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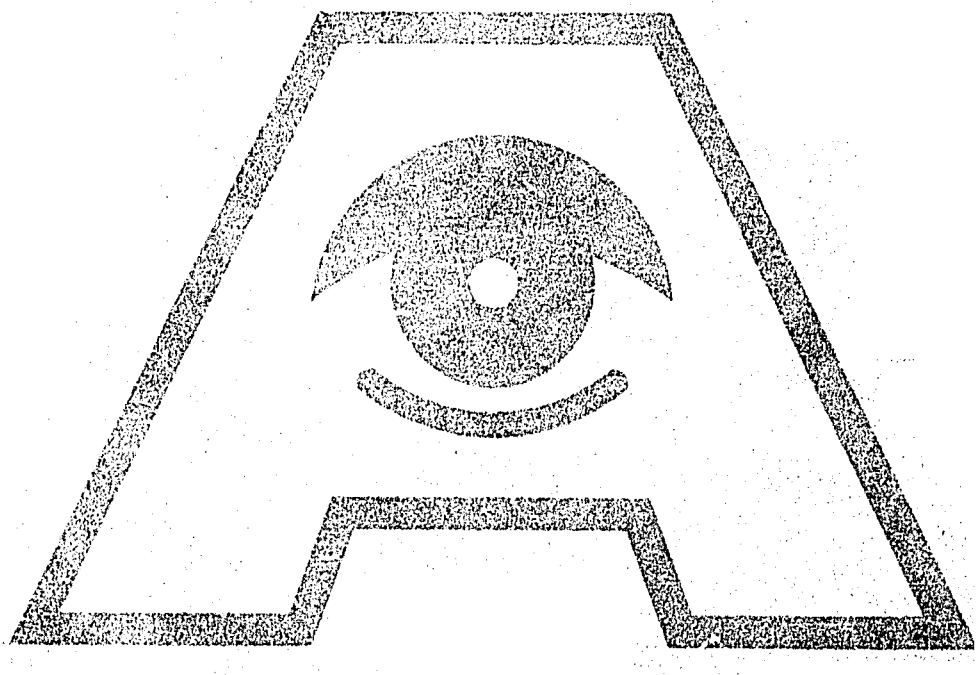

The purpose of the International Vitamin A Consultative Group (IVACG) is to guide international activities aimed at reducing vitamin A deficiency in the world. The group offers consultation and guidance to various operating and donor agencies who are seeking to reduce vitamin A deficiency and its accompanying blindness. As part of this service, IVACG has prepared guidelines and recommendations for:

—Assessing the regional distribution and magnitude of vitamin A deficiency;

—Developing intervention strategies and methodologies to combat vitamin A deficiency;

—Evaluating effectiveness of implemented programs on a continuing basis so that the evaluation of the effectiveness of intervention techniques is a continuing and dynamic procedure;

—Research needed to support the assessment, intervention and evaluation of programs.

Other task force reports of the International Vitamin A Consultative Group (IVACG) which have been published in *Guidelines for the Eradication of Vitamin A Deficiency and Xerophthalmia* are:

I. Assessment of Vitamin A Status (1977)

II. Selection of Intervention Strategies (1977)

III. Evaluation of Selected Vitamin A Intervention Strategies (1977)

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THE SAFE USE OF VITAMIN A

A REPORT OF THE
INTERNATIONAL VITAMIN A CONSULTATIVE GROUP
(IVACG)

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Table of Contents

"The Safe Use of Vitamin A"

INTRODUCTION

The purpose of this report is to provide suggestions or guidelines on the safe use of vitamin A, to encourage its proper use in intervention programs, for meeting the optimal nutritive needs of people in developed and developing countries and to avoid hypervitaminosis A.

Hypervitaminosis A is the consumption of excessive amounts of vitamin A orally or intramuscularly, either as a single dose or by successive doses, causing biochemical and clinical abnormalities in body tissues, many of which cause discomfort and pain. Davis[1] has commented on the difficulty of informing and protecting the public from hypervitaminosis without either fostering unrealistic apprehensions or ironically and tragically encouraging enthusiasts to believe that all apprehensions are unrealistic. The authors of this report hope to put the subject in proper perspective so that the potential benefits of supplementary vitamin A where needed can be fully and safely realized.

SUMMARY OF REPORT

Vitamin A is an essential nutrient occurring in foods in two forms as preformed vitamin A (in animal foods) and as the provitamin A carotenoids (primarily in plant foods). Additionally, synthetic preformed vitamin A identical to that in nature is available to be taken orally, administered intramuscularly or added to foods consumed by man.

While too much vitamin A consumed too frequently or too extensively causes tissue changes, pain and discomfort (vitamin A toxicity or hypervitaminosis), inadequate consumption (hypovitaminosis A) results in loss of visual acuity, blindness, lack of growth, related morbidity and even death. Although hypervitaminosis and its resulting problems occur occasionally in developed nations, hypovitaminosis A in developing countries poses a far greater health problem. The goal, of course, is to provide all populations with the recommended daily allowances for vitamin A while avoiding both extremes of vitamin A nutriture.

One achieves the goal by consuming vitamin A at safe levels. Consumption of animal and plant foods in the usual dietary pattern offers no toxic hazard unless one consumes significant amounts of the livers of certain exotic animals (polar bear, walrus, seal or shark, for example), which feed on fish and marine life. Nor does the addition of vitamin A in a prescribed manner and amount to foods such as cereal grain products or sugar to improve the vitamin A nutriture of a population experiencing hypovitaminosis A present any danger of vitamin A toxicity, as proven by vitamin A nutrification practices of the last 60 years.

When high level concentrates of vitamin A are taken orally or by intramuscular injection, part of the vitamin A is quickly metabolized and excreted, part is used for current body tissue needs and part is retained in the liver for future needs. This liver storage of excess vitamin A permits the maintenance of a normal vitamin A status even when too little is consumed daily for an appreciable period. The slow physiological release of these liver stores of vitamin A permits intermittent massive or high-level oral dosing of preschool children and infants to be used safely as a prophylactic approach, when done in a prescribed manner and amount, against vitamin A deficiency when adequate daily diets are not consumed. Similarly, vitamin A supplements for treatment of xerophthalmia, in a prescribed manner and amount, can cure vitamin A deficiency without danger of vitamin A toxicity.

Guidelines for safe use of vitamin A are included in this report. Based on current knowledge, the authors judge that these are safe, effective procedures which offer a minimum of transient untoward reactions. An assessment of the literature on hypervitaminosis A is also included.

PART A
CONSIDERATIONS IN INTERVENTION PROGRAMS

INTRODUCTION

Vitamin A is an essential nutrient for man since it cannot be synthesized within the body. It is usually supplied in the daily diet either as vitamin A, as carotenoid vitamin A precursors (provitamin A) or as a mixture of the two. Vitamin A ingested in amounts greater than daily needs is stored in the liver.

This liver storage phenomenon permits man and animals to store sufficient vitamin A to enable them to live for months consuming low vitamin A daily intakes without developing clinical signs of deficiency. The natural occurrence of preformed vitamin A (retinol and retinyl esters) is confined to foods of animal origin. The majority of man's intake of vitamin A is in the retinyl ester form when he consumes animal products and by-products. Carotenoid vitamin A precursors present in plant foods such as ingested β-carotene are converted to vitamin A mainly in the small intestine during the absorption process. Of the several dozen natural carotenoid vitamin A precursors known, β-carotene has the highest biological activity. Other frequently recognized and valuable ones but of lower biopotency in natural foods are other carotenes (α, γ), the apo-carotenals, the monohydroxycarotenes (cryptoxanthin), the monketo-β-carotenes (echinenone) and mono-epoxy-β-carotenes.

For an understanding of the physiological role of vitamin A in the body, an examination of varied intake levels of this vitamin is helpful. Three stages of vitamin A nutrition as depicted by Miller & Hayes[2] are shown in Figure I.

Deficiency or Hypovitaminosis A

An inadequate intake of vitamin A results in insufficient levels of the nutrient for optimal cell formation and functions. Depending upon the degree of insufficiency, mild or severe biochemical and clinical signs will develop, and growth, reproduction and resistance to infections will be affected. The most important manifestation of severe vitamin A deficiency is the irreversible loss of eyesight. Together with greater susceptibility to infections and other accompanying nutritional deficiencies, the condition frequently leads to death.

Sufficiency or Adequacy

An individual's exact quantitative need for vitamin A has rarely been determined. The amount of vitamin A estimated to meet the needs of most individuals in a given group is referred to as a recommended dietary allowance (RDA). The RDA for a given group depends on age and physiological status. For proper vitamin A nutrition, a diet which provides the daily recommended intake should be consumed whenever possible. Recommended daily allowances of vitamin A for humans established by expert committees of the Food and Agriculture Organization/World Health Organization (FAO/WHO)[3] and the National Research Council of the National Academy of Sciences (NRC-NAS)[4] are shown in Tables I and II.

Toxicity or Hypervitaminosis A

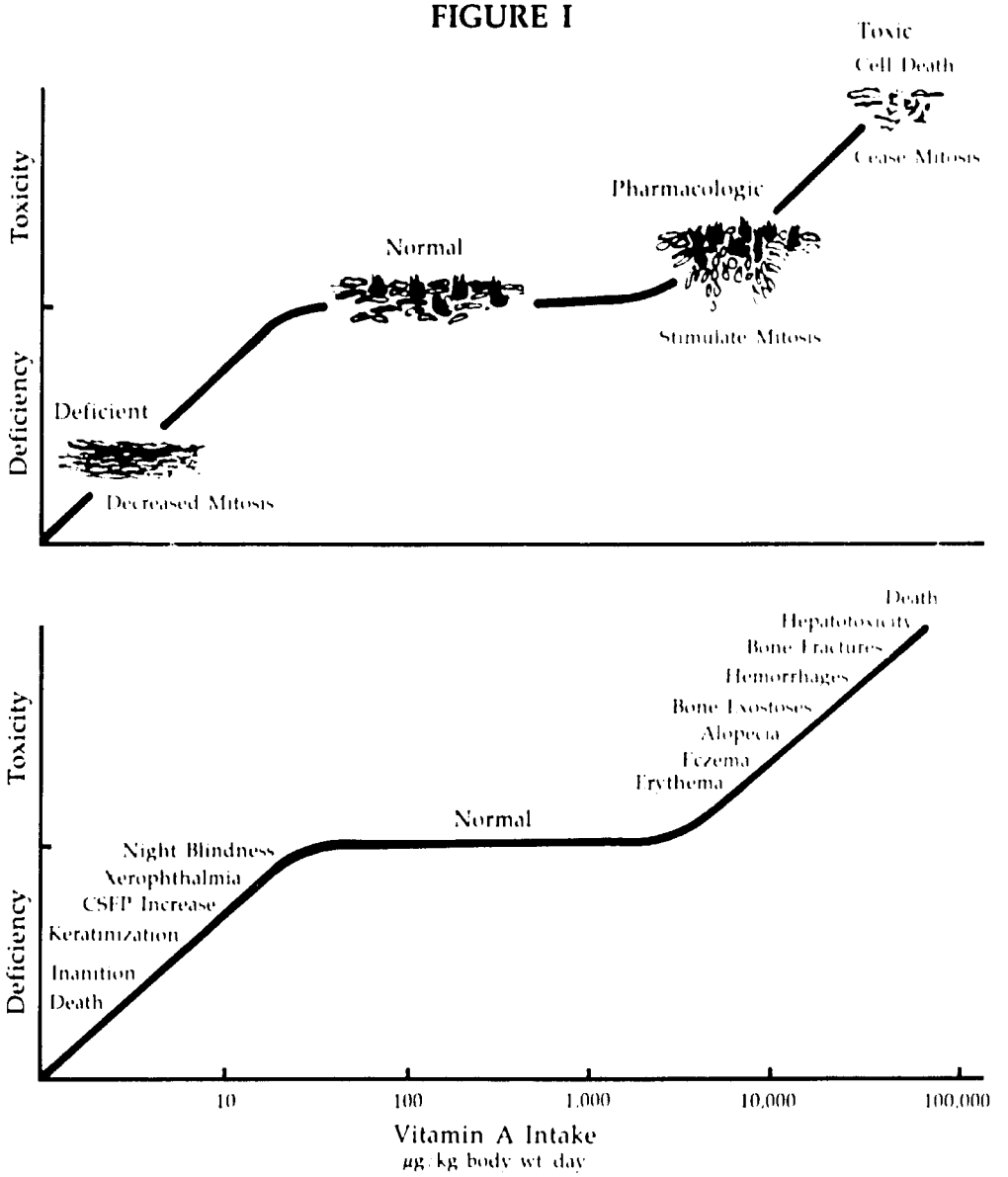
The intake of vitamin A above that which an individual can metabolize, either in a single excessively high intake or very high intakes for prolonged periods, causes very high blood levels resulting in nausea, headaches, irritability, and abnormal responses of the blood, skin, hair and bone. A rapid recovery usually results when excessive intakes are discontinued. Hypervitaminosis A, then, is the result of abuse of this essential nutrient.

