July 2001 Issue | Ranjit Kumar Chandra, MD

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Welcome to *Functional Medicine Update* for July 2001. This month we continue our discussion of the prevention of diseases of age, with specific emphasis on healthy aging. We will focus on nutrition and immunity related to protection against age-related diseases, and the way single nutrients and complex nutrition in our diet influence both cell-mediated and non-cell-mediated immunity.

We begin with a perspective from a recent White Paper published by the Institute for the Study of Aging and the International Longevity Center. This report, titled "Achieving and Maintaining Cognitive Vitality with Aging," is available through the Institute for the Study of Aging. It reviews a workshop with international experts in the field who studied how to prevent cognitive decline with aging. You can secure a copy of this monograph by writing to the Institute for the Study of Aging, 767 Fifth Avenue, Suite 4600, New York, NY 10153. The fax is 212-572-4094.

The workshop report defined a number of important areas in protecting against loss of cognitive function. They include intellectual stimulation and lifelong learning, continued and regular exercise, and daily activities that provide social stimulation. Stress reduction, another factor on this list, goes back to Dr. Robert Sapolsky's description of chronic stress and brain aging. Six to eight hours of regular sleep are also important for protection against premature brain aging, as is emotional stability. Nutrition should contain adequate levels of specific nutrients necessary to promote brain function and immune balance. The report also contains a discussion of antioxidants, which we will discuss with our Clinician of the Month. How do specific nutrients, such as antioxidants, play a role in protecting immune and cognitive function?

Additional Agents to Promote Brain Function in Aging

Others have suggested other agents that may be important for protection against loss of cognitive function. Included are DHEA, melatonin, testosterone, human growth hormone, and various types of herbal and botanical materials. Suggested herbal remedies include hypericum in St. John's Wort for depression, silymarin for oxidative stress, and *Ginkgo biloba*for protection of cognitive function.

Although these substances have met with enthusiasm in some quarters, they probably pale in comparison to the other factors I have described as impacting on brain function through decades of living. Lifelong learning, exercise, daily activities, stress reduction, sleep, emotional stability, and nutrition, probably play the principal roles in shaping the genotype into its phenotype, or urging a phenotype of healthy brain aging and its association with healthy immune function.

Genes and Cognitive Decline: A Cross-Cultural Study

Many people have assumed that diseases of premature brain aging are hard-wired into the genes, and we can do little to overcome our genetic destiny that codes for premature brain-aging and immunologically related disorders like autoimmune disease.

That association was the subject of a paper that appeared in the *Journal of the American Medical Association*. This cross-cultural study looks at the incidence of dementia and Alzheimer's disease (AD) in two communities. One group consisted of black ethnic individuals residing in Nigeria; the other was African Americans living in Indianapolis, Indiana. The study attempted to see whether genes or environment were major predictors for loss of cognitive function with aging.

A number of confounding variables exist when comparing individuals living in Nigeria to African Americans in Indianapolis. Taking several of these factors into account through good statistical methods, the researchers found some interesting differences between the two groups. This is the first report of differences in the rate of incidence of dementia and AD in studies of two populations from nonindustrialized and industrialized countries using identical methods and the same group of investigators at both sites. Further exploration of the population differences may identify potentially modifiable environmental or genetic factors to account for site differences in dementia and AD, which appeared much higher in the Indianapolis African Americans than in their counterparts in Nigeria.

The editorial that follows this article causes us to reflect upon the genetic determinism view of the diseases of aging. The population of African Americans older than age 65 and therefore at risk for AD and other dementias is increasing even faster than in the white population in the United States. In general, studies have found rates of dementia in African Americans comparable to or higher than in whites. This is in contrast to developing countries, such as the individuals in Nigeria, where vascular dementia is much more prevalent and is seen as a greater risk for dementia than AD.

Familial Alzheimer’s Risk—the ApoE4 Allele

Whereas the familial risk to AD appears similar in African Americans and whites, the specific factors conferring genetic susceptibility and their mode of action may differ between these groups. The most widely accepted genetic determinant in white Americans for AD is the apoE4 allele. This particular allele can be homo- or heterozygous. If it is homozygous, you have inherited the apoE4 allele from both your mother and your father. In this case, you have a risk of AD between 12.5 and 14.9 times that of your peers who do not possess this allele. In the heterozygous form, in which you have only one of the two alleles, you have between 2.7 and 3.2 times the risk of developing AD compared to those who do not carry the apoE4 allele.

The apoE4 allele provides the strongest association between a genetic marker and the onset of AD discovered thus far. The E4 association is also evident in Japanese cross-cultural studies. The association with E4 homozygosity also exists in African-Americans, but is greatly reduced relative to that seen in Americans of European descent. The frequency of the E4 allele cannot explain the differences in AD seen between the Nigerian and American cohorts, since it was virtually the same in both. Curiously, the AD/E4 connection does not seem to apply in two African cohorts, Nigerian and Tanzanian. This could argue for either environment/gene interaction, or be the result of genetic ad mixture brought about by the

forced emigration of West Africans.

Ratio of AD to Vascular Dementia

Comparing the ratio of AD to vascular dementia is also informative. In Western nations, the prevalence of moderate to severe dementia among those older than 65 years is 4.6 percent, with an Alzheimer's-to-vascular dementia ratio of 1.7:1, meaning AD occurs almost twice as often as vascular dementia. In Japan, the prevalence of dementia is similar, about 4.5 percent, but the ratio is reversed. The rate of AD to vascular dementia is 0.5, which means vascular dementias occur almost twice as often as AD. Although the rate of dementia is similar, the breakdown into the different types of the etiology is absolutely reversed.

This difference has an obvious association with the greater numbers of strokes in Japan versus in the U.S. In cross-cultural evaluations of Japanese Americans in Hawaii and Washington State, researchers found that as people migrated from Japan to Hawaii or Washington State, the ratio of vascular dementia to Alzheimer's dementia changed. In Japan there was a higher vascular dementia/ low Alzheimer dementia ration, and in one generation that ratio had become the same as it is in the United States, a higher AD/lower vascular dementia ratio.

Genes and Alzheimer’s Disease

That information strongly suggests AD is modifiable based on environment. The individual’s genes did not change as he or she moved from Japan to the United States. What changed was the environment in which the genes were bathed. We now have a much more plastic construct around the development of age-related diseases, based on this concept that genes are bathed by different experiences, nutrition, and environment, which creates an phenotypical outcome in their expression. We now are focusing on what you might call functional neurology.

