For more than 40 years it has been known that vitamin D is essential for maintenance of normal calcium metabolism in man. Efforts over this period have been directed toward establishing an adequate intake of vitamin D throughout the population. National advisory committees in many countries have formulated recommended allowances for the various age groups, public health education programs have stressed the need for the vitamin and the value of sunshine, and the vitamin has been made available to the population at large through provision of inexpensive vitamin supplements and, more recently, the enrichment of milk and a number of commonly used foodstuffs. In consequence, vitamin D deficiency rickets, once a common pediatric problem, is now relatively rare in the United States and other parts of the world.

On the other hand, it has also long been known that vitamin D is potentially dangerous in very high dosage. It had been thought originally that the margin of safety between the requirement of vitamin D and its toxic dosage was very great. However, reports from Great Britain and Switzerland in 1952 drew attention to a group of infants with unexplained hypercalcemia. Additional cases of infantile hypercalcemia began to appear throughout the British Isles, and patients with mild or severe manifestations have been reported in the United States, Canada, and elsewhere. On the basis of circumstantial evidence, vitamin D was implicated in the pathogenesis of the disease, and, as a result, there has been a growing question about the safety of vitamin D intakes which appreciably exceeded the 400 I.U. daily allowance currently recommended for prevention of vitamin D deficiency during growth, pregnancy, and lactation.

In 1963, the Committee on Nutrition of the American Academy of Pediatrics published a report entitled “The Prophylactic Requirements and the Toxicity of Vitamin D.” The Committee summarized the evidence then available regarding the cause of infantile hypercalcemia and made certain recommendations designed to promote an intake of vitamin D by the population at large which would meet the recommended dietary allowances for prevention of rickets as well as minimize the likelihood of excessive intakes. Since the publication of that report, it has been shown that the severe form of infantile hypercalcemia frequently has its inception in utero. It has also been shown that there exists a seriously incapacitating syndrome of older children and adolescents which represents, at least sometimes, the late normocalcemic stage of previously unrecognized infantile hypercalcemia of the severe form.

The present report re-examines the rela-
tion of vitamin D and infantile hypercalcemia in the light of these recent discoveries, and it attempts to assess the dangers of vitamin D to the population at large.

**CLINICAL FEATURES OF INFANTILE HYPERCALCEMIA**

The clinical aspects of infantile hypercalcemia (also referred to as idiopathic hypercalcemia of infancy) have been reviewed in detail elsewhere. To summarize briefly, idiopathic hypercalcemia can be classified roughly into two forms—mild and severe. However, cases with intermediate manifestations are seen. Some authors consider that these two forms represent the ends of a spectrum of the same pathological process; others disagree. This important question is not yet settled. It has been stated in Britain that at least 8% of the patients had the severely affected form, but it is often impossible to categorize a given patient with certainty.

**Mild Form**

Hypercalcemia is the principal disturbance in patients with the mild form. Characteristically, there is failure to thrive, usually of sudden onset between 3 and 7 months of age. Mild azotemia occurs on occasion. These sequelae of hypercalcemia are normally completely reversible with therapy and probably even without treatment. However, a few patients have died during the acute hypercalcemic phase. Treatment consists of marked restriction of calcium intake, temporary elimination of vitamin D and sunlight, and, occasionally, administration of cortisone. Long-term prognosis is excellent.

**Severe Form**

Infants with the severe form have hypercalcemia and failure to thrive of a degree similar to or greater than that observed in the mild cases. In addition, several other more serious features occur. A characteristic "elfin" facies, impairment of renal function, severe mental defect (often with strabismus), dense mineralization of the base of the skull and metaphyses of the long bones, and usually an aortic systolic murmur are present in varying degrees. Originally it was thought that the murmur was caused by thickening or calcification of the aortic valve cusps. However, it is now evident that the systolic murmurs heard in the upper parasternal region may frequently, perhaps always, denote supravalvular aorticstenosis or peripheral pulmonary artery stenoses.

Recent publications have pointed out that, in contrast to the mild form, the severe form of infantile hypercalcemia frequently has its inception in utero, and with further study it may turn out that this feature is a fundamental aspect. The low mean birthweight, the frequent detection of systolic murmurs in the neonatal period, the peculiar facies occasionally noted at birth, and the extent of the anatomical lesions at the time of diagnosis are consistent with a prenatal onset.

