SPECIAL ISSUE

Immunology

The Oral Health-Alzheimer's Connection
Vitamin D Suppresses Immune Reactions
Elderberry for Travel-Related Respiratory Illness

Egg Introduction in Food Allergy Mediation
Immune Processes in Brain Health
The Root Cause of Food Sensitivities
SUPPORT
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SPECIAL ISSUE IMMUNOLOGY
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MESSAGE FROM THE PUBLISHER

Impacting Immunity with Integrative Medicine

Thanks for reading this special issue of the *Natural Medicine Journal*. This issue is devoted to the topic of immunology—an expansive and complex field of medicine. Our goal with this issue was not to publish an exhaustive resource on immunology; rather it was to provide an update on recent research in the field, as well as unique perspectives on an integrative approach to immune system enhancement.

Immunity touches many aspects of medicine as integrative practitioners work to shore up function in a diverse and expanding population.

In this issue, you’ll find an overview on immunology by naturopathic immunologist Eric Secor, ND, PhD, LAc, as well as an enlightening audio interview with *Natural Medicine Journal* editorial board member, immunology researcher Heather Zwickey, PhD. Our sponsored podcast features Todd Born, ND, talking about integrative diagnosis and treatment of food sensitivities. From a research perspective, our authors provide insight into several new studies involving egg immunotherapy, elderberry, vitamin D, and the connection between periodontitis and Alzheimer’s disease.

We’d like to thank the authors and reviewers who assisted with this special issue and we hope you enjoy this glimpse into the fascinating and complex world of immunology. Please share it with your colleagues!

In good health,

Karolyn A. Gazella
Publisher, *Natural Medicine Journal*
ABSTRACT
A healthy and intact immune response requires coordination between skin, mucosal barriers, and both the innate and adaptive aspects of immune response. With an overarching mandate of protection, the blueprints of individual immune surveillance systems are inherited through family history and fashioned through interactions with the environment, including lifestyle choices and chemical exposures. The goal of this article is to provide an overview of the immune response and opportunities for assessment, treatment, and management from an integrative medical perspective.

INTRODUCTION
In biology immunity is the “ability of an organism to resist disease, either through the activities of specialized blood cells or antibodies produced by them in response to natural exposure or inoculation (active immunity) or by the injection of antiserum or the transfer of antibodies from a mother to her baby via the placenta or breast milk (passive immunity).”

Our immune system must continually balance a state of readiness, having all the necessary biological responses prepared to defend us from infection, disease, or invasion of organisms while simultaneously maintaining a state of tolerance or trained immunity.

Ideally, vigilance is tempered by tolerance as the immune system needs to avoid mounting attacks on self (ie, autoimmune diseases), reprogramming recognition molecules (ie, cancers cells), and overreacting with exposure to food and environmental antigens (ie, allergies and sensitivities). Clinical management includes an understanding of the functional aspects of the immune system and development of treatment plans that include targeted therapies to modulate immunity. Many of the treatment modalities help support the pillars of our immune system, which include barrier function as well as the innate and adaptive responses.

OVERVIEW OF IMMUNE SYSTEM STRUCTURE AND FUNCTION
The immune system comprises a complex network of organs, vessels, cells, and proteins. The skin and mucosal surfaces create a mechanical and functional barrier to protect against and eliminate environmental debris and foreign invaders. For example, in the lungs mucus and the mucociliary “escalator” system work together with columnar epithelium to mechanically whisk microbes upward and outward. Columnar epithelial cells also secrete cytokines and host-defense molecules (human β-defensins, lysozyme, lactoferrin, cathelicidin LL-37, and surfactant proteins A and D) resulting in near-sterile airways when fully functional. Bodily secretions (eg, saliva, stomach acid, and tears) also combine with biological reflexes such as coughing, sneezing, vomiting, and diarrhea in an attempt to eliminate potentially dangerous organisms or irritants (antigens).