During the last 100 years or more interest in hypervitaminosis A has been maintained by occasional case reports by physicians or scientists of chronic or acute symptoms from an excessive intake of vitamin A. Present-day concern about safe use of vitamin A revolves around a) the current practices of intermittent oral or intramuscular administration of massive or high-level doses of vitamin A as a preventive measure and as an emergency or short-range approach to the eradication of vitamin A deficiency blindness in children in some of the developing countries and b) the growing practice of daily ingestion of dietary vitamin supplements, some containing high vitamin A levels, to assure a full daily intake of essential nutrients in developed countries.

POPULATION USAGE OF VITAMIN A

In societies which consume both plant and animal foods, vitamin A needs are met by the

FIGURE I



The logarithmic plot of vitamin A intake is depicted as a function of the biological response of man and animals in terms of deficiency, normalcy and toxicity. The scheme at the top illustrates the response of a typical mucous epithelium, but is probably applicable to other undifferentiated blast-cell populations as well. The bottom curve indicates the clinical manifestations resulting from the altered cell function in deficiency and toxicity of vitamin A[2].

combined consumption of carotenoid vitamin A precursors and vitamin A (retinol and retinyl esters). In a 1974 publication[5] the NRC-NAS states that the usual foods available to the U.S. consumer are estimated to provide about half of the total vitamin A activity as preformed vitamin A and half as carotenoid vitamin A precursors. Witchi et al.[6] in a diet-

TABLE I
FAO/WHO Recommended Daily Allowances for Vitamin A[a]

Group	Age (years)	FAO/WHO Vitamin A Values* (μg/day)	Group	Age (years)	FAO/WHO Vitamin A Values* (μg/day)
Infants	0-½	[a]	Children	7-9	400
	½-1	300		10-12	575
Children	1	250		13-15[b]	725
	2	250		16-19[b]	750
	3	250	Adults[c]	All ages	750
	4-6	300			

* To convert to IU, multiply by 3.3
[a] Satisfied by breast feeding by a well-nourished mother.
[b] Boys and girls.
[c] Men and women.

TABLE II
NRC Recommended Daily Allowances For Vitamin A[4]

Group	Age (years)	Weight (lbs)	NRC-NAS Vitamin A Values* (μg/day)
Infants	0-1/2	13 (6)[a]	420
	1/2-1	20 (9)	400
Children	1-3	29 (13)	400
	4-6	44 (20)	500
	7-10	62 (28)	700
Males	11-14	99 (45)	1000
	19-22	145 (66)	1000
	23-50	154 (70)	1000
	51+	154 (70)	1000
Females	11-14	101 (46)	800
	15-18	120 (55)	800
	19-22	120 (55)	800
	23-50	120 (55)	800
	51+	120 (55)	800
Pregnant	---	---	1000
Lactating	---	---	1200

* To convert to IU, multiply by 3.3
[a] Weight in kg.

ary study of 156 American adults of varied ages of both sexes, in various stages of activity and over a 6 to 12 month period, found that approximately equal amounts of carotenes and vitamin A made up their total vitamin A intake. Fruits and vegetables accounted for two-fifth's of the total A activity. Greaves and Tan[7] and Thompson[8] conclude that the British receive about a third of their vitamin A requirements in the form of carotenoid vitamin A precursors.

Due to various reasons, rich sources of provitamin A are not always consumed in adequate amounts, and vitamin A deficiency, including blindness, is prevalent in many parts of Africa and in parts of the Far and Middle East, South Asia, and Central and South America.[9] In Africa and the Far East, little milk, and, in some areas, few vegetables and fruits are consumed. The diets consist mainly of cereals such as rice, millet, cassava and wheat, which supply less vitamin A activity than is required. A similar situation has been described by Flores et al.[10] in many parts of Central and South America, where the diets often supply far less than the recommended allowance of vitamin A and the major part of it is in the form of carotenoid vitamin A precursors. Those following these food consumption practices, not surprisingly, may experience hypovitaminosis A.

Vitamin A Preparations

In addition to vitamin A present in some natural foods, modern science and engineering have produced pure vitamin A which may be used in nutritional intervention programs. Preparations of vitamin A may be taken orally, or by intramuscular injection, or may be added to widely consumed foods (nutrification or fortification) to make them important dietary sources of vitamin A.

For Oral Use: Vitamin A, in crystalline form as retinol or as retinyl esters, is quite labile when exposed to oxygen or air and must be kept in a vacuum or under inert gas. Since it is oil-soluble, dissolving either the acetate or palmitate ester in a vegetable oil helps to stabilize it against oxidation. The vitamin dissolved in oil is readily absorbed from the alimentary tract. Liquids, capsules and tablets of various vitamin A potencies are available for oral ingestion.

For Intramuscular (IM) use: Vitamin A injected intramuscularly should be in a vehicle which permits rapid translocation from the muscle site, by way of the circulatory system within the body, to the liver where part of the dose is used for tissue needs and part is stored for future needs. Animal experiments and human trials have indicated that oil solutions of the vitamin are not efficiently utilized by intramuscular injection and should be avoided. Aqueous dispersions have been developed which are highly effective when used as recommended in hospitals by trained personnel.

For Nutrification of Food: The application form of vitamin A to be added to food depends on the type of food product. Because many manufactured food products are in a dry particle form before preparation for consumption, there is a demand for dry, stable vitamin A forms in a range of particle sizes and forms. These are referred to as dry stabilized vitamin A beadlets, powders, etc. Some disperse in cold and/or hot water during the preparation of the nutrified food product for consumption.

Usage in Developed Countries

Vitamin A deficiency occurs rarely among population groups in developed countries. Three surveys in the United States between 1965 and 1972, however, indicated that a small percentage of the population either did not ingest the recommended daily allowance for vitamin A or, by biochemical assessment, had low serum retinol levels. Similar findings were noted in a Canadian survey. In developed countries, therefore, the concern is to assure an adequate intake of vitamin A for all individuals, a task probably best approached by consuming diets better balanced in vitamin A rich foods or by including vitamin A nutrified foods in the diet. Daily supplements of vitamins are also consumed in developed countries as an alternate method of meeting recommended daily allowances.

Usage in Developing Countries

In developing countries, a number of nutritional intervention strategies may be employed to prevent or overcome hypovitamin-

osis A, depending on the objectives. The goal may be a) to eliminate blindness (keratomalacia) or b) to improve the vitamin A nutrition of the population segment at high risk, namely preschool children, or c) to improve the vitamin A nutrition of the entire population. The primary goal determines the chosen approach.

Foods or food ingredients which currently are serving or are being tested as food vehicles for added vitamin A in developing countries include wheat flour, maize meal, milk powder, fats, oils, sugar (refined sucrose), tea dust and/or leaves, seasoning (monosodium glutamate, MSG) and weaning foods.

Oral dosing of vitamin A may be given by the intermittent massive or high level oral dosing program (2 to 4 times yearly) as is practiced in several countries where contact with preschool children can be made only periodically and where dietary improvement cannot be achieved readily.

Frequent low-level dosing is suggested where conditions permit. In the case of pregnant women, for example, vitamin A administered daily, several times weekly or monthly can be given in amounts in the range of the daily recommended dietary allowance (RDA) levels or slightly above.

Where prolonged vitamin A deficiency in a child or adult has resulted in hospital admission, at a critical stage of keratomalacia, rapid therapeutic action is necessary to save the sight of the eye. For this purpose, an injectable aqueous form of the vitamin may be kept on hand for intramuscular administration.

FACTORS INFLUENCING SAFETY

In assessing the safety of high dosage intake of vitamin A, several factors influencing its absorption, metabolism and utilization in the body should be considered. Drugs and/or chemicals with a potential for interacting with vitamin A or modifying physiological vitamin A patterns should be avoided, or taken at different time intervals as recommended by physicians. Other influencing factors include age, state of nutrition and health, biochemical individuality, the nature of vitamin A preparation and interrelated dietary nutrients.

Adequacy of Protein Intake

There is a close link between vitamin A metabolism and protein metabolism. For normal synthesis and functioning of retinol transport proteins, namely RBP and PA (prealbumin), an adequate intake of good quality protein is necessary.[11] Except in severe protein deficiency, synthesis of carrier proteins is not a limiting factor in the utilization of vitamin A.[12] An inadequate intake of good quality protein will impair vitamin A absorption[13] from the alimentary tract. Yet in spite of altered vitamin A absorption in severe protein deficiency, a substantial portion of a high-level oral dose of vitamin A will be absorbed in children. Under these conditions high-level dosing should be accompanied or followed by protein supplementation of the diet, if possible. Report VI of the IVACG series on *Guidelines for the Eradication of Vitamin A Deficiency and Xerophthalmia* may be consulted for a more detailed review of the metabolism of vitamin A.

Physical Form of Vitamin A

The physical form of an oral vitamin preparation will influence its rate of absorption. One of the earliest groups of investigators[14,15] studied both oily and aqueous vitamin A preparations in humans and animals. Their vitamin A data demonstrated that higher plasma values, higher liver values and lower fecal losses resulted when the aqueous dispersion was used in trials with animals, infants, children and adults.

The ingestion of 200,000 IU of vitamin A by 29 subjects was followed in a study by Kalz and Schafer.[16] Significantly higher values in blood sera were achieved with a water miscible emulsion of retinyl palmitate than with retinyl palmitate in oil solution in capsules (Table III). Upon examining the literature on hypervitaminosis A, Koerner and Voellm[17] concluded that with comparable doses, the symptoms of chronic toxicity appear significantly earlier following ingestion of aqueous dispersions or emulsions than of oil solutions of the vitamin.

Influence of Vitamin C

Humans, guinea pigs and fish require ascorbic acid in their diet since they do not have the complete enzyme system to synthesize it. About 50 years ago some toxic manifestations from excessive vitamin A consumption were observed in guinea pigs to resemble scurvy or

TABLE III
The Effect of Ingestion of 200,000 I.U. of Various Vitamin A Preparations on the Vitamin A Serum Level (I.U.)[16]

	Preparation 1 Vitamin A Palmitate in Watermiscible Emulsion			Preparation 3 Vitamin A Palmitate in Capsules		
	A	B	C	A	B	C
	117.1	242.2	208.0	81.8	157.0	97.0
	119.4	530.4	324.0	63.0	128.0	73.0
	57.2	557.0	232.0	96.0	131.5	153.6
	94.0	580.0	650.0	87.0	213.0	73.0
	101.0	663.3	572.8	88.0	209.0	95.0
	32.3	606.0	187.8	65.0	231.0	195.0
	32.0	227.0	290.0	77.0	180.0	163.0
	53.0	576.0	303.0	61.0	111.0	81.6*
	81.0	508.0	663.0	58.0	99.0	74.0*
	60.0	610.0	746.0	46.3	72.3	79.3
				50.0	80.0	68.3
Mean	74.7	510.1	426.6	70.2	146.5	103.9
Standard Error	10.3	47.8	65.4	5.0	16.7	13.6

A: Fasting Level. B: Three hours after ingestion of vitamin A. C: Six hours after ingestion of Vitamin A

* Data were missing and were obtained by using the formula proposed by Allan and Wishart, and modified by Yates.

vitamin C deficiency. Rodahl[18,19] noted that ascorbic acid was reduced in the liver and blood sera of hypervitaminotic guinea pigs and rats. He also noted that the toxic effect of excessive doses of vitamin A was greater in guinea pigs on a scorbutigenic diet than on one furnishing adequate amounts of vitamin C. Wendt and Schroeder[20] observed favorable action of administered ascorbic acid on symptoms of hypervitaminosis A and in delaying liver deposition of the vitamin. Symptoms of hypervitaminosis A in rainbow trout, which resemble those of vitamin C deficiency, were counteracted by Primbs et al.[21] by increasing the dietary intake of ascorbic acid. Conflicting data exist on the value of vitamin C in reducing hypervitaminotic symptoms in animal species synthesizing vitamin C such as the rat.

In humans, data of Andre et al.[22] presented by Mayer demonstrated that under conditions of hypervitaminosis A, urinary excretion of ascorbic acid was enhanced indicating that high intakes of vitamin A reduce tissue storage of ascorbic acid. Hence, while some data exist on the vitamin C-vitamin A interaction in humans, further studies are desirable for a clarification of the significance of this interaction.

Role of Vitamin E

The vitamin A-E interrelationship has been reviewed by Arnrich[23] and by Bauernfeind et al.[24] Vitamin E protects against disruption of membrane lipoprotein structure caused by high-level vitamin A intakes.[25,26] In chickens, hypervitaminosis A caused by continuous feeding of excessive vitamin A was significantly reduced by incorporating high levels of vitamin E in the diet.[27] Retarded growth, a result of high vitamin A intake, has been overcome by the incorporation of vitamin E in the

diet of growing chicks[27] and growing rats.[28-30] Soliman[31] observed fewer congenital anomalies in rat pups when vitamin E was incorporated into a diet containing high levels of vitamin A. In experimental animals, vitamin E enhances the intestinal absorption and liver storage of vitamins, as most recently confirmed by Yang and Desai.[32] Oaks et al.[33] showed, in humans ingesting 30,000 IU of vitamin A daily, that 200 IU of vitamin E daily reduces serum vitamin A values while maintaining plasma RBP and PA. They suggested that vitamin E enhances the tissue uptake of vitamin A. Under other conditions, Jajadeesan and Reddy[34] noted in children that administration of vitamin E significantly increases the plasma vitamin A concentration both in normal children (not receiving high vitamin A intakes) and in those with vitamin A deficiency, while there was no change in the control group.

