty years ago that vitamin D_2 is significantly more toxic than is vitamin D_3, particularly as regards cardiovascular and renal toxicity.[96,97]

It is significant that the high incidence of "idiopathic" hypercalcemia of infancy in England in the years 1953-1957 was correlated with the excessive fortification with vitamin D_2 of National Dried Milk for infant formulas, and of other Welfare and proprietary foods during that period[7,87] (see Table II). In 1956, the British Pediatric Association recommended reconsidering the vitamin D needs of normal infants before advising on the amount of vitamin D to be added to milk; they suggested its omission from infant cereals, as well as from milk until more data were obtained.[87] The Government recommendation, in 1957,[99] was that (1) the vitamin D content of dried milk be reduced to a minimum of 90-100 units/dry ounce, (2) the vitamin D content of infant cereals be reduced to 300 units/dry ounce, and (3) the vitamin D content of cod liver oil be reduced to 400 units/teaspoonful. Consumption of only one of these sources provides the maximum daily intake or more. Intake of either fortified cereal or oil may be marginally safe in hyper-reactive children; intake of fortified milk with or without the other sources may be toxic.

The compromise of providing vitamin D at a level that protects against rickets in the majority of the population, and that causes disease only in the minority of infants with lower than normal tolerance for this vitamin was approved editorially in 1964.[100] Halving the amount of vitamin D in fortified foods and supplements, was reported to halve the incidence of hypercalcemia;[101] it did not increase the incidence of rickets (in an analysis that considered the colored immigrants separately, since they had not been fed the fortified foods to the same extent as had the native British children[101,102]). Coleman,[47] who reported ECG changes in 12 of 13 Scottish infants with hypercalcemia (admitted to a hospital in the year 1962-1963), has cautioned that it is necessary to make responsible inquiry into the nature of the residual effects of vitamin D deficiency and toxicity, in selecting prophylactic dosage.

In North America, where the Council on Foods and Nutrition of the American Medical Association has long considered acceptable only milk containing no more than 400 units of vitamin D[103], there have been many published reports on infants with hypercalcemia[7,17,19,33-41,43-45,50,56,57,104-106], and other reports on the Williams' Syndrome.[8,44,48,62,63,67,67A,69,70,73,78,106] The American Academy of Pediatrics accepted, in 1963, the likelihood that vitamin D intake is related to infantile hypercalcemia and supervalvular aortic stenosis.[90] In 1965, they recommended public health measures which may reduce one form of congenital mental retardation

TABLE II

FORTIFICATION OF NATIONAL DRIED MILK
(Great Britain)

Date	I.U. Vitamin D per Dry Ounce	Recommendation by
1945	280	Ministry of Health [99]
1953	500	Ministry of Food [87]
1957	90-100	Ministry of Health [99]

CALCULATED DAILY INTAKE OF VITAMIN D (1956) [87]

1 1/2 pints dried milk (460 U/dry oz.):	1,725 I.U.
1 ounce cereal (1,000-1,500/dry oz.):	1,000 - 1,500 I.U.
1 tsp. cod liver oil	700 - 800 I.U.
Total	3,525 - 4,025 I.U.

(Top): Changes in amounts of vitamin D added to dried milk in Great Britain. **(Bottom):** Possible intake of vitamin D at time of peak fortification, if all three sources were consumed.

and heart disease, provided a much larger population was not simultaneously placed in jeopardy of rickets.[107]

Readily detectable, early bone changes of rickets are reversible; the cardiovascular, renal and brain lesions of hypercalcemia are not. It is infinitely preferable to prevent both diseases, rather than to weigh the sociologic value of preventing one or the other. The minimum toxic dose of vitamin D for infants has been given by Stewart et al.[108] as only five to ten times that recommended for optimum growth. If the potency of vitamin D_2 in milk is increased only five fold, and the work cited indicates that it may be increased even more, and may be more toxic than "natural" vitamin D_3, a toxic dose may be reached for the more susceptible children in one quart of milk/day without any other source — as supplement, food, or sunlight. Our objective should be to identify hyper- and hypo-reactive infants, and to see to it that they ingest the amount of vitamin D that they can tolerate and/or that they require.

Identification of Hyper-reactive Infants

It is noteworthy that with only one exception, all of the children with infantile hypercalcemia reported in the literature reviewed in this paper were fair-skinned. That hyper-reactivity is not limited by race, however, is indicated by the fact that generalized infantile arteriosclerosis (which most resembles acute vitamin D toxicity) has been reported in two Negro infants[45] although most affected infants have been white.[85] Daeschner, et al.[109] reported that in a clinic with a significant proportion of Negro or Latin American children, there was a much higher incidence of urinary tract calculi in the white children. As for Williams' syndrome, it was initially described as a disease seen in fair-skinned children.[60] Several dark-skinned children with supravalvular aortic stenosis, however, have been reported.[67,69]

Warkany and Mabon[110] have tested blood samples from 34 white children and 26 Negro children (See Table III) and found that the average value of 122.6 anti-rachitic units for the white children was about 15% higher than that for the Negro children (106.5 units). Perhaps more significant in considering factors that may play a role in diseases caused by either hypersusceptibility to vitamin D or hyposusceptibility, is the distribution of values. The highest blood levels reported (165 units) were seen in 18% of the white and 4% of the black children; levels half that high were found in only 9% of the white, and in 36% of the black children.