Additionally, prebiotics, probiotics, and synbiotics may have the greatest health effects when they are incorporated into the diet early in life.

The bone marrow, thymus, and lymphocytes are the primary lymph organs; secondary organs include the lymph nodes, spleen, mucosal membranes, and the intestinal gut-associated lymphoid tissue (GALT), which includes the tonsils, Peyer's patches, and immune aggregates of the esophagus, stomach, and lamina propria. Together these organs function and orchestrate the maturation of immune cells and provide access to the non-immune privileged (eyes, placenta, fetus, testes, and central nervous system) systemic circulatory environment. In addition, normal human flora (the microbiota) work synergistically with skin and mucosal surfaces to maintain the functional barrier and create as healthy an ecosystem as possible. Although the exact distribution, content, phenotype, and genotype of prebiotics and probiotics have yet to be fully understood, it is clear that significant disruption of the microbiota modulates gut, brain, and immune function. For example, recent research suggests that short-term restriction of short-chain fermentable carbohydrates (the low-fermentable oligosaccharides, (continued on page 8)
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disaccharides, monosaccharides, and polyols [FODMAP] diet), which directly impacts the microbiota, may be clinically useful. Additionally, prebiotics, probiotics, and synbiotics may have the greatest health effects when they are incorporated into the diet early in life.

**CELLULAR COMPONENTS, INNATE AND ADAPTIVE ARMS**

All immune cells are derived from hematopoietic stem cells found in the bone marrow. Stem cells give rise to both the mature myeloid cells (red blood cells [RBCs], platelets, neutrophils, eosinophils, basophils, and mast cells) and lymphoid (natural killer [NK], B, and T) cells, key players in the innate and adaptive immune responses. Although traditionally these were distinct arms, many overlapping and intersecting functions of the humoral or cell-mediated response are now being discovered.

However, we can still define the role of each arm with some distinction. The innate immune system is fast-acting (~0-15hrs) and composed of epithelial barriers, phagocytic granulocytes, dendritic, and NK cells as well as plasma proteins of the complement cascade (C1q, C2, C3, C3c, C4, and C4d). The overarching clinical symptoms of classic inflammation (calor, dolor, rubor, tumor) are indicative of the innate response. The responding innate immune cells have the unique capacity to recognize and respond to evolutionarily conserved patterns upon exposure to foreign stimuli, therefore they act immediately. Pattern-recognition receptors (PRRs) embedded on macrophages and dendritic cells can detect or read patterns found in components of bacterial and fungal cell walls and viral nucleic acids. These PRRs include Toll-like and C-type lectin receptors. Pattern recognition receptors are reinforced by the complement cascade. The complement cascade is a complex of proteins produced by the liver and activated in plasma. The complement cascade modulates the systemic responses (inflammation, anaphylaxis) and is now believed to bridge and inform both innate and adaptive immunity.

