Vitamin A was chemically identified in 1931 and synthesized in 1947, but the multiple effects of this vitamin are only now being recognized. The term vitamin A is used for each molecule showing the same structure or biological activity as the basic trans retinol molecule. The term provitamin A is used for all carotenoids showing the same biological activity as that of vitamin A.

An insufficient dietary vitamin A supply is considered as the primary cause of blindness in the world and is, therefore, a major public health problem. Blindness has dramatic consequences not only for the individual, but also for the entire population. Several million persons are also affected by a moderate vitamin A deficiency, considered as directly responsible for increased infant morbidity and mortality.

EPIDEMIOLOGICAL DATA

Vitamin A deficiency is associated with underdevelopment, and is generally observed in the poorest, least educated social classes. In terms of the overall population, socioeconomic development is a good indicator of vitamin A supply. Vitamin A deficiency is frequently concomitant with protein-energy malnutrition. In the absence of clinical symptoms of xerophthalmia, and according to WHO criteria [1], vitamin A deficiency is considered as a serious public health problem when more than 5% of children have a plasma vitamin A concentration of less than 10 μg/dl.

Based on surveys over the last ten years, it is possible to draw a world map of countries in which xerophthalmia constitutes a serious public health problem [2]. In more than 37 countries, enough data is available to confirm the existence of xerophthalmia. The problem is sometimes limited to defined areas of a country, as

Key Words: vitamin A deficiency, cell-mediated immunity, humoral immunity, resistance to infections

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is the case in some African countries where ecological and climatic conditions are very different in the north and south. In other countries, where xerophthalmia is widespread, the prevalence may vary significantly between the different areas (in Indonesia and India, for instance). The area of Asia situated between Afghanistan and the Philippines, the Sahal and Eastern Africa, Central America and northeast of Brazil represent the regions most affected by xerophthalmia. In addition, in a number of other countries in which direct evidence based on official studies is not available, there are strong signs that vitamin A deficiency and xerophthalmia represent significant public health problems. The total number of subjects suffering from vitamin A deficiency is not precisely known. Nonetheless, if a global projection were to be made on the basis of estimates for Bangladesh, India, Indonesia, and the Philippines, this would exceed 500,000 new cases annually of active corneal lesions, and 6 to 7 million cases of non-corneal xerophthalmia [2]. These are conservative estimates; they do not include other children who do not present active signs of xerophthalmia and vitamin A depletion, a condition associated with decreased resistance to infectious diseases and increased morbidity and mortality [1, 3, 4].

ASSOCIATION BETWEEN VITAMIN A DEFICIENCY, PROTEIN-ENERGY MALNUTRITION, AND INFECTIONS

Ocular lesions due to vitamin A deficiency are often associated with protein-energy malnutrition in children. It has been clearly demonstrated that mortality rates after keratomalacia were higher in severely undernourished children. The younger the child, the higher the mortality rates. Protein-energy deficiency in itself decreases vitamin A and carotenoid absorption. It may also reduce the transformation of carotene and carotenoids into vitamin A [5]. During malnutrition, and especially in kwashiorkor, decreases in plasma retinol, retinol binding protein, and prealbumin concentrations are generally noted. These biochemical parameters are usually normalized with a protein- and energy-rich diet, even without vitamin A supplementation [6].

Malnutrition is frequently associated with infection, which has deleterious effects on vitamin A absorption. Infectious diseases, especially measles, and gastrointestinal, respiratory, and urinary infections bring on xerophthalmia in children having depleted or inexistant hepatic vitamin A stores. Numerous cases of xerophthalmia have been observed after diarrhea or respiratory infectious episodes. Anorexia, and thus a decreased vitamin A supply, is common in several infections, and is especially severe in measles.

