

The role of nutrition in viral disease

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Malnutrition has been associated with a decrease in immune function. Impairment of immune function may lead to increased susceptibility to infection with viruses. Although there are many studies documenting the effect of host nutritional status on immune functions, fewer studies have examined the effect of host nutritional status on viral pathogenesis. This review examines the relationship between viral infection and the nutritional status of the host, and documents that not only can the nutritional status of the host affect immune function, but can have profound effects on the virus itself. One mechanism by which nutritional status affects the virulence of the viral pathogen involves selection for virulent viral genotypes. Other mechanisms remain to be elucidated. © Elsevier Science Inc. 1996 (J. Nutr. Biochem. 7:683–690, 1996.)

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Introduction

It has long been observed that the nutritional status of the host can affect the illness outcome as the result of a viral infection.^{1,2} For example, rotavirus infection in well-nourished children leads to mild diarrhea. In contrast, malnourished children who are infected with rotavirus develop severe diarrhea; the mortality rate is high for these children. The association between famine and epidemics of infectious disease and high rates of mortality have been noted throughout history.

The relation between nutrition and viral infection is postulated to be caused by changes in immune function. That is, the nutritional deficiency impairs the immune response; therefore, exposure to virus results in increased susceptibility to viral infection. This relationship can be depicted as:

Deficient host nutrition → decreased host immunity → increased susceptibility to viral infection.

However, recent data from collaborative studies between my laboratory and Orville Levander's laboratory at the United States Department of Agriculture (USDA) have suggested that this unidirectional model of nutrition-virus interaction may not be adequate. In this review, I present a new paradigm to describe host nutrition and viral interaction. This review will not focus on the effect of nutrition on

immunity, as there are several excellent published reviews that already cover this area.^{3,4} Rather, this review will examine the effects of host nutrition on specific viruses, using both human and animal studies. Although there are many studies examining the effect of nutrition on human immunodeficiency virus (HIV) infection, I will not cover HIV in this review, as this subject has recently been reviewed.⁵

General malnutrition and viral infection

As mentioned previously, rotavirus-induced diarrhea is much more severe in malnourished children as compared with well-nourished children.^{6,7} Rotaviruses are the major etiologic agents of serious diarrheal illness in infants and young children under 2 years of age. Although the frequency of rotavirus-induced diarrhea in developed countries is high, the mortality rate is low. In the United States, over 1 million cases of severe diarrhea occur from infection with rotavirus each year, with up to 150 deaths attributed to the infection. In developing countries, over 125 million cases of rotavirus diarrhea occurs each year, with 18 million of these cases classified as severe, and an estimated 873,000 deaths occurring in infants and children under the age of 4.

Acute respiratory tract infections (ARI) caused by viruses are also more severe in malnourished individuals. ARI are responsible for 4.5 million deaths among children each year, predominantly in developing countries.⁸ Viruses are the dominant etiological agent for ARI in developing countries, and the most commonly isolated viruses are respiratory syncytial viruses (RSV), followed by parainfluenza viruses, influenza A and B viruses, and adenoviruses.^{9,10}

Although there are a number of risk factors associated with an increase in severity and mortality due to ARI in

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developing countries, such as crowding, poor sanitation, low birth weight, parental smoking, etc., malnutrition clearly plays a major role. Malnutrition affects the host in a number of ways, including a diminished immune function, weakness in the muscles that control breathing, and changes in normal lung growth.^{3,11-14} A number of studies have shown that malnourished children (underweight) have an increased likelihood of developing pneumonia post infection, as compared with normal-weight children,⁹ and increases in mortality from ARI in malnourished children have also been documented.¹⁰ Keusch¹⁵ found that malnutrition and respiratory disease often occur together in developing countries, and that the immune defects induced by the malnutrition may affect vaccine responsiveness.