When bacteria, viruses, or allergens (antigens collectively) evade innate responses, the adaptive system is engaged. The adaptive arm of the immune system is delayed (up to 5 days) and consists of critical antigen presenting cells (APCs), which orchestrate responses; T and B lymphocytes; plasma cells; and the antigen-specific antibodies they produce. Dendritic cells are considered the primary “professional APCs” in addition to macrophages and nonprofessional APCs, such as B cells and epithelial cells. Antigen-presenting cells are responsible for antigen engulfment, uptake, processing, and presentation to the adaptive cells through engagement with receptor cells such as the T cell receptor (TCR). Once antigen-rich APCs engage T helper (Th) cells via their TCRs, the Th0 cells (precursors to all Th types) activate, proliferate, and expand within a skewed inflammatory milieu. T helper 1 (Th1) cells produce interferon gamma (IFN-γ), interleukin-2 (IL-2), and granulocyte-macrophage colony-stimulating factor (GM-CSF) and modulate cell-mediated responses. Classically, Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-13, and IL-25 and drive the IgE-mediated antiparasite, anti-allergy, and antibody responses commonly seen in clinic. Regulatory T cells (Tregs) with a cell phenotype of CD4+CD25+FoxP3+ produce IL-10 and transforming growth factor (TGF)-β and are intimately involved in chronic inflammation, scar formation, and the control of other cell types. There are numerous other sub lineages (Th17, Th22, Th9) being evaluated in the scientific literature that are generated by variations in the degree of antigen resistance.
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Numerous integrative therapies, dietary supplements, and botanicals (and their extracts) are being investigated for their ability to affect dendritic and Th cells, their activation status, and their ability to modulate the cytokines and chemokines they produce. For example, previous work in my laboratory in preclinical models has demonstrated that the pineapple extract bromelain is a potent antiallergy and asthma therapy. Our group has demonstrated in a mouse model that bromelain lessens immune response to an antigenic stimulus.\textsuperscript{21} Specifically, bromelain ingestion led to significant inhibition of allergic sensitization (egg antigen) via direct modulation of dendritic cells (CD11c+) as determined by reduced ovalbumin-specific IgE, antigen-specific CD8 T cells, and CD44 (a critical T cell receptor involved in allergic immune response).\textsuperscript{22,23} Ongoing studies will determine bromelain’s optimal dose in allergies and asthma in humans. Other groups are also actively evaluating how dendritic cells can be affected by natural products\textsuperscript{24,25} such as vitamin D\textsuperscript{26,27} and probiotics,\textsuperscript{28} and what clinical impact these findings will have. When possible all treatment modalities should be evaluated in the context of patient care and backed up with objective diagnostics and laboratory measures.

LABORATORY MEASUREMENT OF IMMUNE SYSTEM AND INFLAMMATORY RESPONSE

Laboratory evaluation and determination of the degree of immune system dysregulation and the contribution of inflammatory responses can be complex and overwhelming. A systematic approach based on the family and personal history (work and environmental exposure, sexual history, prescription and recreational drug use), review of symptoms (ROS), and physical exam findings is fundamental. Detailed personal and family history may also reveal multiple chronic immune-mediated conditions or conditions that follow a distinct inheritance pattern (for example, through males on the maternal side). In pediatric patients, the ROS may indicate delayed growth, failure to thrive, malabsorption, or developmental issues. In adults, common underlying symptoms may include frequent, recurrent colds and flus, less common infections, iron-resistant anemias, severe eczema, allergies, and hyper-IgE or allergic eosinophilic syndromes. Collecting a detailed history (classic homeopathic interview) will reveal the cause much of the time. These are the patients who present with “textbook symptoms” that will lead directly to laboratory testing that confirms the diagnosis, such as anemia revealed by a complete blood count (CBC)/iron panel. However, clinical presentations are often not straightforward and labs are unremarkable. Recently I had a patient present with a rash, mild irritable bowel syndrome, difficulty concentrating, and fatigue. Although my first thoughts were food-related allergy or atopy, all allergy tests were negative; testing eventually revealed a genetically altered uridine diphosphate glucuronosyltransferase enzyme (UGT1A1) and the subsequent diagnosis of Gilbert’s syndrome. Therefore, a stepwise diagnostic approach coupled with patient feedback throughout clinical interventions is warranted.

Table 1 outlines several options to consider when embarking on a standard laboratory evaluation of inflammatory and immune-mediated conditions. Even when immune dysregulation is not the chief complaint, several of these lab findings may be positive in patients who present with common symptoms such as pain, fatigue, insomnia, depression, anxiety, gastrointestinal complaints, and stress response. All labs in Table 1 can be ordered from any local or regional Quest Diagnostics lab (or similar lab).