VITAMIN A METABOLISM AND FUNCTION

Biochemical aspects

The term "vitamin A" is employed for all derivatives, except carotenoids, that
possess a biological activity similar to that of the basic molecule trans-retinol (or retinol). The term "provitamin A" is used for all carotenoids that possess a biological activity comparable to that of vitamin A. The most important carotenoid is trans-beta carotene.

Sources

The major form of vitamin A present in foods is retinyl esters. These esters are found only in animal foods such as liver, milk, butter, cheese, eggs, and fish. Provitamins (carotenoids) are found in fruits and vegetables. Some green leafy vegetables (spinach, green cabbage, cassava leaves) and yellow-orange vegetables (carrot, squash) and fruits (apricot, papaya, mango) are particularly rich in beta-carotene [7]. Food concentrations depend upon conservation and cooking methods.

Units

Preformed vitamin A and carotenoids in food or meals are conventionally expressed in terms of micrograms of retinol. To provide a basis for describing the vitamin A activities of carotenoids and retinol on a common basis, the joint FAO/WHO expert group [8] introduced the concept of the "retinol equivalent" (RE), which established the following relationships among dietary sources of vitamin A:

\[ 1 \mu g \text{ retinol} = 1.0 \text{ RE}; \quad 1 \mu g \text{ beta-carotene} = 0.167 \text{ RE}; \quad 1 \mu g \text{ other provitamin A carotenoids} = 0.084 \text{ RE}. \]

In food composition tables, international units (IU) are often used. One IU of retinol represents 0.3 \( \mu g \) of retinol, whereas one IU of beta-carotene equals 0.6 \( \mu g \) beta-carotene. The following formula is commonly employed to evaluate the total amount of RE in a meal or diet:

\[ \text{RE} = \mu g \text{ retinol} + \mu g \text{ beta-carotene}/6 + \mu g \text{ other carotenoids}/12. \]

Vitamin A needs

Recommended dietary allowances are meant to cover the needs of 97.5% of the population. They have recently been reviewed by FAO and WHO [2]. Taking into account age and sex differences, mean human needs are around 450–500 RE daily per capita. They are probably greater in developing countries because of the younger demographic structure. Vitamin A availability varies among the different countries, and is greatly influenced by socioeconomic development. The worldwide availability of vitamin A for human consumption is approximately 220 \( \mu g \) of preformed retinol per person per day, and 3,000 \( \mu g \) of carotenoids per person per day, a total of more than 700 RE. However, these figures should be considered as referring to vitamin A that is supplied, rather than consumed, since losses usually occur during food storage and processing, both industrially and in the home. In all countries in which there is a marked difference between seasons, the vitamin A supply may be sharply reduced during the dry season, becoming one-fourth that of normal.
Vitamin A hepatic stores in babies are low (10 to 40 μg/g liver); babies thus represent a group at risk for vitamin A deficiency. Babies born with limited vitamin A stores are highly dependent upon maternal milk. If the mother is deficient in vitamin A, then infant stores and the maternal milk supply will be reduced.

Metabolism

Absorption. A standard diet supplies vitamin A derivatives (mainly retinol ester forms) and provitamins (mainly beta-carotene). These components are liposoluble and undergo the successive effects of gastric and/or pancreatic and intestinal secretions. Retinol esters are hydrolyzed by biliary-salt-activated enzymes, and are absorbed by enterocytes. Retinol is esterified once again inside the intestinal cell and then incorporated into chylomicrons which finally enter into the general circulation. Provitamin A is directly absorbed and hydrolyzed into retinaldehyde inside mucosal cells. Retinal is subsequently reduced to retinol, which is then incorporated into the chylomicrons. In normal individuals, 80% of dietary vitamin A component and 50% of provitamin A are absorbed in the intestine [9].

Hepatic stores. In a well-nourished person, the liver contains 90% of total body vitamin A; 40% of the intake is rapidly metabolized and excreted, while the remainder is stored in the liver in the form of retinyl esters. Hepatic palmitate retinol undergoes various transformations that are not yet fully understood.