The study in *JAMA* found the age-adjusted prevalence rates of AD and dementia are significantly lower in Yoruba, Nigeria, than in African Americans living in Indianapolis. Therefore, we start seeing a three- to four-fold difference in the overall prevalence of dementia in individuals who are genetically similar. The AD-versus-vascular dementia ratio also changes, suggesting a great degree of plasticity in the way these genes are expressed in different environments. The age-standardized annual incidence rates for both dementia and AD are two to three times lower in Yoruba than among African Americans in Indianapolis, based upon this study.

Environmental Factors and Alzheimer’s Incidence

The explanation is obviously very complex. We could use a number of variables to describe these differences. If the estimates are accurate, they imply a significant non-genetic factor for vulnerability to AD as it relates to environment. This explanation indicates interesting associations with the apoE4 genotype. The penetration, both herterozygous and homozygous, of the apoE4 allele is the same in blacks living in Indianapolis and those in Nigeria, Tanzania, or Kenya, suggesting the E4 allele prevalence argument is insufficient to explain AD differences in the two cultures.

This leads to other questions. Could other risk-enhancing or risk-protective genetic factors account for

some of the differences in incidence rates that are modified by the environment in their expression? Could things like diet and exercise increase or decrease the risk of expression of AD in these individuals?

Dietary Fat and Modifying E4 Expression

As we have said in previous editions of *FMU,* the apoE4 allele may not be fully expressed in its genotype of oxidative stress until it is exposed to a diet very high in saturated fat. This may mean the person who inherits the E4 allele genotype is exquisitely sensitive to saturated fat. If that individual consumes the American diet high in saturated fat, he or she may have increased risk of developing AD through increased oxidative stress, effects on macrophage attachment to endothelia, and other influences on cell immunological function. When transgenic mice that are prone to developing AD were fed a hypercholesterolemic diet high in saturated fat, for example, they developed significantly higher levels of amyloid beta peptide.

This result suggests alterations in amyloid precursor protein associated with increased oxidative stress that are in response to a high-fat, high-cholesterol diet. The expression of these genetic factors, which we may have thought of as "death sentences," may be more modifiable if we recognize them and pattern the individual’s environment, nutrition, and lifestyle to be consistent with his or her specific genetic needs.

Possibility of Modifiable Factors in AD

In summary, the authors of the editorial about the epidemiological cross-cultural study in Ad state the following:

"If modifiable factors such as diet were found conclusively to modulate the risk of AD to the degree suggested by this research, then we would all indeed rejoice at the implications. And in the seemingly endless tug-of-war between genetic and nongenetic influences in disease, new emphasis will emerge not only on the environmental factors, but also on the complex interactions between genetic predisposition and environmental triggers. While this research is only one step and the first of many needed to establish such a connection, the possibility that unique genetic and environmental risk factor profiles could be established could substantially alter our current understanding of AD. If such profiles could be established, cognitive enhancing treatments might be tailored to a particular risk group."

Functional Medicine Approach to AD

That editorial provides an excellent example of the functional medicine approach to disease prevention and management and leads into the discussion with Rajit Kumar Chandra, MD, this month's Clinician of the Month. Dr. Chandra is a pioneer researcher in the area of nutrients and immunity. He has helped us understand the gene/nutrient relationship, with specific focus on immunological status through the aging process.

In an editorial in the *Journal of the American Medical Association*, titled "Graying of the Immune System. Can Nutrient Supplements Improve Immunity in the Elderly?", he wrote:

"It is recognized that nutrient intake should not only prevent the classic deficiency diseases, but also could reduce illness and improve health. The type of nutrients and the quantity required to achieve such a

beneficial effect varies with the index being studied and whether more than one nutrient is being administered simultaneously. For some nutrients, the amounts proposed as being healthful apparently cannot be provided by a reasonable quantity and variety of natural foods. Thus, nutrient supplements may be important for health promotion and prevention of certain chronic diseases. This view goes against the prevailing dogma in nutritional science that a balanced diet is sufficient to achieve all nutritional objectives. Aging is associated with a reduction in many immune responses in most, but not all, elderly individuals."

Immune Function in the Aging Process

Immune dysfunction, as assessed by the prevalence of autoantibodies, also increases in the elderly. Dr. Chandra goes on to state:

"The era of nutrient supplements to promote health and reduce illness is here to stay. In selected groups such as the elderly, there is overwhelming evidence of immunologic enhancement following such an intervention. Some data suggest that a reduction in the incidence and duration of infection may also occur. In North America, a year's supply of micronutrient supplementation costs less than 3 visits to a physician and much less than hospitalization for 1 day. Thus, these preliminary data suggest that a micronutrient supplement may be cost-effective prevention intervention in old age."

"Deficiencies of vitamins and trace elements are observed in almost one third of all elderly. It is expensive and impractical to estimate dietary intake or blood levels of various nutrients in individuals. Since there is no evidence to suggest that physiological amounts of vitamins and trace elements given for prolonged periods have any toxic or adverse consequences and given the high prevalence of deficiencies of several micronutrients in old age, it would be prudent to opt for a suitable micronutrient supplement in modest amounts for all elderly individuals in order to achieve the maximum physiological and health benefit with the least risk of toxicity.

INTERVIEW TRANSCRIPT

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JB: Each of us has mentors to whom we look for guidance in our thinking. One of my mentors is Dr. Ranjit Chandra, the University Research Professor at Memorial University of Newfoundland, and Director of Immunology at the Janeway Child Health Centre in St. Johns. In the past 20 years, he has been a leader in the area of nutritional immunology. He is the director of the World Health Organization Centre for Nutrition and Immunology and is currently the first Carnegie Visiting Professor at Johns Hopkins University. His combined role as doctor/medical researcher has helped us understand the role of nutrition on various aspects of cell-mediated and non-cell-mediated immunity.

Welcome to FMU, Dr. Chandra. How did you move from pediatrics to nutritional immunity as the focus of your professional career?

RC: The story began in India where I was working in a medical school in the Department of Pediatrics. As most people working in such a setting would know, there were many children admitted each day with infection. We would often lose at least 10 or 15 percent of them within a day, mainly because of the underlying malnutrition. This led to the thinking that nutrition is a key element of immunity and resistance to infection. Beginning in the 1960s, we started to investigate this on a more systematic basis.

