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Nutrition, Immunity, and Infectious Diseases in Infants and Children

An Overview

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In 1959, Scrimshaw *et al.* published a landmark review of the interactions of nutrition and infection, including a critical evaluation of the vast literature from both animal and human studies (1). Although they concluded that "few areas of investigation are more replete with unsupported statements of opinion, impression and speculation" and noted that many older studies could be disregarded because they failed to meet acceptable standards of modern research methodology, their systematic and critical review led them to conclude that malnutrition and infection interacted in one of two manners: *synergistic* or *antagonistic* (Table 1). Most often, the interaction resulted in a heightened severity and worsened outcome of infection, a relationship they termed *synergistic*. However, in certain situations malnourished individuals appeared to be protected when infected with particular infectious agents, a relationship they termed *antagonistic*. Now, 40 years after the publication of the Scrimshaw *et al.* review, at this workshop we are asking how much have we learned since then and how has this knowledge affected clinical and public health practice. This chapter reviews the *big picture*, and the detailed investigations of different states of malnutrition will be presented in subsequent chapters.

MALNUTRITION WORSENS INFECTIOUS DISEASES

Scrimshaw *et al.* clearly stated that chronically undernourished children are at great risk of infection and that repeated infections could trigger the rapid deterioration of nutritional status. They pointed out that "children who are basically undernourished

TABLE 1. *The nature of malnutrition-infection interactions*

Synergism: The situation where a nutritional deficiency results in increased frequency or severity of an infection.
Antagonism: The situation where a nutritional deficiency results in decreased frequency or severity of an infection.

are an easier prey to many infections and may die. Further, stress of any kind is likely to be followed by the development of . . . the kwashiorkor syndrome," overt protein-energy malnutrition with edema, a clinical presentation known to be associated with high case fatality rates. In addressing the underlying mechanisms of this interaction they noted that whereas "kwashiorkor can originate in dietary deficiency alone, . . . most cases are the result of synergism between infection and protein malnutrition" (1). Although noting the particular impact of diarrheal disease, whooping cough, malaria, and acute respiratory tract infections, they also emphasized that socioeconomic stress of many types (*e.g.*, social changes in the family, loss of a job, the death of a parent, or separation of the family) could also precipitate this deterioration in nutritional status. The likely consequence of such noninfectious stress was a deterioration in socioeconomic status leading to a secondary impact on nutritional intake. However, the idea that social stress might be a factor in precipitating overt protein-energy malnutrition was a remarkably prescient perspective in view of the current interest in the potential role of the neuroendocrine system in modulating the functional capacity of the immune system (2).

These relationships have been re-examined many times with increasingly sophisticated epidemiologic or laboratory methods in the past two decades in both developing country settings and in hospitalized adult surgical and medical patients in the industrialized world. The results have been consistent—malnutrition predisposes to greater susceptibility to infections and significantly worsens their consequences. However, the classification of malnutrition has usually been based on clinical, rather than laboratory, criteria, resulting in the lumping together of patients differing considerably in individual nutrient status. Biochemical assessments of specific nutrients now allow further classification according to individual mineral and vitamin status (3), whereas the use of body composition analysis, made possible by methodologic and technical developments, gives promise of further subclassification of subjects according to the impact of nutrient levels on the major body metabolic compartments (4). These refinements allow greater correlations of nutritional status with the risk of adverse consequences and streamline the development of preventative and corrective strategies, especially in the resource-limited developing countries.

INFECTION WORSENS NUTRITIONAL STATUS

Scrimshaw *et al.* also noted that the deleterious effect of infection on nutritional status is "a fact insufficiently recognized" (1). Unfortunately, 40 years later we can still say that this relationship remains insufficiently recognized. Scrimshaw *et al.*

used metabolic balance methods to assess nitrogen metabolism during infection, and showed clearly that clinical infections (*e.g.*, chickenpox) or even the mild infection induced by the attenuated live yellow fever vaccine virus, led to a state of negative nitrogen balance (5,6). They observed that nitrogen loss "may begin during the prodromal period before fever . . . appears" or "continue long after fever subsides" (1). The source of the nitrogen loss was subsequently demonstrated to be muscle protein by measuring the excretion of 3-methyl histidine, which is selectively released following catabolism of muscle protein and excreted in the urine. The breakdown of muscle protein releases amino acids into plasma; however, circulating amino acid levels do not rise (except for non-reutilized amino acids) because they are rapidly reutilized for the accompanying increased protein biosynthesis (7,8). However, this new anabolic activity is not directed toward the same proteins made in the preinfectious state. Rather, a transcriptionally regulated major shift occurs in the priorities for protein synthesis away from structural and transport proteins (*e.g.*, albumen or transferrin) to acute phase response proteins (*e.g.*, C-reactive protein, mannose-binding protein, α1-acid glycoprotein, and others) (Table 2) and the proteins of host defense and immune response (*e.g.*, complement, immunoglobulins and others) (9).