Plasma transport. Retinol circulates in plasma bound to the retinol binding protein (pRBP). Free RBP (apoRBP) is synthesized in the liver. The retinol-RBP complex is bound to prealbumin as soon as it reaches the plasma [10-13]. At the peripheral level, the complex is recognized by a specific membrane receptor. Retinol enters the target cell while RBP returns to the circulation. Inside the cell, retinol is bound to specific cytoplasmic carriers (cRBP) that carry the molecule to its sites of action [14].

Physiological role

Vitamin A and vision. Adaptation to darkness is a physiochemical process related to the presence of rhodopsin in the retina. This pigment is synthesized from 11-cis retinal arising from rhodopsin decomposition, and from plasma retinol.

Cellular functions. The systemic role of vitamin A is related to growth maintenance, general health and life itself. The molecular basis of this vital function remains unknown. Retinoic acid, issuing from irreversible retinol oxidation, may act directly on genome expression through specific receptors and may play a crucial role in mechanisms of embryogenesis. Retinol may also possess a specific receptor. These essential functions explain the importance of vitamin A in cell regulation and differentiation, and may explain its role in tumor development. Synthesis of certain proteins may thus depend directly upon vitamin A.

Vitamin A and cancer. Results of epidemiological surveys and experimental studies on animals and human populations suggest that nutritional factors may
influence the incidence of tumoral diseases. Vitamin A and beta-carotene exert a protective effect against tumor development. Prospective studies have shown that the previous dietary beta-carotene intake of subjects suffering from pulmonary cancer was lower than that of non-cancerous subjects [15, 16] and that decreased blood retinol levels were correlated with an increased risk of pulmonary or digestive tract cancer [17]. Similarly, the prophylactic effect of vitamin A and its analogues has been demonstrated for several spontaneous or induced animal tumors.

Relationships between vitamin A and other vitamins and oligoelements. Vitamin E, iron, and zinc metabolism are related to that of vitamin A. Vitamin E protects vitamin A from intraluminal and intracellular oxidation, and could play an important cooperative role, along with vitamin A, at the photoreceptor cell level by protecting retinal aldehyde. Vitamin A deficiency creates anemia and hyposideremia, which are not corrected by iron treatment. Zinc deficiency decreases plasma retinol and increases hepatic vitamin A. Zinc can also affect plasma RBP synthesis.

VITAMIN A AND IMMUNITY

Vitamin A deficiency is one of the most synergistic nutritional deficiencies in terms of infectious and parasitic diseases [18, 19]. Intestinal vitamin A absorption is also affected by infectious diseases. A decrease in the plasma vitamin A level during infection, and its rapid normalization thereafter, suggest that vitamin A delivery from hepatic stores and its transport into the plasma may be directly affected by infectious processes [18].

Despite some controversy, most studies suggest that retinoids can modulate several immunological responses both in vivo and in vitro [20].

Vitamin A and infections

It is now well recognized that the simultaneous existence of infectious diseases and vitamin A deficiency significantly contribute to mortality [21], but the importance of vitamin A in the prevention and treatment of infections remains hypothetical.

Animal studies. Several authors [21-25], and a review of 50 experimental studies on vitamin A-deficient animals [19], have reported decreased resistance to infection and increased severity and incidence of viral, bacterial, and parasitic infections in these animals. Retinoid supplementation was shown to have an effect against experimental infections by different microorganisms, including Listeria, Pseudomonas and Candida, in mice pretreated with high doses of palmitate retinyl [26, 27]; the same was true of Angiostrongylus in rats [23] and Newcastle virus in chickens [28, 29].

The plasmatic prealbumin (vitamin A carrier associated with pRBP) concentration markedly decreased during acute inflammation in the rat because of
blocking of synthesis (degradation rate unaffected).