Nutrition and the Elderly

JB: In the 1980s and 1990s, you published a number of papers I consider to be primary resources in the field. In one that appeared in the Lancet, you looked at the effect of vitamin and trace element supplementation on immune responses and infection in elderly subjects. That paper opened the minds of a lot of doctors to the realization that a diet of variety and moderation may not be enough to support the immune systems of aging individuals whose diet intakes are questionable. Would you tell us about this evolving story of nutrition in the elderly?

RC: Yes. I will take a few minutes first to review the background. We know that as many as 40 percent of seniors, even in industrialized countries like the United States, Canada, and Western Europe, have low levels of many nutrients. Their status would be defined as nutritional deficiency. We also know that many of them have more frequent and prolonged infection. Putting the two things together, we looked at a group of 96 subjects, apparently healthy and living independently, and divided them into two groups. One group received a supplement of all the vitamins and trace elements; the other group was on a placebo. The amounts of supplements we gave them were within physiological limits; they were not mega doses.

Not unexpectedly, we found improvement in immune responses like cell-mediated immunity, NK cell number and activity, interleukin 2 production, and antibody response to flu vaccine in the supplemented group. What came to some extent as a surprise, however, and was most heartening, was that the group receiving the supplements had less infection—23 days in a period of 12 months, compared with 48 days in the placebo group. I think this clearly showed in a fairly well designed trial, that a supplement is needed in elderly people.

Immune System Changes with Nutritional Relationships

JB: In your McCollum Award lecture, published in 1991 in the American Journal of Clinical Nutrition, you wrote about lessons from the past and insights into the future regarding nutrition and immunity. Many practicing physicians have probably not studied the impact of nutrition or specific single nutrients on the immunological system. Dr. Beisel, in a paper in the Journal of the American Medical Association, wrote about single nutrient effects on immunological function. What kinds of changes in the immune system might one suspect have nutritional relationships?

RC: I think every aspect of immunity can be affected, depending on the nutrient involved and the extent or severity of deficiency. Some nutrients, like zinc, have a very wide-ranging effect on immune responses and risk of infection. Others, such as iron, may have more effect of phagocyte function, compared with, let us say, the complement system. I think there is no doubt that most essential nutrients, both vitamins

and trace elements, affect the immune system.

I had the privilege of being in the group that Dr. Beisel chaired, based on that report in JAMA. Most members of the medical community now do believe that in hospital settings, especially in more serious situations like intensive care units, or after surgery, nutrition plays a key role in maintaining immunity and preventing serious infection.

Autioantibody Increases and Aging

JB: As you've explained, delayed hypersensitivity, reduced interleukin production, decreased lymphocyte response to mitogens, low sero-conversion, and decreased antibody production are associated with aging and nutritional status. One factor that may seem paradoxical to some people is the increased level of autoantibodies observed in aged individuals. How do we explain what appears to be the immune system working overtime, while it is also, in certain aspects, not working effectively?

RC: Although it may seem paradoxical, it is quite logical if you look at how the immune system works and how interactions take place between different aspects of immunity. Some parts of the immune system have a surveillance function. They keep the balance. The so-called good immunity is mainly mediated by T cells and depends on these cells producing various cytokines like interleukins and gamma interferon. Other aspects of the immune system are kept in check by this good immunity. You mentioned autoimmunity. It makes sense that if your protective immunity is reduced, then the surveillance is lost to some extent, and diseases like autoimmune disorders and cancer will increase. In the last five years, we have also learned that a balance exists between the TH1 cell and the TH2 cell. If your immunity to infection is impaired, you may have more allergies as well. It's an interesting new concept that young children should be exposed to some infection, because this will protect them from developing later allergies.

Autoimmune as Complex Defense Mechanism

JB: Clinicians often believe the suppression of cell-mediated immunity doesn't necessarily correlate with autoimmunity. This cross-talk you're describing between suppression of localized immune defense and its effect on the lack of recognition of self versus non-self is clinically very interesting. We are currently seeing more and more autoimmune disorders appearing in younger individuals.

RC: You are right. We have to recognize the immune system is a complex host defense mechanism, and all its aspects don't necessarily move in the same direction. Given certain environmental factors, like diet, some aspects may be impaired, but others may be working overtime and produce disorders as a result.

Allergen Exposure in Childhood or Infancy

JB: You raised an interesting point about nutrition and allergen exposure in youth or even in infancy. You wrote an interesting article, titled "Food Allergy and Nutrition in Early Life: Implications for Later Health," which appeared in the Proceedings of the Nutrition Society last year. Would you describe that paper for us?

RC: Briefly, we recognize that in the last 15-20 years, there has been an increasing incidence of allergic

diseases in children. The reasons are not entirely clear. It may be our houses, which are now very tightly constructed. Substances like house dust mites and tobacco smoke are all trapped within the house. Also, of course, genetic factors are important. A child with a family history of allergy should be put on a restricted diet from the time of birth. By this I mean he should be breast-fed, if possible, and then introduced to other types of protein like cow's milk, in a very gradual fashion. The most serious food allergies are due to egg, fish, and peanut, would indicate that these food items should be introduced much later. For example, we now all believe that peanut products should not be given until three years of age. All this makes a difference, in addition to the environmental control of dust, tobacco smoke, and so on.

Soy Formula and Food Allergies

JB: Do you believe soy formula is less likely to cause allergy in infants than other types of infant formula, based on its immune potential?

RC: Many people have used soy as an alternative to cow's milk formula to prevent allergies, but more than 25 well-designed studies have all shown this does not happen, that soy formulas are not protective against food allergy. In fact, soy itself can be quite allergenic. If you take children who already have allergy to milk and put them on soy, as many as 40 percent will developed hypersensitivity to soy, as well. I strongly feel that the best formula to go for in such a situation, whether you are talking about prevention or treatment, is a hydrolyzed or a predigested formula. Depending upon the situation, you may use a partially hydrolyzed formula, which is available in two or three different brands, or you can go for the highly hydrolyzed formulas. Instead of soy, the evidence supports the use of a hydrolyzed formula, which would be beneficial not only for treatment, but even for prevention.

Nutrition and Exercise

JB: We've talked about nutrition and aging, and then we've gone to the other end of the continuum, nutrition in infancy, as it relates to the immune system. I think that leaves an interesting story in between which is nutrition for the strenuously exercising athlete. Many athletes have wondered whether their heavy exercise program increases their immunological potential or causes immune suppression. If so, at what level does that occur? In female athletes, does it relate to the loss of their menstrual period, and difficulties with late or certain hormone balances? What have you learned about the nutritional status of young female athletes and its relationship to their immune system?