Whittle and Greenwood¹⁶ studied 30 malnourished children and 25 well-nourished children for 31 days after the onset of a measles rash. At 31 days, the measles virus could be isolated in 40% of the malnourished children, but in none of the well-nourished children. The relationship between measles and vitamin A deficiency will be discussed further.

A number of animal studies have examined the effect of both malnutrition and protein deficiency and its effect on host susceptibility to viral infection. Similar to what is found in humans, Riepenhoff-Talty et al.^{17,18} found that undernourished mice infected with rotavirus develop more severe diarrhea, which persists longer when compared with well-nourished mice infected with rotavirus. Noble et al.¹⁹ found that pups born to dams that had been fed either low-calorie or protein-deficient diets developed more severe diarrhea when infected with rotavirus than pups born to dams fed adequate diets.

Esa and Reissig²⁰ reported that a strain of mouse genetically resistant to mouse hepatitis virus became susceptible to the virus when weaned on a low-protein diet. Transfer of spleen cells from well-nourished resistant mice to the susceptible malnourished mice could restore resistance to the virus.

Woodruff and Kilbourne²¹ found that mice fed a protein-deficient diet developed more severe heart pathology when inoculated with coxsackievirus B3 as compared with well-nourished mice. The severity of the coxsackievirus B3-induced pathology was in general proportional to the severity of the malnutrition. Price et al.²² and Teo et al.²³ found that mice fed a protein-deficient diet had higher virus titers and increased lung pathology post murine cytomegalovirus infection. However, Pena-Cruz et al.²⁴ found that mice fed protein-deficient diets were not more susceptible to respiratory syncytial virus infection. That is, the lung pathology and the virus titers recovered from the lungs of infected mice were identical between well-nourished and malnourished groups of mice. In contrast, malnourished mice infected with Sendai virus developed more severe pathology and higher lung titers than well-nourished mice.²⁵ Thus, it appears that malnutrition does not produce a uniform response to viral infections.

The effect of nutrition on virus infection in mosquitoes mirrors what occurs in vertebrates. Grimstad and Haramis²⁶ found that female mosquitoes that had been reared under deficient dietary conditions were more susceptible to La Crosse virus. In addition, mosquitoes reared under deficient conditions were able to transmit more La Crosse virus dur-

ing a blood meal than mosquitoes raised under optimum dietary conditions. This study demonstrates how nutrition affects not only the host, but viral vectors as well.

Zinc deficiency and virus infection

A number of studies have examined the effect of zinc deficiency on immune function (for a review, see Ref. 27). Fewer studies have examined the effect of a zinc deficiency on susceptibility to viral infection. Al-Nakib et al.²⁸ demonstrated decreased clinical symptoms in volunteers given zinc gluconate lozenges before challenge with rhinovirus. Similarly, zinc gluconate lozenges provided to rhinovirus-infected volunteers once cold symptoms appeared also had reduced clinical symptoms when compared with the untreated, rhinovirus-infected controls.

In animal models, Singh et al.²⁹ found that mice treated with zinc acetate survived for longer periods of time when infected with the yeast *Candida albicans* or with Semliki Forest virus. Steers fed diets with added zinc methionine for 7 days before challenge with bovine rhinotracheitis virus had less severe symptomology than did infected steers fed normal diets.^{30,31} In contrast, work in vitro with a continuous cell line demonstrated that supplementation of the culture with ZnSO₄ increased susceptibility of the cell line to infection with *Autographa californica* nuclear polyhedrosis virus.³²

Vitamin A

Vitamin A is perhaps the best studied nutrient with regards to viral infection. Recently, much attention has been focused on the relationship between vitamin A deficiency and infection with measles virus. In developed countries, measles is generally a mild disease that rarely results in severe complications, such as encephalitis. Access to vaccination against measles infection also reduces the incidence of disease in developed countries. However, in developing countries, infection with measles often leads to what is termed "severe measles." Children with severe measles develop a lower respiratory tract infection, which is associated with a high rate of mortality. Measles remains a major cause of mortality in children in developing countries.

