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# VITAMIN A, INFECTION, AND IMMUNE FUNCTION*

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■ **Abstract** In populations where vitamin A availability from food is low, infectious diseases can precipitate vitamin A deficiency by decreasing intake, decreasing absorption, and increasing excretion. Infectious diseases that induce the acute-phase response also impair the assessment of vitamin A status by transiently depressing serum retinol concentrations. Vitamin A deficiency impairs innate immunity by impeding normal regeneration of mucosal barriers damaged by infection, and by diminishing the function of neutrophils, macrophages, and natural killer cells. Vitamin A is also required for adaptive immunity and plays a role in the development of both T-helper (Th) cells and B-cells. In particular, vitamin A deficiency diminishes antibody-mediated responses directed by Th2 cells, although some aspects of Th1-mediated immunity are also diminished. These changes in mucosal epithelial regeneration and immune function presumably account for the increased mortality seen in vitamin A–deficient infants, young children, and pregnant women in many areas of the world today.

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## INTRODUCTION

Physicians and nutritionists have long known that malnutrition increases the severity of infection and that serious or repeated infections increase the risk of malnutrition (91). This is certainly true of vitamin A. In 1928, not long after its identification (62, 74), vitamin A was termed "the anti-infective vitamin" (43). This description was not entirely accurate, however, as more recent work has shown that vitamin A does more to enhance recovery from infection than it does to prevent infection in the first place. Perhaps in recognition of this fact, the therapeutic use of vitamin A became an area of great research interest during the 1930s (for a review, see 94). The advent of antibiotics in the 1940s dampened interest in this area for many years, but interest was rekindled in the 1980s, when the critical role of vitamin A in preventing mortality from infectious diseases was demonstrated anew in clinical and community studies (51, 111). Mechanistic research on the role of vitamin A at the cellular and molecular level also received a substantial boost in the 1980s, when the nuclear receptors for the vitamin A metabolites all-*trans* and 9-*cis* retinoic acid (RA) were discovered (41a, 59, 76). These receptors regulate gene transcription and include the RA receptors (RAR) $-\alpha$, $-\beta$, and $-\gamma$, and the retinoid X receptors (RXR) $-\alpha$, $-\beta$, and $-\gamma$. Thus, the decade of the 1990s was incredibly productive for both public health nutritionists and molecular biologists working on vitamin A.

This review presents an overview of the infection-malnutrition cycle as it applies to vitamin A. As this review is brief, it cannot cover all the relevant research of the past decade. This should not be a shortcoming, however, because many recent review articles (37, 88, 89, 118, 130, 138), as well as the proceedings of a symposium (53) and a comprehensive book covering the health effects of vitamin A deficiency (113), have been published in the past several years.



## INFECTIOUS DISEASE AND VITAMIN A STATUS

### Infectious Diseases Impair Vitamin A Status

Clinicians have long known that preschool age children presenting with xerophthalmia (the ocular disease caused by vitamin A deficiency) often have a concurrent infection or a history of recent infection. Diarrhea, pneumonia, and, in particular, measles are commonly seen preceding or presenting with xerophthalmia (113). This association of xerophthalmia with a history of infection has also been seen in retrospective, case-control studies among pregnant women (24) as well as in prospective, observational studies of children (112). A follow-up of Bangladeshi

children who received vitamin A supplements demonstrated that a high incidence of respiratory infection was associated with a failure of the supplements to improve vitamin A status [as assessed by the relative dose-response (RDR) test] just one month after supplementation (80). Similar observations have been made for chickenpox (16). Finally, direct measurement of tissue vitamin A levels in animal studies have shown that acute viral infections can deplete liver vitamin A stores (133). It is thus evident that severe or recurrent infections can lead to the development of vitamin A deficiency, at least in subjects who have a low-to-marginal intake of vitamin A in the first place.

How might infections cause vitamin A deficiency? In general, a micronutrient deficiency may be produced by infectious diseases in five ways: first, by decreasing food intake (anorexia); second, by impairing nutrient absorption; third, by causing direct nutrient losses; fourth, by increasing metabolic requirements or catabolic losses; and fifth, by impairing utilization (e.g. by impairing transport to target tissues) (47, 61, 110). The first three mechanisms certainly affect vitamin A status, although the latter two are not known to be important. These five pathways to deficiency are illustrated in Figure 1.



## Mechanisms

***Decreased Intake*** Acute infections cause anorexia, thus decreasing nutrient intake. In a community study in Guatemala, children with acute respiratory infections or diarrhea consumed 8% and 18% fewer calories per day, respectively, than did asymptomatic children (60). More severe infections have a greater impact on intake. Thus, Kenyan children with severe measles consumed 75% fewer calories when ill than they did after recovery (33). It is important to note that intake of breast milk (a good source of vitamin A) is not diminished by infection. Although total energy intake from non–breast milk sources in a cohort of Peruvian infants decreased by 20%–30% when they had diarrhea or fever, no measurable decrease was seen in breast milk intake (14).

***Malabsorption*** Enteric infections, such as diarrhea and gut helminth infections, directly affect the integrity, morphology, and function of the absorptive mucosa of the intestine and thus may cause malabsorption of vitamin A (61, 110). Impaired digestion and direct competition by parasites may also decrease the availability of some nutrients. It is thus not surprising that infection with the gut helminth *Ascaris lumbricoides* increased the risk of having xerophthalmia in a Nepali case-control study (30). A prospective community study in Indonesia found that diarrhea increases the risk of xerophthalmia (112) whereas a retrospective study in Peru showed that children with longer episodes of diarrhea have lower serum retinol concentrations, which suggests that liver stores may be depleted by infection (3) (although the depressive effect of infection on serum retinol concentration complicates this interpretation, as discussed below). In addition, a recent study found decreased vitamin A absorption in rats with lactose-induced diarrhea, a model of

chronic diarrhea in children. The apparent absorption [(intake-fecal loss)/intake] in controls was 90%, compared with 40%–80% in the diarrhea group over the 3-week study period (57). This is a substantial decrease and is similar in magnitude to that seen in isotopic studies, which found that uninfected Indian children absorb 99% of a tracer dose of vitamin A whereas children with diarrhea and *Ascaris* infection absorb 70% and 80%, respectively (106, 107). However, at least one recent study from Bangladesh has shown that intensity of *Ascaris* infection is not associated with impaired vitamin A absorption (using fecal loss as an indicator of absorption) (2), although uninfected controls were not examined. This negative result may also be due to the lower intensity of infection in these study subjects compared with subjects in the earlier study (107). If ascariasis can lead to vitamin A malabsorption, then one would suppose that treating ascariasis should improve vitamin A status. However, a recent study found that treatment of ascariasis did not improve vitamin A status unless supplemental vitamin A was also administered (123). This negative result may not be surprising, as the short time period between deworming and assessment of status (4 weeks) may not have allowed significant increases in vitamin A stores from the unsupplemented diet.