RC: I think we have to consider several confounding factors in this particular relationship. If you look at young female athletes who are participating in very vigorous programs, or ballet dancers who intentionally keep their weight quite low, there are other consequences. There could be psychological problems. They could develop frank anorexia nervosa or bulimia. In studies we conducted in Spain last year, we found the immune systems of these girls are significantly impaired. They are not impaired to the extent we find in protein energy malnutrition or severe nutrient and micronutrient deficiencies in developing countries, or even in the elderly, but there is a substantial reduction in responses. Many of them get more infections. It's a common experience among marathon runners, for instance, that after they run the race, within about 24-48 hours, most of them will come down with a cold. I think this could reflect the adverse effects of very severe, prolonged exercise on immunity.

On the other hand, moderate, sustained exercise actually boosts the immune system. We have shown this

quite clearly in the elderly who, if they exercise gently, say walking or swimming, even 25 minutes three or four times a week, have a better immune system compared with those who are sedentary. Once again, we have to talk of a balance, neither too little nor too much.

Zinc as Important Micronutrient

JB: I'd like to discuss some single nutrients and their relationship to the immune system. A number of years ago Dr. Lucille Hurley at the University of California at Davis conducted research on zinc nutrition in primates. She found, I believe, that zinc deprivation of the mother adversely impacted the immune systems of the offspring. It took something like two to three generations of repletion to bring them back to the F0 generation. Tell us about the importance of zinc for the developing immune system and how that relates to infant and child nutrition in today's world.

RC: I think zinc is among the four most important micronutrients that have a profound effect on the immune system. The late Lucille Hurley certainly showed that if mothers were deprived of zinc, even pre-gestation and certainly during pregnancy and lactation, then their offspring had reduced antibody responses to antigens. When these offspring were mated with healthy males, even though they were no longer deprived of zinc, the second generation, or grandchildren, if you will continued to show some depression of the immune system. It wasn't as profound as in the animals that were actually starved or deprived of zinc. So, it is true that nutrition during pregnancy, or even pre-pregnancy, has a very important and perhaps a prolonged effect on the immune system of infants. That's been shown in rodents, in primates, and in humans.

Zinc Supplementation in Infancy and Childhood

JB: In your opinion, based on your work and observations, is any need for zinc augmentation in infants' and children's diets throughout development, even into adolescence?

RC: It's a good question. I would have no hesitation in recommending it for low-birth-weight infants, whose weight is less than 2.5 kg at the time of birth. For the first 6 to 12 months, their immunity is low. Giving them extra zinc, approximately .5 to 1 mg per kg body weight, will boost their immune response and bring it back to normal in a shorter time than if they were not given zinc. There is also some evidence that infants and young children, particularly boys, if they are given zinc, they have a greater gross velocity for height. It has not been shown conclusively whether it will also help their immune system in that age group. In adolescents, I think it's not so much zinc, but iron that seems to be the common problem. If you give them iron, it not only improves their immune responses, but also increases cognitive function and abstract thinking, and in particular, their performance in mathematics.

Vitamin E

JB: Moving from trace elements to the fat-soluble vitamin family, what are your thoughts on the Meydani and Blumberg work at Tufts and the USDA Human Nutrition Center on Aging? They wrote a paper that was published in JAMA in 1997, on vitamin E supplementation and in vivo immune responses in healthy elderly subjects. Do you feel vitamin E is an important part of this picture?

RC: Vitamin E is among the group of vitamins that are important for the immune system. Gradually, we

are increasing the recommendation for the amount of vitamin E that should be consumed, from about 10 mg some years ago to now perhaps 30-40 mg. I wrote a commentary in the same issue of JAMA on their paper and on vitamin E in general. Basically, after reviewing their paper and other literature, I concluded that somewhere between 50 and 100 mg might be the amount of vitamin E needed for optimal immune response. I don' t feel that giving amounts more than that would substantively benefit immunity or affect the incidence of infection. We certainly need more studies to confirm what has been found in Boston, but even with the present evidence, some extra vitamin E would be justified in the elderly. Their study was done in old people, so in that age group, I would have no hesitation in recommending anywhere from 50 to 100 mg.

Optimal Dosage of Vitamin E

JB: In their paper, as I recall, they had a significant increase in immune response, or titers to hepatitis B. It was several times higher in the vitamin E-supplemented group, and they used graded doses. The question is where does the curvilinear dose/response curve show maximum improvement for some of these functions?

RC: They used four different doses, including a placebo. For three responses, including the response to hepatitis that you mentioned, 200 mg gave the best response. For other responses, for example, lymphocyte transformation or other things, 60 mg was the best. The group given the largest amounts of 800 mg was probably the worst. In fact, sometimes it performed worse than the placebo. With nutrients we must recognize there is always a bell-shaped curve for each nutrient and immunity. Where the peak will be has to be determined for each nutrient by careful long-term, well-designed studies.

Human nutrition means that we should look at all nutrients. Even though some nutrients may be more important than others, I think balanced food and supplements that include all essential nutrients would be my recommendation, rather than focusing only on one nutrient.

The Gut/Immune System Connection

JB: I think your construct of the bell-shaped dose/response curve is something for all clinicians to keep in mind. If a little is good, a whole lot may not be better. You recently published a paper in the European Journal of Clinical Nutrition regarding the effect of enteric flora on immune function in the individual. That paper was titled "Enhancement of Natural Immune Function by Dietary Consumption of Bifidobacterium Lactis (HN019)." What is the connection between the gut and the immune system?

RC: Studies on infants who were breast-fed or not breast-fed revealed that breast-fed infants have more of these lactic acid bacteria compared with the other microflora in formula-fed babies. The breast-fed babies have fewer infections and fewer allergies. This has now been extrapolated to other age groups. In the paper to which you just referred, we studied elderly people and gave them a particular strain of bifidobacterium for six months. Even within three months, however, we found a very significant increase in cell-mediated immunity, natural killer cell activity, and also to some extent, in phagocytic function.

This kind of approach is also being used in two other areas. One is in prevention and treatment of diarrhea, including travelers' diarrhea. If you are travelling to a developing country in Asia, Africa, or Central America, then taking a dose of lactobacilli, and it could be any one of the strains, is helpful in

preventing diarrhea. Similarly, if an infant already has diarrhea, giving the baby these bacilli will help reduce the duration of the diarrhea. We have a couple of papers that have been tests confirming this, and also another paper showing that it may even prevent eczema and respiratory problems in infants who may be genetically prone to developing allergies.