While a vitamin A-E interrelationship exists under certain circumstances, an explanation of how vitamin E ameliorates some of the toxic manifestations of excessive vitamin A dosing is not apparent. One view suggests that vitamin E stabilizes or otherwise protects cell membranes. Since vitamin E as α-tocopherol has antioxidant properties, both *in vitro* and in the alimentary tract, and since vitamin A is poorly absorbed in vitamin E deficiency, the addition of a small amount of vitamin E (40 mg or IU) to the 200,000 IU of vitamin A in the gelatin capsule used in intermittent high level oral dosing is judged to be a justifiable practice.

Antagonism of Vitamin K

The appearance of hypoprothrombinemia in chronic hypervitaminosis in both animals and humans suggests a possible antagonism between excess vitamin A and K. Experiments with rats[35] indicate that the antagonism can occur quickly: decreased clotting time has been observed after five days of feeding of excessive vitamin A levels. Normal clotting time has been quickly restored[36] by feeding supplementary levels of vitamin K. Whether antagonism is due to a direct effect of the vitamin A on the intestinal synthesis of vitamin K in the alimentary tract, on an inhibition of vitamin K absorption or on other factors is not clear. While hemorrhaging of various types occurs in hypervitaminosis A, correction quickly follows cessation of chronic, high-level vitamin A dosing.

Mineral Interrelationships

Altered bone formation, bone fracture and hypercalcemia reported in some cases of chronic hypervitaminosis A indicate a vitamin A-calcium interrelationship or antagonism. Hypercalcemia has been reported in a 31-year-old female[37], given 3,500,000 IU daily for 21 days, in an 18-year-old male[38] ingesting 200,000 IU daily for two years, in a 16-year-old male[39] taking 100,000 IU daily and 300,000 IU plus a multi-vitamin tablet every fourth or fifth day for six months and in an 18-year-old female[40] consuming 150,000 IU of vitamin A plus a multi-vitamin tablet daily for three years. In some instances excessive supplementary vitamin D was taken as well.

Hypercalcemia has also been reported in animals suffering from hypervitaminosis A. Bone ash was low[41] and bones with thinner cortices and less trabecular structure[42] were observed. Addition of calcium[41] or porcine calcitonin[42] to the dietary program prevented the changes. In other studies the calcium and phosphate levels in the blood of hypervitaminotic rats were reported to be normal,[43] and in other trials no reduction in bone ash[44,45] could be demonstrated in rats dosed with large amounts of vitamin A. The significance of the vitamin A-calcium interrelationship is difficult to unravel at this time.

Within the last 10 years, data supporting an interrelationship between zinc and vitamin A have appeared. In most cases, however, the interaction concerns low levels of vitamin A and zinc rather than the toxic state.[46-48] Zinc sulfate and vitamin A have been used as treatments for acne patients. Vahlquist et al.[49] treated acne patients daily both with 300,000 IU in an aqueous vitamin A preparation and with 45 mg zinc given orally for 12 weeks without untoward side reactions. Zinc alone was as effective as vitamin A plus zinc in improving acne lesions. Based on short-term studies of zinc sulfate on plasma and hepatic concentration of vitamin A, Ette et al.[50] propose that zinc may be used to treat not only patients with depressed plasma vitamin A levels but also those with liver damage from hypervitaminosis A. Definitive clinical studies

involving subjects with hypervitaminosis A must be conducted before any conclusions can be made regarding the possible effect of zinc on this syndrome.

While anemia is occasionally mentioned as a sign in hypervitaminosis A, it is not among the more prominent indicators.[51,52] Hypovitaminosis A is often associated with anemia in malnourished children and interventions to correct vitamin A deficiency are reported also to decrease the prevalence of anemia. It is not known whether there is any iron-vitamin A interrelationship in hypervitaminosis A.

EFFECT OF INFECTION AND DISEASE

No nutritional deficiency is more consistently synergistic with infectious and parasitic disease than that of vitamin A. Vitamin A deficiency renders the subject more susceptible to attack by disease, and the diseased subject in turn is less able to make proper use of dietary provitamin and vitamin A.[51,53-57] In acute infectious diseases, plasma vitamin A levels usually are depressed and transport mechanisms become more efficient.[55] Subjects dying of chronic infections have significantly lower vitamin A liver values than those subjects dying of other causes.[56] In patients with liver disease, the levels of vitamin A, RBP and PA are all markedly decreased.[58]

Sivakumar and Reddy[59] observed the absorption of labelled vitamin A given as a single dose in two children, once when they were healthy and later when they were ill with respiratory infection. The absorption of vitamin A decreased by 20 per cent and 69 per cent and urinary excretion of vitamin A metabolites increased during illness. Reddy and Sivakumar[60] also reported on the vitamin A absorption pattern of groups of normal, healthy children, those with respiratory infections, and those with diarrhea (Table IV). The ill children absorbed less of an oral dose and excreted more vitamin A in feces and urine than healthy children. In developing countries, vitamin A deficiency associated with malnutrition appears to be more common when ascariasis is also present.[56] Lower serum values for vitamin A are frequently found in subjects suffering from parasitic diseases. When Mahalanabis et al.[57] investigated vitamin A absorption in ascariasis (*Ascaris lumbricoides*) in 28 patients given a single oral dose (5000 IU/kg body weight), malabsorption of vitamin A was demonstrated in over 70 per cent of the patients. Immediately after expulsion of the worms, vitamin A absorption improved in 13 out of 14 patients tested. Awadalla et al.[61] reported poor vitamin A absorption from a 200,000 IU oral dose in boys with parasitic infestations of giardia and ascaris. Araiyo et al.[62] found in Brazilian children that internal parasites strongly interfere with utilization of vitamin A.

The literature on intermittent high-level vitamin A dosing of children indicates that less of the dose will be absorbed in ill children. While this should not decrease safety of administration, it certainly influences the effi-

TABLE IV

Absorption of Labelled Vitamin A* in Children with Infection[60]

Group	No.	% of Dose Absorbed from the Gut	% of Absorbed Label Excreted in Urine	% of Dose Retained in the Body
Normal children	5	99.2 ± 0.47	17.0 ± 1.58	82.2 ± 1.99
Children with respiratory infection	8	74.3 ± 6.83	23.3 ± 2.96	57.6 ± 5.96
Children with diarrhea	3	70.2 ± 5.92	16.0 ± 3.24	58.9 ± 4.39

* 4 μCi (11, 12-H_2) retinyl acetate + 3,000 I.U. unlabelled retinyl acetate.
Mean ± S.E.

cacy of the procedure. If possible, ill children should be followed up and given a second dose of oral vitamin A as soon as they are well again.

GUIDELINES ON RISK ASPECT

Guidelines for the safe administration of a high dose of vitamin A require an evaluation of influencing factors. It must be recognized at the start that the evolutionary pattern has been to provide the individual's vitamin A requirement in small quantities daily in the diet. McLaren[55] over a decade ago suggested that the body treats vitamin A, when received in massive oral dose amounts, in a special manner. Large doses enable storage of a sizable portion in the liver for future use. The rapidity with which the liver store disappears, however, is directly proportional to the amount stored. Therefore both practical and physiological aspects must be considered in recommending the oral or parenteral dose in a given instance. The ideal solution would be to provide vitamin A in the diet in small and regular amounts which are in balance with the intake of other essential nutrients. In developing countries where prevalence of hypovitaminosis A is high, recommended daily intakes of the vitamin are not always provided in the diet, particularly of children. In these situations other ways of meeting the crucial nutritional needs, such as intermittent high level oral dosing, must be considered. Two approaches are discussed below for determining guidelines for the safe oral use of vitamin A in high dosages.

Dose Tolerance/Recommended Daily Allowance Ratio

As previously stated by Moore,[63] the human body is able to tolerate doses of vitamin A which are at least 100 times greater than the daily requirement for its physiological needs. The dose cannot be increased indefinitely without injury, however. A maximum of 150 times the RDA is a useful indicator of the largest single oral dose of retinyl ester in oil solution which might be tolerated by a subject of a given age and sex (Tables I and II). This rule of thumb would not be applied to pregnant women or infants less than one year of age. The NRC-NAS recommended dietary allowance (RDA) of vitamin A for children ages 1 to 3 years is 400 μg of vitamin A or 1320 IU. A dose 150 times that amount would equal 198,000 IU. A single oral dose of 200,000 IU of vitamin A ester in oil solution is regarded as acceptable and relatively safe judged by field experience over the past 10 years. Using the same calculation, the largest single dose in oil for adult males would be 495,000 IU and for adult females would be 396,000 IU. The literature on high-level dosing would support these as tolerated single oral intakes.

How far beyond the amount of 150 times the RDA levels and how many times and how often one can repeat these dose levels without encountering significant toxicity depends on influencing factors previously discussed. The literature indicates that when a group of subjects is given similar high-level doses of vitamin A, a few individuals are more sensitive and may have a fleeting hypervitaminotic symptom, such as a headache or nausea, which the majority do not. Based on observations in animal research, variability in utilization of vitamin A among human individuals might be expected.

Daily Dose/Body Weight Ratio

The calculation of a daily dose of vitamin A based on body weight may be a better guideline for frequent or multi-dosing of individuals. Recorded oral doses of vitamin A preparation which have been reported to induce toxic reactions vary from approximately 2,500 to 50,000 IU (750 to 15,000 μg) per kilogram of body weight or a twenty-fold variation where duration of dose varied from days to years. In view of the many influencing factors already mentioned, giving a rigid single guide that would hold universally would be impossible. Assuming that the daily ingestion of vitamin A at 2500 IU per kilogram of body weight is near the beginning of toxicity given over a time period, the following intakes of vitamin A are proposed (Table V) as maximal for oral prophylactic and therapeutic use of retinyl ester such as vitamin A acetate or vitamin A palmitate in solution, tablet or capsule form for the given age group. Pregnant women are not included in the proposed tabulation.

Therapeutic levels should be administered only under a physician's care. Furthermore it is suggested that the prescribing physician

TABLE V
Proposed Daily Vitamin A Maxima for Oral Prophylactic and Therapeutic Use

Age Group	Prophylaxis Daily Maximum[a]		Therapeutic Daily Maximum[b]	
(yr)	(IU)	(μg)[c]	(IU)	(μg)[c]
Infants, age 1-3 mo.	3,000	900	6,000	1,800
Children, age 1-3	6,000	1,800	12,000	3,600
Children, age 4-6	10,000	3,000	25,000	7,500
Children, age 7-10	15,000	4,500	50,000	15,000
Adolescents, age 11-17	20,000	6,000	100,000	30,000
Adult females[d], age 18-65+	25,000	7,500	125,000	37,500
Adult males, age 18-65+	30,000	9,000	150,000	45,000

[a] Exceeds NRC-RDA by a factor of 2-9 times
[b] Exceeds NRC-RDA by a factor of 4-45 times
[c] Retinol equivalents given in the form of retinyl ester
[d] Non-pregnant females

consider a break or vitamin A-free period of 1 to 2 weeks between courses of therapeutic treatment. If for any reason the prescribing physician exceeds these daily levels or time intervals for individual patients, weekly checkups on the patients should be made and treatment stopped if significant signs of hypervitaminosis A appear.

SAFETY OF IVACG RECOMMENDATIONS

The IVACG recommendations listed below are judged to be safe procedures for intervention programs:

For Treatment or Therapy:

Give one capsule on diagnosis; repeat the dose on the second day; and give a final dose of one capsule on discharge, or after approximately two weeks. These capsules contain 200,000 IU (60,000 mg retinol equivalents) vitamin A and 40 IU vitamin E in oil. Infants less than 1 year of age or very small or very low weight children are given one-half capsule under the above schedule.

In severe case of keratomalacia and danger to loss of sight 100,000 IU of vitamin A palmitate in a water dispersible formulation should be administered intramuscularly in place of the first oral capsule on diagnosis; only give one-half the dose (50,000 IU) to infants under one year or very small or very low weight children.

For Prevention or Prophylaxis:

Give one capsule (200,000 IU) every three to six months. After delivery, nursing mothers may also be given one capsule on the above schedule as an aid to increasing the vitamin A content of their milk. Infants less than one year or very small or low weight children should be given one-half of the capsule dose (100,000 IU).

For Pregnant Women:

Adequate vitamin A should be assured by provision of vitamin A-rich food in the diet or by supplements of vitamin A not to exceed 10,000 IU (3000 μg retinol equivalents) daily. Although there is no conclusive evidence of harm in humans, massive or high-level doses of vitamin A should not be given until further evidence has been accumulated on its safety for pregnant women.

Labeling of Capsule and Ampule:

IVACG recommends that the above dosing schedules become a part of the label of the product where this is feasible or become a package insert to be included in the smallest unit package of the product.

Support for the IVACG recommendations can be found in the literature. Intermittent massive or high-level dosing was first suggested in 1964[64] and at an early stage put into practice in Jordan and India.[65] Other countries have followed. The Indian National Program in India, now about 10 years old, currently treats about 20 million children annually.[51] Initially one annual oral dose of 300,000 IU was given, but reversible toxic reactions were too frequent particularly if administered in an aqueous preparation instead of an oil solution. The program was quickly changed to 200,000 IU of retinyl ester in an oil solution given at least once every six months. Currently a gelatin capsule containing 200,000 IU of vitamin A palmitate with 40 IU of vitamin E in an oil solution is widely used throughout the world, although India still uses an orange-flavored oil solution of which 200,000 IU are administered by measured doses.