The severe form of infantile hypercalcemia has a bad prognosis. The mental defect is permanent and usually severe, cardiovascular and renal lesions are probably never reversible even with good therapy, and a number of patients have died.

**The Late Normocalcemic Stage of Severe Infantile Hypercalcemia**

Although formerly not distinguished from valvular aortic stenosis, a rare condition characterized by stenosis of the supravalvular segment of the aorta has recently been receiving increasing interest from cardiologists. It now appears that there are at least two syndromes with this vascular anomaly as a feature. In one syndrome, often familial, stenosis of the aorta is the only obvious abnormality. In the other apparently more common syndrome, children and adolescents with supravalvular aortic stenosis also manifest severe mental defects, a peculiar facial appearance, and often abnormalities in tooth formation. This grouping of features in association with a history of unsatisfactory progress in infancy suggested to Black and Bonham-Carter, et
al., 16 and Beuren, et al. 17 that the syndrome might represent the late manifestation of the severe form of infantile hypercalcemia. However, none of the patients were hypocalcemic at the age when diagnosed. Thus, this astute speculation remained unconfirmed until the report of Garcia, et al. in 1964.17 These authors described a 9-month-old infant with supravalvular aortic stenosis, probable mental retardation, and typical elfin facies who had unquestionable hypercalcemia. Supravalvular aortic stenosis has subsequently been demonstrated in a few additional patients with severe infantile hypercalcemia; 5,11,12 in some of these patients hypoplasia of the pulmonary or renal arteries and other vascular lesions have also been found.

It is clear that the syndromes consisting of supravalvular aortic stenosis, severe mental defect, and peculiar facies may represent previously unrecognized severe infantile hypercalcemia. However, such conditions as intrauterine rubella can produce mental defect and pulmonary artery stenosis.18 Thus, it is by no means certain that all instances of the juvenile syndrome can be attributed to the severe form of infantile hypercalcemia.

Epidemiological Evidence

VITAMIN D INTAKES OF INFANTS: By 1953 to 1954, approximately 200 cases of infantile hypercalcemia (mainly of the mild form) had been reported in Great Britain. Many suggestions were advanced to explain the increasing incidence of the condition. The most widely accepted of these implicated vitamin D as the underlying causative agent; in support of this possibility, British investigators pointed to the observation that, in the mid 1950's, the normal infant in Britain might readily acquire as much as 4,000 I.U. of vitamin D per day by ingesting nationally subsidized or commercial milk powders, infant cereals, and specific vitamin D supplements.20

Four thousand I.U. of vitamin D was 10 times the presently recommended prophylactic dosage of vitamin D. On the other hand, ingestion of this amount of vitamin D obviously was not the only factor, since the great majority of British infants receiving such intakes of vitamin D were unaffected and a considerable number of cases of infantile hypercalcemia were known to have occurred with intakes below 1,000 I.U. per day.21 It was, therefore, proposed that hypersensitivity to the vitamin, 22 a defect in cholesterol metabolism, 23 or defective removal of vitamin D24, 25 were other possibilities to be considered in the etiology.

By the mid 1950's British health authorities had become alarmed at the high incidence of infantile hypercalcemia in the United Kingdom. As a result of the joint recommendations of the British Ministry of Health Subcommittee on Welfare Foods 26 and of the British Paediatric Association Committee on Hypercalcaemia, 27 and with the cooperation of industry, reductions were made in the vitamin D content of various infant foods and supplements. According to estimates at the time 27, 28 and subsequently the daily intake of British infants younger than 1 year of age had been approximately halved by 1957 to 1958. Editorials in the British Medical Journal 27 and Lancet 28 in 1960 stated that the incidence of idiopathic
hypercalcemia was believed by many British pediatricians to have decreased since the institution of vitamin D curtailment. Although it was generally inferred that a causal relation between vitamin D and infantile hypercalcemia had been established, epidemiological proof that there had been a reduction in incidence was not available at that time.

In 1964 the British Paediatric Association (BPA) reported the results of three surveys of incidence of infantile hypercalcemia in Great Britain—one in 1953 to 1955 at the time when the greatest number of cases was being reported; one in 1959, approximately 1 to 2 years after the major reduction in vitamin D intake had taken place; and one in 1960 to 1961. The results of the BPA Committee on Hypercalcaemia survey are shown in Table I. The Committee's interpretation of the data was guarded: “The marked decline in hypercalcaemia (1960 to 1961) does not correspond in time with the major reduction in vitamin D allowances which took place in 1957 to 1958, but followed it after an interval of two to three years. . . . Unfortunately, the results of these surveys do not provide a positive answer to the question of the part played by excessive intake of vitamin D in the pathogenesis of infantile hypercalcemia. . . . It remains speculative whether the decrease in hypercalcaemia noted from 1960 is a consequence of reduced vitamin D intake.”

