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Vitamin A deficiency. New knowledge on diagnosis, consequences and therapy*)

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Zusammenfassung: Durch die Entwicklungen der biochemischen Analytik in den letzten zehn Jahren sind eine Vielzahl von Substanzen, so auch Vitamin A, dessen Stoffwechsel und Wirkungsweise weitgehend aufgeklärt schien, erneut untersucht worden. Dabei haben sich neue Erkenntnisse ergeben, die für die menschliche Gesundheit von Bedeutung sind und hier in Kurzform zusammengestellt sind. So konnte festgestellt werden, daß ein auch in Industrienationen möglicher leichter Vitamin-A-Mangel durch übliche Blutanalysen nicht sicher zu erfassen ist. Die Ursache dieses marginalen Vitamin-A-Mangels kann einerseits durch Erkrankungen bedingt sein, andererseits aber auch durch streng einseitige Ernährung. Folge einer solchen einseitigen Ernährung kann nach epidemiologischen Untersuchungen eine höhere Krebserkrankungsrate bestimmter epithelialer Gewebe ein. Allerdings können Überdosierungen mit Vitamin A auch zu Nebenwirkungen führen. Es ist nicht auszuschließen, daß Vitamin A auch beim Menschen teratogen wirkt. Aus Sicherheitsgründen sollten daher Frauen im gebärfähigen Alter eine Substitutionsempfehlung, über das Zweifache der empfohlenen täglichen Dosis für Schwangere in USA (10 000 I.E./Tag) hinaus, nur bei klarer Indikation gegeben werden. Andererseits sind Mißbildungen infolge eines Vitamin-A-Mangels nicht auszuschließen.

Summary: Due to the rapid development of biochemical analyses in the last 10 years different substances like vitamin A, with an apparent clarified metabolism and action, were re-estimated. As a result, new knowledge was presented which could be essential for human health. Some details and consequences are reviewed in this paper. Marginal deficiency, which also may occur in industrialized nations, cannot be determined with certainty by usual blood analyses. The reasons for marginal deficiency are either different diseases or unbalanced nutrition. From epidemiological research it is argued that low vitamin A intake is associated with a higher incidence of cancer in different tissues. However, vitamin A may lead by over-dosing to toxic side effects. There exists a possibility that vitamin A is teratogenic also in humans. Thus, for safety reasons, woman who can become pregnant should not be advised to supplement the vitamin more than twice the RDA of the US Food and Nutrition Board for pregnant women (10 000 I.U./day) if there is no clear-cut indication. On the other hand there are indications that malformations may also caused by vitamin A deficiency.

Schlüsselwörter: Vitamin A, Übersicht, Risiken

Key words: vitamin A, review, benefits, risks, teratogenicity

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Introduction

Vitamin A, an essential dietary component, has increasingly been the focus of experimental research and clinical applications in the last few years. Not the least of the reasons for this has been the fact that more and more research has widened the spectrum of functions with which the derivatives are being credited. In particular, the different modes of action of the various compounds as regards the transformation, differentiation, and proliferation of normal and neoplastically modified cells are extremely complex. This explains why vitamin A deficiency is accompanied by so many symptoms and, consequently, why it affects various organs and tissues to different extents that depend on the duration of the insufficiency. For instance, even marginal vitamin A deficiency can affect the respiratory epithelium although the typical, clinical symptoms only occur when the deficit persists. Whereas chronic vitamin A deficiency can be diagnosed from the clinical symptoms, its marginal counterpart can elude diagnosis and consequently proper therapy.

The importance of determining serum retinol for diagnosing the vitamin A status

The vitamin A status is established by determining the amount of retinol (vitamin A) circulating in the blood. Together with its transport protein, retinol binding protein (RBP), the retinol is flushed out of the main store, the liver, bound in the blood to transthyretin (TTR), and absorbed through a cellular receptor by the target cell. In the absence of regular intake, the liver can act as a source of vitamin A for as long as supplies last. Although it is generally held that the stores last for 1–2 years in an adult, recent studies have revealed that this supposition is invalid. Above all, a normal plasma vitamin A level cannot be used as a basis for assessing available stores in the liver because it is homeostatically regulated until the stores are almost totally depleted. The rate of depletion depends on numerous factors that govern the requirements for, availability of, and metabolism of the vitamin (e.g., hormones, trace elements, medicines, etc.) (67).