The large number of clinical and field studies compiled in Table VI provide evidence that a dose of 200,000 IU for children over 1 year of age and one-half the dose (100,000 IU) for infants under one year of age or for very small or very low weight children is an acceptable effective dose with a high degree of safety and a very low incidence of temporary reactions. Where the oral dose is used therapeutically it is safe to administer the same dose the following day. The oral dose can also be safely given again when ill children have recovered from viral, microbial or parasitic infections.

Because of the suddenness with which corneal necrosis can occur in xerophthalmia, the condition is a clinical emergency requiring immediate attention. The most common form of vitamin A therapy currently used in the clinical situation is the intramuscular (IM) injection preparation, an aqueous (water-dispersible) vitamin A palmitate product capable of providing 50,000 and 100,000 IU per dose. Several studies (Table VII) demonstrate that the IM injection of 100,000 IU can be safely given to children over one year of age and that 50,000 IU can be given to infants less than one year of age or to very small or very low weight children. Reddy [51] cites the rapidity of injection therapy over oral treatment.

However, the recent data of Sommers et al.[76] indicate therapy provided by use of either the oral capsule or IM injection is satisfactory. In the experience of Pereira (1980 private communication), small marasmic infants (3 to 5 kg) with keratomalacia displayed toxic signs of vomiting and intracranial tension when 100,000 IU of aqueous vitamin A palmitate was injected IM, thus supporting the need of the lower level of 50,000 IU for very small or low-weight infants.

The literature records[89] congenital malformations in animals due to hypovitaminosis and hypervitaminosis A during gestation but does not reveal its clear significance in the human experience. Gal et al.[90] reviewed the human congenital literature including level of vitamin A in blood obtained 7 days postpartum from women delivering babies, but since no information was available on the blood vitamin A levels or the dietary intake during the pregnancy, no significant correlations could be established. Bernhardt and Dorsey [91] record a case in which a mother who had taken 50,000 IU of vitamin A daily for the last two trimesters of pregnancy and a lesser amount the first trimester gave birth to a child with congenital renal anomalies. Pilotti and Scorta[92] reported an Italian mother who declared to have ingested 400,000 IU vitamin A and 600,000 IU of vitamin D daily for about a month during the early phase of pregnancy and who gave birth to a malformed child. Whether excessive vitamin A or vitamin D caused the malformation is not clear.

Geelan[93] describes two other infants with congenital anomalies alleged to have resulted from very high intakes of vitamin A by the mother at some stage of pregnancy. In view of these few human data and the well-tested evidence in animals it is most wise to continue to proceed cautiously with low-level vitamin A administration to pregnant women until further data are accumulated on the subject.

The nutritional status of the mother during pregnancy has long been known to influence the vitamin A adequacy of the child at birth. In pregnant women in the poorer communities of developing countries the serum vitamin A values usually fall as the pregnancy progresses.[94] Dietary survey and blood assay for vitamin A can establish whether the pregnant mother should be given some supplementary vitamin.

TABLE VI
Review of Some Experiences with Intermittent High Level Oral Dosing of Vitamin A and Incidence of Hypervitaminosis A

Reference	No. of Children	Age of Children	Form of Vitamin A Chemical	Physical	Conc. of Dose[a]	Toxic Observations
Pereira & Begum, 1973 [65]	6	4-5 yr	palmitate	oily	330,000 IU	none reported
Susheela, 1969 [67]	94	2-6 yr	palmitate	oily	330,000 IU	none reported
Pereira & Begum, 1969 [68]	43	2-5 yr	palmitate	oily	330,000 IU	no hypervitaminosis observed
Samsudin et al., 1974 [69]	175[b]	children	palmitate	aqueous	300,000 IU (100 IU vit. E)	no complaints, gastro-intestinal or neurological
Swaminathan et al., 1970 [70]	1785	1-5 yr	palmitate	oily	300,000 IU	4% toxic manifestations
Srikantia & Reddy, 1970 [71]	15	1-½-4 yr	palmitate	oily	300,000 IU	none reported
Reddy, 1969 [72]	100	½-5 yr	palmitate	aqueous	300,000 IU	nearly 25% toxic manifestations
Patwardhan & Kamel, 1967 [73]	90	1-6 mo	palmitate	aqueous	300,000 IU	no untoward reactions
Arroyave et al., 1959 [74]	12	1-½-3 yr	palmitate	oily	250,000 IU	none reported
Simmons et al., 1973 [75]	179	pre-school	palmitate	aqueous	225,000 IU	no clinical toxic effects
Sommers et al., 1980 [76]	69[c]	children	palmitate	oily	200,000 IU (day) (40 IU vit. E) 200,000 IU (day 2) (40 IU vit. E)	no toxicity except occasional asymptomatic papilledema
Reddy, 1977 [51]	10-20MM	1-4	palmitate	oily	200,000 IU	1-4% transient signs, such as malaise or vomiting
Salon et al., 1979 [77]	About 500	1-16 yr	palmitate	oily	200,000 IU 40 IU vit. E	3.4% reporting complaints of vomiting, headaches or fever
Sinha and Bang, 1976 [78]	153	2-6 yr	palmitate	oily	200,000 IU	Six of 153 vomited after first dose, none in subsequent doses
Guanzon-Hinojales et al., 1976 [79]	1773	½-5 yr	palmitate	oily	200,000 IU (40 IU vit. E)	none reported
Tarwotjo et al., 1975 [80]	2812	1-5 yr	palmitate	oily	200,000 IU (40 IU vit. E)	some unconfirmed effects[d]; acceptable dosage
Tarwotjo et al., 1974 [81]	40,063	pre-school	palmitate	oily	200,000 IU (40 IU vit. E)	acceptable dosage: no hypervitaminosis A identified
Kusin et al., 1974 [82]	17	3-6 yr	acetate	oily	200,000 IU (0-500 IU vit. E)	no hypervitaminosis
Karyadi et al., 1973 [83]	709	under 6 yr	palmitate	aqueous	200,000 IU	no hypervitaminosis
Reddy & Mohanram, 1971 [84]	15	3-7 yr	palmitate	oily	200,000 IU	dose effective, low clinical toxicity, insignificant cellular toxicity
Pereira & Begum, 1971 [85]	23	2-6 yr	palmitate	oily	165,000 IU	none reported
Reddy & Srikantia, 1966 [86]	15[e]	2-5 yr	palmitate	oily (butter)	100,000 IU (daily for 6 days)	no toxicity reported

[a] Given as a single dose, unless otherwise indicated.
[b] 75 with xerophthalmia, 100 normal
[c] Clinic children with xerophthalmia, about one third with diarrhea, about one half with protein-energy malnutrition
[d] Field report claimed some instances of vomiting and diarrhea, investigations by physician indicated illness was not related to vitamin ingestion; 200,000 IU dosage was judged acceptable
[e] Ten with kwashiorkor, five normal

TABLE VII
Review of Some Experiences With High Level Intramuscular Injection (IM) of Vitamin A and Incidence of Hypervitaminosis A

Reference	No. of Children	Age of Children	Form of Vitamin A Chemical	Physical	Conc. of Dose	Toxic Observations
Sommer et al., 1980 [76] **Venkataswamy et al., 1977** [77]	45[a]	Children	palmitate	aqueous	100,000 IU	None reported
	34	Avg. 2-¼ yr.	palmitate	aqueous	100,000 IU	None reported
Srikantia & Reddy, 1970 [71]	10	1-½-4 yr	palmitate	aqueous	100,000 IU	None reported
Pereira et al.[b], 1967 [70]	12	6 with kwashiorkor, 6 normal	palmitate	aqueous	100,000 IU	A recommended treatment; no vomiting, no intracranial tension

[a] Clinic children with xerophthalmia, about one third with diarrhea, about one half with protein-energy malnutrition.
[b] One child given 100,000 IU I.M. for six consecutive days showed no toxicity; another child below one year of age given 100,000 IU intramuscularly had symptoms of bulging fontanelle and vomiting.

Pereira and Begum[91] have indicated that vitamin A supplements of the order of 10,000 IU per day have maintained the blood level of the pregnant mother without enhancing the blood level of the newborn (and thereby presumably not endangering the newborn.)

High potency vitamin A supplements may be safely administered intermittently to nursing mothers if there is concern that the mother does not consume an adequate diet. Hrubetz et al.[95] supplemented the diets of 42 lactating women with 50,000 or 200,000 IU of vitamin A daily over a period of months and increased the vitamin A content of the milk proportionately. No mention was made of any toxic reaction. The subject is reviewed by Rodriquez and Irwin.[59]

For Nutrification of Food:

Since food is the usual carrier of vitamin A for humans, it may be desirable to add vitamin A to one or more specific foods or dietary items indigenous to a geographic area. Foods feasible for nutrification are those centrally processed which are consumed by a high percentage of the population at risk. Since the amounts of vitamin A added are adjusted to permit the recipient to receive the approximate recommended daily allowance for vitamin A, there is no risk of potential hypervitaminosis A. Foods to which vitamin A has been successfully added are fats, oils, dry skim milk, maize meal, wheat flour, sugar and monosodium glutamate (MSG). Table VIII may be consulted for some foods nutrified with vitamin A.

The staple food selected for nutrification in a given population group will depend upon the outcome of dietary surveys. The disappearance of the nutrified product at the point of consumer distribution can be used to monitor population intake. To date there are no indications clinically or biochemically that hypervitaminosis A has resulted from any of the nutrification projects currently in operation.

REPORTING OF HYPERVITAMINOSIS A

Although vitamin A toxicity remains a very minor clinical or nutritional problem, as recently concluded by Davis,[1] physicians and nutritionists should exercise caution and remain alert to signs of toxicity in the future. There may be unreported and undetected cases yet not observed. When one or more signs are noted, the observer should be stimulated to: a) check further for other typical signs, b) take a roentgenogram to reveal possible bone changes, if bone pain or tenderness exists, c) elicit a history of vitamin A consumption, and d) determine retinol and ester

TABLE VIII
Some Vitamin A – Fortified Supplemental And Weaning Foods Consumed By Young Children

Product	Approximate Year Initiated	Country	IU/Vitamin A/100 g
Supplemental			
Margarine	1918	many countries	1500-5000
Dry skim milk*	1965	—	5000
Wheat flour*	1969	—	900-1300
Corn meal*	1968	—	900-1300
Corn-soy-milk (CSM)*	1964	—	1700
Wheat-soy-blend*	1969	—	1650
Soy fortified corn meal*	1973	—	750
Weaning			
Bal-Amul	1967	India	1500
Cerealina	1965	Brazil	2200
Cerex	1979	Guyana	1700
Duryea	1969	Colombia	2000
Incaparina	1961	Guatemala	4500
Laubina	1970	Lebanon	2500
Lisha	1978	Tanzania	1700
Nutri-Soy	1979	Costa Rica	1700
Peruvita	1966	Peru	3000
Pronutro	1962	South Africa	3500
Superamine	1967	Algeria	2600

* U.S. Government Food Donations.

blood content tests for altered biochemical status. If overdosage is ascertained, all vitamin supplements should be removed and the patient confined, if necessary, to watch for alleviation of symptoms. Relief of many of the symptoms usually occurs within a few days or a week, and full recovery usually follows within one to several months.

If overdosage is detected from the patient's history, the actual amounts, the frequency and regularity of administration, the type of product and the declared label content of the product must be ascertained and included in any published report. Other medicant and food supplements must be reported in detail. Further information on the patient such as body weight and progress information during the recovery stage would be desirable.

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PART B
LITERATURE ASSESSMENT

HYPERVITAMINOSIS A VERSUS HYPOVITAMINOSIS A

Hypovitaminosis A or *vitamin A deficiency* is a major pediatric public health problem[56,96] in many developing countries of the world. In 1976, the World Health Organization (WHO) listed 74 countries and territories where hypovitaminosis A is considered a public health problem. Hypovitaminosis A, caused by insufficient vitamin A in the diet, is a major cause of blindness with an associated high rate of mortality. Over 1,000,000 children are estimated[96] to develop xerophthalmia throughout the world yearly; of these, 100,000 become permanently blind.

Hypervitaminosis A or vitamin A toxicity is the result of misuse or over-consumption of vitamin A, either out of ignorance or carelessness or out of the misconception that continued excessively high intakes will provide some unusual health benefit. No deaths have been attributed solely to hypervitaminosis A and in most instances hypervitaminosis A causes tissue changes, pain and discomfort, all of which are reversible. While difficult to estimate, several hundred instances worldwide probably occur annually, 90 percent of which cause fleeting side effects (from intermittent massive oral dosing programs) which are self-correcting within hours or a day after a single high level dosage. The remaining cases (from causes indicated in Table XI) may cause sufficiently severe symptoms to require weeks or months to reverse; of these, five to ten cases, on the average, are reported in the literature. These relatively few case reports attract attention and lead some readers to conclude that hypervitaminosis A is a more serious problem in the world than is actually the case. The simple remedy for this condition is to stop dosing the patient with excessive vitamin A. Table IX contrasts hypervitaminosis A and hypovitaminosis A.