**Human studies.** In agreement with experimental studies, vitamin A deficiency in humans is associated with increased frequency and severity of several infections [30, 31]. A study of 3,000 pre-school children in a rural zone in Indonesia showed that morbidity and mortality risks increased in vitamin A-deficient children [32]. Mortality (respiratory infections, diarrhea) was 3 times higher in children presenting hemeralopy, 7 times higher in those with Bitot's spot, and 9 times higher in those having both symptoms, than in non-vitamin A-deficient children, with or without protein-energy malnutrition. This indicates that the major risk was associated with vitamin A deficiency rather than with generalized nutritional deficiencies.

On the other hand, a single or chronic infection accelerated the depletion of vitamin A stores in non-deficient pre-school children [33, 34]. Serum vitamin A and pRBP concentrations decreased during acute bacterial and viral infections [35], and these levels were normalized during convalescence [36]. The decrease in plasma prealbumin was greater than that of pRBP [37].

In most studies, the causal relationship between retinoid deficiency and infection remains unexplained. A primary factor could be epithelial changes and the resulting reduced mucus production. Indeed, vitamin A plays a crucial role in the maintenance of anatomic barriers. Vitamin A deficiency may increase susceptibility to mucosal infections [38-43] because of defective post-mitotic cellular differentiation of epithelial and mesenchymatous cells; i.e., fiber proteins instead of mucus would be synthesized [44, 45] and this would lead to keratinization and metaplasia of epithelial areas [43].

The second factor that could explain the effect of vitamin A deficiency upon resistance to infection is the alteration in certain immune functions. However, none of the quoted studies reported a defect in humoral or cell-mediated immunity related to vitamin A deficiency. Arguments in favor of an effect of vitamin A deficiency on the immune system are based on macroscopic observations of lymphoid organs and on functional studies of immune cells (lymphocytes and polymorphonuclear cells).

**Vitamin A and lymphoid organs**

Retinoids appear to influence lymph organs, either by decreasing the cell number (at toxic doses) [46] or by increasing it (at subtoxic doses) [47, 48]. Results from animal studies are contradictory and may differ according to the lymph organ studied.

Several authors observed atrophy and diminished cell number of thymus, spleen and other lymphoid tissues during vitamin A deficiency [22, 43, 49, 50]. However, in most of these animal studies, it was difficult to separate the effects of vitamin A deficiency alone from those of more generalized protein-calorie malnutrition.

In other reports, vitamin A deficiency in mice and rats did not affect lymph
organ weight [51-54], except at the late stage of vitamin A deficiency at which cervical and mesenteric lymph node weights increased [52, 53]. The splenic lymphocyte yield (per mg of tissue) decreased in stationary and late stages of deficiency in rats (increased hematopoiesis?); whereas the cervical lymph node cell concentrations increased following the increase in organ weight at the late stage of deficiency; and weight, but not lymphocyte yield, increased in mesenteric lymph nodes. The distribution of T lymphocyte subsets in these organs was not altered.

In mice, increased lymph organ weights (of spleen, thymus and lymph nodes) were observed after 8 weeks of vitamin A-deficient diet. High B lymphocyte and macrophage numbers (without modification of the mature T lymphocyte number) would explain this increased weight [53].

**Vitamin A and cell-mediated immunity**

**Blastogenic responses to T lymphocyte mitogens**

*Animal studies.* Most experimental studies report an alteration in the lymphocyte response to several mitogens in vitamin A-deficient animals. The blastogenic response of circulating lymphocytes decreased in mildly deficient chickens. Severe vitamin A deficiency in these animals increased the number and blastogenic response of circulating lymphocytes; however, concomitant protein-energy malnutrition could represent a confounding factor [49].

Lymphocyte blastogenic transformation after PHA (phytohemagglutinin), ConA (concanavalin A) and LPS (bacterial lipopolysaccharide) stimulation also decreased in the spleen of vitamin A-deficient rats [54], even at early stages of deficiency (arrest of body weight gain) [51]. Responses to PHA and LPS were lowered in the thymus, but this was not the case for the response to ConA, whatever the concentration of the mitogen [51, 55]. Dose-response curves and stimulation kinetics were not altered, and the response was normal in the pair-fed group. Moreover, 3 days of repletion with retinyl acetate corrected the responses, even when the energy and protein supplies were limited [54, 55].