Aside from the general biological survival rationale for the shift from the synthesis of maintenance proteins to the production of urgently needed defense proteins under the stress of infection, the significance of most other aspects of acute phase changes is not well understood. One important acute change is the alteration in metabolism toward the utilization of amino acids for energy, either through metabolism of branched chain amino acids in muscle or the production of glucose in the liver by a number of mechanisms not, as previously thought, limited to hepatic gluconeogenesis (10). Scrimshaw *et al.* noted that "loss of urinary nitrogen is partly from greater energy requirements imposed by higher body temperature, but mainly from toxic destruction of protein. Nitrogen loss may continue long after fever has subsided or may begin during the prodromal period before fever . . . appears" (1). This has been well demonstrated in experimental human volunteer studies in which a mild infection has been induced and nitrogen balance is measured before, during,

TABLE 2. *Acute phase proteins in the inflammatory response*

Acute phase protein	Postulated role in host defense
Marked increases in concentration	
C-reactive protein	Fixes complement, opsonizes
Mannose-binding protein	Fixes complement, opsonizes
α_1-acid glycoprotein	Transport protein
Serum amyloid A	? Immunosuppressive
Moderate increases in concentration	
α_1-proteinase inhibitors	Limit proteolytic damage
C3, factor B of complement system	Increase complement activity
Ceruloplasmin	Oxygen scavenger to limit damage
Fibrinogen	Coagulation
Fibronectin	Cell adherence, opsonization

and after the febrile acute illness (6). Such studies clearly show that nitrogen losses are cumulative and maximal at the point at which the fever disappears and clinicians and patients consider the convalescent period to have begun. However, it takes much longer to restore nitrogen stores than it does to cause the losses, requiring both an infection-free period and adequate intake of good quality protein for efficient correction of acquired deficits (10,11). Neither of these conditions is likely to be satisfied for children in the developing world, and the next infectious insult will most likely add to the residual nutritional deficit from the prior episode. Repeated infectious diseases then result in the downward cyclical interaction observed between infection and nutritional status in these children, leading ultimately to the acute condition, kwashiorkor (10).

Another facet of the acute phase response is a rapid reduction in the concentration of serum iron, zinc, and vitamin A at the onset of infection, which is caused by the enhanced synthesis of transport proteins for the intracellular uptake of these nutrients (12). An increase in serum copper is also observed as increased synthesis of the copper transport protein ceruloplasmin carries copper in the reverse direction from the intracellular to extracellular compartments. The reduction in iron and zinc has been interpreted by some to be a natural defense mechanism designed by nature to reduce the availability of these essential nutrients to invading microorganisms, an attributed host response termed "nutritional immunity" (13).

A number of reasons are seen to doubt this explanation. For example, in the case of iron, microbial pathogens actually use the reduced availability of free iron as a signal to upregulate their own iron acquisition mechanisms, including the rapid production of high affinity iron-binding acquisition and uptake proteins. These systems compete extremely well with mammalian host iron-binding proteins to ensure an adequate supply for the pathogen. Hypoferremia, therefore, does not deprive the organisms of the needed iron. In addition, many pathogens also use low free iron as a signal for transcriptional upregulation of virulence genes. This commonly occurs through an iron-responsive gene called *fur*. The product of this gene, the Fur protein, is an iron-binding protein that, in the presence of adequate iron, binds to a consensus sequence in the promoter region of iron-regulated genes, thereby blocking transcription. Iron-depleted Fur does not bind to its consensus sequence, allowing the transcription of the iron-regulated genes. Use of these mechanisms for low free iron as the regulatory signal for gene regulation is clearly counterproductive to any role hypoferremia might play in host defense.

On the other hand, the cellular uptake of iron, zinc, and vitamin A can have important direct and positive effects on host defense. For example, iron- and zinc-containing metalloenzymes are essential for the synthesis of DNA, which must precede cell replication. Therefore, uptake of iron and zinc by cells of the immune system will promote cell division, a necessary event to the expansion of cell populations involved in host defense responses to invading microorganisms. Diminished antigen-specific amplification of lymphocyte, lymphocytes, and phagocytic cells is likely to be the difference between an asymptomatic or mild infection and a severe or even fatal one. Furthermore, zinc metalloproteins produced by the thymus (*e.g.*, thymulin) are criti-

cal for the functional maturation of one T lymphocyte, which is not only involved in cell-mediated immunity but also provides help to B cells in the differentiation to antibody-producing plasma cells.