On the other hand, not all authors have made such a non-committal assessment of these data. A leading article in the same issue of the British Medical Journal stated: “[It] seems reasonable but perhaps not finally proved that excess of vitamin D is, in fact, the essential cause of hypercalcaemia.” In a third article in that issue, Bransby, et al. acknowledged the use of many data from the above survey but gave the impression that they had concluded that vitamin D intake and infantile hypercalcemia were causally related.

These epidemiological data apply in the main to the mild form of infantile hypercalcemia. For the purposes of the present consideration, it might be questioned whether a decline also occurred in the incidence of the severe form specifically. The BPA Committee was not able to decide this question. From what is now known of the usual prenatal onset of the severe form of infantile hypercalcemia, alteration in infant feeding practices might be expected to have little or no bearing upon the incidence of this form of the condition.

### Table I

<table>
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<td>17</td>
<td>50</td>
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</table>

* In 1957 to 1958, the overall intake of vitamin D intake was estimated to have been halved.

VITAMIN D INTAKES AND METABOLISM DURING PREGNANCY: Studies of vitamin D metabolism in normal human pregnancy have hitherto been almost completely neglected. Clinical experience in China has demonstrated a need for vitamin D during pregnancy in excess of the requirement of the normal adult. The total vitamin D allowance recommended for the later stages of pregnancy by advisory committees in the United States and Canada is 400 I.U. per day. There is no question that this quantity is sufficient to protect the normal mother and fetus in all instances. However, the recommended allowance seems to have been arrived at empirically, for there is practically nothing known of the minimum requirements during the various stages of pregnancy.

The published case reports of infantile hypercalcemia have usually failed to record the specific vitamin D intakes of the mothers of affected infants. Referring to the mild form of the disease, Black states without...
further documentation, “thorough investigation of the maternal diet during pregnancy has never revealed an excessive intake of vitamin D.”

Evidence that the severe form of infantile hypercalcemia may often commence in utero has recently focussed attention upon maternal vitamin D intake and metabolism during pregnancy. Although there must be many pregnant women who ingest much more than the recommended allowance of vitamin D (400 I.U./day), the evidence thus far does not prove that excessive maternal intake is a factor in causing the severe form of infantile hypercalcemia. The total vitamin D intakes of the mothers of two Canadian infants with the severe form of infantile hypercalcemia did not likely exceed 200 I.U. per day, since the dairy milk did not contain added vitamin D, the mothers did not regularly consume any of the vitamin D-enriched foods then on the market, and they did not take vitamin supplements during pregnancy. The infants each received a total of 800 I.U. vitamin D per day. Kenny, et al. calculated that the total daily intake of a mother who bore an asymptomatic hypercalcemic infant was 600 I.U. per day for the last 7 months of pregnancy. This mother had previously borne a severely affected infant but the vitamin D intake during the earlier pregnancy was not stated. Black and Bonham-Carter stated that the mothers of four normocalcemic juvenile patients with peculiar facies, mental defect, and supravalvular aortic stenosis had had normal vitamin D intakes during pregnancy. Thus, if vitamin D plays a role in the intra-uterine development of the severe form of infantile hypercalcemia, it must do so either by placental transfer of the vitamin from the mother to the excessively vitamin D-sensitive fetus or alternatively by producing a response in the excessively sensitive mother which is deleterious to the fetus. To date there have been no published studies of the vitamin D metabolism of the pregnant mothers of severely affected infants.

**Biological Tests of Vitamin D Excess and Hypersensitivity in the Affected Infant**

If epidemiological evidence for a direct causal relation between vitamin D and infantile hypercalcemia still remains inconclusive, so also does evidence obtained in individual cases by direct biochemical study of vitamin D concentrations of blood and metabolism of the vitamin. Two types of studies have been carried out in attempting to clarify this question: (1) measurement of vitamin D concentrations in serum and other tissues, yielding data which would indicate either excessive intake or abnormally slow disappearance of vitamin D, and (2) assessment of response of patients to vitamin D administration, yielding evidence regarding hypersensitivity.