Table III

U. S. P. Units per 100 Cc. of Blood Serum	Total No. Tested	White Adults	White Children	Negro Children
165	9	2	6	1
132	27	10	11	6
110	31	14	10	7
94	8	2	4	2
83	13	1	3	9
66	1	1	0	0
	—	—	—	—
Total	89	30	34	25
Average vitamin D level, units per 100 cc.	116.4	117.6	122.6	106.5

Frequency Distribution of Persons According to Levels of Vitamin D in Blood Serum

(Reproduced by permission of J. Warkany and H. E. Mabon and Amer. J. Dis. Children, 60:606-614, 1940.)

The possibility that the generally higher anti-rachitic blood levels and greater response to vitamin D in white than in heavily pigmented children may be a consequence of the screening of ultra-violet rays by the skin pigment must be considered. On the basis that one square centimeter of white human skin synthesizes 18 units vitamin D in three hours, Loomis[111] has calculated that 400 units/day can be synthesized by the cheeks of Northern European infants exposed to the sun. On the other hand, Negro stratum corneum filters out 50-95% of the solar ultra-violet irradiation. That this explanation can account solely for the extremes in vitamin D-reactivity, however, seems unlikely. Generalized infantile arteriosclerosis and infantile hypercalcemia at one end of the distribution curve, and familial vitamin D-resistant rickets at the other, probably reflect mutations which cause changes in the metabolism of vitamin D, and which can occur irrespective of skin pigment.

Routine diagnostic tests to detect reactivity to vitamin D, preferably in the first week of life, should be developed. Since vitamin D toxicity is known to cause hypercalcemia and hypercholesterolemia (particularly of the free fraction),[22] perhaps a simple screen for the serum calcium and free cholesterol response to a standard dose of vitamin D in

milk, may suffice. The range of responses should be established—with special attention directed to new-born siblings of children with supravalvular aortic stenosis or of children with familial vitamin D-resistant rickets, as well as of the patients themselves, and of their parents (fathers, as well as mothers). More complicated tests, as of serum levels of antirachitic factors, including the recently discovered 25-HCC,[10,11] may provide important additional data on the nature of individual differences in response to vitamin D.

With such data, individualized vitamin D requirements should be able to be determined early in life. Until suitable tests are available and widely employed, milk should be made available in two forms; one that is free of added vitamin D, and one that is fortified, preferably at the same price so that economics not play a role in the milk bought. The private or public health physician should then recommend the source and dosage of vitamin D to be taken.

SUMMARY

1. Disease states or genetic differences that cause altered intestinal absorption or renal excretion of calcium and phosphorus, or altered synthesis or metabolism of Vitamin D, affect individual requirements of Vitamin D or susceptibility to its toxicity.

2. Vitamin D requirements are not uniform, white children generally requiring significantly less Vitamin D than do black children for prevention or cure of the skeletal lesions of hypovitaminosis D.

3. Hyper-reactivity to Vitamin D has been widely implicated as a pathogenic factor in infantile hypercalcemia, a disease that results in irreversible damage to kidneys, heart, arteries and brain.

4. There is evidence that the Williams' Syndrome (supravalvular aortic stenosis, usually associated with renal damage, severe mental retardation, and peculiar facies) is a late expression of infantile hypercalcemia.

5. The cardiovascular and renal lesions of generalized arteriosclerosis of infancy resemble those of infants dying early in the course of infantile hypercalcemia, and of animals with experimental hypervitaminosis D.

6. Renal tubular acidosis and nephrocalcinosis infantum, diagnosed only at autopsy, have also been associated with either Vitamin D overdosage or hyper-reactivity to Vitamin D.

7. The three- to ten-fold enhanced activity of Vitamin D in milk, as compared to the same unitage in oil, and the greater toxicity of Vitamin D_2 as compared with Vitamin D_3, results in consumption of potentially harmful amounts of Vitamin D by those drinking milk freely.

8. Four hundred units in oil has been shown to be prophylactic even in the group most susceptible to rickets; 90 units in milk has been reported to be prophylactic in the population group most reactive to Vitamin D.

9. There is urgent need for development of tests for reactivity to a standard dose of Vitamin D, to be applied in infancy.

10. Milk should be provided in 2 forms; (1) free of added Vitamin D, and (2) fortified as at present, the physician to recommend the source and amount of Vitamin D to be taken.

11. The question of how best to protect against rickets should be reinvestigated, with greater individualization of dosage considered a vital objective.

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[This paper is an updated adaptation of the article mentioned in Reference No. 7, above.]