HISTORY OF HYPERVITAMINOSIS A

Hypervitaminosis A in humans was not discovered initially from the over-consumption of pure vitamin A or of high vitamin A pharmaceutical doses. For centuries, Eskimos and arctic travelers have known from past experiences and folklore that the ingestion of polar bear and seal liver caused illness and must be avoided. Even the sled dogs or huskies and

TABLE IX
Relative Significance of Hypervitaminosis A Versus Hypovitaminosis

Item	Hyper	Hypo
Type of affliction	symptoms reversible	early symptoms reversible later stage irreversible
Persons afflicted annually world-wide	200 estimated	1,000,000 (estimated)
Severity of affliction	20 of which a few are publicized	100,000 permanently blind (estimated)
Deaths due to affliction annually world wide	None known	thousands (estimated)
Patient age of affliction	total life cycle	usually infants and preschool children
Associated conditions	usually none	protein-energy malnutrition infections and parasitic disease, poor growth

the raven of the north will not readily eat the liver. One of the earliest descriptions of illness (somnolence, stomach pain, nausea, headache, diarrhea, vertigo, peeling of skin) due to the eating of polar bear liver appeared in the logbook of Gerrit de Veer, written during the hibernation of the Dutch explorer, Willem Barentz, on Nova Zembla in 1596.[98] Not until the research of Rodahl and Moore[99] in 1943 and Rodahl[100] in 1949 did it become known, however, that as a result of the chain of consumption of marine life by polar bears their livers were exceedingly rich in vitamin A (containing 18-27,000 IU per g). A meal of a quarter or half kilo of bear liver could result in the intake of 3 to 13 million IU of vitamin A, well over 1000 times the daily recommended allowance.

Early reports[100-102] on hypervitaminosis A in humans as a result of consuming natural vitamin A concentrates were Czerny (1912), Ward (late 1930's), Spiesman (1941) and Josephs (1944), involving fish liver oil or oil concentrates. Animal tests in the early 1940's[100,101] with orally administered crystalline vitamin A confirmed the hypervitaminotic symptoms at very high dosage levels.

FREQUENCY OF HYPERVITAMINOSIS A REPORTS

A tabulation of approximately 200 literature reports covering about 600 individual cases from 1850 to 1979 (Table X) uncovered 182 reports, accounting for 505 individual cases, since 1948. The 74 cases of hypervitaminosis A reported prior to 1948 primarily were due to single meal consumption of the liver of the polar bear, seal, walrus, shark, halibut, husky, etc.

Table X shows two peak periods since 1948 (1952 to 1955 and 1970 to 1972) when the number of individual case reports was highest.

During the earlier period (1952 to 1955) two pharmaceutical preparations on the market, one containing 350,000 IU of vitamin A with 300,000 IU of vitamin D and another containing 400,000 IU of vitamin A with 600,000 IU of vitamin D per dose, when administered by prescription to infants, caused acute symptoms of hypervitaminosis A within 6 to 24 hours. Many of these cases of hypervitaminosis A occurred in Europe, primarily in France and Spain. In the second period (1970 to 1972), many of the cases of hypervitaminosis A may be traced to high daily intakes of vitamin A (more likely without vitamin D) prescribed as a therapy for dermatological disorders. In other instances the regime for therapy for the

TABLE X
Annual Occurrence of Literature Reports on Hypervitaminosis A

Period	Reports	Cases
(year)	(No)	(No)
1850-1899	4	25
1900-1938	5	38
1940	1	8
1941	1	1
1943	1	1
1944	1	1
1948	2	3
1949	2	19
1950	6	27
1951	8	9
1952	11	24
1953	17	60
1954	7	37
1955	10	18
1956	5	17
1957	12	38
1958	3	5
1959	4	6
1960	3	5
1961	5	10
1962	2	8
1963	2	4
1964	2	2
1965	7	17
1966	3	5
1967	4	4
1968	5	5
1969	4	13
1970	9	31
1971	8	47
1972	11	51
1973	5	6
1974	12	16
1976	4	8
1977	5	5
1978	4	5
Total	195	579

skin condition originated in self-diagnosis and self-medication by the subject.

CAUSES OF HYPERVITAMINOSIS A

Hypervitaminosis A results not from public health intervention programs, but from a) lack of knowledge and/or proper communication by either or both patient and physician and b) the enthusiasm of the public, principally parents, grandparents and health enthusiasts, who assume (without consulting knowledgeable resources) that "if a little is good, more must be better." As noted in Table XI which categorizes the different motivations or chains of events which lead to the reported cases of hypervitaminosis A, about an equal number of cases result from prescriptions as from layman abuse of vitamin A preparations. Over-dosing of children by parents or grandparents was the primary example of hypervitaminosis A caused by laymen. Some of the preconceptions or misunderstandings which led to overdosing were:

1) Belief that if a little is good, more should be better.

2) Confusion of products, for example, cod liver oil (850 IU vitamin A and 85 IU vitamin D per g) was confused with the higher potency oleum percomorph (60,000 IU vitamin A and 8,500 IU vitamin D per g), or another similarly potent product.

3) Confusion with instructions.

a. Confusion of "drops" with "droppers full"

b. Confusion of "drops" with "teaspoonsful"

c. Confusion about proper dose for a given age or weight.

4) Lack of understanding of the role of vitamin A in the nutrition of the child.

The literature reports on self-medication usually involve one case per report where excessive amounts of vitamin A were taken for a dermatological condition, usually acne, or for miscellaneous reasons such as cold prevention.

The causes of prescription-related hypervitaminosis A appear to be a) failure to recognize the three stage phase of vitamin A nutrition; b) failure to stress to parents the dangers of giving excessive vitamin A levels

TABLE XI
Causes of Hypervitaminosis A

Category	Reason for Toxic Condition		Reports	Cases
Laymen	parental overdosing		63	146
	self-medication		35	40
	incorrect dose		11	14
		sub-total	109	200
Physician	prescription (PP)		38	160
	PP and parental dosing		12	35
	PP and self-medication		15	20
		sub-total	65	215
Other	Experimentally induced		4	35
	Polar bear, seal, walrus, husky, halibut, shark liver consumption		17	129
		sub-total	21	164
		TOTAL	195	579

to the child; c) failure to warn dermatological patients not to exceed a given time period in taking high level daily intakes of vitamin A, without expecting toxic manifestations; and d) acceptability of a minimal degree of transient hypervitaminotic A symptomology if there were significant alleviation in the treatment of dermatological conditions. After the physician discharges the patient following an acceptable period of dermatological therapy under his supervision, the patient may renew the therapy for an extended time period or at an increased dosage and become hypervitaminotic at a later date through self-medication.

TYPES OF HYPERVITAMINOSIS A

For nearly four decades the scientific literature has shown that excessive intakes of vitamin A can have harmful effects in animals and man. Communication of these findings to medical practitioners and the lay public has not been successful. From the approximately 200 reports (Table X) of hypervitaminosis A which have appeared in the literature to date, the major toxic symptoms are tabulated in Table XII. Signs mentioned in less than four instances in the 200 reports were not tabulated.

Hypervitaminosis A can be divided into two categories: acute and chronic, based on toxic manifestations following the ingestion of a very high dose over days or on hypervitaminotic symptoms resulting from continued ingestion of high doses for months or years. Acute or chronic vitaminosis A may occur in infants, children and adults.

Acute

Acute hypervitaminosis A in adult humans has occurred primarily from the consumption of cooked or fried livers of animals (polar bear, seal and husky) or large fish (halibut, shark) high in vitamin A content and probably high in vitamin D content. Nater and Doeglas,[105] as late as 1970, cite an instance of acute vitamin A toxicity in fishermen after the fishermen consumed 20 to 300 g of fried halibut liver (2—30 million IU of vitamin A). The largest amount was eaten by a 90 kg man. Symptoms starting five hours after the meal were dull heavy headaches, dizziness, nausea, vomiting and immobility. Symptoms the following day included redness and desquamation of skin of the face, trunk, and eventually palms and soles. Recovery followed within a few weeks.

Acute toxicity has also been observed following excessive daily doses of vitamin A administered for the treatment of dermatological conditions. Frey and Schock,[106] in observing adult patients with psoriasis given high oral doses of retinyl acetate manufactured by chemical synthesis, noted that 400,000 IU daily were well tolerated but doses of 1,000,000 IU caused dryness, scaling and fissuring of lips; 2,000,000 to 4,000,000 IU produced redness and scaling of skin as well as nausea and dizziness when given for three to six days. Furman[107] reported a case in which a 28-year-old woman, after ingesting 1,300,000 IU of vitamin A over 27 hours to avoid sunburn, developed an intense headache, ataxia, nausea, blurred vision, vertigo, edematous skin, skin exfoliation, papilledema, and loss of hair. As reported by Leicht et al.[37] in 1973, a 31-year-old woman who consumed 3,500,000 IU of vitamin A daily as an aqueous emulsion for three weeks (73,500,000 IU total) suffered from persistent headaches, loss of appetite and weight, repeated vomiting, increased thirst, anemia, general weakness, hepatosplenomegaly, complete alopecia, lamellar scaling of skin, scabbed lips, dry tongue, pain over kidneys upon micturition, toxic hepatitis and hypercalcemia. The patient recovered within 5 to 30 days. Goeckenjan et al.[108] reported on a 30-year-old man consuming 51,000,000 IU of vitamin A in the form of an aqueous dispersion over a 22-day period who developed headaches, dizziness, vomiting, visual disturbances, itchy skin, lip and gum changes, scaling of skin, body weakness, clouding of consciousness, anemia, hyperglycemia, renal failure, hepatomegaly, prolonged hypoprothrombinemia, hypercalcemia, hyperlipidemia and high serum vitamin A. Foelsch et al.[109] in 1976 described a 22-year-old man consuming 70 to 75,000,000 IU of vitamin A over a 38-day period as a treatment for psoriasis, who had to cease treatment because of signs of hypervitaminosis A: headache, itching, vomiting, fatigue, anorexia, vertigo, nervousness, psychomotor unrest, weakness, pain extremities and joints, reddening of skin, gingivitis, conjunctivitis, swollen and ulcerated lips, swelling in lymph nodes, light and noise sensations, renal

TABLE XII
Symptoms of Hypervitaminosis A in Cases in Literature Reports

Symptoms	200 Report Survey (TM)
Alopecia	32
Hair sparse and/or coarse	18
Anemia	10
Anorexia	46
Atexia	
(vertigo, dizziness, giddiness, equilibrium or walking problems)	34
Blood changes	
Elevated serum lipids	4
Elevated serum vitamin A	50
Elevated serum alkaline phosphatase	18
Elevated serum transaminase	5
Prolonged prothrombin time	7
Hemorrhages, petechia (bleeding gingivae, membrane, nose, skin)	25
Bone aspects	
Joint pains	25
Long bone thickening, widening, hyperostosis	18
Extremeties tenderness, aching, swelling	31
Brain and skull change	
Cranial hyperostosis, increased head size	18
Bulging fontanel	51
Elevated CSF pressure, cranial hypertension, pseudotumor cerebri	33
EEG anomalies	5
Headache	56
Calcemia, hyper	13
Diarrhea	11
Edema, face, eye lids, abdomen, leg	20
Fatigue, malaise, lethargy, somnolence, weakness, asthenia	64
Fever	11
Insomnia	11
Irritability	37
Menstrual changes	6
Nausea, vomiting	68
Nervous complications	8
Organ changes	
Hepatomegaly, palpable or tender liver	32
Splenomegaly	11
Skin anomalies	
Mouth or lip fissures or chapping	41
Pruritis, itching	29
Pigmentation	12
Pale, dry or dry scaly	34
Rash, erythema or scaly rash	22
Desquamation, exfoliation, eruption	16
Nails, brittle or soft	7
Thirst, polydipsia	4
Urination, altered pattern	9
Vision	
Diplopia, distorted or blurred vision	27
Papilledma	24
Exophthalmos	10
Conjunctivitis	5
Weight loss	18

* TM = times mentioned

tubular failure, altered micturition and hypercalcemia. Recovery occurred about 12 days after cessation of the vitamin A treatment.

Another instance of a stage between acute and chronic hypervitaminosis A is the well controlled research project of Hillman.[110] In his first test, Hillman consumed 1,000,000 IU of vitamin A in an aqueous emulsion daily for 13 days and 2,000,000 IU on the 14th day. A second test, some five months later, a 25-day series, involved consuming 1,000,000 IU daily. In general, the clinical observations were similar to those reported previously: severe headaches, dizziness, nausea, anorexia, muscle weakness, pain and tenderness over the long bones, thinning of hair, dermatitis, cheilosis, epistaxis, visual disturbances, increased fragility of nails, and alternating constipation and diarrhea. Liver function tests and dark adaptation measurement were not significantly influenced. Clinical responses differed qualitatively and quantitatively in the two treatment periods and were less severe in the second test. Factors influencing the responses may have involved duration of dose, adaptive response, degree of apprehension, weather conditions, and unnoted infections.