Malnutrition had long been noted to be associated with severe measles.³³ Further investigations led to the discovery that a deficiency in vitamin A often accompanied the development of severe measles.³⁴⁻³⁸ Double blind placebo studies were carried out in a number of developing countries with vitamin A.³⁹⁻⁴⁵ The majority of these studies found a significant decrease in pneumonia and a decrease in mortality associated with measles infection in children given vitamin A supplements, as compared with children given a placebo. These trials led the World Health Organization to recommend treatment of all measles virus-infected children in developing countries with vitamin A. It is also recommended that supplements of vitamin A be given at the time of vaccination for measles. However, some studies suggest that providing the vitamin A supplement at the time of vaccination reduces the efficacy of the vaccine.⁴⁶

Studies in the United States have found that in 50% of

children infected with measles were vitamin A deficient.⁴⁷ Other studies have demonstrated that children in U.S. hospitals treated with vitamin A for severe measles have a shorter duration and less severe course of illness.^{48,49} This has led to Committee on Infectious Diseases of the American Academy of Pediatrics to recommend vitamin A treatment for infants and children (up to age 2) hospitalized with severe measles.⁵⁰

Although the mechanism of potentiation of measles virus virulence in vitamin A-deficient children is not known, it is thought to be caused by decreased immunity.⁵¹ Increased levels of measles-specific IgG and increased total numbers of lymphocytes have been found in vitamin A-treated measles-infected children as compared with placebo treated measles-infected children.⁵² A decrease in the immune response induced by a deficiency in vitamin A would, therefore, allow the virus to replicate to higher virus titers and, thus, induce more severe disease.

Deficiency in vitamin A has also been associated with increased severity of RSV infection.⁵³ RSV causes worldwide annual epidemics of lower respiratory tract illness and is the most important cause of viral-induced lower respiratory tract illness. Several studies have found that children hospitalized in the U.S. with RSV-associated illness had decreased serum vitamin A levels.^{54,55} More severe disease was associated with the lowest levels of vitamin A. The vitamin A deficiency was not present before illness, suggesting that the viral infection itself is responsible for the decline in vitamin A levels. The mechanism of depletion is not known, but it may be due either to increased utilization of vitamin A during a viral infection, or a change in the distribution of vitamin A. A trial with oral vitamin A supplementation in children hospitalized with RSV infection did not demonstrate any benefit as compared with placebo-treated children.⁵⁶ However, the authors of the study suggested that several factors may have been involved in the inability to detect a benefit from vitamin A treatment including the dose given, the small size of the study, and the fact that the levels of vitamin A, although depressed, were not as depressed as levels seen in children in Africa with severe measles.

In animal studies, rats deficient in vitamin A develop more severe herpetic keratitis when infected with herpes simplex virus, as compared with rats fed a diet adequate in vitamin A.^{57,58} Vitamin A-deficient mice infected with influenza virus have decreased mucosal and serum antibody levels to influenza virus, although lung pathology and virus titers are not different between deficient and supplemented groups.^{59,60} Vitamin A-deficient adult mice challenged with rotavirus also develop decreased antibody responses as compared with vitamin A-adequate mice.⁶¹ However, because adult mice do not develop diarrhea post rotavirus infection, it is not known how the vitamin A levels affect illness.

Keshan disease

Keshan disease is an endemic cardiomyopathy that was first described in Keshan County, Heilongjiang Province, North-east China in 1935.⁶² The heart pathology is characterized by foci of necrosis throughout the myocardium and the le-

sions can exhibit varying degrees of cellular infiltration and calcification.⁶³ Keshan disease was predominantly found in women of childbearing age and post-weaned children. Distribution of Keshan disease suggested an environmental factor was involved, and further investigations led to the finding that the soils in Keshan disease endemic areas had low concentrations of the trace element, selenium (Se).⁶⁴ Testing of individuals in Keshan disease endemic areas found low Se concentrations in both hair and blood. A randomized, placebo-controlled treatment trial with sodium selenite found a significant drop in Keshan disease in the treatment group⁶⁵ when compared with the group receiving the placebo. Therefore, all children at risk of Keshan disease were supplemented with sodium selenite.