A major drop in the serum retinol value to below normal levels – 60 μg/dl in men, 50 μg/dl in women, 25 μg/dl in babies and infants – will only occur when the liver stores (normal value: 20–300 μg/g liver) are depleted to below the critical point of 10 μg/g liver (20, 45, 67). By this stage, at the very latest, the vitamin A stores (6, 44) in such peripheral tissues as tracheal and bronchial mucous membranes, tongue and reproductive glands, all of which depend on a supply of vitamin A, are so depleted that there is insufficient vitamin A to maintain their structural integrity (8, 37, 38,. 57, 77).

A marginal deficiency that is not accompanied by a pronounced drop in the serum retinol level could therefore already have been preceded by morphological and biochemical changes, especially in the mucous membranes of the respiratory and gastrointestinal tracts (8, 37, 38).

When the serum retinol level falls as a result of further depletion of the liver, thereby acting as a symptom, it is then too late.

Given suboptimal dietary intake of vitamin A, it is quite possible for a marginal deficiency to elude diagnosis for a long time.

Aetiology of vitamin A deficiency

1 Dietary insufficiency

In Third World countries, extensive vitamin A deficiency, which is often the result of a lack of protein and thus inadequate RBP formation, is one of the most common deficiency illnesses and is clearly recognizable by its symptoms: Bitot's spots and xerophthalmia. By contrast, this form of vitamin A deficiency is much rarer in industrial countries in which there are adequate food supplies. There, marginal insufficiency exists and is easily overlooked owing to a lack of detectable symptoms, and it is caused by poor dietary habits and illnesses that restrict the availability of the vitamin by various means. Studies by the United States Department of Agriculture (16, 17, 68) of the dietary habits of 21 500 U.S. citizens revealed that only half of them consumed the recommended daily allowance (RDA) of 5 000 I.U. vitamin A; women at the age of 23–34 years were found to be intaking only 40 % of the RDA. A state of marginal deficiency is said to exist when the intake provides less than 70 % of the RDA (68) and such a state was diagnosed in 31 % of the probands as a whole and in 41 % of women. Although the vitamin stores in the liver mostly compensate for fluctuations during intake, inadequate consumption, even by healthy people, can lead to marginal insufficiency in the long-term and thus to an undersupply to the peripheral tissues.

If illnesses occur that affect absorption of the vitamin or increase consumption of it, marginal insufficiency can develop much more rapidly, especially if the stores are low (as is the case with infants, sufferers of consumptive illnesses and chronic alcoholics). Again, a repeatedly detected reduction in serum retinol levels to below normal can, as a result of homeostatic regulation, be interpreted as a sign of marginal vitamin A insufficiency (20, 45).

2 Illnesses that can induce insufficiency

Here we must distinguish between those illnesses which impede absorption of the vitamin, thereby causing demand to outstrip supply, and those which increase consumption or disrupt metabolization of it.

Illnesses that inhibit absorption of vitamin A

Reduced serum retinol and RBP serum values as a result of restricted absorption of vitamin A have been reported (7, 39, 54, 59, 61, 69) in cases of maldigestion and malabsorption syndromes, Morbus Crohn and parasitic intestinal ailments. Wechsler (71) reported a case of vitamin A insufficiency as a result of intestinal factors in which a 15-year-old girl who had undergone by-pass surgery of the small intestine as a treatment for obesity and returned for treatment because she had developed therapy-resistant follicular keratotic lesions of the extremities and also nyctalopia. Although the plasma vitamin A level was markedly down at 16 μg/dl – a

value nevertheless above that of 10 µg/dl defined by the WHO as constituting insufficiency – her nyctalopia and skin symptoms rapidly receded after administration of high doses of vitamin A. This case shows that symptoms of vitamin A insufficiency need not necessarily be accompanied by drastically reduced serum vitamin A levels and that supplements of vitamin A should be considered during protracted illnesses or resection of the small intestine. Impaired absorption of fat-soluble substances has been reported, particularly in cases of feverishly ill infants (19, 59).