In cervical and mesenteric lymph nodes, the lymphocyte response to mitogenic stimulation was unchanged at the early stage of the deficiency; however, responses to ConA and PWM (pokeweed mitogen) increased at the stationary and late stages of deficiency in cervical lymph nodes, and at the late stage of deficiency only in the mesenteric lymph nodes [52].

High doses of vitamin A may influence the response to mitogens in mice and rats. Beta-carotene given to rats at a high dose (2 mg/kg) for 10 weeks had an immunostimulatory effect, which could be related to its antioxidizing function [56, 57]. Lymphocytes from mice first sensitized to Bacillus Calmette-Guérin (BCG) and then specifically stimulated with PPD (protein-purified derivative), or non-specifically stimulated with PHA (whole T lymphocytes), were significantly more responsive in animals treated with a high dose of vitamin A (3,300 IU, non-toxic dose) than those in controls. Moreover, vitamin A normalized the cell-mediated immune response (and humoral responses) in mice pre-treated with immune
depressors (prednisolone or cyclophosphamide) [58].

Results concerning the in vitro effect of retinoids are controversial, in that lymphocytes were found to be both markedly stimulated [59] or unaffected [46].

**Human studies.** Very few surveys have focused on lymphocyte responses to mitogens in human subjects. The results are in general agreement with those of experimental studies, but more investigation is needed before any conclusions can be drawn.

The numbers of circulating T lymphocytes decreased in vitamin A-deficient children, but their blastogenic response to PHA was normal [60]. Treatment of vitamin A-deficient individuals with retinoids increased lymphocyte reactivity to T-lymphocyte mitogens and to allogeneic lymphocytes. These reactions could implicate the T helper subset, both in the proliferative response and in the induction of cytotoxic lymphocytes.

This hypothesis seemed to be confirmed in the following reciprocal experiment: beta-carotene given orally at a high dose (180 mg/day for 2 weeks) significantly increased the proportion of cytotoxic/suppressor T lymphocytes [61]. Retinoic acid in vitro also increased the proliferative response of human thymic and tonsil lymphocytes after PHA or allogeneic lymphocyte stimulation [62]. The retinoic acid effect appeared to be dose dependent. In the presence of retinoic acid, the circulating lymphocyte response to PHA was increased in one study [63], unaffected in another [62], and inhibited at a high dose of retinol in a third [64]. Splenic lymphocytes were unaffected [62].

**Delayed hypersensitivity**

Delayed hypersensitivity is a good indicator of functional cell-mediated immunity in vivo. However, this parameter has been poorly investigated in vitamin A deficiency.

**Animal studies.** Early vitamin A deficiency in mice (5 weeks of diet; appetite and body weight gain unaffected) decreased the delayed hypersensitivity response to dinitrofluorobenzene (DNFB). The decrease became more pronounced as vitamin A deficiency progressed. No modification in lymphocyte number or distribution could explain the alterations [53].

On the other hand, high doses of retinoids in mice could also influence the hypersensitivity reaction. It was not stimulated in mice receiving intraperitoneal injections of gradually increasing doses of retinoic acid and having been presensitized with sheep red blood cells (SRBC) [46]. But delayed hypersensitivity was stimulated in another study on mice receiving retinyl palmitate or retinoic acid and simultaneously sensitized with SRBC [65]. Retinoids would therefore appear to affect sensitization and induction steps of delayed hypersensitivity, through direct or indirect T-lymphocyte stimulation [65].

**Human studies.** One study on vitamin A-deficient children reported a weaker delayed hypersensitivity reaction to BCG [66].