**Vitamin D Concentrations in Serum and Other Tissues:** Most of the studies of serum vitamin D concentrations have been carried out on severely affected infants. However, Cuthbertson and Thomas, et al. carried out bioassays on the sera of six and two mildly affected infants, respectively, and found normal values in each. One mildly affected infant in Cuthbertson’s series, who died during the hypercalcemic phase, had lower vitamin D concentration in the liver than that of a control subject of the same age.

In patients with the severe form of infantile hypercalcemia results of various studies are contradictory. Cuthbertson could not detect an elevation in the plasma vitamin D concentration in any of five severely affected infants. One patient was studied while still hypercalcemic before restricting vitamin D. The intake was estimated to be 1,500 I.U. per day. A second patient had a normal vitamin D level and was still hypercalcemic when studied 10 days after instituting vitamin D restriction. A third severely affected infant had a normal vitamin D concentration and was still hypercalcemic 25 days after instituting restriction. Two others with normal vitamin D levels had been off vitamin D for 18 days and 200 days, but
they were normocalcemic when tested and these findings are, therefore, probably not significant.

Kenny, et al. found a level of 3 units per ml (normal for their assay 0.7 to 3.1 units per ml) in the serum of the asymptomatic sibling of a patient with the severe form while the former was receiving a low vitamin D intake. When the infant was given 400 I.U. vitamin D per day for 10 days, the vitamin D level was 4 units per ml. A subsequent value of 8 units per ml is in question, because technical difficulties were experienced with this assay.

On the other hand, several investigators have recorded findings at variance with the foregoing reports. Fellers and Schwartz studied the concentrations of vitamin D (or vitamin D-like substance) in serum by rat bioassay in three patients with severe infantile hypercalcemia, each of whom appears to have been receiving approximately 1,200 to 1,500 I.U. vitamin D per day until the time of diagnosis. The concentrations of vitamin D were recorded as 31, 60, and 20 units per ml, respectively, at diagnosis; levels of 17 and 27 units per ml were recorded during a 14-month follow-up after discontinuing vitamin D in the first patient and a value of 36 was recorded after a 6-month follow-up in the second patient. Fellers and Schwartz quoted their normal range as 1.10 to 1.95 units per ml; they concluded that the patients’ concentrations of vitamin D were abnormally high and persisted for an unduly long time. The severely affected hypercalcemic infant reported by García, et al. was considered to have a significantly elevated serum vitamin D concentration of 15.4 units per ml, as compared to a normal range of 0.6 to 4.0 units per ml. In one patient with the severe form who was receiving 4,000 I.U. per day, Smith, Blizzard, and Harrison estimated a serum concentration of 23 units per ml, but this must be considered with some reservation since only four rats were used for the assay. After restriction of vitamin D intake for 6 months and 21 months, the values were 5 and 2 units per ml, respectively. They considered all these values to be elevated, but, for some unexplained reason, their normal range was 0.6 to 1.65 units per ml, compared to the range usually quoted (0.6 to 4.0 units per ml).

The reason for the discrepancies in the various results on patients with the severe form of hypercalcemia is not clear.

**RESPONSE OF AFFECTED INFANTS TO VITAMIN D ADMINISTRATION:** The response of patients to loading doses of vitamin D has not been extensively studied to date, and, when assessed, the effect on the calcium level in serum has been variable. To date, apparently, none of these investigations have been carried out in patients with the severe form of hypercalcemia.

Challenge with excessive doses of vitamin D in several studies on mildly affected patients produced no alteration in the clinical or biochemical status. Forfar, et al. reported on a patient in the actively hypercalcemic phase who had no aggravation of symptoms, and the serum calcium appeared to decrease while receiving 50,000 to 100,000 I.U. per day for 1 week. Two 2-year-old patients of Hubble, who were in complete remission, received 6,000 I.U. vitamin D per day for 90 days and 70,000 I.U. per day for 30 days, respectively, with no symptoms and no hypercalcemia. Similarly, the administration of 2,000 I.U. vitamin D per day to a patient with the mild form for about 1 month produced inconsistent and probably insignificant alterations in serum calcium levels and did not result in exacerbation of symptoms.