***Direct Loss*** Even after nutrients are absorbed they may still be lost in sweat, vomit, stool, or urine. Vitamin A losses from the first two routes are probably negligible. Loss into the stool can occur during enteric infections that damage the gut mucosa. Such losses may be most pronounced in postmeasles *Shigella* dysentery because of the development of protein-losing enteropathy (90), or during hookworm infection, which causes significant blood loss. However, the amount of vitamin A lost via such routes is probably small. For example, an adult hookworm can cause a loss of up to 0.30 ml of blood/day (49). Even in a heavy hookworm infection (10 adults), this would result in a loss of $<0.003$ $\mu$mol of retinol/day (with serum retinol of 1.0 $\mu$mol/liter), or $<1\%$ of the US recommended dietary allowance for a young child. Urinary retinol losses during severe infection, on the other hand, can be substantial. Adults in intensive care with pneumonia and sepsis lose up to 10 $\mu$mol/day, or nearly three times the recommended dietary allowance, whereas healthy adults lose $<1\%$ of the recommended dietary allowance per day (116). The magnitude of urinary retinol loss is strongly associated with fever and severity of disease. Although children with mild, afebrile infections typically lose little vitamin A in the urine, Bangladeshi children with watery diarrhea, dysentery, pneumonia, or sepsis had maximum observed retinol losses of 0.18, 0.63, 0.38, and 0.60 $\mu$mol/day, respectively, giving maximum estimated losses for each episode (of 10 days estimated duration) of 1.8, 6.3, 3.8, and 6.0 $\mu$mol. In a 2-year-old boy with nearly depleted liver stores (8.6 $\mu$mol), the loss of 6.3 $\mu$mol would represent 73% of reserves (65), indicating that an episode of severe infection could precipitate an episode of xerophthalmia in a child with minimal vitamin A reserves. A principal cause of this urinary retinol loss is impaired tubular reabsorption of low-molecular-weight proteins, including retinol binding protein (RBP) (64), the principal serum transport protein for retinol. Such proteins normally pass from the glomerular capillaries into the collecting tubules and are reabsorbed by the proximal tubular

epithelium, as shown in Figure 2. This process is disrupted during febrile episodes when RBP and other low-molecular-weight proteins are lost in the urine. Because most RBP in the blood is normally retained in the serum by its noncovalent association with transthyretin (TTR), a disruption in this association, or decreased TTR production during the acute-phase response (APR), may also contribute to this loss in the most severe cases. Fortunately, children receiving high-dose vitamin A supplements during infection do not have substantially higher urinary retinol losses than do children not receiving vitamin A (C Stephensen, H Hernandez, & LM Franchi, unpublished observations).



***Increased Requirement*** Some nutrient requirements may be increased during infection but this has not been well documented for vitamin A. It is possible, however, that metabolically active tissues that require vitamin A (e.g. lymphoid tissue) may have increased turnover rates during infection, or that retinol may be lost to oxidative cleavage at sites of inflammation. One recent publication suggests that this might occur in children undergoing an APR. Following accidental kerosene ingestion, serum retinol decreased more rapidly after the insult than did serum RBP. The authors suggest that increased tissue uptake rather than decreased liver secretion accounts for this disparity, although this suggestion remains speculative (142).

***Impaired Utilization*** It has been suggested that the APR may impair utilization of vitamin A by decreasing mobilization and transport of retinol from its primary storage site, the liver, to vitamin A–requiring peripheral tissues. The APR is induced when infection or tissue trauma causes the activation of macrophages and neutrophils. The release of tumor necrosis factor (TNF)-$\alpha$, interleukin (IL)-1, and IL-6 by these and other cells at the site of inflammation initiates the systemic APR (8). These cytokines trigger the induction of fever and production of cortisol (to down-regulate inflammation) by the central nervous system and, in the liver, increase the transcription and translation of positive acute-phase proteins [e.g. C-reactive protein (CRP) and $\alpha$-1-acid glycoprotein] while decreasing the production of negative acute-phase proteins, which include transferrin, albumin, TTR (115), and RBP (83). Because RBP is the principal transport protein for delivering vitamin A from liver stores to peripheral tissues (77), this decrease could cause deficiency in peripheral tissue. However, retinol is not a metabolic substrate, like glucose, or precursor for synthesis of macromolecules, as are essential amino acids, and it is not clear that transient decreases have any immediate, detrimental impact on vitamin A–sensitive tissues.

On the other hand, some data do suggest that low serum retinol, even with adequate liver stores of vitamin A, can produce vitamin A deficiency in at least one peripheral tissue, the retina. Very low serum retinol and RBP concentrations are seen in human subjects with specific point mutations in the human RBP gene. These subjects also have night blindness and retinal dystrophy but few other signs of vitamin A deficiency (11). RBP-knockout mice, which have high liver vitamin A stores but low serum retinol concentrations, appear to be largely "normal" but

also have impaired retinal function (77). Recent work has also shown that women in Nepal are at significant risk for developing transient night blindness during pregnancy (23). Nepali women with night blindness are more likely to have low serum retinol in association with an active APR than are women without night blindness. Similar observations have been made for children with xerophthalmia (97) and transient retinal whitening during severe episodes of malaria (56). These studies suggest that transient depression in serum retinol causes night blindness. However, as these studies were cross-sectional in design, our ability to make causal inferences is limited. Thus, the impact of the APR on tissue retinol availability remains uncertain.



## THE ACUTE PHASE RESPONSE AND ASSESSMENT OF VITAMIN A STATUS

### Serum Retinol Decreases During the Acute-Phase Response

The decrease in serum retinol which occurs during the APR is seen following trauma as well as infection (for a review, see 37). The greater the severity of infection (as measured by body temperature or serum concentration of a positive acute-phase protein), the greater the decrease in serum retinol. This decrease is transitory and serum retinol typically returns to preinfection levels within a few days (66). Several mechanisms probably contribute to this transient decrease. Increased vascular permeability at sites of inflammation may allow leakage of RBP into extravascular space and thus decrease serum levels. In addition, some retinol will be lost into the urine during infection. In hospitalized children with dysentery, those who lost 0.1 $\mu$mol of retinol per day in the urine (8% of subjects; 15% of the Food and Agriculture Organization/World Health Organization basal requirement) had significantly lower serum retinol concentrations than did subjects who excreted less retinol (66), which suggests that urinary loss contributed to lower serum retinol levels. But this effect may only be significant in severe infections. The lack of significant urinary retinol excretion during mild infections may explain why bacterial lipopolysaccharide (LPS) injection in rats was sufficient to depress serum retinol and liver RBP levels but did not cause a significant urinary retinol excretion (84) (although rats and humans may also have different renal responses to infection). It is likely that the principal reason for decreased serum retinol during relatively mild infections is that synthesis of RBP mRNA by the liver is decreased during the APR, resulting in decreased release of retinol-RBP by the liver (83).

### Impact of Acute Phase Response on Assessing Vitamin A Status

***Serum Retinol Cannot Be Used Uncritically as an Indicator of Vitamin A Status in Subjects with an Active APR*** Serum retinol concentrations are useful in identifying individuals (or, more typically, the percentage of individuals in a population)

who have normal liver reserves of vitamin A (serum retinol >1.05 $\mu$mol/liter), marginal reserves ($\leq$1.05 $\mu$mol/liter), depleted reserves ($\leq$0.70 $\mu$mol/liter), or depleted reserves with frank deficiency ($\leq$0.35 $\mu$mol/liter) (128). Transient changes in serum retinol that occur during the APR do not reflect changes in liver reserves. Thus serum retinol concentrations cannot be used to assess vitamin A status during an active APR in the same manner they are used in other subjects. This is obviously true in clinical populations, but community studies of children in Ghana (38) and adults and children in the United States (121) have also found that a significant percentage of asymptomatic subjects with active APRs also have low serum retinol concentrations.