Acute hypervitaminoses in infants and children occur quickly and show typical responses. Boniver[111] observed 10 infants and children, ages 9 months to 6 years, with bulging fontanels following single oral doses of 300,000 to 900,000 IU. Marioni and Panizon[112] recorded a group of 22 infants and children ages 6 months to 7 years who developed headaches, bulging and pulsations in the fontanels, nausea, vomiting, anorexia and somnolence following oral doses of 300,000—750,000 IU (with vitamin D). Recovery from symptoms followed 1½ days after cessation of treatment. Marie and See[113] noted a four-month-old boy who developed a bulging fontanel about 12 hours after he had ingested 350,000 IU of vitamin A. The youngster vomited once after drinking and maintained the bulging fontanel the following day and experienced a slight loss of weight. The following day all abnormalities disappeared. The case reported by Hoefer-Janker et al.[114] of a 12-year-old boy also deserves mention. About 22,000,000 IU were administered over a 21-day period, the daily dose intake varying from 300,000 to 1,500,000 IU (in divided doses), as treatment of ichthyosis congenita. Beginning on the ninth day, severe headaches, increased cerebrospinal fluid pressure, desquamation of skin, and a drop in alkaline phosphatase were observed.

The foregoing citation of cases indicates that the ingestion of one to several million or more IU of vitamin A within one-half day in the case of adults, and 300,000 or more IU in children can cause the manifestation of acute hypervitaminosis A. Trials are tabulated where both oil solutions and aqueous dispersions of vitamin A have been orally administered. Oil solutions are better tolerated than aqueous dispersions.

Aqueous dispersions, depending on the specific formulation, are absorbed more rapidly than oil solutions and may accelerate the degree and timing of the manifestations. These general comments are supported by the individual cases discussed and the summary table on acute hypervitaminosis in children based on over 40 literature reports covering 125 cases (Table XIII).

Chronic

Chronic hypervitaminosis A in young children and infants commonly results in anorexia, dry, itchy skin or pruritus, (sometimes a rash), alopecia and coarse hair, intracranial pressure, angular fissures or cracking of lips, irritability, tenderness and swelling of extremities, hyperostosis, hepatomegaly, weight loss or growth failure. Although in adults milder joint and bone pains, less hepatomegaly and more alopecia, skin and nail changes, pigmentation of skin, hemorrhages, occasional menstrual alteration, insomnia, malaise or fatigue occur, symptoms between the two groups are quite similar. Chronic toxicity may occur at any age from an infant two months of age or younger to adults over eighty years of age.

Some unusual cases of chronic hypervitaminosis A are reported in the literature, one of which well illustrates the difficulty experienced by medical practitioners in diagnosing and treating the condition. Gerber and his associates[115] reported an unusual case of a 21-year-old woman who was admitted to five hospitals over nine years before her illness finally was diagnosed as hypervitaminosis A in the sixth hospital.

Initially, when she complained of head-

TABLE XIII
Acute Hypervitaminosis* in Infants and Children (125 Cases)

Reports	Type Product	Daily Dose Vitamin A	Daily Dose Vitamin D	Duration	Age	Cases
(No.)		(IU)	(IU)	(days)	(mo.)	(No.)
1	aqueous	600-900,000	?	1	9-72	10
1	aqueous	700,000	600,000	1	7	1
1	oil	600,000	large	1	3	1
1	?	500,000	500,000	1	36	1
10	7 aqueous 3-?	400,000	600,000	1	1-22	25
12	4-aqueous 8-?	400,000	?	1	1-60	29
1	?	350-500,000	300,000	1	4½-18	8
10	3-aqueous 7-?	350,000	300,000	1	6-36	11
1	aqueous	350,000	?	1	6	1
1	?	300-750,000	?	1	6-84	22
1	aqueous	300-350,000	300,000	1	3-7½	5
1	aqueous	200,000	300,000	1	5-6½	3
1	?	187,000	?	2	4½	1
1	?	150,000	?	1-2	5-6	2
1	?	100-200,000	100-600,000	1	4-6	4

* Reported as hypervitaminosis A but in many instances, the vitamin preparation also contained high levels of vitamin D making it impossible to differentiate between the toxic manifestations of the two vitamins.

aches, double vision and nausea, hospital "A" tentatively diagnosed a brain tumor. Shortly thereafter she signed out of hospital "A" and entered hospital "B" where it was learned for the first time that she had been taking vitamin A in large amounts for 18 months to treat a skin disorder from which she had suffered since childhood. Because of continued evidence of increased pressure within the cranium with no associated signs of tumor, serous meningitis was diagnosed. At hospital "C" her condition was diagnosed as chronic encephalitis. A month later she entered a fourth hospital where her sparse eyebrows, pigmentation of the skin of the abdomen, enlargement of the liver and spleen, anemia, and pain and spasm of the muscles in the low back area were noted. In a readmission to the same hospital an inflammation of the nervous system and of the roots of the sensory nerves leaving the spine was diagnosed. The skin was uniformly hyperpigmented, dry and scaly and itching was a serious complaint. A third admission to hospital "D" elicited several more tentative diagnoses, among them Addison's disease. During this period she had continued to consume 500,000 units of vitamin A per day and this "medication" was administered during her hospital stay as well. She was subsequently discharged from hospital "D" without a clear diagnosis. Five months later she entered hospital "E" with multiple severe joint pains and marked difficulty in walking. Since X-ray studies showed "arthritic" changes of the spine, she was subsequently discharged with a diagnosis of infectious arthritis. During the next five years she was treated by chiropractors and osteopaths without improvement. She continued to consume 500,000 units of vitamin A faithfully each day for eight years.

When at hospital "F" a relationship between her intake of vitamin A and her symptoms was suspected, her fasting vitamin A

blood level proved to be 2,000 μg/dl. Immediately thereafter the patient was admitted to the hospital and all vitamin A medication was stopped. At the end of one month her skin texture had improved and her bone pains were markedly diminished. Within two months spontaneous pain had disappeared and no further sedation was needed. Thereafter, she gained weight and improved steadily until all evidence of vitamin A toxicity had vanished.

Moore[63] cites the case of a three-year-old boy who had taken 250,000 IU of vitamin A daily since infancy. Although biochemical studies indicated a plasma vitamin value of 2,000 μg per dl, the child made a good recovery, and in an examination a year later was judged to be normal.

Another case, reported by Krause[116] concerns a 79-year-old man who had consumed 50,000 IU of vitamin A daily for 17 years, a practice known to his physician, before his death. Thus, the subject consumed a total of 310,000,000 units of vitamin A during this period without developing any signs of hypervitaminosis A. At an autopsy conducted immediately after death, during which the liver was washed free of blood and analyzed, vitamin A concentration was 12,960 IU per g or a total of 17,820,000 IU (5.4 g retinol) in the 1,375 g liver. No blood analyses were made.

An examination of 75 cases of chronic hypervitaminosis A in adults (Table XIV) indicates that the toxic manifestations develop in a shorter period of time when very high levels of vitamin A are consumed than when moderate levels are taken. Daily intakes of 1,000,000 IU or more cause manifestations within days or several weeks, while daily intakes of 400,000 to 700,000 IU give toxic reactions after 1 to 36 months. Daily intakes of 150,000-200,000 IU usually produce signs after 6 to 85 months, while ingestion of 100,000 IU daily yields toxic signs after 6 to 108 months. In most cases of reported hypervitaminosis A the vitamin A intake values cited are obtained only by patient inquiry; hence they should be treated as alleged values.

In children and infants, as previously indicated, continued ingestion of high levels of vitamin A causes such symptoms as anorexia, irritability, headache, and skin lesions. Infants are less tolerant than children. A tabulation (Table XV) of 65 cases of hypervitaminosis A in infants and children shows an amazing tolerance and rate of recovery from hypervitaminotic symptoms of children who have ingested excessively high level vitamin A intakes daily for a major portion of their lives. With discontinuance of high vitamin A dosing given for short periods, the hypervitaminotic symptoms quickly abate. Of the numerous clinical defects and subjective symptoms (23) in prolonged or chronic hypervitaminosis A, those involving bone changes are among the more lasting ones, although permanent bone malformations appear to be relatively rare. Bone abnormalities in children include retarded growth of long bones, long bone thickening (hyperostosis) and premature closure of the epiphyses. Within some months the abnormal roentgenographic signs disappear and recovery seems complete. Other skeletal anomalies such as fractures, short stature and length discrepancies of lower extremities have been observed in patients with chronic hypervitaminosis A.[117,118] Negative calcium balance with increased urinary calcium excretions also has been reported in hypervitaminosis A in human subjects.[38,39] Since toxic levels of vitamin D are usually given together with vitamin A in the cases of chronic hypervitaminosis in children, the effects of excessive vitamin D intakes are difficult to separate from those of hypervitaminosis A (Table XV).

Chronic hypervitaminosis A in children and infants involves intakes of vitamin A varying from about 2,500 to 50,000 IU (7,500-15,000 μg) per kilogram of body weight, with more sensitivity shown by infants. Aqueous preparations seem to induce toxic manifestations more readily than oily preparations.

HYPERCAROTENEMIA OR HYPERCAROTENOSIS

Excessive consumption of carotenoids such as the carotenes and other carotenoid vitamin A precursors does not generate a correspondingly high vitamin A tissue content and does not cause hypervitaminosis A. Two physiological mechanisms protect the body from carotenoid toxicity: a) the efficiency of intestinal absorption falls rapidly and b) the rate of conversion of carotenoids to vitamin A is relatively slow within the body. Thus, although

TABLE XIV
Chronic Hypervitaminosis in Adults (75 Cases)

Type Product	Daily Dose Vitamin A (IU)	Daily Dose Vitamin D (IU)	Duration (Mo)	Age (yrs)	Sex
Aq. Vit. A prep.	3,500,000	no	21 days	31	F
Aq. Vit. A prep.	51,000,000(total)	no	22 days	30	M
Vit. A prep.	75,000,000(total)	?	24 days	31	F
Aq. Vit. A prep.	70-75,000,000(total)	38	38 days	22	M
Aq. Vit. A prep.	1,200,000	no	56 days	36	M
Aq. Vit. A prep.	1,000,000	no	14-21 days	40	M
Vit. A prep.	700,000	?	13	35	M
Vit. A capsules	600-2,000,000	no	18	44	F
Vit. A prep.	600,000	?	36	51	F
Vit. A capsules	600,000	no	18	44	F
Vit. A prep.	600,000	?	12	75	M
Aq. Vit. A prep.	600,000	no	7	17	M
Vit. A troches	600,000	no	35 days	33 F, 69 F, 70 M,	68 F, 75 F, 83 M
Vit. A prep.	600,000+	no	96	28	M
Aq. Vit. A prep.	500,000	no	2	39	F
Vit. A prep.	450,000	?	12	28	F
Multi-Vit. prep.] Vit. A prep.	410,000	?	156 (also liver and carrots)	68	M
Vit. A prep.	400,000	?	6	42	M
Vit. A tablets	75-150,000	?	96] 101½	39	F
	375,000	?	5½		
Aq. Vit. A prep.	300-600,000	no	18	20	F
Vit. A prep.	300-400,000	?	10	17	M
Vit. A prep.	300,000	?	48	24	F
Vit. A prep.	300,000	?	36	15	M
Vit. A prep.	300,000	?	24	19	F
Aq. Vit. A prep.	300,000	no	12+	18	F
Vit. A prep.	300,000	?	12	16	F
Aq. Vit. A prep.	300,000	no	6+	14	M
Aq. Vit. A prep.	300,000	no	6	16	M
Aq. Vit. A prep.	300,000	no	5	46	F
Aq. Vit. A prep.	300,000	no	2	19	F
Vit. A prep.	250,000	?	4½	16	M
Vit. A prep.	240,000	?	6+	31	F
Vit. A prep.	200-300,000	?	12	15	F
Vit. A capsules	200-275,000	no	2	25	M

TABLE XIV
(continued)

Type Product	Daily Dose Vitamin A (IU)	Daily Dose Vitamin D (IU)	Duration (Mo)	Age (yrs)	Sex
Vit. A prep.	200,000	?	96	62	M
Aq. Vit. A prep.	200,000	no	36	21	F
Aq. Vit. A prep.	200,000	no	29	47	M
Vit. A prep.	200,000	?	25	adolescent	F
Vit. A prep.	200,000	?	24	18	M
Vit. A tablet	200,000	no	24	15	F
Vit. A prep.	200,000	?	18	17	M
Vit. A prep.	200,000	?	18	18	F
Vit. A prep.	200,000	?	10	14	F
Vit. A prep.	200,000	?	14 days	14	F
Vit. A capsules	160-130,000	no	7	21	F
Vit. A prep.	150,000	?	12	17	M
Vit. A prep.	150,000	?	12	17	M
Vit. A prep.	150,000	?	85	32	F
Vit. A tablets	150,000	no	48	18	F
Aq. Vit. A prep.	150,000	no	22	16	F
Vit. A prep.	150,000	?	18	20	F
Vit. A prep.	150,000	?	15	adolescent	F
Aq. Vit. A prep.	80,000	?	8] 12	36	F
Multi-Vit. prep.	125,000	?	4]		
Vit. A prep.	100-500,000	?	48	30	M
Aq. Vit. A prep.	100-300,000	no	18	18	F
Vitamin prep.	100-150,000	?	6+	18	F
Vit. A prep.] Multi-Vit. prep.]	100-300,000	?	6	16	M
Vit. A prep.	100,000	?	long time	38	F
Vit. A prep.	100,000	?	108	52	F
Vit. A prep.	100,000	?	42	20	F
Aq. Vit. A prep.	100,000	no	24	15	F
Vit. A prep.	100,000	?	6	41	F
Vit. A prep.	90,000	?	120 also dessicated liver and carrot juice	42	F
Vit. A prep.	90,000	?	48	57	F
Vit. A prep.	90,000	?	48	16	F
Vit. A prep.	75,000	?	24	adult	F
Vit. A prep.	50-5,000,000	?	60	24	M
Vit. A capsules	50-200,000	?	4	16	M