Reduced serum retinol and RBP levels are characteristic of measles (29, 32) and chicken pox (2). Whether or not the cause is impaired absorption, increased consumption or changes in the hitherto unknown regulator of serum retinol homoeostasis is still uncertain. The consequence, however, is restricted supplies of the vitamin to the peripheries, a situation that can lead to deficits accompanied by the corresponding changes. Evidence for this comes from the fact that, in cases of vitamin A insufficiency, an additional measles infection markedly increases the extent of corneal changes induced by the deficiency (29).

Utilization problems

Frequently, patients suffering from liver disorders have low plasma vitamin A and RBP levels (55) that are occasionally connected with clinical symptoms (nyctalopia) of vitamin A insufficiency. In a comprehensive study, Smith and Goodman (60) showed that the plasma levels of vitamin A, RBP, and TTR are greatly reduced in cirrhosis and cases of chronic, active, and acute hepatitis. Bioptic material from the patients consistently produced low vitamin A stores that were still within the normal range. It is suspected that the lower serum level is caused by less synthesis or impaired flushing of RBP or both. In another study, however, rats that were chronically administered alcohol were found to have low liver vitamin A values and simultaneously raised serum retinol (52, 53). Despite slightly impaired liver cell metabolism (degeneration of liver) subsequent to chronic alcohol intake and almost totally depleted liver stores, normal plasma retinol levels have been recorded in humans (34, 35). Mobarhan et al. (40) have demonstrated, moreover, that chronic alcohol consumption eventually depletes not only the central (liver) stores but also the peripheral stores. As already mentioned, these illnesses or insufficient intake of vitamin A can create states of marginal insufficiency that elude diagnosis because of a lack of symptoms. Even tolerance tests can only give some indication of the situation if marginal vitamin A insufficiency has existed for a longer period of time. It must therefore be presumed that certain, unspecific symptoms can signify peripheral vitamin A deficiency and necessitate appropriate (i.e., prophylactic) therapy. Foremost among these symptoms are illnesses of the tracheobronchial tract.

Consequences of marginal deficiency

Against the background of low plasma retinol levels and inadequate stores in the liver of neonates, especially those who are premature (56), one illness that frequently leads to serious complications at this age deserves

special attention because of the close correlation that exists between vitamin A availability and changes which are typical of vitamin A insufficiency, viz. bronchopulmonary dysplasia.

Vitamin A influences regular growth and differentiation of epithelial cells. Pronounced insufficiency of it causes typical changes in the tracheobronchial epithelium, such as basal cell proliferation, which results in necrosis of the overlying tissue and ultimately in squamous metaplasia (37, 74). The consequence of the cellular changes is more or less pronounced loss of cilia (8, 24) and hence impaired mucociliary clearance. As Born et al. (12) have demonstrated, the degree of ciliary loss varies with the extent of the vitamin A insufficiency.

Similar morphological changes (necrotizing bronchiolitis and squamous metaplasia of the tracheobronchial epithelium) occur in the illness known as bronchopulmonary dysplasia (BPD), which is observed especially in neonates and is a result of hyaline membrane deficiency (HMD; 43). It reduces mucociliary clearance and thus induces a predisposition for serious recidivating infections (48, 70).

In the light of these morphological similarities and the special situation regarding vitamin A supply in neonates, it has been proposed that BPD can be caused by vitamin A deficiency or its progress, at least, influenced by it (28, 56). However, the etiology of BPD is governed by many parameters and both exogenous (mechanical respiration, additional O_2 therapy) and endogenous (e.g., HMD) factors are currently the subject of discussion (9, 43, 65).

From the studies carried out by Shenai et al. (56), vitamin A might exert a protective effect in the healing of necrotizing bronchiolitis and squamous dysplasia, both of which are concomitant with BPD. They found that neonates with BPD have much lower plasma retinol levels than comparable neonates without it. Whereas the plasma levels of the healthy babies remained constant or rose slightly after birth, the already low levels in the babies with BPD fell markedly in weeks 1–3. Possible causes for this may lie both in increased consumption or impaired utilization of vitamin A and in the fact that the sick babies were generally fed artificially for longer than were the healthy neonates. Low liver reserves can therefore be regarded as a predisposition factor for BPD.