For ease of use and clinical application, several options for laboratory evaluation of common immune-mediated conditions are grouped from A (fundamental) through D (more advanced). This is not meant to be an exhaustive list but will provide context and reminders as you proceed with diagnosis and clinical management. Group A represents fundamental assessment beginning with a CBC to evaluate anemia. A helpful tool to remember when eval-
Evaluating CBC results (sometimes referred to as the “rule of 3”) is that hemoglobin equals approximately 3 times the RBC count, and hematocrit equals approximately 3 times hemoglobin. For example, using typical values for an otherwise healthy adult man, if the RBC count is $5 \times 10^6$/$\mu$L, hemoglobin would be roughly 15 g/dL and hematocrit roughly 45%. When reviewing the white blood cell (WBC) count, consider both the total count and the differential (percentage of each type of WBC), and platelets. Variation in WBCs and their subtypes (either too low or high)

### Table 1. Options for Laboratory Evaluation of Immune Mediated Conditions

<table>
<thead>
<tr>
<th>Laboratory Testing</th>
<th>Group</th>
<th>Associated Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC &amp; Differential</td>
<td>A</td>
<td>Fundamental (RBC, WBC) immune evaluation</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation Rate (ESR)</td>
<td>A</td>
<td>Marker of active inflammation (nonspecific)</td>
</tr>
<tr>
<td>C Reactive Protein (CRP, hsCRP)</td>
<td>A</td>
<td>Marker of active inflammation (nonspecific)</td>
</tr>
<tr>
<td>Zinc (RBC, plasma or 24hr)</td>
<td>A</td>
<td>General immune function &amp; wound healing</td>
</tr>
<tr>
<td>Vitamin B6, Plasma</td>
<td>A</td>
<td>General immune function, metabolic disorders, Rx, ETOH</td>
</tr>
<tr>
<td>25-OH Vitamin D</td>
<td>A</td>
<td>Dietary deficiency, liver metabolism, gut immunity</td>
</tr>
<tr>
<td>CoQ10</td>
<td>A</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>DHEA, Pregnenalone</td>
<td>A</td>
<td>Hormone-associated stress response &amp; resiliency</td>
</tr>
<tr>
<td>Cortisol</td>
<td>A</td>
<td>Generalized stress response and resiliency</td>
</tr>
<tr>
<td>B12 &amp; Folate</td>
<td>A</td>
<td>Poor diet, malabsorption, Rx, ETOH</td>
</tr>
<tr>
<td>Iron and Ferritin</td>
<td>A</td>
<td>Dietary, metabolic deficiency or excess</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>A</td>
<td>Surrogate marker leukocytes &amp; intestinal inflammation</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>A</td>
<td>Decreased in inflammation of the liver</td>
</tr>
<tr>
<td>Protein, Total</td>
<td>A</td>
<td>Autoimmune hepatitis, inflammation</td>
</tr>
<tr>
<td>Amino Acid Analysis</td>
<td>A</td>
<td>Proteins, neurotransmitters, hormone precursors</td>
</tr>
<tr>
<td>Hemoglobin A1c (with MPG)</td>
<td>A</td>
<td>Diabetic and nondiabetic inflammation</td>
</tr>
<tr>
<td>Amylase &amp; Lipase</td>
<td>A</td>
<td>Elevated in gastrointestinal, pancreatic inflammation</td>
</tr>
<tr>
<td>Immunoglobulins (IgG, IgM and IgA)</td>
<td>A</td>
<td>Acute and chronic inflammation, autoimmune diseases</td>
</tr>
<tr>
<td>Celiac Disease (HLA Typing)</td>
<td>B</td>
<td>Dx immune-mediated gluten intolerance</td>
</tr>
<tr>
<td>Tissue Transglutaminase (TG-IgA, IgG)</td>
<td>B</td>
<td>Gluten-sensitive immune-mediated enteropathies</td>
</tr>
</tbody>
</table>