By contrast, in the studies of Kenny, et al. on the asymptomatic hypercalcemic sibling of a severely affected patient, the serum calcium level was normal on a vitamin D intake of 40 I.U. per day but rose to hypercalcemic levels after 10 days on 400 I.U. per day. Other investigations have yielded similar increases in the concentration of serum calcium levels, but the interpretation is not clear since the stressing dosages of vitamin D were unreasonably
INFANTILE HYPERCALCEMIA

excessive. Bonham-Carter, et al. reported a rise of serum calcium levels from 10.6 to 11.9 mg/100 ml and deterioration in the clinical condition of a 9-month-old infant in remission during administration of 10,000 I.U. vitamin D per day for a 12-day period. The child was considered to have the mild form of the disease. A second, mildly affected patient of Forfar, et al., who was still actively hypercalcemic, showed an increase in the serum calcium level of approximately 2 mg/100 ml, an increase in the urine calcium output and a weight loss during a 1-week period while receiving 100,000 I.U. per day.

With the probable exception of the atypical patient of Kenny, et al., evidence of abnormal responsiveness of mildly affected patients to reasonable vitamin D challenges has been unconvincing.

Vascular Lesions Produced in Experimental Animals by Toxic Dosages of Vitamin D

Vitamin D, administered in high dosage to experimental animals, has long been known to produce lesions in various parts of the vascular system. In particular, the findings of Hass, et al. and of Gillman and Gilbert in mature rabbits and rats, and recently of Friedman and Roberts in newborn rabbits, are of interest with respect to supravalvular aortic stenosis in humans.

In mature animals, doses of 25,000 to 125,000 I.U. per day for periods of up to 21 days produced various vascular lesions. Those in the aortas were of particular interest. In both species, the proximal aorta was found to be the most susceptible to damage; the lesion progressed distally from that point. Early signs consisted of subintimal edema and damage to the elastic lamina. More severe lesions were of greater depth and occasionally formed solid calcified or cartilage-like plaques in the deeper layers of the artery wall, but stenoses were not mentioned. Intimal proliferation or vegetative accumulations of polymorphonuclear leucocytes on the intimal surface sometimes occurred. Calcification, if it took place, frequently became resorbed after vitamin D had been withdrawn. Actual stenosis of the aorta has not been reported in studies on mature animals.

Working on the assumption that supravalvular aortic stenosis of humans occurs in early infancy, probably in utero, Friedman and Roberts recently studied newborn offspring of rabbits fed very large doses (1.5 million units) of vitamin D throughout gestation. The finding of very elevated levels of vitamin D in the offspring demonstrated its transplacental passage. A significant number of the offspring had generalized vascular lesions; some animals showed aortic changes reminiscent of supravalvular aortic stenosis in humans.

Although serum calcium concentrations were not reported in the three studies cited, such large doses of vitamin D would almost certainly produce hypercalcemia. Therefore, it is not possible to be certain whether vitamin D per se, or the resultant hypercalcemia, produced the vascular lesions observed in the experimental animals or their offspring.

Assessment of the Evidence Impugning Vitamin D in the Pathogenesis of Infantile Hypercalcemia

There is no valid reason to give more weight to one of the foregoing studies of vitamin D metabolism than to another. Considering patients with either the mild or the severe form of infantile hypercalcemia, and taking all the data at face value, consistent results have not been obtained with any of the tests. Although there is a certain amount of circumstantial evidence that vitamin D may play an important role in causing infantile hypercalcemia, this hypothesis has not yet been proved for either form of the disease.

It has been suggested that the severe form of infantile hypercalcemia might be caused by an abnormality of maternal vitamin D intake or metabolism during pregnancy. Although animal studies have produced intriguing results, there is as yet no
direct clinical evidence for the hypothesis. It is possible that application of more specific or more accurate methods for studying vitamin D metabolism, or more careful study of the importance of dietary calcium intake, may help to elucidate the pathogenesis of this disease in the future. On the other hand, it is also possible that vitamin D may eventually prove not to be directly involved in the pathogenesis of this bizarre symptom-complex, particularly in the severe form of infantile hypercalcemia.