Hustead et al. (28) came to similar conclusions. They found that neonates with BPD have much lower plasma retinol values than are normal. As possible reasons, they cite: low initial values (at birth), insufficient vitamin A intake (after birth) and reduced mobilization or increased utilization of the vitamin. Low initial values in the sense of low liver stores occur in neonates and, especially, premature neonates when intake of the vitamin is very inadequate during pregnancy, which is a period of increased requirements. This phenomenon can be observed in industrialized nations (18).

Vitamin A and cancer

Metaplastic changes and ciliary loss are symptoms of a number of tracheobronchial ailments. Squamous metaplasia with ciliary loss also occurs in neoplastic lung ailments, such as those following chronic inhala-

Table 1. Prospective and retrospective studies that establish a link between carcinoma incidence and serum retinol values relative to a healthy control group.

Country	Average serum values µg/dl		Number and localization of the neoplasms
	Number of ill patients	Control	
India	31	48	555 oral
Pakistan	22	40	203 oral
England	55	59	35 multiple
England	46	66	28 lung
England	47	60	26 lung
USA	25	48	51 gastro-intestinal tract

tion of cigarette smoke (3), chronic (51) and acute infections of the respiratory tracts (25, 27, 49, 75).

Since such squamous metaplastic changes of the type observed in cases of vitamin A deficiency and following chemical or physical noxae are often discussed in connection with the development of precancers (41, 42) and since vitamin A in vitro and in vivo exhibits clear antineoplastic effects (63), there have been a great many attempts to try and establish a link between carcinoma formation and individual vitamin A supplies.

Epidemiological studies on vitamin A deficiency and carcinogensis

Given the above discussion on the unreliability of obtaining an objective view of plasma retinol levels, epidemiological studies (see Table 1) should be interpreted cautiously. More information on postulated links between vitamin A supply and the incidence of carcinomas is provided by studies of dietary behavior (see Table 2). Especially interesting are those studies

Table 2. Studies in which the incidence of carcinoma was primarily obtained by determining the dietary intake of provitamin (beta-carotene) A and vitamin A.

Country	Relative risk (low:high intake)	Number and localization of the neoplasms	Dietary component assessed
Norway	2.6:1	36 lung	Vitamin A
Norway	1.7:1	228 stomach	Green vegetables
	1.4:1	278 colorectal	Green vegetables
USA	1.5:1	83 stomach	Green vegetables
	1.4:1	373 colorectal	Green vegetables
USA	1.7:1	292 lung	Vitamin A
USA	2.1:1	569 bladder	Vitamin A
USA	1.9:1	122 esophagus	Vitamin A
USA	3.0:1	421 larynx	Vitamin A
Singapore	2.2:1	233 lung	Green vegetables
England	1.4:1	104 lung	Vitamin A
Japan	1.5:1	807 lung	Green vegetables

which have examined the influence of vitamin A and beta-carotene intake on the development of carcinomas in known risk categories, such as smokers, or in groups suffering from alcohol-induced, impaired vitamin A metabolism.

When the groups investigated by the various researchers are randomized, it turns out that the incidence of carcinoma, particularly of the lungs, is significantly higher in smokers with a low dietary intake of vitamin A than in those who consume much more of it (13, 22, 23, 31). The risk of developing carcinoma shows a marked dependency on the total vitamin A and provitamin intake, especially in regular consumers of alcohol (31). In this risk category, too – as with smokers – there is a correlation between the relative amount of the vitamin consumed and the risk of carcinoma. In other words, a high vitamin A intake reduces the risk of carcinoma in spite of alcohol consumption and a low intake increases the risk in chronic abusers. That regular alcohol intake indisputably impairs the liver cell metabolism to give rise to vitamin A deficiency (to an extent depending on the degree of liver damage) seems to have been confirmed by Kvale et al. (31), who examined the serum retinol of all categories and only found a clear negative correlation with carcinoma incidence in alcoholics. Stähelin et al. (64) also noted a clear correlation between alcohol intake and lung carcinoma incidence in 4222 men, whereas they were unable to establish a link between serum retinol levels and lung carcinoma incidence in the group as a whole.