Vitamin A metabolites play important roles in the intracellular milieu where they serve as critical transcriptional regulators affecting, among other genes, many involved in immune function and host defense. Vitamin A plays a role as an antioxidant to limit tissue damage from oxidative processes initiated by host defense cells. For example, neutrophils and monocyte or macrophages produce oxidative metabolites to kill infectious microorganisms or virus-infected cells but these can initiate *bystander* damage as well unless contained. Thus, the acute shift of all three of these micronutrients directly enhances host defense mechanisms whether or not any indirect effect is exerted through the reduction in plasma levels of these micronutrients that results in a diminished capacity of invading organisms to multiply (14).

GENERAL HOST RESPONSES AND THEIR RELATION TO IMMUNE ACTIVATION

Infections are associated with a set of common clinical manifestations, including fever, chills, anorexia, myalgia, and fatigue. These events are initiated by small peptide cytokine mediators, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, released from inflammatory cells activated by infection and acting on the temperature regulatory centers in the hypothalamus (15). Fever may have beneficial effects on host defense by enhancing the speed of metabolic reactions and inflammatory and immune cell function; however, increased temperature also significantly increases energy consumption. Chills are a manifestation of involuntary muscle contractions, initiated by neural pathways activated by cytokines to generate the heat required to raise body temperature. Anorexia, which results in a reduction in nutrient intake in the face of increased metabolic demands, means that an alternate source of nutrients is needed. This source is found in body stores—initially glycogen, stored in the liver—and once that is exhausted, in the conversion to glucose of amino acids derived from muscle catabolism (16). Myalgia is the physical manifestation of proteolysis (17). IL-1 also induces slow wave sleep by a central action in the brain, which accounts for the feeling of fatigue. This has the benefit of reducing energy needs and partially compensating for the reduced food intake caused by anorexia.

This is a remarkable coordination of host responses that, on the surface, appear to be unrelated clinical events. The coordination is even more striking, because these cytokines also are essential in the activation of the immune response (18). However, cytokine responses are impaired in the malnourished host (19,20), accounting for many of the altered immune responses in the malnourished host (21,22). We are at the beginning of our understanding of the mechanisms involved (23), but because of the remarkable increase in our knowledge of cytokine regulation of metabolism and immune responses, we are finally able to move from phenomenologic to mechanistic studies (24), as will be summarized in this symposium. These studies will provide

the basis for future therapeutic interventions in malnourished hosts, leading to an improvement in both nutritional status and immune function (25).

SUMMARY

Nutrition–infection interactions are complex and bidirectional; they lead to progressive deterioration in both body composition and host defenses. Impaired host defenses condition the host to more frequent and more severe infections, thus increasing the spiral of nutritional deterioration. Over the past two decades, the remarkable intertwining of the metabolic and host defense responses to infection has been linked to mediator peptides released during the inflammatory response. The role of specific nutrient deficiencies, alone or in combination, can now be studied because of improved tools for defining nutritional status, better measures of host defense, and aids to assess the production and effect of cytokine mediators. Forty years after the landmark first review by Scrimshaw *et al.* we are on the brink of really understanding and then controlling the pathophysiology associated with infection and malnutrition.