Subjects from the US Third National Health and Nutrition Examination Survey (NHANES III) with active APRs (CRP $\geq$ 10 mg/liter) were significantly more likely to be classified as having marginal liver reserves of vitamin A (odds ratios ranged from 3.1 to 8.6, depending on age and sex) than were subjects without active APRs. [This cross-sectional analysis assumes that serum retinol concentrations were transiently decreased during an active APR, as has been demonstrated in many other studies (66).] Elevated CRP levels were found in from 1% to 14% of the NHANES III population, depending on age and sex, and were associated with infection as well as various chronic diseases, including arthritis, gout, bronchitis, and diabetes. Other tests of vitamin A status that depend on measurements of serum retinol are probably also affected by the APR. For example, a preliminary report indicates that the RDR test does not correctly identify subjects who have recently received high doses of vitamin A as having adequate vitamin A stores when the CRP concentration at the time of the test was $\geq$10 mg/liter (119).

***Can Acute-Phase Proteins Be Used to "Correct" Serum Retinol Levels During the APR?*** Because an active APR may cause misclassification when serum retinol is used to assess vitamin A status, it is reasonable to ask whether serum levels of positive APR proteins might be used to correct this misclassification. Clearly, appropriate cutoff values should be identified for the various positive APR proteins (CRP, $\alpha$-1-acid glycoprotein, $\alpha$-1-antitrypsin, and others) that can be systematically applied in nutrition surveys. But can serum levels of a positive acute-phase protein be used as a correction factor to predict what the "real" concentration of serum retinol would be in the absence of an active APR? Rosales et al have recently suggested that using acute-phase proteins will not adequately correct for transient changes in serum retinol during malaria (86). Furthermore, regression equations to predict serum retinol for NHANES III subjects included age, sex, CRP, and several interaction terms, which suggests that correction for an APR in this manner would be problematic (121).

***Use of the RBP:TTR Ratio to Assess Vitamin A Status*** A better approach to this problem would be to develop an indicator of vitamin A status that is not affected by the APR. Rosales & Ross (85) have recently suggested that the ratio of RBP to TTR may serve this purpose. The basis of the proposed test is as follows:

RBP and TTR form a noncovalent macromolecular complex in serum and have a relatively constant molar ratio, even during the APR. However, serum TTR levels are not affected by vitamin A deficiency whereas serum RBP decreases. This decrease in RBP results in a lower RBP:TTR ratio. This ratio seems not to be affected by the APR and correctly identifies groups of rats on marginal vitamin A diets (as compared with supplemented diets) in both the presence and absence of LPS-induced inflammation (85). Similarly, in a post hoc analysis of samples from children with measles who received vitamin A supplements or placebo, only children in the vitamin A group had a significant increase in the RBP:TTR ratio. A more recent study evaluated the RBP:TTR ratio in children recovering from accidental kerosene ingestion (39). None of these subjects received vitamin A supplements, but their vitamin A status was assessed using the modified RDR (MRDR) test after recovery. The RBP:TTR ratio did not strongly predict categorization of the subjects as adequate or deficient based on the MRDR test. However, some of the subjects had an active APR at the time of the MRDR. Thus, if the MRDR is compromised by an active APR, as occurs with the RDR, the analysis done in this study may underestimate the utility of the RBP:TTR ratio in assessing vitamin A status. Further work on this method is clearly warranted.



## VITAMIN A AND IMMUNE FUNCTION

### Innate Immunity

***Overview*** The innate immune system is, in evolutionary terms, our oldest defense against infection. It consists of epithelial barriers, circulating phagocytes (primarily neutrophils and macrophages), and other cytotoxic cells [e.g. natural killer (NK) cells], as well as constitutive and inflammation-induced serum proteins (e.g. complement proteins and positive acute-phase proteins, respectively). This system is regulated by proinflammatory cytokines produced primarily by macrophages and neutrophils, such as IL-1, TNF-$\alpha$, IL-6, and IL-12, as well as antiinflammatory cytokines, such as IL-10, which down-regulate inflammation once pathogens have been eliminated.

***Barrier Functions*** The skin is an important barrier to infection. Vitamin A deficiency causes a thickening of the outer, keratinized layer of the skin (hyperkeratosis) (25) but does not obviously compromise its barrier function. However, vitamin A deficiency does significantly compromise the mucosal epithelial barriers found in the conjunctiva of the eye as well as in the respiratory, gastrointestinal, and urogenital tracts. One key change caused by vitamin A deficiency is the loss of mucus-producing goblet cells. This loss of the protective mucus blanket diminishes resistance to infection by pathogens that would ordinarily be trapped in the mucus and swept away by the cleansing flow of mucus out of the body (see Figure 3). In addition, vitamin A deficiency can result in squamous metaplasia (113).

However, vitamin A deficiency that is not complicated by infection causes only minimal epithelial changes. In the respiratory tract, squamous metaplasia is seen only at sites where tissue damage (e.g. caused by viral infection and inflammation) has destroyed the normal epithelium, which is then replaced by metaplastic foci. In the intestine, destruction of epithelial cells in vitamin A–deficient mice results in more severe pathologic changes than is seen in control animals, but squamous metaplasia does not occur (89, 131). It is difficult to directly demonstrate that vitamin A deficiency impairs regeneration of enteric mucosa in humans. However, in a recent preliminary report, Thurnham et al (125) used an indirect test of gut mucosal integrity (lactulose:mannitol differential sugar absorption test) to demonstrate that Gambian children recovering from diarrhea who received vitamin A supplements regained normal mucosal integrity more rapidly than did children receiving a placebo.

The inability of vitamin A–deficient mucosal epithelia to regenerate adequately following damage may allow easier penetration of the gut mucosal barrier by pathogenic bacteria. In support of this argument, increased bacterial translocation from the intestine into regional lymphoid and other tissue has been observed in vitamin A–deficient rats (137). Supplemental vitamin A treatment of rats on normal diets also inhibits bacterial translocation from the gut during lectin-induced diarrhea, a model for chronic diarrhea in humans (102). In the respiratory tract, pathogenic bacteria that would ordinarily be cleared by mucus are able to adhere to damaged epithelium or sites of squamous metaplasia (21) and thus may increase the chance of invasive disease, such as septicemia. Given the importance of the mucosal barriers to infection, it is likely that squamous metaplasia and impaired recovery of normal mucosal integrity—as depicted in Figure 3 —directly contribute to the increased severity of disease and greater risk of mortality that are caused by vitamin A deficiency.

***Neutrophils*** Neutrophils and other granulocytes develop from myeloid stem cells in the bone marrow. RAR-mediated modulation of gene expression controls the development of neutrophils (for a review, see 55). This is illustrated by the fact that a translocation that fuses the RAR-$\alpha$ gene with a gene known as PML (for promyelocytic leukemia) is found in patients with the disease acute promyelocytic leukemia. This fusion disrupts normal neutrophil maturation, triggering the proliferation of promyelocytes. RA therapy for acute promyelocytic leukemia patients can cause reversion of the disease by restoring maturation of promyelocytes to neutrophils.

Vitamin A deficiency also disrupts normal neutrophil development and can result in decreased phagocytosis and killing of bacteria (127). These defects may lead to the decreased clearance of bacteria from the bloodstream that has been seen in vitamin A–deficient rats (73). Recruitment of neutrophils from blood into the site of inflammation may also be affected by vitamin A, as is indicated by the observation that retinoid treatment diminishes neutrophil migration into the skin from capillaries. In addition, treatment with RA and synthetic retinoids can

decrease oxidative metabolism that is associated with killing ingested bacteria and promoting inflammation (75).