In this context, long-term vitamin A deficiency in the peripheral stores, and the respiratory epithelium especially, is quite conceivable since alcohol depletes not only the liver but also the extrahepatic stores (40, 53). Leo and Lieber (35) have demonstrated with various categories suffering from minor to major impairments of the liver cell metabolism (chronic, persistent hepatitis, alcohol-degenerated liver, and cirrhosis) that the liver can be depleted to levels far below normal. In none of the cases was there a significant drop in plasma retinol levels or RBP values, with the result that the vitamin A deficit eludes clinico-biochemical diagnosis, and this fact accounts for the missing correlation between plasma value and lung carcinoma incidence in the study by Stähelin et al. (64). However, as already mentioned, it does mean that structural changes (squamous metaplasia) in the respiratory epithelium can be expected in alcoholics as the consequence of vitamin A insufficiency. These epidemiological findings leave room for the tentative conclusion that vitamin A deficiency increases the risk of carcinoma without it necessarily being implied that vitamin A deficiency alone can cause neoplasms.

The results of numerous in vivo and in vitro experiments in recent years have demonstrated that vitamin A is essential for the structure of skin and mucous membranes and the respiratory epithelium especially and that it intervenes in particular in structural repair processes when the tissue has been damaged by physical and chemical noxae. This underlines the special role of vitamin A in preventing neoplastic changes of the epithelium and has encouraged many clinical studies of the vitamin's mode of action during therapy of neoplasms of the lungs, nasopharynx, the bladder, cervix, and the gastrointestinal tract.

This picture of an influence possibly being exerted on the respiratory epithelium by vitamin A in the prevention of precancers or the induction of neoplasms is only a minor aspect of the vitamin's "antineoplastic action". Extensive in vivo and in vitro experiments have clearly revealed that the vitamin plays an immediate regulatory role in differentiation processes, which are connected with the induction and growth phases of neoplasms.

This type of picture has been presented in surveys in recent years (14, 73) and shows that vitamin A influences genetic expression glycoprotein synthesis and the immune system at the most diverse nuclear and extranuclear levels, thereby intervening in specific differentiation and transformation processes. Above all, it has also been shown that tumor induction and growth in vitro and in vivo can be inhibited by vitamin A (5, 63).

Toxicology

In most cases (mainly children aged 1–5) in which a single, oral dose of 300 000 I.U. in oily or aqueous solution was used to treat vitamin A insufficiency, there were no reports of any side effects having occurred (46, 50, 62). Such temporary side-effects as dizziness, headache, and vomiting did occur in individuals (47, 58). Children aged 9 months to 6 years were reported by Bonvier (11) as developing slight swelling of the fontanelle after a single dose of 300 000 or 900 000 I.U. Marioni and Panizon (36) described the case of a group of 22 children aged 6 months to 7 years who were given one dose of 300 000 I.U. and 150 000 I.U. (with vitamin D); they developed swelling of the fontanelle, headache, vomiting, and dizziness, all of which symptoms receded completely after 36 h.

Bauernfeind (4) made an extensive analysis of the literature and concluded: "A study of 75 known reports of chronic hypervitaminosis A in adults reveals that the symptoms of intoxication develop more rapidly when very high doses are taken daily. Daily intake of 1 million I.U. or more manifests itself in symptoms of intoxication within days or several weeks. Intake of 400 000–700 000 I.U. per day produces the symptoms within 1–36 months and 150 000–200 000 I.U. per day, within 6–85 months."

The occurrence and severity of symptoms of intoxication depend strongly on the vitamin A status of the individual concerned, with the result that high doses can be tolerated more readily when the liver stores are depleted than when they are sufficiently full.

Owing to the dependency of the symptoms of intoxication on such various boundary conditions as liver store status, age, protein supply, or assorted primary illnesses, it is virtually impossible to establish a therapeutic spectrum. The studies by Goodman et al. (21) show that a daily intake of 200 000 I.U./m^2 body area (≙ 330 000 I.U. per person) for up to 4 months does not give rise to major side-effects. The situation is different for pregnant women or those of child-bearing age who are undergoing vitamin A therapy or supplementing.

Teratogenicity of vitamin A

Both definite underdosing and massive overdosing with vitamin A cause teratogenic damage in animals. A clear distinction must be made

between retinoic acid derivatives, which are used for therapeutic purposes, and retinol or retinyl esters, which are used for supplementing. The question as to teratogenicity pursuant to overdosing with vitamin A cannot therefore address the damage caused by retinoic acid therapy.