Table data represents standard laboratory test available through national labs such as Quest Diagnostics.
can indicate immune compromise (low total numbers, lymphocytes, or neutrophils), allergic response (elevated eosinophils), autoimmune disorder, and cancer. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels provide evidence of an active inflammatory process that may require further evaluation. Patients can also be evaluated for nutrition-related immune status by testing for levels of zinc, vitamin B6, 25-OH cholecalciferol, coenzyme Q10, vitamin B12/methylmalonic acid (MMA), folate, iron, ferritin, and protein (total, albumin, and globulin) and ordering an amino acid analysis. Any of these can be used in combination to determine if nutrient absorption and/or metabolism are issues. Systemic stress or resiliency can be determined with salivary or serum cortisol (morning and evening) and hormone cascades such as dehydroepiandrosterone (DHEA) and pregnenolone and their downstream products. The addition of hemoglobin A1c (with mean plasma glucose) will direct therapeutic goals toward sugar regulation, and amylase and lipase abnormalities may prompt a referral to a specialist in gastroenterology for further work-up.

(continued on page 14)

**TABLE 2. ALLERGY TESTING BY REGIONS**

<table>
<thead>
<tr>
<th>Designation</th>
<th>Geographic Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region I</td>
<td>CT, MA, ME, NH, NJ, NY, PA, RI, VT</td>
</tr>
<tr>
<td>Region II</td>
<td>DC, DE, MD, NC, VA</td>
</tr>
<tr>
<td>Region III</td>
<td>Northern FL, GA, SC</td>
</tr>
<tr>
<td>Region IV</td>
<td>South of Orlando, FL</td>
</tr>
<tr>
<td>Region V</td>
<td>IN, KY, OH, TN, WV</td>
</tr>
<tr>
<td>Region VI</td>
<td>AL, AR, LA, MS</td>
</tr>
<tr>
<td>Region VII</td>
<td>MI, MN, WI</td>
</tr>
<tr>
<td>Region VIII</td>
<td>IA, IL, MO</td>
</tr>
<tr>
<td>Region IX</td>
<td>KS, ND, NE, SD</td>
</tr>
<tr>
<td>Region X</td>
<td>OK, TX</td>
</tr>
<tr>
<td>Region XI</td>
<td>AZ (Mtn), ID (Mtn), NM, CO, MT, UT, WY</td>
</tr>
<tr>
<td>Region XII</td>
<td>Southern AZ, SE CA Desert</td>
</tr>
<tr>
<td>Region XIII</td>
<td>Southern Coastal, CA</td>
</tr>
<tr>
<td>Region XIV</td>
<td>CA Central Valley</td>
</tr>
<tr>
<td>Region XV</td>
<td>Nevada, Southern Idaho</td>
</tr>
<tr>
<td>Region XVI</td>
<td>Central &amp; Eastern WA &amp; OR</td>
</tr>
<tr>
<td>Region XVII</td>
<td>NW CA, Western OR, WA</td>
</tr>
<tr>
<td>Region XVIII</td>
<td>Alaska</td>
</tr>
<tr>
<td>Region XIX</td>
<td>Puerto Rico</td>
</tr>
</tbody>
</table>

**TABLE 3. COMMON IGE-BASED ALLERGY TEST PROFILES**

<table>
<thead>
<tr>
<th>Three Panels to Diagnose IgE-Mediated Allergies</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Food Allergy</strong></td>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Clam, f207</td>
<td><em>Alternaria alternata</em>, m6</td>
</tr>
<tr>
<td>Cod fish, f3</td>
<td><em>Aspergillus fumigatus</em>, m3</td>
</tr>
<tr>
<td>Corn (Maize), f8</td>
<td><em>Bermuda grass</em> (<em>Cynodon dactylon</em>), g2</td>
</tr>
<tr>
<td>Egg white, f1</td>
<td><em>Birch</em> (<em>Betula verrucosa</em>), t3</td>
</tr>
<tr>
<td>Milk, f2</td>
<td><em>Cat dander</em>, e1</td>
</tr>
<tr>
<td>Peanut, f13</td>
<td><em>Cladosporium herbarum</em>, m2</td>
</tr>
<tr>
<td>Scallop, f338</td>
<td><em>Cockroach</em>, i6</td>
</tr>
<tr>
<td>Sesame, f110</td>
<td><em>Common ragweed</em> (<em>Short</em>; <em>Ambrosia elatior</em>), w1</td>
</tr>
<tr>
<td>Shrimp, f24</td>
<td><em>Cottonwood</em> (<em>Populous deltoides</em>), t14</td>
</tr>
<tr>
<td>Soybean, f114</td>
<td><em>D. farinae</em>, d2</td>
</tr>
<tr>
<td>Walnut, f256</td>
<td><em>D. pteronyssinus</em>, d1</td>
</tr>
<tr>
<td>Wheat, f4</td>
<td><em>Dog dander</em>, e5</td>
</tr>
</tbody>
</table>