Although Keshan disease is essentially eradicated in China, there are aspects to the epidemiological pattern that suggest that an infectious agent, in addition to a Se deficiency, may be required for the development of Keshan disease. Keshan disease has a seasonal and annual incidence, and not every individual with low Se status developed the disease. A number of enteroviruses, including coxsackieviruses, have been isolated from blood and tissue samples from individuals with Keshan disease.⁶⁶ A coxsackievirus B4 isolated from a Keshan disease victim caused increased heart damage when inoculated into Se-deficient mice as compared with mice fed a Se-adequate diet.⁶⁷ Using the polymerase chain reaction technique, Li et al.⁶⁸ found 87.5% of myocardial specimens from Keshan disease patients were positive for enteroviral RNA, whereas only 3% of controls were positive. Similarly, again using the polymerase chain reaction, Roath et al.⁶⁹ found that 30% of blood samples from Keshan disease victims were positive for enteroviral RNA. Taken together, these results suggest a possible role for enteroviruses in the etiology of Keshan disease.

Coxsackieviruses, enteroviruses in the Picornaviridae, are known etiological agents of viral-induced myocarditis, or heart inflammation. To further investigate the role of coxsackieviruses and Se deficiency in Keshan disease, my laboratory, in collaboration with Orville Levander at the USDA, used a well-characterized murine model of coxsackievirus B3 (CVB3)-induced myocarditis.

CVB3-induced myocarditis and Se deficiency

To determine if a Se deficiency would affect the pathological outcome of an infection with coxsackievirus B3, we fed mice a diet adequate in Se (0.2 µg/g) or deficient in Se (no Se added to the diet) for 4 weeks.⁷⁰ At the end of the feeding period, mice were inoculated with a myocarditic strain of CVB3, CVB3/20. This virus has been cloned and sequenced.⁷¹ At 10 days post-inoculation, hearts from mice fed a diet adequate in Se had mild to moderate pathology. However, mice fed the diet deficient in Se had much more severe myocarditis. The heart lesions were larger and had more extensive regions of calcification than lesions in Se-adequate mice. Virus titers in the heart and liver were higher in the infected Se-deficient mice when compared with Se-adequate mice. Although both groups of mice were able to clear virus, viral clearance took longer in Se-deficient mice.

In a second series of experiments,⁷² we inoculated Se-

deficient and Se-adequate mice with CVB3/0, a strain of CVB3 that is normally avirulent in mice, although virus can be recovered from the heart tissue of infected, asymptomatic mice.⁷³ CVB3/0-infected mice fed Se-adequate diets did not develop any myocarditis post-infection. However, mice fed Se-deficient diets developed moderate myocarditis. As found for CVB3/20, CVB3/0 virus titers were elevated and persisted longer in Se-deficient mice as compared with Se-adequate mice.

To understand how the Se deficiency caused a change in the expression of virulence of the two CVB3 viruses, we examined various immune parameters. Nutritional deficiencies have long been known to cause immune dysfunction, and a deficiency in Se has been found to increase susceptibility, due to immune suppression, to parainfluenza 3 virus in lambs⁷⁴ and infectious bovine rhinotracheitis virus in steers.⁷⁵

Neutralizing antibody titers at 14 days post-infection were equivalent between Se-adequate and Se-deficient mice. However, splenic T cell proliferation against both mitogen and CVB3 antigen were depressed in the Se-deficient mice. Natural killer cell activity was not affected by the Se deficiency. Thus, it appeared that the immune system was negatively affected in the Se-deficient animals. Using the unidirectional model presented in the Introduction, our results suggest that the Se-deficiency impaired the immune system of the host such that the CVB3 virus could now cause increased pathology in the compromised host. However, a second alternative was conceivable. Was it possible that the virus itself had changed its phenotype as a consequence of replicating in a Se-deficient host?