Although neutrophil function is impaired by vitamin A deficiency, increased numbers of granulocytes have been seen in the peripheral blood of vitamin A–deficient rats (69, 143), and a recent study found that vitamin A deficiency in SENCAR (a strain selectively bred for increased sensitivity to chemical-induced skin carcinogenesis) mice causes an expansion of granulocytes in the bone marrow and peripheral blood, apparently by decreasing neutrophil apoptosis (54). Treatment of these mice with RA returned neutrophil levels to normal, as was also seen in deficient rats (143). Not all mice strains develop neutrophilia during vitamin A deficiency (63), indicating that a genetic predisposition may exist.

Thus, vitamin A deficiency has two disparate effects on neutrophils: It increases numbers but impairs function. On balance, these studies suggest that the protective function of neutrophils is impaired by vitamin A deficiency and will diminish protection against bacterial infections.

***Macrophages*** Macrophages are activated during inflammation and, like neutrophils, are professional phagocytes. Vitamin A deficiency may lead to a significant increase in the total number of macrophages in the secondary lymphoid organs of mice (109), whereas RA treatment can cause a decrease in the number of monocytes found in the bone marrow and spleen (63). In addition to affecting cell numbers, vitamin A deficiency also leads to increased transcription of IL-12 (18), whereas RA inhibits IL-12 production by primary macrophages in vitro (67). IL-12 produced by macrophages, acting as antigen-presenting cells, promotes development of T-helper (Th) 1 cells, which produce interferon (IFN)-$\gamma$ (as discussed below). Increased IFN-$\gamma$ production by Th1 cells can, in turn, lead to increased macrophage activation. Such activation may lead to the higher spontaneous release of nitric oxide (a reactive oxygen metabolite involved in killing ingested bacteria) by peritoneal macrophages that has been observed in vitamin A–deficient mice (136), although this difference disappears after stimulation with LPS. In addition, corneal abrasions in vitamin A–deficient rats result in greater inflammatory damage and production of IL-1 (100). These studies suggest that vitamin A deficiency causes increased inflammation mediated by cytokines from macrophages.

Although data from humans are scarce, a recent clinical study found that patients with common variable immunodeficiency had low serum retinol levels that were increased by supplementation, which suggests a preexisting vitamin A deficiency. The vitamin A supplementation also diminished serum levels and in vitro production of the proinflammatory cytokine TNF-$\alpha$ while increasing serum levels and production of the antiinflammatory cytokine IL-10 (4). Although these data indicate that some macrophage-mediated inflammation is increased by vitamin A deficiency, the phagocytic capacity of macrophages can be impaired by deficiency. For example, vitamin A deficiency decreases the phagocytic activity and bacteria-killing ability of peritoneal macrophages for *Staphylococcus aureus* (141). Peritoneal macrophages from vitamin A–deficient chickens do not have

decreased phagocytic ability for yeast but do have reduced oxidative metabolic capacity (104), which is important in bacterial killing. Vitamin A supplementation can also enhance the phagocytic activity of macrophages (for a review, see 88).

These data indicate that vitamin A deficiency enhances macrophage-mediated inflammation by increasing production of IL-12 and IFN-$\gamma$ but impairs the ability of macrophages to ingest and kill bacteria. This latter deficit may lead to increased pathogen replication at sites of infection, thus causing increased pathology, inflammation, and secondary immune responses, as has been observed for bacterial (141) and viral (68) infections in vitamin A deficiency. Thus, macrophage-associated defects in the initial control of infection may lead to more severe infection whereas the enhanced production of proinflammatory cytokines (due both to vitamin A deficiency and increased pathogen load) may also exacerbate inflammation, at least during infections that trigger Th1-mediated responses.

***NK Cells*** NK cells are lymphoid cells originally characterized by their anti–tumor cell lytic activity. It is now appreciated that these cells play an important role in innate immunity by killing virus-infected cells as well as tumor cells. Several studies have demonstrated that vitamin A deficiency decreases both NK cell number and lytic activity (for a review, see 89). More recently, these observations have been extended to include aging rats chronically fed diets that produced marginal vitamin A status (31). The protective benefits of NK cells in the early stages of viral infection, or in antitumor responses, clearly is diminished by vitamin A deficiency.

## Pathogen-Specific Immunity

***Overview*** Pathogen-specific immunity depends on the recognition of antigen either by antibody produced by plasma cells (which develop from B-cells) or by T-cell receptors on CD4+ Th cells or CD8+ effector T-cells. Antigen-presenting cells (APCs) take up antigen at a site of infection, process it, and display the processed antigen on their surfaces using major histocompatibility class II molecules. When APCs arrive at a regional lymph node, they expose naive T-cells to antigen and initiate proliferation and maturation, as outlined in Figure 4. Memory T-cells develop and persist after primary stimulation to allow a more rapid response on subsequent exposure to the same antigen. Memory Th cells provide help to antibody responses as well as cell-mediated immune responses, such as the development of virus-specific CD8+ cytotoxic T-lymphocytes (CTLs). Some antibody responses to antigens, such as bacterial LPS, do not require help from T-cells. Memory Th cells develop along one of two pathways: Th1 or Th2 (see Figure 4) (92). Put briefly, vitamin A deficiency impairs Th2-mediated antibody responses but does not impair, and may even enhance, Th1-mediated responses.

Th1 cells respond to intracellular pathogens, such as viruses, by producing IFN-$\gamma$ and IL-2. They stimulate CTL responses, macrophage activation, and

the delayed-type hypersensitivity (DTH) response and provide limited help to stimulate B-cell development and antibody production [e.g. IFN-$\gamma$ stimulates immunoglobulin (Ig)G2a in mice]. These activities of Th1 cells can be down-regulated by Th2 cytokines. Th2 cells respond to extracellular pathogens and produce IL-4, IL-5, and IL-10, which stimulate B cell help (e.g. for IgG1, IgE, and IgA production), eosinophil and mast cell development, and macrophage deactivation. These activities can be down-regulated by IFN-$\gamma$. The Th1/Th2 patterns are not completely dichotomous. For example, the response to influenza A virus infection elicits a strong IgG2a response, which is driven by IFN-$\gamma$, and a strong secretory IgA response, which is driven by Th2 cytokines.



***Vitamin A Deficiency Diminishes Th2-Mediated Antibody Responses*** Vitamin A deficiency impairs antibody responses to antigens that require Th2-mediated help (for a review, see 88). The serum IgG1 antibody response to purified protein antigens (87, 109) and the serum IgG1 and IgE responses to the intestinal helminth *Trichinella spiralis* are impaired by vitamin A deficiency (20), as is the salivary IgA response to influenza A virus infection (41, 122) and the intestinal IgA response to cholera toxin (139). These changes are caused by a decrease in the number of antigen-specific plasma cells; the amount of antibody produced per cell is not affected (41, 108). Although few human studies have been done, Semba et al (96) have shown that vitamin A supplementation increases the serum antibody response to tetanus toxoid in vitamin A–deficient children, and Rahman et al have made similar observations for the diphtheria vaccine (81).