**Graft rejection, antitumoral activity, and cytotoxic T lymphocytes**

**Graft rejection.** Bearing in mind the potential action of retinoids on cellular
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differentiation and proliferation [67-74], several experimental investigations have
focused on the effects of vitamin A on graft rejection. Studies were not performed
on vitamin A-deficient animals, but rather concerned normal animals receiving
vitamin A, or else were in vitro studies of retinoid effects in cell cultures.

In vivo supplementation of mice with retinyl acetate stimulated the immune
reaction of cutaneous graft rejection, whether the graft was of syngeneic [75, 76]
or allogeneic [77] origin. Oral beta-carotene given to mice for a limited period of
time (2 weeks) at 6 dietary levels (0 to 270 mg/kg) also stimulated allograft
rejection, but this reaction did not occur if beta-carotene was substituted by
retinoic acid [47].

The mechanism of action of retinoids on graft rejection is controversial. Enhanced
rejection might be caused by direct cytotoxicity rather than by stimulation
of cell-mediated immunity: mice treated with retinoids did not seem to express
immunological memory [76]. Alternatively, retinoids may stimulate cytotoxic T
lymphocytes starting with the primary reaction, and may play a role in induction
of suppressor T cells starting with the secondary reaction. Retinoic acid appears to
have no effect upon the effector step of cell-mediated cytotoxicity [46, 61, 78] but
stimulates the induction step of cytotoxic T cells. The vitamin would thus act prior
to rather than during the sensitization step of cell-mediated immunity.

In vivo or in vitro retinoic acid effects appear to be antigen dependent. This
does not indicate non-specific stimulation or polyclonal activation of cytotoxic T
cells, but true adjuvant action [79].

Antitumoral activity, and cytotoxic T lymphocytes. Retinoids in vivo were
shown to prevent induction or growth of chemically induced tumors [80-82].
Retinoic acid in mice stimulated cytotoxic T lymphocytes rather than natural
killer (NK) cell activity [83, 84]. Retinoids might immunologically control the
neoplastic stages and these cells would then be eliminated; thus, retinoids might
directly affect pre-neoplastic cells.

Vitamin A and humoral immunity

Vitamin A deficiency in humans would seem to have little effect on the
specific antibody response, though this has not been confirmed in animal experi-
ments [85].

Animal studies. Experimental studies on vitamin A-deficient animals sensi-
tized with different antigens reported decreased antibody responses [59, 86]. This
was observed in vitamin A-deficient rats immunized against Salmonella pullorum
[87], diphtheria, and human red blood cells [86, 88]. It was also the case when
vitamin A-deficient rats sensitized with SRBC, tetanus or diphtheria were com-
pared with pair-fed controls [50].

Other studies on vitamin A-deficient rats, rabbits, and pigs reported increased
total serum immunoglobulins [89, 90] and decreased serum antibody responses
against specific antigens [86, 88-93]. Treatment with retinol restored normal
immunoglobulin levels [90]. The intestinal secretary IgA level and intestinal
antibody responses were low in vitamin A-deficient rats, whereas serum antibody production was normal [94].

Five weeks of a vitamin A-deficient diet in mice significantly depressed the serum IgM response to hemocyanin antigen [53]. This alteration could be explained by a decrease in the number of IgM-producing B lymphocytes, rather than by a decrease in the secretory rate of IgM per cell. The low B-lymphocyte content in the spleens of vitamin A-deficient animals would favor this hypothesis [51]. However, vitamin A could also play a role in immunoglobulin biosynthesis [95].

On the other hand, healthy animals supplemented with retinol, palmitate retinyl, or retinoic acid produced higher antibody titers after immunization with soluble or particle antigens than non-supplemented controls [26, 94, 96-101].