Award for Pioneering Work in Nutrition and Immunity

JB: I can certainly understand why you have been named an Officer of the Order of Canada, the highest award given to Canadian citizens, for your contributions in this field. You have inspired countless numbers of students, including myself, in studying this field. People who have followed your work have been able to manage their patients with a better sense of nutrition and immunity that has resulted in better outcome for their patients. I thank you on behalf of all the clinicians who have benefited from your work.

RC: Thank you so much. You've been very generous in your comments and it's been a privilege talking to you.

Conclusion

JB: It has been a privilege. We wish you the best in your continued work. We will follow you closely in your publications.
In our discussion of nutrition and immunity, Dr. Chandra raised several interesting points about various aspects of nutrient intake that could have positive roles on immune status. One was our discussion of antioxidants and the work of Drs. Simin Meydani and Jeffrey Blumberg at the Tufts USDA Human Nutrition Center on Aging in Boston. These investigators conducted a study to determine if long-term supplementation with vitamin E in vivo enhances clinically relevant measures of cell-mediated immunity in healthy elderly subjects. The published report of that study is titled "Vitamin E Supplementation and In Vivo Immune Response in Healthy Elderly Subjects." This randomized, double-blind, placebo-controlled intervention study concerned a total of 88 free-living, healthy subjects age 65 or older. Subjects were randomly assigned to a placebo group or to groups consuming 60, 200, or 800 mg per day of vitamin E for 235 days.

The main outcome measures used to evaluate nutritional impact on immunity include delayed-type hypersensitivity skin response (DTH); antibody response to hepatitis B, tetanus and diphtheria, and pneumococcal vaccines; and autoantibodies to DNA and thyroglobulin. Researchers assessed these measures before and after supplementation to examine autoimmunity in comparison to immune cell recognition.

Determining Optimal Dosage of Vitamin E

As Dr. Chandra pointed out in his review of this paper, different effects occurred at different dose levels to the different parameters. Optimization of all parameters studied probably occurred somewhere between the 100 and 200 mg per day level. At the arbitrarily selected very high dose intake of 800 mg per day, the subjects had the most suppression of autoantibodies. This result suggests that high doses of vitamin E may have a suppressive effect on autoantibody production, whereas lower levels of vitamin E intake may more favorably increase cell-mediated immunological function and B cell function. The curves cross to maximize the benefit somewhere between the 100 and 200 mg per day level. At that dose they got

improvement of response to various vaccinations and also reduced levels of autoantibody to thyroglobulin.

Elevated autoantibodies to the endocrine glands indicate the person becomes allergic to his or her own endocrine glands. If there is a principal factor of accelerated biological aging associated with autoantibodies to the endocrine glands, then this study implies that proper antioxidant vitamin E intake helps stabilize the immune system against crosstalk with the immune and endocrine systems. By crosstalk we mean loss of the ability to distinguish friend and foe and starting to respond to the body as a foe.

Antioxidants taken in higher doses also play a role in cardiovascular protection and other positive health benefit outcomes. Controversy surrounds vitamin E supplementation and heart disease. A paper in the Lancet, titled "Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE): Randomised Placebo-Controlled Trial," discusses using 800 IU per day of vitamin E or placebo. The investigators pointed out that excess cardiovascular mortality occurs in individuals on hemodialysis. They suggest this fact is interrelated to oxidative stress, which is much greater in hemodialysis patients with increased blood malondialdehyde levels, meaning higher levels of lipid peroxidation, as measured in their blood with the TBA test.

They investigated the effect of high-dose vitamin E supplementation on cardiovascular disease outcomes in hemodialysis patients with preexisting cardiovascular disease. They saw a significant improvement in outcome for those patients who received 800 IU per day. Vitamin E reduced the composite cardiovascular disease endpoints and myocardial infarction significantly to less than half of that observed in the placebo group.

Conflicting Study Reports

This paper created a series of responses in later issues of the Lancet, including one from Sarah Nuttall and her colleagues from the Division of Medical Sciences, Queen Elizabeth Hospital in Birmingham, England. According to Nuttall’s group, the paper by Boaz and colleagues showed regular supplementation of vitamin E reduced the risk of composite cardiovascular endpoints, myocardial infarction, ischemic stroke, and peripheral vascular disease in patients on hemodialysis.

This finding seems to be in contrast with a recent Heart Outcomes Prevention Evaluation Study (HOPES). In the HOPES study, vitamin E seemed to have no significant effect in patients at high risk to cardiovascular disease. In the Cambridge Heart and Antioxidant Study (CHAOS), however, there was an effect on non-fatal myocardial infarction, but not on mortality. In the GISSI-Prevenzione trial, the opposite seems to have been shown.

No Clear Message

The Nuttall group wrote, "The lack of a clear message might promote confusion and skepticism, which is unfortunate but predictable if varying doses of antioxidants are given to different populations and several endpoints are reported. Surely the time has come when oxidant stress (ie, the imbalance between free-radical production and antioxidant defences) should be studied in high-risk patients who are given an antioxidants regimen that restores plasma or tissue antioxidant activity to normal. Appropriate endpoints should be identified and the effect of antioxidant treatments documented. The establishment of an

association between correction of oxidant stress and clinical endpoints would have improved the Boaz study."

They went on to say they suspect that if the effects of oxidant stress had been assessed, the results would have been confounded by the prescribed cocktail. That cocktail included not only vitamin E, but an additional level of substances including folate (5 to 10 mg or 5000-10,000 m g per day), vitamin B6 at 10-250 mg per day, and vitamin B12 250 m g per day. This combination would lower homocysteine concentrations. High homocysteine is associated with increased free radical production. Therefore, are we looking at single variables or multiple variables?

Antioxidant Synergy

"Vitamin C supplements 100-500 mg per day, have also been shown to have a synergistic action with vitamin E," the Nuttall report continued. "Boaz and colleagues do not discuss the relevance of these other antioxidants and primary or secondary endpoints, nor reveal where more endpoints were reached in patients who received only vitamin E or placebo. The distribution of the other antioxidants was near equal, although the doses are not given."