THE INCIDENCE OF INFANTILE HYPERCALCEMIA

Overall Incidence

Although cases of infantile hypercalcemia have been reported from many parts of the world, the nationwide surveys conducted in Great Britain provide the only quantitative estimates of the incidence of this condition. From the 1960 to 1961 survey, the computed incidence of infantile hypercalcemia for the British Isles was 35 cases per year. Since in 1960 there were 785,000 births in Great Britain, the incidence of infantile hypercalcemia of all forms was 0.045 cases per 1,000 live births, or approximately 1 case for every 20,000 live births. Clearly, these figures may not be applicable to North America. For one thing, about 8% of the cases in Great Britain were estimated to be severely affected, whereas almost all of the 50 odd cases reported in North America during the past 14 years have been classified as severely affected. However, the British figures serve to emphasize the overall rarity of the condition, since there is no reason to suggest that the incidence of infantile hypercalcemia is greater in any other country.

Incidence of the Severe Form

The obvious difference in the seriousness of the two forms of infantile hypercalcemia emphasizes the importance of attempting to derive some estimate of the incidence of the severe form of infantile hypercalcemia per se. The British reports point out the difficulty in clearly distinguishing between the two forms of the disease. However, if one accepts the suggestion made by the BPA Committee on Hypercalcemia that approximately 8% of the British cases were severely affected, the incidence of the severe form of infantile hypercalcemia appears to have been approximately 0.0036 cases per 1,000 live births, or approximately 1 case for every 275,000 births.

The incidence of the severe form of infantile hypercalcemia can be arrived at in a different way by computing the incidence of supravalvular aortic stenosis in the pediatric population. The latter calculation was possible using data available from the Toronto Heart Registry and the Cardiology Service of The Hospital for Sick Children. By including all mentally defective patients with supravalvular aortic stenosis and peculiar facial appearance and all patients with the severe form of infantile hypercalcemia, a total of 11 presumptive cases were diagnosed in the course of studying 8,000 consecutive cases of congenital heart disease during a 16-year period. Accepting 6 cases per 1,000 births as an estimate of the incidence of all forms of congenital heart disease in the pediatric age group, the approximate incidence of severe infantile hypercalcemia was calculated at 0.008 cases per 1,000 births. This yields an incidence of 1 case per 120,000 births. Possibly this estimate is erroneously high since it is not yet proved that all mentally defective children with supravalvular aortic stenosis previously had severe infantile hypercalcemia.

It is obvious that the foregoing estimates are open to criticism. Nonetheless, they confirm the general impression that infantile hypercalcemia, especially in its more serious form, is an extremely rare condition. As a cause of heart disease in the population at large, infantile hypercalcemia plays a very small role. As a cause of mental defect, its contribution is much less than, for example, that of phenylketonuria, itself a rare condition in the population.
PROPHYLACTIC REQUIREMENTS OF VITAMIN D AT DIFFERENT AGES

The recommended dietary allowances for vitamin D, as set forth by the Committee on Nutrition of the American Academy of Pediatrics are similar to those of the National Academy of Sciences and National Research Council Food and Nutrition Board in the United States and the Canadian Council on Nutrition and are based on present knowledge of the minimum requirements and the toxicity of vitamin D at different ages. These recommendations constitute suitable guidelines upon which to base public health nutrition policy. A total intake of 400 I.U. vitamin D per day is recommended for prematures, infants, children, and adolescents; an allowance of 400 I.U. per day is recommended for women during the later part of pregnancy and during lactation. It is clearly stated that the amounts recommended refer to the total ingested vitamin D from all sources. No supplemental vitamin D is considered necessary for adults, over and above that acquired from the ordinary diet and casual exposure to sunlight.

There is no question that these amounts of vitamin D are sufficient to meet the requirements of virtually all normal individuals, even in the absence of ultraviolet irradiation. Furthermore, it is considered from present evidence that intakes of this order carry no risk of toxicity for normal individuals at any age, whether during infancy, childhood, or adult life. On the other hand, the lower limit of intake that can be depended upon to provide effective prophylaxis is very difficult to ascertain. In infancy, intakes of 100 I.U. per day have been shown to be sufficient to prevent deficiency. In older children living under modern conditions, a daily intake of 400 I.U. apparently provides considerably more vitamin D than is necessary for prophylaxis. Vitamin D deficiency rickets is virtually non-existent beyond infancy in North America, despite the fact that the great majority of high school children and adolescents do not take specific vitamin supplements (with the result that many children ingest a total of less than 100 I.U. per day without obvious consequence).

It is clear that the recommended allowance of 400 I.U. vitamin D per day amply provides for the total vitamin D requirements of normal infants, children, and pregnant women. From the standpoint of preventing rickets, there is no reason for the normal individual to ingest more than this total amount. From the standpoint of avoiding hypercalcemia in the population at large, there is no compelling necessity for physicians or public health authorities to strive for lower overall intakes.