Adult mice vaccinated against tetanus or BCG and injected intramuscularly with vitamin A (3,300 IU) 6 days later produced higher antibody titers than non-treated mice. When mice were immunodepressed 7 days after vaccination, vitamin A administered on the 6th day partially prevented suppression of antibody production [58]. These results are in accordance with those of several investigators: slightly increasing the dietary level of vitamin A stimulated the antigen-specific antibody response [98, 100-103].

The stimulatory effect of retinoids upon secondary IgG and IgE responses, in contrast to that upon primary antibody responses (which remained essentially unaffected), appears to be adjuvant-like [97, 102, 103]. This concept is supported by a possible action of retinoids on B lymphocytes [104]. However, the vitamin A stimulation of antibody production would be greater with T-dependent than with T-independent antigens [105]. One study on mice reported antibody titers proportional to vitamin A doses, but these were toxic levels when extrapolated to humans [106]. Subtoxic doses may sometimes be necessary in order to obtain immunostimulatory effects [107].

Finally, vitamin A and its analogues can stimulate the humoral response in normal animals; however, some questions remain unanswered: (1) Which are the target cell, B and/or T lymphocytes or polymorphonuclear cells? Vitamin A may influence T lymphocytes that cooperate with B cells, and this would explain the effect of retinoids upon humoral immunity [108]. Recently, Buck et al. [109] found that human cells are critically dependent for optimal growth in cell culture on an external supply of retinol. (2) Is the stimulatory effect similar for the three vitamin A analogues? The hypothetical adjuvant effects of vitamin A appear to be stronger with the alcohol form than with the acid, aldehyde and ester forms [58].

**Human studies.** Observations of humoral function in vitamin A-deficient children contradict those reported in experimental studies. Indeed, in two surveys, vitamin A-deficient children had normal circulating B lymphocytes, immunoglobulin levels, and antibody production after vaccination against tetanus or diphtheria [110]. Intramuscular injection of 200,000 IU of retinyl palmitate into vitamin A-deficient children in Bangladesh did not increase the immune response to tetanus, nor the intradermal reaction to tuberculin or *Molinia* extract [106].
However, it is difficult to verify the existence of past or recent infections in human studies. This could explain the "high" reactivity of some vitamin A-deficient children in the surveys quoted.

**Vitamin A and complement**

Few studies have attempted to relate vitamin A status to complement levels or activity, and the results are controversial. In one animal study (in rats), vitamin A deficiency was associated with a reduction in complement level and activity [41], but this was not confirmed in another study [111]. The properdine level (factor P) would appear to decrease in vitamin A deficiency states, and retinol may play a crucial role in the maintenance of an adequate non-specific opsonin concentration in the serum [85].

**Comments.** The controversial results concerning the effects of retinoids upon humoral and cell-mediated immunity may be explained by the fact that the time, doses, and pathway of administration of these components all are of crucial importance in subsequent stimulating or inhibiting effects [107]. Moreover, stimulating or inhibiting effects observed *in vitro* are not always found *in vivo* [46]. The effects of retinoids upon a lymphocyte population are not necessarily reproducible in a population from a distinct organ or from another individual to another.

One well-known role of vitamin A is in glycoprotein synthesis [112]. These proteins are constituents of cell membranes and participate in several functions that may be altered during vitamin A deficiency [69, 113-116]. The hypothesis for the mode of action of vitamin A is based on this observation: glycoproteins represent important cellular receptors for numerous biological effectors, in particular mitogens and recognition molecules that determine lymphocyte distribution in lymph nodes and spleen [117-119]. It has been chemically proven that these glycoproteins cover T- and B-lymphocyte membranes [120]. Lymphocyte treatment with a glycosidase, trypsin or neuraminidase before intravenous transfusion significantly alters the normal mode of circulation of these cells [117-119]. In rats, for example, the redistribution of some lymphocyte subpopulations could deplete splenic lymphocytes which respond to ConA, PHA or LPS and reveal the existence of a suppressor T lymphocyte population responsible for the inhibited blastogenic response [51].