It is clear that when you start using complex mixtures of antioxidants, you get the antioxidant "buddy system," the electron transfer system starting to have potentially synergistic effects you would not see with single antioxidant supplementation. This redox buffering, so to speak, the reduction/oxidation buffering provided by complex antioxidant mixtures can potentially have a much different influence on oxidative stress from that of single antioxidants. The results of the Boaz study are certainly of interest. Trials may show, however, that antioxidants can help patients with renal disease as a consequence of increased oxidative stress, and this may be most beneficial with complex array of antioxidants.

Importance of Whole-Food Nutrition

Dr. Chandra talked about complex mixtures of nutrients found in whole foods. Nutritional supplements can certainly be of value, but food provides an array of redox-active substances, particularly the phenols and the flavonoid compounds, which work together with the water- and fat-soluble antioxidants to deliver redox protection. Therefore, when we start looking at the role of antioxidants and the protection against age-related diseases, complex mixtures may be more significant than single agents.

Another recent paper, published in the Journal of the American Medical Association, is titled "Effects of Vitamin E and Lipid Peroxidation in Healthy Persons." In this study, oxidative stress was evaluated before and after vitamin E supplementation. To assess the effects of vitamin E, investigators used a randomized, controlled trial of 30 healthy men, aged 18-60 years. Participants were randomly assigned to receive either placebo or a vitamin E alpha tocopherol supplement at doses of 200, 400, 800, 1200, and 2000 IU a day for eight weeks, followed by an eight-week washout period. The researchers looked at indices of lipid peroxidation by urinary 4-hydroxynonenal, 2-isoprostanes, as well as at the TBA thiobarbituric acid-active material.

Solo Vitamin E Study

Circulating vitamin E levels, as you can imagine, increased in a dose/response-dependent manner during

the study. They found no significant effect of vitamin E at any levels on urinary 4-hydroxynonenal or isoprostane. They concluded that the vitamin E supplementation did not appear to reduce the indices of oxidative stress that they measured. They suggest, therefore, that vitamin E may not, in itself, be a preventive supplement for defense against oxidative stress.

I think that conclusion is a little premature and certainly not warranted on the whole. As I mentioned, vitamin E works as a redox buddy in the "buddy system" of electron exchange. If the electron that goes from the tocopheroxy radical lacks the ability to be transferred to something else, (glutathione or the regeneration from glutathione disulfide of glutathione, or lipoic acid), then you stop the chain-breaking mechanism that is found with vitamin E as part of its radical protection against free radicals. You are then less effective in realizing its oxidant stress protection than if it was given along with the other agents that work as part of the buddy team for diffusing oxidative stress.

Antioxidants in the Complex Human Physiological Model

Research of the future is likely to move away from the pharmacological model of nutrition, which measures one agent against one endpoint. It will move toward what really happens in human physiology, which is complex arrays of similar molecules with similar function, and how they function against a variety of physiological outcome parameters. What would happen if the above study had been done with vitamin C, vitamin E, selenium, N-acetylcysteine, lipoic acid, and some polyphenols? Would the results have been the same, or would we have seen something different on the production of 4-hydroxynonenal or the isoprostanes?

What was the level of stress these individuals were under? Was there already a significant amount of oxidative stress? Could we have looked at the degree of 8-hydroxy-deoxyguansine (8OHDG), which is a measure of oxidative damage to DNA, and correlated it with oxidative stress markers before and after the supplementation with a complex array of antioxidants? One needs to be cautious when setting up an experiment to test a favored hypothesis. A rationale may be incorporated within the study design that has predetermined the results. As Dr. Chandra pointed out, when looking at complex outcome variables like immunological function against complex inputs from multi-nutrient diets, we need to have pattern recognition protocol, to evaluate the impact of a complex diet on complex immunological parameters, and even on oxidative stress.

Allergic Disorders on the Rise

Dr. Chandra also talked about allergic disorders. More and more people seem to be becoming allergic to their world—to their diet, their environment. As a result, allergy medications are among the most prescribed medications as the population becomes more asthmatic, more atopic, more allergic. Antihistamines and the allergy relief medications are becoming much more widely used.

Allergy and allergic diseases were the topic of a recent review in the *New England Journal of Medicine*. Allergic rhinitis is characterized by episodes of sneezing, itching, rhinorrhea, and nasal obstruction. Current drugs used to treat allergic rhinitis are antihistamines and anticholinergic agents, principally for the relief of symptoms, and topical corticosteroids to suppress allergic inflammation. Histamine H2 receptor antagonists, which are less sedating and more pharmacologically selective than other earlier antihistamines, are now getting more attention. Some H2 receptors and H1 receptor antagonists

reportedly inhibit allergen-inducing filtration of tissues by eosinophils. We are beginning to look at the biological basis of allergy and modulating some of these processes.

Modes of Immunotherapy

Specific immunotherapy, which has been used for the treatment of allergic diseases for nearly 100 years, consists of desensitizing a person to an allergen by administering increasing concentrations of extract to the allergen over a long period of time. This approach has been successful for some patients with seasonal allergic rhinitis, but others do not respond favorably to the desensitization approach using concentrations of extracts of allergen.

The mode of action of specific immunotherapy is complex and still a subject of study. You would think that by this time, with our increasing knowledge of the immune system, we would understand how one brings about desensitization at the immunological level. Really, the story is still being unraveled.

Mast Cell Degranulation Process

Immunoglobulin G (IgG) blocking antibodies compete with IgE for allergen. They may also have the ability to prevent the aggregation of complexes of IgE and the a chain of the high-affinity IgE receptors on MAST cells by altering the steric confirmation. In addition, they may interfere with antigen trapping by IgE bound to antigen-presenting cells. Several studies, I believe, have shown that specific immunotherapy can inhibit the release of pharmacological mediators, like interleukins, leukotrienes, and proinflammatory prostanoids from MAST cells and basophils. This inhibitory activity prevents infiltration of allergic lesions by inflammatory cells and decreases the number of MAST cells in tissues.

This MAST cell degranulation process, in which an IgE is bound to the surface of a MAST cell, causes a confirmational transformation of an inactive phospholipase to an active phospholipase. Upon activation, fatty acids are released from the sn-2 position of phospholipids. One of these fatty acids, arachidonic acid, is a key player in the inflammatory process.

Arachidonic Acid Cascade

The release of arachidonic acid is the rate-limiting step in the initiation of inflammation by the MAST cell. The process delivers the arachidonate to lipoxygenase, which can convert it into leukotrienes like leukotriene B4, which are about 1000 times more proinflammatory than histamine. These leukotrienes, when released from the MAST cell without white cells, and cause swelling, water retention, pain, and the responses we normally associate with allergies. So the MAST cell degranulation process and the activation of the arachidonic acid cascade play an important role in the pathogenesis of allergy. IgG blocking antibodies can compete with IgE for allergen and attenuate this process.