In contrast, the IgG2a response to influenza A infection is increased in vitamin A–deficient mice (122), and most animal studies find that serum antibody responses to viral infection are not impaired (89). With regard to human studies, vitamin A supplements have been shown to increase the serum IgG response to measles infection (27) and to measles immunization (9), although decreases have also been seen (98; for a review, see 132). The serum antibody response to polio vaccine is not affected by vitamin A supplements given at routine immunization visits (95). The studies using measles and polio vaccine in humans were designed primarily to determine whether administration of high-dose supplements at vaccine visits interfered with the development of protective serum antibody titers (135) and were not designed to examine the role of vitamin A in immune function. In addition, the lack of effect of vitamin A supplements in such studies may also reflect better underlying vitamin A status than in studies that examined the effect of vitamin A deficiency on immune function (96).

In addition to affecting antibody responses, vitamin A deficiency also changes the pattern of Th1/Th2 cytokine production in animal studies. When lymphocytes isolated from the draining lymph nodes of *T. spiralis*–infected mice were restimulated with antigen in vitro, cultures from vitamin A–deficient mice produced more IFN-$\gamma$ and less IL-4, IL-5, and IL-10 than did cultures from control mice (17, 20). Depletion experiments found that CD4+ Th cells were the principal source of the IFN-$\gamma$ (19, 140). Higher IFN-$\gamma$ and IL-2 production have also been seen following mitogen stimulation of lymphocytes from vitamin A–deficient rats (140).

Thus, production of Th2 cytokines is diminished by vitamin A deficiency, whereas production of Th1 cytokines is increased.

***High Dietary Vitamin A May Enhance Th2-Mediated Responses*** Although vitamin A deficiency diminishes the secretory IgA response, we have recently found that high dietary vitamin A significantly enhances the IgA response and IL-10 production, as well as diminishes the serum IgG response and IFN-$\gamma$ production (29). Similarly, RA treatment of mice with experimental allergic encephalomyelitis, a disease mediated by Th1-like T cells following immunization with myelin basic protein (MBP), decreases the severity of disease. In addition, in vitro treatment with all-*trans* RA decreases MBP-specific IFN-$\gamma$ production and increases MBP-specific IL-4 production by lymph node cells (78). Thus, high-dose retinoid treatment can increase the production of Th2 cytokines while decreasing the production of Th1 cytokines.



***How Does Vitamin A Affect the Th1/Th2 Balance?*** The mechanisms underlying the ability of vitamin A deficiency to impair Th2 responses are not fully defined, but work currently in the literature suggests that RA decreases the production of the Th1-enhancing cytokines IL-12 and IFN-$\gamma$ and, thus, indirectly enhances Th2 development because these cytokines down-regulate Th2 responses (as shown in Figure 4). As discussed above, in vitro treatment with RA decreases production of IL-12 p40 by stimulated macrophages (67) and IFN-$\gamma$ production by stimulated Th1-like cells and NK cells (18, 40). In addition, vitamin A–deficient mice have higher levels of IL-12 p40 and IFN-$\gamma$ transcripts in unstimulated lymph node cells than do control mice (18). Higher IFN-$\gamma$ production by CD8+ cells has also been documented by ELISA (18). These data suggest that a lymph node environment conducive to Th1 development is created by vitamin A deficiency. However, because the predominant effect of vitamin A deficiency is to decrease Th2-mediated responses, often without increasing Th1 responses, a direct effect of vitamin A on Th2 development is plausible. A recent preliminary report (117) indicates that RA can directly enhance Th2 development from antigen-naive Th0 cells in vitro. This effect is independent of IL-12 and IFN-$\gamma$ but requires IL-4. Thus, vitamin A may affect Th1/Th2 development by multiple mechanisms.

***Vitamin A Deficiency Can Impair Th1 Responses*** As indicated in Figure 4, data on vitamin A diminishing Th2 and enhancing (or not impairing) Th1-mediated responses are not completely consistent. For example, in three studies, the DTH response to dermal contact sensitization in mice (1, 109) and subcutaneous ovalbumin administration in rats (140) was diminished in vitamin A–deficient rodents. More recently, the DTH response to ovalbumin immunization was enhanced in vitamin A–deficient rats (136). The reasons for these differences are not clear, but taken together, the studies suggest that vitamin A deficiency impairs DTH responses. One human study also found that high-dose vitamin A supplements enhance the DTH response in infants who had improved vitamin A status (as indicated by serum retinol $>0.70$ $\mu$mol/liter) after supplementation (79).

With regard to another Th1-mediated response, one study has reported that vitamin A deficiency impairs CTL function during Newcastle disease virus infection in chickens (105). In addition, vitamin A deficiency has been shown in some experiments to decrease IL-2 production (20), whereas high-level dietary vitamin A (26) and RA treatment in vitro can enhance IL-2 or IL-2 receptor expression (6), which could enhance proliferation of Th1 cells if this occurs in vivo as well. It is clear that the impact of vitamin A on pathogen-specific immunity is not completely represented by the alterations in Th1/Th2 balance discussed above. Other factors are at work that also impair some aspects of Th1-mediated responses.

***Direct Effects of Vitamin A on B-Cells*** The observation that the antibody response to LPS is not impaired by vitamin A deficiency suggests that B-cell development might be unaffected by vitamin A status. However, the proliferative response of splenocytes to B-cell mitogens is decreased in cells isolated from vitamin A–deficient rats (129). In addition, retinol is a required growth factor for Epstein-Barr virus–transformed B-lymphoblasts, and the retinol metabolite 14-hydroxy-retroretinol has been identified as the required compound (15; for a review, see 88). In contrast, retinol has also been shown to inhibit the proliferation and differentiation of primary human B-cells (12), raising the question of which competing activity is relevant in vivo. In addition, retinoic-acid treatment of B cells can induce greater IgG secretion in vitro (5), can direct class-switching to IgA (126), and affects B-cell apoptosis (58). Clearly, B-cell activity is modulated by vitamin A, but there is not a clear picture of how these different activities come together to regulate B-cell function in vivo.



## VITAMIN A, MORBIDITY, AND MORTALITY

### Community Mortality Studies

It is now well accepted that vitamin A supplements will decrease early childhood mortality in areas of the world where vitamin A deficiency is a public health problem. Very large, placebo-controlled community intervention trials done in Africa and Asia showed an overall decrease in mortality of 30% in children 6 months to 5 years of age. Benefits for infants $<6$ months of age are less certain. These studies have been reviewed and analyzed together in at least three meta-analyses (34, 42), including one published recently (130). In addition, recent analysis of morbidity and mortality associated with use of immunization visits in infants from Ghana, India, and Peru to deliver vitamin A supplements saw no effects on morbidity or mortality but did show improved vitamin A status (135). Vitamin A supplements have also recently been found to protect against AIDS-associated mortality in this age group (35). The findings of these studies are not recapitulated here other than to highlight a few key points. Not all studies showed a significant benefit and differences between the different study sites (Indonesia, India, Nepal, Sudan, Ghana, Peru) in underlying nutritional status, morbidity patterns, and use of

primary and preventive health care no doubt affected the response to vitamin A treatment. When vitamin A was provided in frequent small doses, mortality decreased more dramatically than when infrequent high doses were administered. These studies often had >10,000 subjects and were done in areas where cause of death could not be rigorously assessed. Thus, although most deaths in these studies were from infectious diseases, it was difficult to determine cause of death with certainty. The available data suggest that the deaths averted were from measles, diarrhea, and infections associated with convulsions (perhaps resulting from high fever) but not from pneumonia (130a). More recently, provision of vitamin A supplements to pregnant women has been shown to decrease childbirth-associated mortality (134), although little specific information is available on cause of death. Fetal and infant survival were not improved by this intervention (52). Clearly, vitamin A diminishes risk of death from infectious diseases, with the benefit being seen with some infections but not others. Unfortunately, the mechanistic studies of vitamin A and immune function do not completely explain why this occurs (discussed below).