Alteration of membrane lymphocyte receptor synthesis and redistribution of lymphocyte populations are not mutually exclusive hypotheses: the former has consequences in terms of the latter [117-119]. Numerous authors support the alternative hypothesis of a vitamin A effect on lysosomal membranes [77, 121-123]: the enzymes would be delivered in the presence of an excess of vitamin A [123-131].

Finally, a recent study on mice placed emphasis on a stimulating effect of vitamin A on undifferentiated immunoblasts [58].

**Vitamin A and polymorphonuclear cell functions**

Several experimental and human studies have been performed in situations of
vitamin A excess or deficiency.

Animal studies. The number of adherent cells decreased in peritoneal exudates from vitamin A-deficient rats [50] and phagocytic activity decreased [132]. However, 5 weeks of dietary vitamin A deficiency in mice did not alter the macrophage proportion in lymph nodes or spleen. Their absolute number was slightly increased compared with that of non-deficient mice. After 8 weeks of diet, vitamin A deficiency was coupled with inanition, and there was a clear increase in splenic macrophage number [53].

In another study, vitamin A increased bactericidal cell activity toward *Listeria monocytogenes* [26]. Oral retinoic acid and retinyl palmitate stimulated peritoneal macrophages in aged mice [133].

Human studies. Two surveys have been performed on vitamin A-deficient children. They reported decreased phagocytic and bactericidal activities [109, 134]. The amount of lysozyme delivered in secretions was reduced [41, 135] as was the amount in lymphocytes [134, 136] from vitamin A-deficient children.

Likewise, vitamin A inhibited interferon-induced monocyte-receptor expression. Beta-carotene had the opposite effect and stimulated the effects of interferon [137, 138].

Results reported in both animal and human studies require further research in order to clarify the influence of vitamin A on polymorphonuclear cell function. The nitroblue tetrazolium (NBT) reduction test has not yet been studied, but is a good indicator of hexose monophosphate shunt activity. No controlled studies of bactericidal capacity against different microorganisms have yet been carried out.

**Vitamin A, NK cells, and LAK cell activity**

Based on a review of the literature, only two studies pointed out the effect of vitamin A on NK cell activity. They observed that vitamin A [139] and beta-carotene [140] stimulated NK cell activity. An enhancement in both *in vitro* and *in vivo* killer T-lymphocyte function and cell-mediated cytotoxicity has been shown as a result of retinoid treatment [46, 84, 141]. Recently, interleukin 2-induced LAK cell activity was demonstrated to be enhanced by retinoic acid [142].

**Vitamin A and lymphokines**

No studies exist on the relationship between vitamin A and lymphokines in deficiency states.

Mice fed a retinyl-acetate-supplemented diet had an increased proportion of interleukin 2-producing T lymphocytes [142]. Retinoids could stimulate cell-mediated immunity by increasing T helper proliferation and/or interleukin 2 (IL-2) production.

However, in humans, retinoic acid did not seem to exert any effect upon IL-2 production by activated T lymphocytes [143]. Retinoic acid inhibits the interferon secretion from PHA-stimulated human peripheral lymphocytes [63, 144].
CONCLUSIONS

Vitamin A plays a crucial role in several immunological mechanisms. The preventive action of retinoids upon tumoral growth and graft rejection have stimulated research on these immunological processes in situations of vitamin A repletion or excess.

Elsewhere the extent of mild or severe vitamin A deficiency throughout the world points out the role of vitamin A in resistance to infections. Vitamin A deficiency in animals is associated with decreased resistance to infections and alterations in cell-mediated and humoral immunity. Some differences have been reported, depending on the organ and duration of deficiency.

Most of these results have been confirmed in humans, but fewer surveys are available and the parameters are more difficult to control because of the presence of concomitant confusing factors.

Some immunological functions have been poorly investigated in relation to vitamin A deficiency; these include polymorphonuclear cell capacities and lymphokine production, both of which intervene in specific and non-specific defense mechanisms.

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