Dr. Vincent Marinkovich, an allergist and immunologist at Stanford University Medical School, and a member of our core faculty for the Applied Functional Medicine in Clinical Practice training programs, has spoken at some great length about the important role of IgG in IgE reactions. He has explained the immune complex association as a balance between too little immune complex formation and too much immune complex formation. In the middle of this continuum, the body has normal surveillance of IgG, kind of putting the brake on IgE.

Thymus-Dependent 1 and 2 Systems

T-lymphocytes (T-cells) originate in the thymus, and are dispersed to secondary lymphoid tissues. The helper T-cells (T_H) provide lymphokines to other immune cells and can be divided into two groups. TH1 cells synthesize IL-2 and IFNg ; the cells make IL-4 and IL-5. Broadly speaking, the former are considered proinflammatory cytokines and are associated with cell-mediated immunity. The latter augment IgG1 and IgE responses. The balance is between TH1 cytokines, interferon gamma, interleukin 12, and TH2 interleukins, which include interleukin 4 and 5. The balance between the TH1 side and the TH2 side is like keeping one foot on the brake and the other on the accelerator. The body can respond to a potential noxious agent with appropriate immune response, but it is not in a brakeless, free-wheeling situation.

TH1/TH2 balance in relation to nutrition plays a role in our understanding. Nutrition interrelates with environmental exposures and relates to genetic predisposition through histocompatibility locus antigen determinants (HLAs). We are beginning to get a molecular picture that may help predict from first principles what patient would respond to what type of allergen and what type of nutritional support he or she may require for optimization of that balance between TH1 and TH2.

Tolerance and Autoimmunity

This theme is discussed in an article titled "Tolerance and Autoimmunity," which appeared in the *New England Journal of Medicine*. The immunological specificity of the antigen receptors of T cells and B cells is a result of this random shuffling of the two genes (a and b) that code for the antigen-binding site. It is remarkable that a single pair of genes could code for so many different variations by this shuffling process. It can respond to molecules in the environment that it never knew it would be exposed to, which that organism had never seen before. How did it have that pluripotentiality?

This process can generate 10^9 different T cell receptors. That’s not infinite, but it is a lot of variation that the body can mobilize and respond to based on the mixing and matching of these many genes that form the DNA code at the antigen-binding site.

Tolerance is the process that eliminates the cells which are autoreactive, i.e., recognize self-antigens. A breakdown of this system can result in autoimmunity. This balance, which distinguishes self from non-self, has everything to do with immune surveillance by the immune system and simultaneous prevention of autoimmunity. As Dr. Chandra pointed out, it is possible for a person simultaneously to have alterations in cell-mediated immunity and increased autoimmunity and the inability to distinguish self from non-self.

Autoantibodies are characteristic of many autoimmune diseases and can be the direct cause of the lesions in some of these disorders. For instance, in Graves disease, thyroid autoantibodies bind to and stimulate the receptor for thyrotropin, which contribute to increased oxidative stress and inflammatory mediation. Autoantibodies against intracellular antigens are not usually pathogenic. Instead, they have been viewed largely as secondary consequences of the autoimmune process and therefore triggered from outside messages of the cell to inside reactions that slow down or alter cellular function.

Autoimmune Processes and Nutritional Balance

These autoimmune processes range from mild symptomatology at the cell-specific level to pathophysiological features of the classic autoimmune diseases—systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, and the like. Depending on where the imbalance is between TH1 and TH2 and how severe it is, one might get increasing pathogenicity that ultimately ends up in end-organ failure or the pathology that we identify as an autoimmune disease. Patients might present with much milder symptoms of more subtle imbalances. This is the point at which nutrition can play an important role. Essential fatty acids, antioxidants, zinc, and other trace minerals, including iron, play some role in balancing these immunological factors. This is an interesting part of the story.

As I mentioned, T cells or thymus-dependent lymphocytes can be categorized according to the cytokines they produce. The type 1 helper T cells produce mainly interferon gamma, tumor necrosis, and interleukin 2. We would normally call these the inflammatory-producing T cells because they elaborate proinflammatory cytokines. On the other hand, the type II T cells produce mainly interleukin 4, 5, 13, which are often considered more antinflammatory cytokines. Therefore, balance between TH1 and TH2 is important, and imbalances on either side of the equation can be associated with specific pathogenicities.

Th1 and TH2 and Pathogenesis of Specific Disorders

TH1 cells are primary mediators in multiple sclerosis and type I diabetes, and TH2 cells mediate allergic diseases. Alteration of the cytokine balance, therefore, is an appealing therapeutic possibility to reset the balance between TH1- and TH2-derived cytokines. Nutrients have been found to play a role in establishing that balance.

Nutrients are not the only factor, obviously. Genes and other environmental factors play an important role, but nutrition is one of the determining variables for establishing the balance between the elaboration and activation of TH 2 versus TH1-mediated effects.

Balancing Nutrients to Provide Immunological Support

In applying the knowledge Dr. Chandra has acquired through his extensive research over the last 40 years, one can look at variables such as antigenic principles in the environment, removing them to the extent possible with an elimination diet or cleaning up the localized environment. One also tries to improve immunological recognition through nutritional support, proper protein levels, balance of carbohydrate to protein to fats, the right kind of fats, less saturated fat and more omega 3 oils and essential fatty acids.

One tries to get adequate trace minerals, particularly zinc and magnesium into the diet. These minerals play important roles in immunological defense mechanisms. We need to establish the proper ratio of calcium to magnesium and balance the ratio of antioxidants—vitamin C, vitamin E, the carotenoids, the flavonoids, polyphenolic compounds, selenium, cysteine, lipoic acid, coenzyme Q10. That whole antioxidant family consists of redox-active substances. Specific amino acids, such as arginine or L-glutamine, may also play an important role in immunological recognition.

Pancreatic Disorders

When you study the literature regarding certain extraordinary inflammatory conditions associated with

autoimmunity or immune hypersensitivity, you can begin to identify a variety of disorders that may in part be exacerbated by imbalances of genes and environment. One of them was recently discussed in the *New England Journal of Medicine* in an article titled "Sclerosing of Pancreatitis." This disorder has been referred to not only as sclerosing pancreatitis, but primary inflammatory pancreatitis, lymphoblastcytic sclerosing pancreatitis, autoimmune pancreatitis, chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct, and sclerosing pancreocolongitis. These are different names for the same condition, which is associated with lymphoblastic inflammation of the pancreas and hypergammaglobinemia in response to glucocorticoid treatment.