## Effect of Vitamin A Supplements on Specific Infections

***Measles*** High-dose vitamin A supplements improve recovery from measles, decreasing mortality, duration of disease, and risk of complications (for a review, see 132). Measles is an acute, immunosuppresive viral infection, and children with severe measles often develop opportunistic bacterial pneumonia and diarrhea due to compromised innate and adaptive immunity. The clinical trials of vitamin A supplements during measles primarily studied children brought to hospitals with severe disease. Many of these children also had secondary bacterial infections. It is thus reasonable to ask whether vitamin A improves recovery by affecting measles itself or by affecting the secondary bacterial infections that result from measles (or both). The answer to this question is not clear. Both neutralizing antibody and CTLs are involved in clearing measles infection. Although there are no data on the impact of vitamin A supplements on the CTL response to measles, vitamin A supplements do not appear to enhance, and may impede, the recovery of DTH responses to recall antigens following measles virus infection (82). However, the serum IgG response to measles infection can be increased by vitamin A supplements (27), although effects on vaccine responses are equivocal, as discussed above. Thus, there is not strong evidence for vitamin A supplements enhancing measles-specific immune function. (It should be remembered that the absence of data is not the same as negative data.) However, vitamin A does enhance recovery of mucosal integrity after viral infection, antibody responses to bacterial antigens, and recovery of neutrophil function. These mechanisms can protect against opportunistic bacterial infections. Restoration of these defenses may contribute significantly to the enhanced recovery caused by vitamin A in measles.

***Diarrhea*** In the case of diarrheal diseases, recovery from infection calls on those defense mechanisms that are compromised by vitamin A deficiency: regeneration

of intact mucosal epithelium damaged by invasive pathogens, Th2-mediated secretory IgA antibody responses against bacterial toxins, intact phagocytic responses to protect against invasive disease, and Th2-mediated serum IgG responses against bacterial toxins. However, clinical studies of diarrhea offer a mixed picture: Subjects with acute watery diarrhea do not benefit from supplementation whereas, in at least one study, subjects with invasive disease (*Shigella* dysentery) do benefit (for a review, see 130). This benefit in invasive disease may be due to the ability of vitamin A to enhance regeneration of damaged mucosal epithelium and enhance the phagocytic activity of neutrophils and macrophages. It has also been shown that vitamin A supplements can reduce the incidence and duration of diarrhea episodes (7) and is of particular benefit among children who are not breastfed (10). A recent clinical study showed that low-dose vitamin A supplements given daily to hospitalized malnourished children decreased the incidence of severe, nosocomial diarrhea in those with clinically evident protein-energy malnutrition (PEM), but that a single high-dose supplement given on admission increased the risk of such diarrhea in children without underlying PEM (32). The reason for the disparate response to the different doses is not clear, but the improvement in recovery caused by vitamin A supplements in children with PEM is consistent with a recent study showing that in mice, vitamin A restored the decline in the intestinal IgA response and Th2 cytokine production that is produced by PEM (70). Vitamin A enhances the secretory IgA response in animals without PEM as well. This increase in pathogen-specific antibody in the gut could increase resistance to secondary infection and improve recovery from primary infection, thus decreasing incidence, duration, and severity of diarrhea.

***Respiratory Infections*** In community studies, vitamin A supplements have increased the risk of symptomatic respiratory infection, whereas in clinical studies, supplements have typically, although not always, failed to improve recovery (for a review, see 130). In some clinical intervention trials, including those using patients with community-acquired pneumonia in Peru (120) and respiratory syncytial virus infection in the United States (13), use of vitamin A supplements has resulted in more severe disease. Recently, a clinical trial in tuberculosis patients has shown no benefit of vitamin A supplements on recovery (44), although the immune response may have been modified (45). It is interesting that a recent community-based study in Equador found that low-dose supplements given weekly decreased the risk of acute lower respiratory infection (ALRI) in children with weight-for-age *z*-scores two standard deviations below the reference standard while increasing risk of ALRI above this level (99). A similar association of vitamin A enhancing recovery only in children with underlying PEM has also been seen in a clinical study of pneumonia in Vietnam (103). The reason for this association with underlying PEM is not clear but may be due to these children having more severe disease or a greater risk of underlying vitamin A deficiency.

A major puzzle that has yet to be explained is how vitamin A supplements increase the apparent incidence of ALRI in community studies and adversely affect recovery in some clinical studies. In the community studies, it is likely that the

incidence of infection is not affected but that the risk of developing disease severe enough to be counted as ALRI (using such indicators as fever, cough, and rapid breathing) is enhanced. How severity is enhanced is not known. However, it is interesting to note that 25%–30% of patients with acute promyelocytic leukemia who receive RA therapy develop what has become known as the RA syndrome (48). This syndrome is characterized by thrombosis, fever, respiratory distress, radiographic evidence of pulmonary infiltrates, and pleural effusions. Although the etiology of the syndrome is unclear, it is known that RA can increase IL-1 production by alveolar macrophages (46), which could, in turn, recruit neutrophils into the lung, thereby increasing inflammation. RA also enhances transcription of the IL-8 gene in respiratory airway epithelium (22). IL-8 is also a chemotactic factor for neutrophils. Could high-dose vitamin A supplements thus produce a low-grade RA syndrome, particularly in children who already have active pulmonary inflammation, including increased vascular permeability and activated macrophages and neutrophils? We do not know the answer to this question, and it is not clear why similar adverse effects are not seen in measles-related pneumonia. However, the possibility that vitamin A enhances some aspect of pulmonary inflammation seems plausible and could explain the adverse effects of vitamin A supplements on respiratory infection in some settings.



***HIV*** HIV, like measles, is a viral infection, and the animal data reviewed above do not predict strong enhancement of antiviral responses by vitamin A supplements. Many studies have examined the association of low serum retinol concentrations with HIV severity or progression of disease in US populations and in the developing world (for a review, see 71, 93). Most data on the association of vitamin A status with severity of HIV infection suffers from the flaw that serum retinol concentrations were used to identify "deficient" subjects. As discussed above, this approach can be unreliable during an ongoing infection. These studies, however, strongly suggested that vitamin A deficiency enhanced the risk of vertical transmission of HIV, at least among women at risk of deficiency in Africa. Placebo-controlled intervention studies in pregnant women at risk of deficiency have now been done, but vitamin A supplementation did not decrease vertical transmission or improve measures of immune function (28, 36). Apart from vertical transmission, short-term interventions in better-nourished adult populations in the United States have also demonstrated no improvement in disease or immune function parameters (50). However, a recent study from Tanzania has shown that vitamin A supplements in HIV-infected children 6 months to 5 years of age reduced diarrhea- and AIDS-related deaths (35). This result is reminiscent of the reduction in deaths seen in HIV-uninfected children and may be attributable to similar mechanisms. Vitamin A supplements may thus diminish the severity of opportunistic infections in popuations at risk of vitamin A deficiency, but direct improvement of HIV-specific immunity has not been demonstrated.