To test this hypothesis, we inoculated Se-deficient mice with CVB3/0 virus.⁷⁶ Seven days later, virus was isolated from the hearts of the infected mice and renamed CVB3/0Se-, to reflect the host the virus was isolated from. As a control, the virus was also isolated from Se-adequate mice, and renamed CVB3/0Se+. These isolated viruses were then passed into Se-adequate mice. If the unidirectional model was correct, then the hearts from the Se-adequate mice inoculated with the CVB3/0Se-virus should not develop lesions. However, if the virus phenotype had changed, then disease should be present in the CVB3/0Se-inoculated animals. We found that Se-adequate mice inoculated with CVB3/0Se- virus developed moderate myocarditis, whereas Se-adequate mice inoculated with CVB3/0Se+ virus did not develop any disease. Thus, the viral passage experiments demonstrated that the viral phenotype had been altered: CVB3/0 virus changed from avirulent to virulent as a consequence of replicating in a Se-deficient host.

To determine if the phenotype change was due to a change in the viral genome, CVB3/0 (the input strain), CVB3/0Se-, and CVB3/0Se+ viruses were sequenced.⁷⁶ The genomic sequence of CVB3/0Se+ was found to be identical to CVB3/0. However, CVB3/0Se- differed from CVB3/0 at six nucleotide positions: nucleotide numbers (5'-3') 234, 788, 2271, 2438, 3324, and 7334 (See Table 1). There are seven known differences in the genome between CVB3/0 and known myocarditic strains of CVB3. All six of the nucleotide changes found in CVB3/0Se- are identical to the nucleotides found in the myocarditic strains. Nucleotide 2690, which is different between CVB3/0 and myocarditic

Table 1 Nucleotide and corresponding amino acid differences between the avirulent CVB3/0 and the virulent CVB3/0Se- viruses and comparison with CVB3/20 (virulent) strain

Nucleotide Number (5'-3')	CVB3 Strain			Amino acid change
	CVB3/20 ¹	CVB3/0 ¹	CVB3/0Se- ²	
234	T	C	T	Non-translated region
788	A	G	A	Arg → Gly
2271	T	A	T	Phe → Tyr
2438	C	G	C	Gln → Glu
2690	A	G	G	None
3324	T	C	T	Val → Ala
7334	T	C	T	Non-translated region

¹CVB3/20 and CVB3/0 are cloned and sequenced strains of CVB3. We sequenced the CVB3/0 preparation used to inoculate both Se-deficient and Se-adequate mice. CVB3/20 is a myocarditic strain. CVB3/0 is an amyocarditic strain.

²CVB3/0Se- virus was isolated from the heart of a Se-deficient mouse inoculated with CVB3/0. The same pattern of nucleotide changes was identified in three other virus isolates. These viruses are myocarditic when inoculated into Se- and vitamin E-adequate mice.

strains, was not changed in the CVB3/0Se- virus. Thus, the myocarditic CVB3/0Se- strain was found to be a hybrid between known myocarditic strains and the amyocarditic CVB3/0. The specific nucleotides important for the change to the virulent phenotype have not been identified. However, this model presents an excellent opportunity to examine the relationship between nucleotide sequence and virulence.

CVB3-induced myocarditis and vitamin E deficiency

Because many of the individuals living in Keshan disease endemic areas were of marginal vitamin E status, and because vitamin E and Se can spare one another's activities, we also infected vitamin E-deficient mice with CVB3.⁷⁷

Similar to what we found with Se-deficient mice, vitamin E-deficient mice also developed much more severe myocarditis when infected with the myocarditic strain, CVB3/20, when compared with vitamin E-adequate animals. Of particular interest, when menhaden oil is substituted for lard as a fat source, heart damage in infected mice is increased when compared with infected mice fed lard-based vitamin E-deficient diets.