According to the article in the *New England Journal of Medicine*, this condition has been found to be associated with IgG4 elevations. IgG4, the rarest of the IgG subclasses, accounts for 3 to 6 percent of the total IgG in the serum of normal subjects. It is unique in the IgG subclasses in its ability to bind complement C1Q and thus activate the classical pathway of complement and its low affinity for target antigen.

High serum IgG4 concentrations were found in a limited number of conditions, including atopic dermatitis, other allergy-related atopic disorders, and pyricytic diseases. IgG4 could perhaps be a useful marker for some of these underlying inflammatory conditions associated with allergy, and it might then be amenable to elimination, environmental hygiene, or nutritional modification in a nutritional allergic response.

Gut Flora and Immune Function

Dr. Chandra also talked about the relationship between gut flora and immune function. Nearly two thirds of the immune system is clustered around the gastrointestinal tract, the gut-associated lymphoid tissue (GALT). A relationship exists between a complex food matrix and bacterial flora. One to one and a half kilograms of living flora of different species in the gut that produce their own chemical personalities and in close proximity to the GALT can result in immunological activation or potentiation based on the chemical exposures the GALT is receiving. We now recognize that bacteria in cultured food products may have varying effects on the immunological function of the gut, the GALT, or the mucosal-associated lymphoid tissue (MALT).

***Lactobacillus acidophilus** NCFM*

A recent paper in the *Journal of Dairy Science* evaluated the scientific basis of one species of oral supplemented probiotic as a functional agent to improve GI and immune function. This was the *Lactobacillus acidophilus* NCFM strain. This strain has a number of favorable personality characteristics when it is given as a supplement. It adheres to the mucus-secreting cells, which is important if it is going to persist after oral supplementation. It produces anti-microbial compounds that help defend against parasitic bacterial levels in the gut. It is amenable to GI survival so it doesn’t just pass on through; it adheres to the mucosal cells and can proliferate. It inhibits aberrant crypt formation in animals that have been exposed to mutagens.

This finding suggests it could decrease the risk of colon cancer. By fermenting nondigestible carbohydrate, such as fructooligosaccharides, NCFM can produce lactic acid. If you administer the appropriate dietary fermentable carbohydrate, non-digestible in the normal human, but fermentable by the

intestinal microflora, then it can produce beneficial organic acids like butyrate.

Beneficial Effects of NCFM Administration

The NCFM strain decreased the incidence of pediatric diarrhea in clinical trials and led to significant decreases in the levels of toxic amines like cadaverine and putricine in the blood of dialysis patients with small-bowel bacterial overgrowth. At adequate daily feeding levels, NCFM may facilitate a range of favorable influences on GI function, including immune benefits. It has also been shown to facilitate lactose digestion in lactose-intolerant subjects, suggesting it has ability to hydrolyze lactose.

We should no longer think of nutrition solely in terms of vitamins, minerals, protein, carbohydrate, fat, and water. We can now look at a variety of other associated agents that work synergistically to give rise to the liberation of nutrients, or the production of other tropic factors. This category includes living flora, called probiotics.

Probiotics and Prebiotics

A paper in the *Journal of the American Medical Association* in 1996 was titled "Biotherapeutic Agents. A Neglected Modality for the Treatment and Prevention of Selected Intestinal and Vaginal Infections." The biotherapeutic methods discussed in this article included probiotics and prebiotics for the management of recurrent vaginal infections and functional GI problems like chronic irritable bowel syndrome. I believe probiotics represent an important new tool in clinical nutrition and perhaps in clinical immunology. Probiotics include *Lactobacillus acidophilus* NCFM strain and numerous other bacteria. Their catabolism of substrates, such as non-digestible carbohydrates like inulin, and oligosaccharide containing substrates upon which they result in the production of favorable fermentative end products like butyrate.

A number of other probiotic species may have different effects on immunological function of the gut. Therefore, one could consider a broad spectrum of replacement bacteria that may have varying effects in different regions within the immunological cascade and produce a very favorable outcome in patients.

Metchnikoff and the Importance of Bifidobacteria Declines with Age

One characteristic associated with aging is the decline of bifidobacteria and the rapid rise in parasitic anaerobic bacteria. Earlier in the lives of most healthy individuals, bifidobacteria were the predominant bacterial species, but they begin to decline rapidly and be replaced by toxic bacteria as we age. We don’t know if this decline is related directly to age-related disorders. In his book, *The Prolongation of Life*, Metchnikoff, a scientist of the late 19th and early 20thcentury, proposed that alteration of gut bacterial flora was a major cause of premature aging. He was director of the Pasteur Institute and won a Nobel Prize in Medicine for his discovery of the macrophage.

Metchnikoff was a primary discoverer of the immune system, looking at the blood microscopically. He believed toxic bacteria in the colon played a significant role in modifying immune function. He thought that by re-instilling friendly bacteria by enemas into hospitalized patients, he could improve their liver and kidney function and their overall vitality.

New Explanations for Old Observations

The idea that toxic bacterial overgrowth has an impact on immune and general function in aged individuals has a long-standing history in medicine. We are only now beginning to understand how this process works through receptor sites, modification of gene expression, influences on colonocyte replication, and the DNA masking effects of histone acetylation influenced by butyrate levels that affect the expression of genes in the colon. We are taking old observational work and creating new molecular explanations for the function. The outcome for the patient may remain the same, regardless of the explanation, and that is improved GI immune function, lowered systemic inflammatory markers, and decreased risk to some immunological dysregulation--the TH1 and TH2 cytokine imbalance.

TH1/TH2 balance is also related to the kind of non-digestible carbohydrate one consumes. A recent report in *Applied and Environmental Microbiology* describes fermentation of fructooligosaccharides by lactic acid bacteria and bifidobacteria. It shows that inulin is metabolized or fermented only by certain species of bacteria. Other bacteria, such as *Lactobacillus GG,* do not ferment these substrates. Therefore, the different types of oligosaccharides have different fermentabilities depending on the type of bacteria present in the gut that produce the outcome and byproducts, such as butyrate. Bacteria, substrate, GI environment, and overall nutrition combine to exert a systemic effect on the immune system. Dr. Chandra has caused us to look closely at this very interesting connection.

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