***Malaria*** One well-controlled study has shown that vitamin A supplements decrease the severity of malaria infection in children 6 months to 5 years of age

(101). Supplementation reduced the number of febrile episodes, the parasite density, and the proportion of subjects with spleen enlargement. The immune response to malaria, an intracellular parasite, involves innate immunity (NK cells) and IFN-$\gamma$ production, as well as Th2 cytokines (72). Antibody plays a key role in diminishing the severity of disease. This response develops rapidly in young children during their first year or two of exposure to malaria. In the study by Shankar et al (101), subjects 6 months to 3 years of age benefited more from the vitamin A supplements than did older subjects. It is thus tempting to speculate that vitamin A enhanced the acquisition of immunity in these children and thus diminished disease severity, whereas older children already had acquired a more mature antibody response. This interpretation suggests that vitamin A supplements could boost the development of immunity among infants and young children in malaria-endemic areas and thus decrease the burden of malaria morbidity in this age group.



## CONCLUDING REMARKS

In conclusion, we have seen that common infections can increase the risk of vitamin A deficiency by decreasing intake, decreasing absorption, and increasing excretion. Vitamin A deficiency, in turn, impairs both the innate and adaptive immune response to infection. In particular, mucosal integrity and Th2-mediated responses are compromised. These alterations in host defense increase the risk of death from common infections in young children and pregnant women. Correcting vitamin A deficiency decreases mortality from measles, diarrhea, and other infections, although the severity of respiratory infections may be enhanced under some circumstances. Much work remains to be done, as the mechanisms by which vitamin A affects immune function have not been carefully examined at the molecular level. On a clinical and community level, nutrition research would benefit greatly from the development of a method to measure vitamin A status that is simple to apply and not adversely affected by the APR. Pursuing these research priorities will advance our knowledge of how vitamin A affects the infection-malnutrition cycle and will also bolster efforts to develop sustainable programs to eliminate vitamin A deficiency, which, for the reasons described above, should remain a top priority of the international health community.



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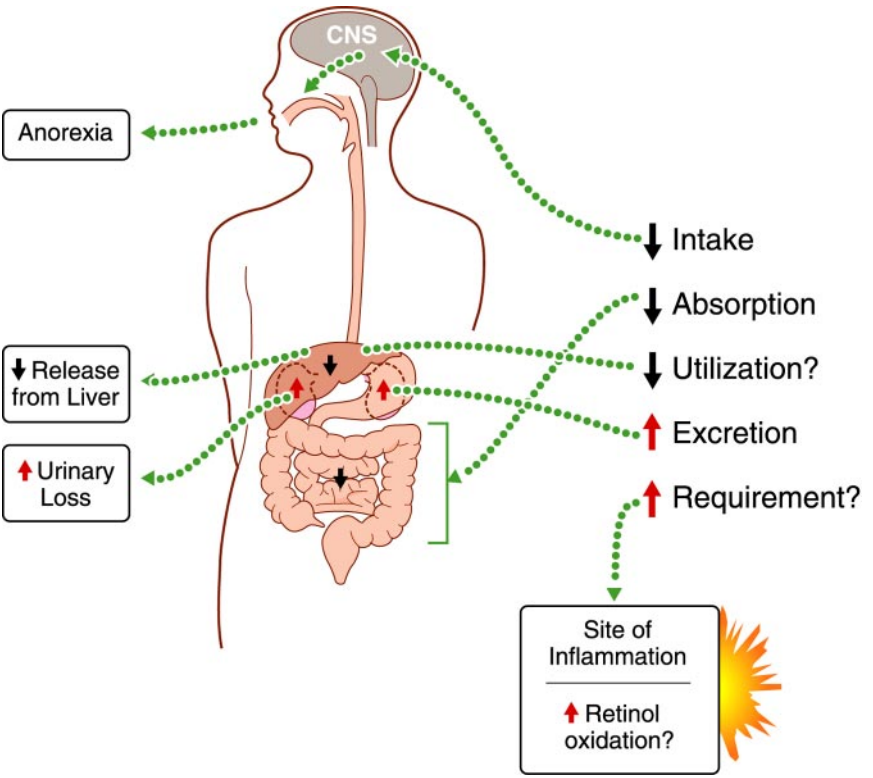


**Figure 1** Infectious diseases impair vitamin A status. This figure illustrates three mechanisms by which infections are known to impair vitamin A status: decreased intake due to anorexia; decreased absorption; and increased urinary excretion. Infection may also affect vitamin A status by impairing utilization of retinol stores in the liver (by diminishing transport from stores to peripheral tissues) or by increasing requirements (e.g. by increasing oxidative degradation of retinol at sites of inflammation), although proof for these two mechanisms is lacking.

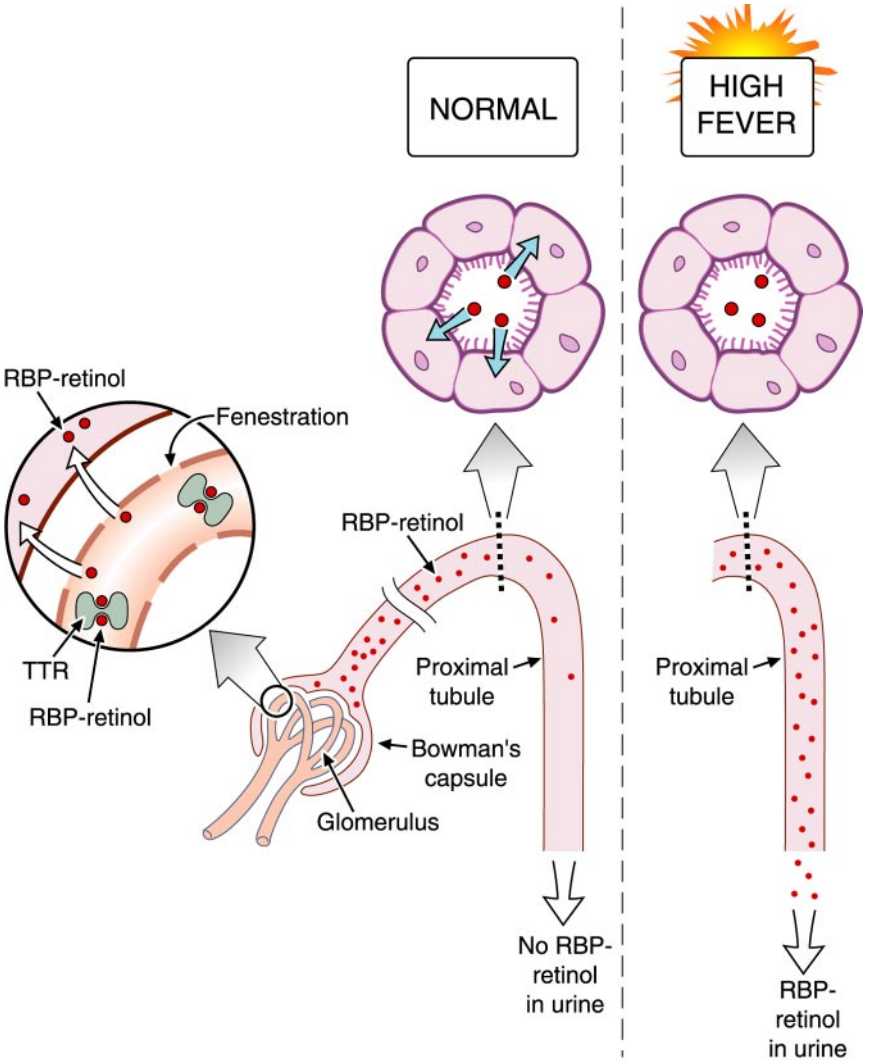


**Figure 2** Mechanism of urinary retinol excretion during infection. Retinol, bound to retinol-binding protein (RBP), is normally retained in the glomerular capillaries by its association with transthyretin (TTR). If not bound to TTR, RBP is small enough to pass through the fenestrations of the glomerular capillaries into the urinary collecting tubules, which begin with Bowman's capsule. Under normal circumstances, RBP passes down the tubules but is reabsorbed by the proximal tubular epithelial cells. During infections, particularly those with high fever, this reabsorption is diminished and RBP, carrying retinol, is lost into the urine.