TABLE XV
Chronic Hypervitaminosis in Infants and Children (65 Cases)

Type Product	Daily Dose Vitamin A (IU)	Daily Dose Vitamin D (IU)	Duration (Mo)	Age (Mo)	Sex	IUA/ kg wt**
Vit. A prep.	300-15,000,000	?	21 days	144	M	7500-37,500
Vit. A prep.	600,000 (less amounts earlier)	?	12+	144	M	15,000
Oleum percomorph	500,000+	100,000+	36-50	84	F	22,900
Multi-Vit. drops + Vit. A prep.	463,040	?	1½	72	M	22,200
Cod liver oil + Multi-Vit. drops	400-625,000	40-100,000	54	72	F	25,600
Oleum percomorph	400-600,000	58-88,000	6	12	M	54,300
Oleum percomorph	400-500,000	60-70,000	24	36	F	32,100
Oleum percomorph	400-500,000	60-70,000	12+	16	M	40,200
Cod liver oil + Vit. A & D prep. + Multi-Vit. drops	400,000	60,000	30	36	F	27,500
Vit. A prep.	400,000	?	14	54	F	23,100
Vit. A prep.	347,280	?	24	48	F	21,200
Oleum percomorph	250,000	35,000	20	23	M	20,000-
	500,000	70,000	3			40,000
Oleum percomorph	250,000	35,000	6	84	F	12,300-
	500,000	70,000	¾	6¾		24,600
Vit. A & D prep.	250,000	40,000	5½	18½	M	21,600
Oleum percomorph + Multi-Vit. drops	250,000	35,000	6	15	F	24,200
Oleum percomorph	250,000	34,000	36	36	M	17,000
Oleum percomorph + Vit. D. prep. + Multi-Vit. drops	240,000	60,000	7	17	F	22,400
Oleum percomorph	240,000	35,000	12	36	F	17,100
Oleum percomorph	240,000	35,000	3	28	M	17,900
Oleum percomorph	240,000	34,000	12	36	F	17,100
Fish liver oil	240,000	large	33	36	M	16,300
Vit. A prep.	240,000	?	14 days	144	F	6,000
Oleum percomorph	220,000	32,000	8½	9	F	25,500
Vit. A & D prep.	200-300,000	40-50,000	17	37	M	16,700
Oleum percomorph	200-300,000	29-44,000	9	21	F	21,900
Oleum percomorph	200-300,000	29-44,000	15	32	M	17,700
Vit. A & D prep.	200,000	40,000	8	20	M	16,800
Oleum percomorph	200,000	30,000	27	28	M	14,900
Vit. A & D prep.	185,000	37,500	9	33	F	13,700
Vit. A & D prep.	160,000	3,000	several	84	M	6,900
Oleum percomorph	150,000	22,000	4	24	F	12,500-
	300,000	44,000	2	6		25,000
Oleum percomorph	150,000	22,000	several	25	F	12,300
Multi-Vit. prep.	150,000	15,000	10	18	M	13,000
Aq. Vit. A prep.	150,000	?	24	86	M	6,400
Oleum percomorph + Multi-Vit. drops	125,000	18,000	5	14	M	11,700
Oleum percomorph	120-180,000	17-25,000	many	24	M	11,900

TABLE XV
(continued)

Type Product	Daily Dose Vitamin A (IU)	Daily Dose Vitamin D (IU)	Duration (Mo)	Age (Mo)	Sex	IUA/ kg wt**
Oleum percomorph	100,000+	14,400+	8] 14	15	F	9,700-
Oleum percomorph] Multi-Vit. drops	115,000+	15,600+	6]			11,100
Vit. A & D prep. *] Oleum percomorph] Multi-Vit. drops]	100,000+	20,000+	18	30	M	7,300
Oleum percomorph Di-cal-phos & vit. D	100,000	14,700	7	24	M	7,900
Oleum percomorph Vit. A prep.	100,000+	5-10,000	6	22	M	8,200
Vit. A prep.	100,000	?	14	114	M	3,300
Vit. A & D prep.	85,000	1,500	24	7	M	10,100
Vit. A & D prep.	80,000	16,000	3⅓	7	M	9,500
Oleum percomorph] Multi-Vit. drops]	80,000+	11,000+	2½	6½	F	10,800
Vit. A prep.	75,000	?	3	4	M	11,000
Vit. A prep.	72,000	?	66	84	M	3,100
Vit. A & D prep.	71,500	10-14,000	4	4	M	11,300
Vit. A prep.	65,000	?	4	63	M	3,400
Oleum percomorph	62,500	9,000	21 days	49 days	M	12,500
Vit. A prep.	60,000	40,000	7] 10½	48	F	3,700-
	75,000	40,000	3½]			4,600
Aq. Vit. A & D prep.	60,000	9,000	2	2½	F	12,000
Variety of Supplements	57,000+	1,000	12	30	F	4,400
Multi-Vit. tablets	50-100,000	800-1,600	12	96	M	3,000
Vit. A prep.	50,000	?	4	42	F	2,800
Aq. Vit. A & D prep.	50,000	50,000	6 days	4-5	M	6,900
Aq. Vit. A & D prep.	50,000	10,000	7	15	F	4,900
Aq. Vit. A prep.	42,500	?	2¾	6	M	3,000
Oleum percomorph	37,500	5,400	17	29	F	2,900
Cod liver oil] Multi-Vit. syrup]	30,000	3,000	6	26	F	2,500
Aq. A & D prep.	25,000?	?	9	12	M	2,500
Aq. A & D prep.	22,500	4,500	2	4½	M	2,400
Aq. A & D prep.	22,500	4,500	25 days	4	M	3,750
Aq. A & D prep.	22,500	4,500	2½	5½	M	3,100
	(not measured)					
Aq. A & D prep.	17,500	10,800	3½	4½	F	2,900
Multi-Vit. prep.	12,000	1,200?	7days	infant (2.2kg)		5,500

* Reported as hypervitaminosis A but in many instances, the vitamin preparation also contained high levels of vitamin D making it impossible to differentiate between the toxic manifestations of the two vitamins.

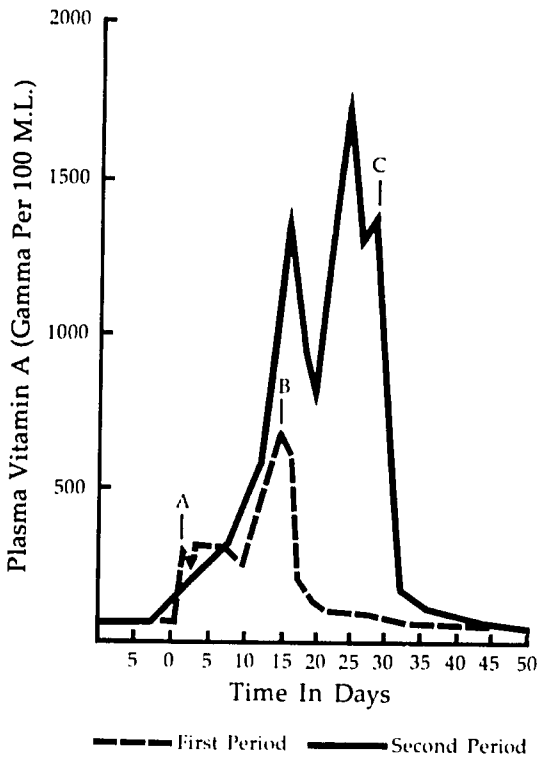
** Calculated value using average weight graphs for reported age.

individuals who consume high levels of carotenoids in pharmacological dosage forms, or as large quantities of red palm oil or green and yellow vegetable or certain yellow fruits, will develop a yellow or orange pigmentation of skin and show high levels of carotenoids in the blood (75-125 μg/dl), these conditions have no effect on health and will slowly disappear following elimination of the carotenoid-containing foods or supplements from the diet.

BIOCHEMICAL ASPECTS OF HYPERVITAMINOSIS A

Vitamin A bound to its carrier protein (RBP) is much less toxic than free vitamin A to organ tissue[119] in *in vitro* culture. The more recent understanding[120,121] of the retinol transport and storage system in hypervitaminosis A has indicated that the capacity of the liver to take up and store orally absorbed retinol and secrete it bound to the carrier, although extensive, is limited.[122] Hypervitaminosis A appears to occur *in vivo* only when the body's intake of vitamin A exceeds the liver's capacity to remove it from the blood stream and store it at a sufficient rate. The resulting contact of membranes and body cells with high concentrations of lipoprotein-bound vitamin A leads to abnormal effects.

FIGURE II
Vitamin A Blood Levels Before and After Ingestion of High Intakes of Vitamin A for a Few Weeks.[110]



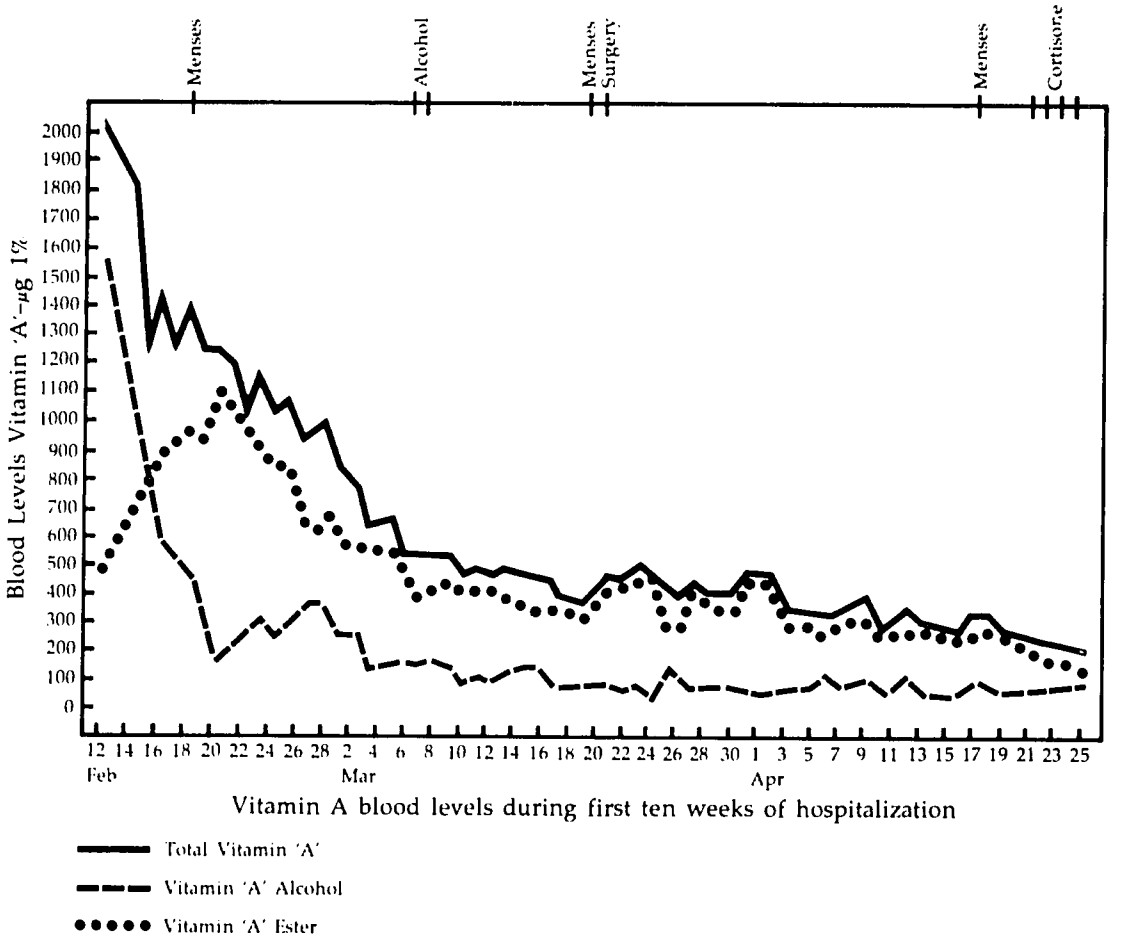
Blood plasma vitamin A levels during two test periods of ingestion (one million units daily*). A. Vitamin A started, both test periods. B. Vitamin A discontinued, first test period. C. Vitamin A discontinued, second test period.

* Two million units on final day, first period only.

Chronic high intakes of vitamin A raise the steady-state serum vitamin A values (Table XII). In the case of Hillman,[110] an adult consuming 15,000,000 and 25,000,000 IU for 13 days and 25 days respectively, the serum vitamin A level approached 700 and 1,800 μg/dl, respectively, as compared to the normal range of 20-80 μg/dl (Figure II). Following cessation of dosing, plasma vitamin A values fell rapidly over a period of a few days. Although in this study the amount of vitamin A ingested correlated with the resultant blood levels, a corresponding correlation between blood levels and clinical manifestations was not observed. The length of convalescence somewhat correlated with the length of consumption. The blood level of vitamin A in chronic hypervitaminosis is similar to that found in acute dosing. In the case reported by Gerber et al.,[115] the serum total vitamin A level of an adult who consumed 500,000 IU daily for eight years fell after the cessation of vitamin intake but not as rapidly as in acute intoxications as described by Hillman. In the early stages of the recovery period retinol fell more rapidly than retinyl esters (Figure III).