Infection of vitamin E-deficient mice with the normally benign CVB3/0 strain results in myocarditis, similar to the pathology seen in CVB3/0-infected Se-deficient mice. Serum neutralizing antibody responses are not affected, although spleen cell proliferative responses to both mitogen and antigen are decreased, similar to what was seen with the Se-deficient mice.

Because both Se and vitamin E act as antioxidants, although by two very different mechanisms, a common mechanism of increased oxidative stress in the host seemed a likely explanation for the increased virulence of the CVB3

viruses. To further test this hypothesis, we fed mice one of three diets: 1) adequate in vitamin E, adequate in Se; 2) deficient in vitamin E, adequate in Se; 3) deficient in vitamin E, adequate in Se, with the addition of N,N'-diphenyl-p-phenylenediamine (DPPD). DPPD is a synthetic antioxidant structurally unrelated to vitamin E, which mimics its antioxidant properties. Serum α -tocopherol levels were depressed in the mice fed a vitamin E-deficient diet ($0.6 \mu\text{mol/L}$) as compared with mice fed vitamin E-adequate diets ($4.5 \pm 0.1 \mu\text{mol/L}$). Mice fed vitamin E-deficient diets supplemented with DPPD also had low serum α -tocopherol levels ($0.8 \pm 0.1 \mu\text{mol/L}$). When the mice were infected with CVB3/20 virus, DPPD-supplemented diets prevented the enhancement of myocarditis due to the vitamin E deficiency.

All of our observations can be readily rationalized on the basis that increased oxidative stress in the host increases myocarditis induced by CVB3 infection: 1) Se deficiency increases the pathology of CVB3-induced myocarditis; 2) vitamin E deficiency increases the pathology of CVB3-induced myocarditis; 3) consumption of peroxidizable fat (menhaden oil) increases the pathology of CVB3-induced myocarditis, and 4) DPPD prevents the increase in pathology due to vitamin E deficiency. In addition, Hiraoka et al.^{78,79} demonstrated protection against CVB3-induced myocarditis when mice are treated with superoxide dismutase.

Viral passage experiments with virus obtained from vitamin E-deficient mice also demonstrated the same nucleotide changes as for virus recovered from Se-deficient animals. This suggests a common mechanism of increased mutation in the deficient animals, which may be increased host oxidative stress. The fact that the changes in the virus were identical between vitamin E and Se-deficient mice suggests that the increase in virulence of the virus may reside in only a few nucleotide positions.

Viral quasi-species and nutritional status of the host

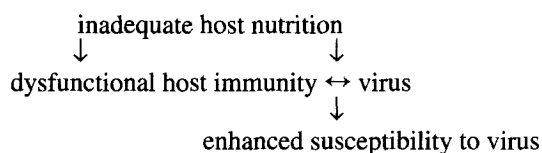
What is the mechanism for the change in viral genotype that occurs during replication in either a Se-deficient host or a vitamin E-deficient host? There are several possibilities. Like other RNA viruses, coxsackievirus has a high rate of mutation. Mutation rates of RNA viruses are in the range of 10^{-3} to 10^{-5} substitutions per copied nucleotide. This rate is at least 10^3 fold larger than the mutation rate for cellular DNA.^{80,81} The high mutation rate of RNA viruses is due to the RNA replicase lacking efficient proofreading and post-replicative repair activities.^{82,83} It has been suggested that RNA viruses replicate near the minimal fidelity compatible with maintaining their genetic information.⁸⁰⁻⁸³ However, not all mutations will be viable, because the success of a mutation depends on its ability to complete an infectious cycle and its overall fitness. Therefore, in an individual virus population, individual genomes that differ in one or more nucleotides will form the average or consensus sequence of the population. Thus, viruses exist as populations, or swarms of mutants, which has been termed quasi-species.⁸³ Thus, quasi-species are enormous and dynamic mutant distributions that have great adaptability.