REFERENCES

1. Scrimshaw NS, Taylor CE, Gordon JE. Interaction of nutrition and infection. *Am J Med Sci* 1959; 237: 367–403.
2. Reichlin S. Neuroendocrinology of infection and the innate immune system. *Recent Prog Horm Res* 1999; 54: 133–81.
3. Hensrud DD. Nutrition screening and assessment. *Med Clin North Am* 1999; 83: 1525–46.
4. Brodie DA, Stewart AD. Body composition measurement: a hierarchy of methods. *J Pediatr Endocrinol Metab* 1999; 12: 801–16.
5. Wilson D, Bresani R, Scrimshaw NS. Infection and nutritional status. I. The effect of chickenpox on nitrogen metabolism in children. *Am J Clin Nutr* 1961; 9: 154–8.
6. Gandra YR, Scrimshaw NS. Infection and nutritional status. II. Effect of mild virus infection induced by 17-D yellow fever vaccine on nitrogen metabolism in children. *Am J Clin Nutr* 1961; 9: 159–63.
7. Feigin RD, Klainer AS, Beisel WR, Hornick RB. Whole-blood amino acids in experimentally induced typhoid fever in man. *N Engl J Med* 1968; 278: 293–8.
8. Beisel WR. Metabolic response to infection. *Annu Rev Med* 1975; 26: 9–20.
9. Suffredini AF, Fantuzzi G, Badolato R, Oppenheim JJ, O'Grady NP. New insights into the biology of the acute phase response. *J Clin Immunol* 1999; 19: 203–14.
10. Keusch GT. Host defense mechanisms in protein energy malnutrition. *Adv Exp Med Biol* 1981; 135: 183–209.
11. Chevalier P, Sevilla R, Sejas E, Zalles I, Bellmonte G, Parent G. Immune recovery of malnourished children takes longer than nutritional recovery: implications for treatment and discharge. *J Trop Pediatr* 1998; 44: 304–7.
12. Thurnham DI. Impact of disease on markers of micronutrient status. *Proc Nutr Soc* 1997; 56: 192–7.
13. Weinberg ED. Nutritional immunity. Host's attempt to withhold iron from microbial invaders. *JAMA* 1975; 231: 39–41.
14. Keusch GT. Micronutrients and susceptibility to infection. *Ann NY Acad Sci* 1990; 587: 181–8.
15. Dinarello CA, Bunn PA Jr. Fever. *Semin Oncol* 1997; 24: 288–98.
16. Chang HR, Bistrian B. The role of cytokines in the catabolic consequences of infection and injury. *JPEN* 1998; 22: 156–66.
17. Cooney RN, Kimball SR, Vary TC. Regulation of skeletal muscle protein turnover during sepsis: mechanisms and mediators. *Shock* 1997; 7: 1–16.
18. Biron CA. Role of early cytokines, including alpha and beta interferons (IFN-alpha/beta), in innate and adaptive immune responses to viral infections. *Semin Immunol* 1998; 10: 383–90.

19. Beisel WR. Infection-induced malnutrition—from cholera to cytokines. *Am J Clin Nutr* 1995; 62: 813–9.
20. Sauerwein RW, Mulder JA, Mulder L, et al. Inflammatory mediators in children with protein-energy malnutrition. *Am J Clin Nutr* 1997: 65; 1534–9.
21. Morlese JF, Forrester T, Jahoor F. Acute phase protein response to infection in severe malnutrition. *Am J Physiol* 1998; 38: E112–7.
22. Woodward B. Protein, calories and immune defenses. *Nutr Rev* 1998; 56: S84–2.
23. Hardin TC. Cytokine mediators of malnutrition: clinical implications. *Nutr Clin Pract* 1993; 8: 55–9.
24. Klasing KC. Nutritional aspects of leukocytic cytokines. *J Nutr* 1988; 118: 1436–46.
25. Moldawer LL, Lowry SF. Interactions between cytokine production and inflammation: implications for therapies aimed at modulating the host defense to infection. In: Cunningham-Rundles S, ed. *Nutrient modulation of the immune response.* New York: Marcel Dekker, 1993: 511–23.

DISCUSSION

Dr. Suskind: One question I have relative to an area you previously touched on is the effect of the microbe on the host in terms of the cytokine response, leading to a change in the production of visceral proteins. Could you comment on that briefly?

Dr. Keusch: I specifically avoided dealing with cytokines in order to present the larger picture. However, I think we are going to hear a great deal about the role of cytokines as the intermediary between the organism and the host. We now understand cytokines to be a set of small peptides that have regulatory properties. We have yet to discover all the cytokines there are—every time you pick up a journal there is a new one. At our present level of sophistication, we now understand that cytokines constitute the intermediary between the organism and the host, both activating and regulating the immune response, as well as altering the priorities for metabolism, changing the transcriptional activation of genes that result in changes in the synthesis of some visceral proteins, and increasing the synthesis of some of the acute phase proteins. To fully understand the system in mechanistic terms and find targets for interventions, we need to be able to meddle in the inflammatory response. We would love to be able to enhance it when it is inadequate, or to suppress it when it is overactive. I believe the promise of being able to do that is just ahead of us, with the completion of the sequencing of the human genome. We are going to find an enormous number of genes for which there is no known function, and where there are no homologies that we can use in animals. The only way we are going to begin to understand those genes is to see when they are present and activated in clinical situations. Thus, we need clinical investigation to tell us when a gene may be related to a human disease, or to human health. Once a gene is identified and the gene product discovered, a wonderful opportunity exists for therapeutic advance. This is the future for the pharmaceutical industry—using genetics to identify specific targets among genes and gene products or receptors for gene products, and, therefore, to manipulate the host response. So you are right: cytokines are at the center of the scientific revolution, because they are at the center of the host response.