In hypervitaminosis A the relative level of retinols and retinyl ester are significant. Smith

FIGURE III
Vitamin A Blood Levels After Cessation of High Intakes of Vitamin A for an Eight Year Period.[115]



and Goodman[123] have examined total vitamin A, retinol, retinyl ester, RBP and prealbumin content of blood plasma in subjects with hypervitaminosis A (Table XVI). In each of the patients, clinical toxicity was associated with increased concentrations of total vitamin A and, more specifically, with markedly increased levels of retinyl esters in plasma. In control subjects of comparable age, the proportion of total vitamin A present as retinyl ester ranged from only 0.1 to 4.7 percent in plasma obtained after a 12-hour fast. In contrast, the initial plasma samples studied in Cases 1 and 2, obtained within four days of the last dose of supplemental vitamin A, showed retinyl esters comprising 67 and 65 percent, respectively, of the total vitamin A present. In Case 3, retinyl esters made up 33 percent of the total vitamin A in the initial sample of plasma, obtained three weeks after the last dose of supplemental vitamin A. The return of plasma retinyl ester concentration to normal levels appears to be an extremely slow process. In Case 3, retinyl esters still represented 10 percent of total plasma vitamin A 286 days after her last known supplemental vitamin A. A similar trend is evident in Figure III.

In contrast to total vitamin A and retinyl ester levels, the concentrations of plasma retinol-binding protein and prealbumin were normal when the patients showed toxic manifestations. In making a diagnosis where hypervitaminosis A is suspected, a blood assay for total vitamin A and determination of the percentage in the retinyl ester form and of retinol-binding protein concentration in plasma, which enable one to calculate the retinol/retinol-binding protein ratio, may be helpful.

Laboratory data, other than altered plasma vitamin A values, gathered from cases of hypervitaminosis A[124] include increased cerebrospinal fluid pressure, anemia, leukopenia and proteinurea. Negative calcium balances and increased urinary calcium excretion have also

TABLE XVI
Plasma Retinol Transport in Vitamin A Toxicity[123]

Case No.	Time Since Last Vitamin A Dosage	Total Vitamin A	Retinol	Vitamin A As Retinyl Ester	RBP	Pre-Albumin	Molar Ratio	
							Total Vitamin A To RBP	Retinol To RBP
	days	*μg.dl*		%	*μg/m*			
1	4	291	96	67	62	226	3.6	1.1
	7	238	80	66	55	220	3.2	1.1
	9	180	75	58	61	305	2.2	0.9
	11	146	69	52	55	237	2.0	0.9
	24	49	34	31	44	185	0.8	0.6
2	3	382	132	65	63	223	4.7	1.5
	7	320	133	58	58	325	4.0	1.7
	13	152	77	49	63	312	1.8	0.9
	18	100	55	45	54	355	1.3	0.7
	42	105	55	48	83	155	0.9	0.4
3	21	128	76	41	46	310	2.0	1.3
	28	81	67	17	107	530	0.5	0.5
	77	58	47	19	130	247	0.3	0.3
	286	62	56	10	74	233	0.7	0.6
Normal controls	—	50.1 ± 31.3†	—	1.6 ± 3.0‡ (range 0.1-4.7)	46.2 ± 20.9†	250 ± 104†	0.82 ± 0.63† (range 0.40-1.62)	—

*Retinol-binding protein. †Mean ± 2 SD values in 109 cases previously reported. ‡Mean ± 2 SD for 14 control subjects 3-23 yr of age.

been observed and may be associated with hypercalcemia. In some cases calcium appears to be excessively mobilized from the skeleton by action of vitamin A on bone. In other cases assessment of the relation between hypervitaminosis A and hypervitaminosis D is difficult because vitamin D also was ingested at high levels. Hyperlipidemia has also been noted on occasions.

While bilirubin, cephalin flocculation, cholesterol, thymol turbidity tests and blood sedimentation values may change in hypervitaminosis A, they do not appear to be dependable criteria based on present data evaluation. Nor do dark adaptation measurement and ophthalmologic examination correlate with hypervitaminosis A. Hypervitaminosis A may also affect gluconeogenic activity and the activity of some important amino acid metabolizing enzymes in the liver, such as hepatic alanine amino-transferase and tryptophan dehydratase ornithine aminotransferase.[125] This line of endeavor could be further examined.

COMMENTS ON THE HYPERVITAMINOSIS A LITERATURE

Between 300 and 400 published reports exist on hypervitaminosis A in humans. Based on such a large literature the establishment of rigid guidelines for avoiding hypervitaminosis A should be relatively easy.

While the literature is obviously helpful, however, it is deficient in revealing all the desired information. There are short and long reviews on the general topic with warnings; there are reviews of cases observed by others. There are instances of several publications of the same cases by different authors and one instance of a group of authors reporting the same case four different times. There are papers dealing in great detail with a single case and those with too few details on a number of cases.

Several problems arise in evaluating the literature. In many cases of hypervitaminosis A, the diagnosis is made in retrospect. Two major factors responsible for this situation are: a) an inaccurate diagnosis by physicians and b) the reticence of the self-medicating patient or dosing parent to admit the actual intakes. Failure to measure or record the dose is not unusual and estimates are tempered by the quite natural desire not to appear foolish. Since many of the reports on hypervitaminosis A are consequently based, in part, on testimonial information, toxic manifestations are unlikely to have occurred at some of the lower vitamin A intakes reported.

The literature on acute and chronic hypervitaminosis A in children and infants indicates that, in many instances, toxic syndromes involve both vitamins A and D. How does one separate the two? Since vitamin A preparations administered to children (Tables XIII and XV) usually contain vitamin D, both are consumed in excess in high level dosing. Hypervitaminosis D symptoms,[126] summarized in Table XVII, compare similarly with many of those cited for vitamin A in Table XII.

Of all the vitamins, vitamin D causes the most serious toxicity. There are no recorded cases of vitamin D toxicity from exposure to sunlight; however, the ingestion of large amounts of fish liver oil or vitamin D concentrate has been incriminated as a cause of hypervitaminosis D. According to Hayes and Hegsted,[127] the dose range to induce toxicity in children varies from daily doses of 10,000 IU for four months to daily intakes of 200,000 IU for two weeks, with most cases ranging from doses of 25,000 to 60,000 IU per day for 1 to 4 months. As much as 2,000 IU of vitamin D per day have been consumed by many infants without adverse effect, although 400 IU per day is regarded as the safe recommended dose.

Arnrich[24] has considered the interaction of vitamins A and D in hypervitaminosis. The pathological impact of excess vitamin D is related primarily to skeletal tissue and secondarily to soft tissue metastasis. The two vitamins together in excess appear to interact antagonistically. Large doses of vitamin A in rats with hypervitaminosis D reduced hypercalcemia, maintained bone ash concentration and reduced calcium in kidney, heart and lung tissue. In chick studies, three categories of biochemical responses to excess vitamins D and A are apparent: a) responses to both vitamins, in which antagonism is marked as noted in plasma calcium, phosphorus, and acid phosphatases; b) responses to excess vitamin A only, in which lysosomal enzymes in plasma and packed cell volume are altered;

TABLE XVII
Hypervitaminosis D[126]

A. Signs and Symptoms

1. Earlier:

Weakness	Headache	Diarrhea	Bone pain
Fatigue	Nausea	Dry mouth	Metallic taste
Lassitude	Vomiting	Muscle pain	

2. Later:

Polyuria	Weight loss	Pancreatitis	Hyperthermia
Polydipsia	Nocturia	Rhinorrhea	Photophobia
Anorexia	Conjunctivitis	Pruritis	Decreased libido

B. Findings

1. Biochemical
   a. Hypercalcemia
   b. Elevated NPN
   c. Albuminuria
   d. Hypercholesterolemia

2. Morphological
   a. Metastatic calcification of kidneys, blood vessels, myocardium, lungs, skin

3. Hepatochemical
   Increased hepatic cholesterol, lipid

4. Behavioral
   Reduced cognitive function

and c) responses to neither, in which calcium absorption is normal. In children, hypervitaminosis A, particularly of the chronic type, is frequently complicated by high vitamin D intakes, a fact to be considered when viewing manifestations and critical dosage intakes.

The analysis of chronic hypervitaminosis A in adults is complicated by other factors. Tabulation of cases in Table XIV can result in one set of conclusions concerning the particular dosage and duration of intake which produce toxic manifestations. In adults, the simultaneous intake of high doses of vitamin A and D is much less common than in children and infants (Table XV).

In the instances where vitamin A has been administered under the supervision of a physician for the treatment of some medical condition, however, manifestations of hypervitaminosis A were abstract or slight (Table XVIII; 365 cases). This difference, which is probably, but not certainly, due to a more accurate estimate of the vitamin A intake of the patients, would indicate a higher tolerated dosage and duration.

Other limitations of the literature include the poor definition of the vitamin A product used in the study. The type of product, the form of vitamin A (whether an oil solution, aqueous dispersion, tablet or capsule) its potency at the time of ingestion, and whether or not it is combined with other vitamins and/or minerals rarely are described in sufficient detail.

SUGGESTIONS FOR FURTHER RESEARCH

A) Proportion of vitamin A in high level dosing taken up in liver by malnourished versus normal child.

B) Effectiveness and safety of IM dose of vitamin A in malnourished versus normal child.

TABLE XVIII
High-Dose Vitamin A Administration Physician Supervised Studies (365 Cases)

Type Product	Daily Dose Vitamin A* (IU)	Duration	Age (Yrs)	Cases (No.)	Comments (side effects)
Vit. A. Prep.	600,000	several days	18	1	none
Ag. Vit. A Prep.	500,000	2 mos.	39	1	initial headache
Vit. A. Prep.	400,000	2 wks.	34	1	none
Vit. A Tabs.	300-450,000	3-36 mos.	38-83	10	none
Vit. A Prep.	300,000	5-100 days	—	36	none
Vit. A. Prep.	300,000	several mos.	40-76	5	none
Vit. A. Prep.	300,000 200,000	6 1 7 (yrs)	43	1	none
Vit. A. Prep.	200-300,000	6-7 wks.	30	2	none
Vit. A Prep.	200,000	2-11 mos.	15-36	27	none
Vit. A. Prep.	200,000	6 mos.	adults	65	none
Vit. A. Prep.	200,000	3 mos.	17	1	none
Fish Oil Conc.	200,000	14 days	41	1	none
Vit. A. Prep.	200,000 50,000	64 4 68 (mos)	26	1	none
Vit. A Prep.	150,000	18 mos.	75-81	11	none
Vit. A Prep.	150,000	12 wks	14-21	42	none
Vit. A Oil Prep.	150,000	67 days	6-10	2	rise in serum vitamin A
Fish Oil Conc.	145,000	3-12 wks.	21-66	5	rise in serum vitamin A
Vit. A Tabs.	150,000	30 days	adults	10	none
Vit. A. Prep.	100,000	12-18 mos.	adults	—	rise in serum A, E & cholesterol phospholipids
Vit. A Prep.	100,000	9 mos.	18-26	35	none
Vit. A Prep.	100,000	4-5 mos.	adults	1	none
Vit. A Prep.	100,000	4-5 mos.	adult	1	none
Vit. A. Tabs.	90-180,000	5-12 mos.	18-26	27	1 with stomach upset, 1 with anorexia
Vit. A. Prep.	50-300,000	8-50 wks.	—	64	none
Vit. A Prep.	50-100,000	8 mos.	50	1	none
Vit. A Prep.	50,000	204 mos.	79	1	none
Ag. Vit. A Prep.	10-400,000	12-33 days	5-80	14	none

*Level of vitamin A administration given in clinical applications.

C) Value of co-administration of additives (antioxidants, etc.) and vitamin A in high level dosing.

D) Influence of vitamin E and/or vitamin K deficiency on hypervitaminosis A.

E) Better definition of biochemical factors such as retinol, retinyl ester and RBP levels and serum ratios in hypervitaminosis A.

F) Status of vitamin A nutrition, particularly hypervitaminosis A, on glycoprotein synthesis and enzymatic activity in cellular breakdown.

G) Better understanding of vitamin A transport system and cellular damage in hypervitaminosis A.

H) Vitamin A supplementation in pregnancy and lactation.

I) Clarification of the extent to which vitamin D has contributed to reported cases of vitamin A toxicity.

GLOSSARY OF TERMS

Vitamin A: Generic term applied to all compounds having vitamin A activity in biological systems. When specific quantities are discussed in the report, such chemical terms as "retinol" and "β-carotene" are employed.

Retinol: Vitamin A (alcohol). Retinol is also used in the report to include retinyl esters (vitamin A esters), provided that the retinol constituent is considered.

Carotene: Provitamin A. The report assumes that other naturally occurring vitamin A-active carotenoids will be included quantitatively on the basis that they have one half of the biological activity of β-carotene.

International Unit (IU): 0.3 μg retinol (0.344 μg retinyl acetate or 0.55 μg retinyl palmitate), 0.6 μg of β-carotene or 1.2 μg of other vitamin A-active carotenoids.

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