Thus, the change in genotype of the CVB3/0 virus in the Se-deficient mice may be due to selection of a new consensus sequence. That is, the Se-deficiency allowed for the pre-existing mutant virus to outcompete the previous consensus sequence, either due to a faster replication rate, or an increase in fitness. Two possible mechanisms may operate in the Se-deficient or vitamin E-deficient animal that alter the pattern of quasi-species evolution. One possibility is that the same mechanism of oxidative stress damage to cellular DNA⁸⁴ also operates on replicating RNA genomes. Se is an essential co-factor for glutathione peroxidase, an enzyme important in limiting oxidative stress in the host. Vitamin E acts as a free radical scavenger. Thus, the pro-oxidant/antioxidant balance is shifted towards pro-oxidant in the Se- or vitamin E-deficient host. This increase in oxidative stress may then lead to direct damage of the RNA genome, increasing the mutation rate.

A second possibility is that the nutritional deficiency led to an impairment of the immune system. A number of nutritional deficiencies, including Se and vitamin E, leads to impaired immune responses.³ Indeed, our study found a decrease in T cell reactivity against both mitogen and specific viral antigen in Se-deficient or vitamin E-deficient animals. This impairment in immune function may lead to increased virus titers, and therefore, an increased probability of generating viral variants with new pathogenic potential. The impairment of immune function may be due to increased oxidative stress in the deficient host. Lipid peroxidation of immune cell membranes may lead to decreased activity. H_2O_2 can permeate cells and inhibit adenosine triphosphate (ATP) synthesis. Thus, generation of oxidants in a Se or vitamin E-deficient animal could damage immune cells, leading to impaired function.

These results demonstrate for the first time that a specific nutritional deficiency in the host can alter the genotype of a virus, thereby resulting in a more virulent pathogen. If these findings are generalizable to other RNA viral infections and other nutrients, then the nutrition of the host should be considered when any viral disease shows unexpected properties. For example, influenza pandemics often originate in China, which has widespread areas of Se deficiency. Human immunodeficiency virus is thought to have originated in Africa, by introduction of virus from a primate population into humans.^{85,86} Africa also has areas of Se-deficiency.⁸⁷

Based on our work, the unidirectional model of host nutrition-virus infection should be modified. The following model may be more appropriate:



This relationship demonstrates the affect of nutrition both on the host and the pathogen. As illustrated above, inadequate host nutrition can not only result in immune dysfunction in the host which may lead to increased susceptibility to viral infection, but can *directly* affect the virus itself. Once the viral genome has been altered, it can now affect not only nutritionally deficient populations, but well nourished populations as well.

Concluding remarks

It has been known for many years that nutritional status of the host can affect immune function. Both in vitro and in vivo studies have demonstrated that many immune functions are affected by either malnutrition or a single nutrient deficiency. It has commonly been assumed that any perturbation of the host immune system caused by inadequate nutrition would increase susceptibility to infectious disease. However, compared with studies examining the effect of nutrition on immune function, there are fewer studies documenting the effect of host nutrition on viral pathogenesis.

This paper has reviewed studies that examined the effects of various nutritional deficiencies on viral pathogenesis and induction of illness. On a mechanistic level, our current understanding of host-nutrition-virus infection interaction is inadequate. Host nutrition could affect 1) host cells by changing their vulnerability to virus infection, 2) host immune system, or 3) the virus itself. Further research is needed to address and clarify these relationships.

Collaborations between nutritionists and virologists, groups with seemingly divergent interests, are required to elucidate the relationship between nutrition and viral infection. Fostering this interdisciplinary research will advance the newly emerged area of "nutritional virology."

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Review

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