Dr. Klish: I was fascinated by your discussion of microbial utilization of iron. You are fully aware that this a very contentious area in the United States, as it relates to iron supplementation in infancy. You started your statement by saying that in theory one should maintain iron deficiency in these children, but I do not think that is what you were actually saying at the end of your paper, when you talked about the way organisms utilize iron. Could you say what you really meant?

Dr. Keusch: Thank you for pointing that out. I am not a fan of the nutritional immunity hypothesis that states that the acute phase reduction in serum iron is geared by nature to remove iron from microorganisms. The microorganism does not care. It has its own mechanisms stim-

ulated by low free iron to activate the systems to acquire the iron it needs, and the low iron can also be used as a signal for the production of virulence factors. So from that perspective, it does not make any difference what the iron level is. On the other hand, iron deficiency in the host impairs the host's immune response. So iron deficiency needs to be dealt with in the same way as other nutritional deficiencies—we need to correct it in populations. The iron and immunity hypothesis proposes that situations of iron excess cause infection. This directs our attention toward iron availability, and the possibility that it might be a good thing for people to be iron deficient. That is a very unsophisticated view of the interaction between high iron and the host, which also impairs the host immune response. High iron results in membrane and DNA damage through oxidative mechanisms, and organisms that thrive under those circumstances are the ones that have failed to evolve an iron-obtaining mechanism. They actually require situations of high iron in order to be able to grow and, therefore, to be virulent. Thus, on the one hand I am not a proponent of keeping the world iron deficient because the consequences of iron deficiency are severe and highly prevalent and they need to be dealt with by public health measures. On the other hand, you do not want to give parenteral iron in the course of an acute infection in individuals who are poorly nourished and have very low levels of circulating iron-binding proteins. These relationships need to be fully understood from the prospective of the host, the microorganism, and the host response.

Dr. Chandra: I think if we were to believe in the iron nutritional immunity hypothesis, we should also have to extend it to most other micronutrients. The basis for the hypothesis is that as serum iron drops during infection, it must be good for the host. Could we not say the same thing about zinc or copper? Most micronutrient levels in the serum fall during infection, and on that basis I do not think we should necessarily accept that a fall in serum iron contributes to increased resistance to infection. Maybe it has some other value for the body. One other comment I want to make is that we also need to consider what form of iron we give, either in prevention or treatment. We know that different forms of iron can have different effects in the oxidative pathways. That could be a third factor in the equation between microorganisms and nutrients. Finally, we may have underestimated the binding between iron and iron-binding proteins in the body. We have always felt that microorganisms are superior in extracting iron from host proteins, but I think that will also need to be re-examined in the light of new observations.

Dr. Suskind: Dr. Keusch, you mentioned something about gastric peptides in the gastrointestinal tract. I am not aware of any such studies in children who are malnourished. Could you comment on whether they may be one of the factors, in addition to decreased gastric acidity, leading to small bowel overgrowth?

Dr. Keusch: I am not aware of any studies on this. It is an area that could be explored. These antimicrobial peptides are not only present in the human gastrointestinal tract, they also form one of the defenses used by amphibians, which have a much more primitive immune system. They are being identified, isolated, and studied as potential therapeutic agents. They are different from other antimicrobial agents that we know about, and relatively little is understood about their regulation in the gastrointestinal tract, or what role, if any, they play in regulating the normal flora. In particular, we do not know whether any deficits occur in the synthesis of these proteins in the presence of protein-energy malnutrition or other circumstances of nutritional deficit. This is another frontier area for us to work on into the next century.

Dr. Marini: I think we should differentiate between iron in the gastrointestinal tract and the iron in the blood, remembering especially that maternal milk contains a lot of lactoferrin, which binds iron in the gastrointestinal tract. Another matter is the question of free radicals. We blame free radicals for disease, and you showed data suggesting that low antioxidant diets in Cuba are associated with increased disease. But consider the model of the full term, normal

neonate, wherein are increased free radicals because of *oxygen shock*. Under these circumstances, the free radicals are said to be good for the baby because they prime the immune system. On the other hand, we have proof that if you give a lot of vitamin E, which is an antioxidant, to preterm neonates, infection increases (1). So I think that an excess of free radicals can be wrong in certain cases. In normal individuals, however, if nature makes free radicals it probably has a good reason (2).

REFERENCES

1. Johnson L, Bowen F, Hermann N, et al. Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enerocolitis in infants with birth weight 1,500 grams or less. *Pediatrics* 1985; 75: 619–38.
2. Guerini RC, Longaretti A, Viani P., Marini A, Cestaro B. Lipid peroxide levels of healthy full term neonates. Role of lipid composition and the mode of delivery. *Developmental Physiopathology and Clinics* 1998; 8: 195–204.