PUBLIC HEALTH IMPLICATIONS

Early in the history of rickets prophylaxis, it became apparent in temperate climates that sunlight could not be relied on to provide protection against rickets during the winter months and, similarly, that the usual foods of infants (including breast milk, cow's milk, egg yolk, and butter) did not contain enough vitamin D to meet requirements in many instances. Therefore, the use of vitamin D supplements was promoted, and there was widespread acceptance of this public health measure in North America and Great Britain. It soon became evident, however, that rickets had not been entirely eliminated, and a decision was made to enrich milk with added vitamin D. This measure, along with other sociological factors, had outstanding success in reducing the incidence of infantile rickets in the United States where practically all evaporated milk and an estimated 85% of all dairy milk now contains added vitamin D. In Canada, where the incidence of rickets has also diminished greatly, only evaporated milk is systematically enriched. However, vitamin D deficiency still occurs with considerable frequency in some metropolitan areas; at least 100 proved infantile cases were admitted to Montreal and Toronto hospitals in a recent 12-month period. There is no doubt that most cases of vitamin D deficiency could have been
prevented by a concerted program of fluid-milk enrichment.

It soon became apparent that vitamin D fortification of milk was an effective means of preventing rickets, and the success of this program gave an impetus for the enrichment of a variety of commonplace foods in the United States and, until recently, in Canada. As a result, the usual diet has recently contained variable and practically unavoidable amounts of vitamin D, and in many instances the amount of vitamin D may be considerable. In recent years, however, the suggestion that vitamin D might be a primary factor in causing infantile hypercalcemia has forced nutritionists and public health authorities to give careful reconsideration to national practices relating to this essential nutrient.

In 1963, the Committee on Nutrition of the American Academy of Pediatrics reviewed the information then available regarding the prophylactic requirements of vitamin D and the evidence for its toxicity. It also made a survey of foods in the United States and Canada that then contained added vitamin D. On the basis of hypothetical food intakes, the Committee demonstrated the theoretical possibility that, by consuming only a reasonable selection of commercially enriched foods, some infants and children might consume several times the recommended daily allowance of 400 I.U. The validity of these hypothetical calculations has since been confirmed by two dietary surveys.

At the time of the report, the Committee considered that the evidence linking vitamin D and infantile hypercalcemia was circumstantial. However, it proposed that measures should be taken which would bring about a reduction in the unnecessarily abundant dietary sources of vitamin D available to both children and adults and provide adequate intakes to prevent vitamin D deficiency in the population at large. The recommendations, which were reiterated and amplified in 1965 can be summarized as follows:

1. Continuance of the enrichment of all types of milk with vitamin D at a level of 400 I.U. per (United States) quart,
2. Discontinuance of vitamin D supplementation of all other foodstuffs,
3. Adjustment of all vitamin D supplements to contain 400 I.U. per recommended daily dose,
4. Assessment by the physician of the dietary intake of vitamin D before prescribing specific vitamin D supplements to the individual patient.

New information about the pathogenesis of infantile hypercalcemia and its incidence has become available since the Committee's report, and an appraisal of current national policies regarding vitamin D is again warranted. There is still a considerable lack of knowledge concerning the metabolism of vitamin D and the limits of its requirement and toxicity. On the one hand, the evidence that the severe form of infantile hypercalcemia may have its inception in utero now places a responsibility on physicians to be alert to possible prenatal factors. On the other hand, it is now obvious that both forms of infantile hypercalcemia are very rare. Furthermore, it is still not proved that vitamin D plays a central role in the pathogenesis of either the mild or the severe form of this disease.

The evidence concerning infantile hypercalcemia does not alone provide justification for extensive changes in national policies relating to vitamin D. The recommendations of the Committee on Nutrition, however, are appropriate in that they embody the principle of sensible moderation in consumption of vitamin D at all ages. Vitamin D is a potentially toxic substance and the possible long-term effects of intakes that exceed requirements by several orders of magnitude are still unknown. Implementation of the Committee's recommendations would have the effect of promoting intakes that closely approximate the recommended allowances. Careful consideration suggests that the Committee's proposals would not increase the incidence of vitamin D deficiency in the infants and children of North America, yet they would have the effect of minimizing the likelihood of high intakes by individuals in all popula-
tion groups, including infants and pregnant women.

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