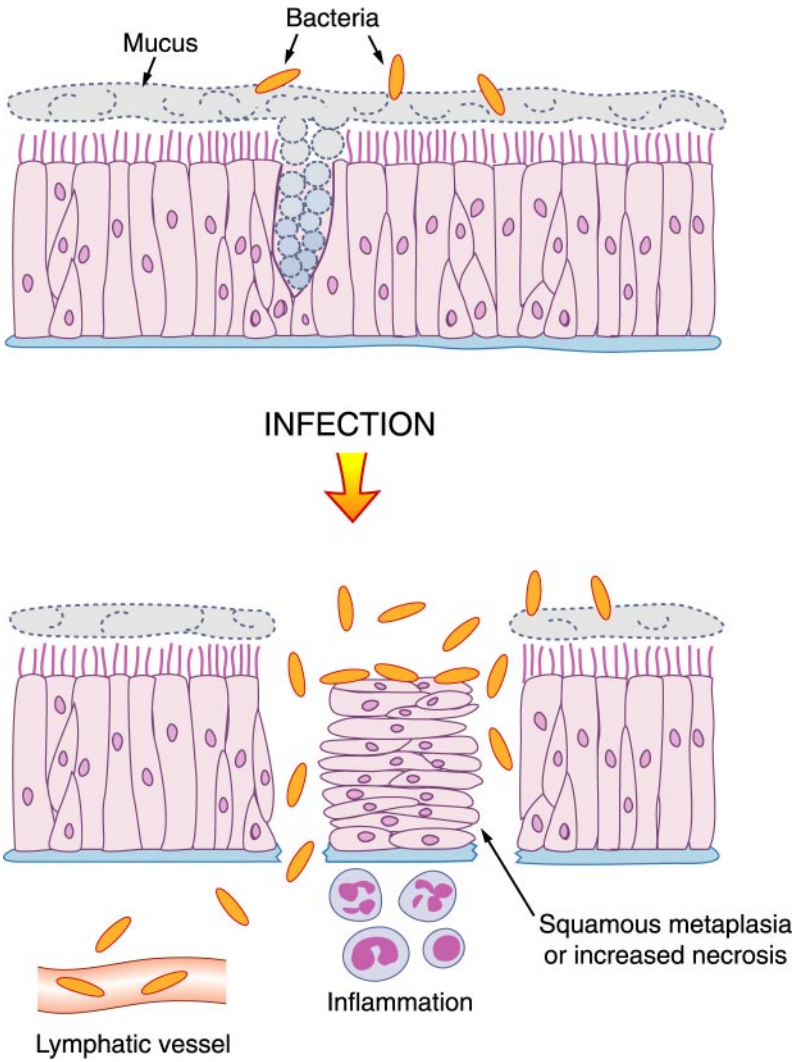


**Figure 3** Vitamin A deficiency impairs regeneration of normal mucosal epithelial barriers during infection. Normal mucosal epithelium (*top*) prevents adherence of many potentially pathogenic bacteria by trapping them in mucus and moving them out of the airways or down the gastrointestinal tract. In vitamin A deficiency, mucosal epithelium that is damaged by infection (and the associated inflammation) does not regenerate normally, and foci of squamous metaplasia (in the respiratory tract) or increased necrosis (in the gut) develop at sites of inflammation. Such foci allow greater adherence of potentially pathogenic bacteria and may allow increased bacterial translocation across the mucosal surface, into lymphatic vessels, and to local lymphoid tissues and beyond, resulting in invasive disease.

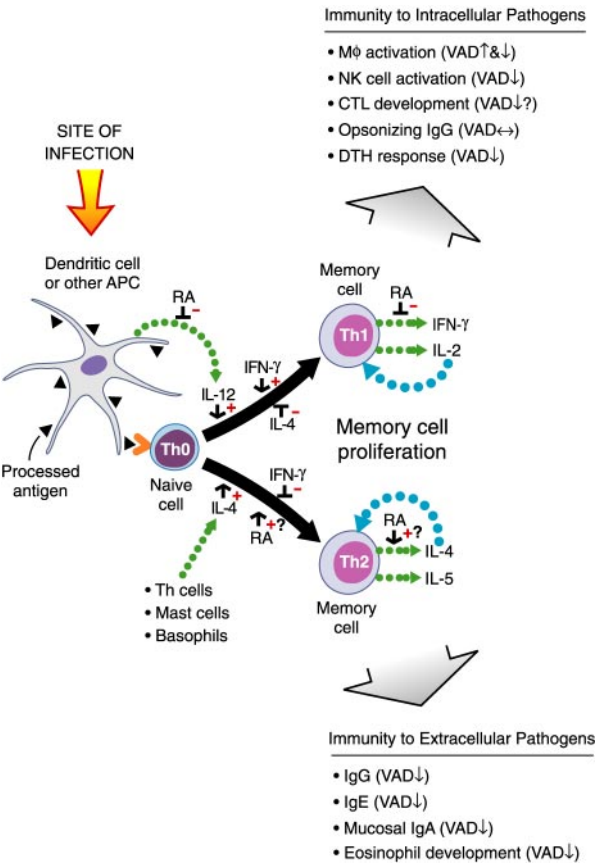


**Figure 4** Effects of retinoic acid (RA) on cytokine production and of vitamin A deficiency (VAD) on mechanisms of immunity. An antigen-presenting cell (APC) arrives in a lymph node carrying processed antigen from an invading pathogen. The antigen-naive T-helper (Th0) cell recognizes the antigen via its T-cell receptor. This recognition, in combination with interleukin (IL)-12 produced by the APC (*green dashed* →), stimulates development of Th1 memory cells or, in the presence of IL-4 (from Th2 cells mast cells or basophils), stimulates development of Th2 memory cells. Th1 cells produce interferon (IFN)-$\gamma$ to stimulate immunity to intracellular pathogens and IL-2 to promote Th1 cell growth (*blue dashed* →). Th2 cells produce IL-4, which stimulates immunity to extracellular pathogens and Th2 cell growth, as well as other cytokines, such as IL-5. IFN-$\gamma$ promotes development of Th1 cells (*black* → *with red* + *sign*) and blocks development of Th2 cells (*black* → *with red* + *sign*). IL-4 has the opposite effects. RA blocks IL-12 and IFN-$\gamma$ production and may enhance development of Th2 cells and IL-4 production (*black* → *with question mark and red* → *sign*). Immune mechanisms are either enhanced (↑), diminished (↓), or not-changed (↔) by vitamin A deficiency (? indicates equivocal data). Mf, macrophage; NK, natural killer; CTL, cytotoxic T-lymphocyte; DTH, delayed-type hypersensitivity; Ig, immunoglobulin.