There are numerous reports in the literature of teratogenic effects, especially in animals (26, 72), of the retinoic acid derivatives (particularly isotretinoin = 13-cis-retinoic acid), which are used to treat severe cystic acne and chronic dermatosis (10). There are also reports that indicate a causal relationship between retinoic acid therapy and increased rates of spontaneous abortions and of malformations (retinoid syndrome) in humans (33).

As for retinol and retinyl esters, there are reports of teratogenicity in animals; however, these effects have not yet been verified in humans (30).

Since so few human cases of teratogenic effects of vitamin A (as retinol or retinyl esters) have been reported, an epidemiological evaluation is extremely difficult to make. Thus, Rosa et al. of the Food and Drug Administration (FDA) analyzed the only 18 reported cases known up to 1986 of malformations as a result of high vitamin A intake long before and during pregnancy (49a). They concluded: "Although the data so far do not provide human dose/risk estimates, findings in laboratory studies and human experience with other vitamin A analogues provide reason for cautioning against long-term exposures of 25 000 units per day or more in women who may become pregnant."

Against the background of animal experiments, experience with retinoids in humans and the few cases of malformations attributable to hypervitaminosis A, various institutions made recommendations in 1987 on vitamin A doses for pregnant women. Pregnant women and women of child-bearing age should restrict their total vitamin A intake to 8 000–10 000 I.U./day. The FDA recommends that pregnant women limit their total daily intake of vitamin A to 8 000 I.U. The Teratology Society (66) and the American College of Obstetricians and Gynecologists (1) recommend 8 000 I.U. vitamin A/day, the Council for Responsible Nutrition (15) and the International Vitamin A Consultative Group (IVACG, 30) quote 10 000 I.U. as the upper limit for diet supplements. IVACG and WHO view 10 000 I.U. vitamin A/day as posing no risk to pregnant women but recommend this dose only in cases of suspected vitamin A deficiency (30). A workshop held at the end of September, 1987, in Little Rock, Arkansas, USA, on the subject of the teratogenicity of vitamin A reaffirmed existing recommendations and defined new, necessary research objectives.

Although there is no scientific basis for limiting daily vitamin A intake by pregnant women to 8 000–10 000 I.U., these limits have been chosen out of a high regard for safety. Another reason for this choice is that normal diet supplementation precludes higher doses.

Conclusions

Vitamin A is crucial to the growth, development, and structural integrity of skin and mucous membranes. If there is a deficit of the vitamin, the mucous membranes, especially, undergo squamous metaplastic changes of the kind that are encountered with other noxae and are generally

viewed as symptoms of precancers. These observations, coupled with the fact that test animals suffering from a vitamin A deficiency frequently develop epithelial tumours, have led to intensive investigations of these parameters in animal experiments and clinical and epidemiological studies. It has been discovered that:

- Squamous metaplasia arising from vitamin A deficiency is reversed through intake of the vitamin.
- There is evidence that, even when vitamin A supplies are adequate, the squamous metaplastic changes caused by other noxae, particularly around the tracheobronchial epithelium can be reconverted into the original epithelium phenotype.
- Vitamin A can inhibit the induction of chemically induced neoplasms.
- Vitamin A prevents the growth of tumour cell lines in vitro and in vivo.
- Vitamin A reduces the incidence of tumour recidivation after surgical, radiological, or cytostatic therapy.
- A high vitamin A intake in the diet considerably reduces the risk of lung carcinomas posed by carcinogens (e.g. inhalation of cigarette smoke, benzo(a)pyrene, etc.).

The significance of this for the prevention of malignant neoplasms is that risk categories in industrialized nations should be advised to take extra amounts of this vitamin in addition to the recommended daily allowance. Chief among the reasons for this is that an evaluation of available literature reveals that there is more and more evidence about the importance of this vitamin in connection with carcinogenesis. Recommendations to the effect that daily intake of more than 10 000 I.U. vitamin A for preventing carcinomas are based more on speculative calculations than on scientific knowledge.

If one takes into consideration the fact that vitamin A and beta-carotene appear to be effective at different stages of carcinoma development, the intake of vitamin A and its provitamins must be balanced. The problem of toxic side effects occurring within the recommended supplement range can be disregarded provided that children and pregnant women do not exceed a long-term daily dose of 10 000 I.U. in the form of diet supplementing (IVACG, 1986).

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