**Food/Environmental**

| *Elm* (*Ulmus americana*), t8                     |
| *Maple* (*Box elder*; *Acer negundo*), t1 |
| *Cat dander*, e1                                  |
| *Maple leaf sycamore* (*London plane*), t11 |
| *Cladosporium herbarum*, m2                       |
| *Mountain cedar* (*Juniperus sabinoides*), t6     |
| *Cockroach*, i6                                   |
| *Mugwort* (*Safebrush*; *Artemisia vulgaris*), w6 |
| *Cod fish*, f3                                   |
| *Mulberry*, t70                                   |
| *D. farinae*, d2                                  |
| *Oak* (*Quercus alba*), t7                       |
| *D. pteronyssinus*, d1                            |
| *Penicillium notatum*, m1                         |
| *Dog dander*, e5                                  |
| *Rough pigweed* (*Amaranthus retroflexus*), w14  |
| *Egg white*, f1                                  |
| *Sheep sorrel* (*Rumex acetosella*), w18         |
| *Milk*, f2                                        |
| *Timothy grass* (*Phyleum pratense*), g6         |
| *Peanut*, f13                                     |
| *Walnut* (*Juglans californica*), t11             |
| *Shrimp*, f24                                     |
| *White ash* (*Fraxinus americana*), t15           |
| *Soybean*, f14                                    |
| *Total IgE*                                       |
| *Walnut*, f256                                    |
| *Wheat*, f4                                       |
| *Total IgE*                                       |

Adapted from Quest ImmunoCAP®.

d=dust mites (house), e=epidermal, f=food, g=grass, i=insect, m=mold, t=tree, w=weed
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Altered immunoglobulins (Igs) may suggest broad compromise in immunity or autoimmunity. B cell production (all Igs reduced), a specific cancer (eg, lymphoma, multiple myeloma), or an autoimmune (eg, rheumatoid arthritis, system lupus erythematosus) diagnosis. Labs that reveal an increase or decrease in selective Igs may suggest an active ongoing infection (IgM); gastrointestinal mucosal involvement (reduced IgA); chronic infection and immunocompromise (IgG increased); allergic, dermatitis, or parasitic activity; or hyper IgE syndrome (increased IgE). Patients who are responding to vaccination may see a 2- to 5-fold increase in immunoglobulin response (4-8 weeks primary; 8-12 weeks memory), so determine if the CBC, WBC differential, or humoral response is altered due to vaccination. Depending on the patient’s symptoms, further evaluation and referral to an appropriate specialist for a more comprehensive immunological evaluation of immune dysregulation may be warranted.

Group B is directed toward immune-mediated gluten intolerance (celiac disease) and enteropathies as well as the initial screen for autoimmunity (testing for antinuclear antibodies [ANA]) and rheumatoid arthritis, metabolic inflammation (IGF-I) and concomitant immunologic response to Candida. If there is indication of immune dysregulation (low or high WBC subtypes), chronic unresolved infection, inflammation, or frequent colds and flus, Group C will help evaluate innate and adaptive arms of the immune response. These tests may identify and enumerate additional lymphocyte cell subpopulations based on flow cytometry and identification of cell surface receptors (such as CD4 and CD8 T cells), or they may be functional tests performed on isolated WBC subsets, which are cultured in vitro and challenged with a variety of antigenic and cellular stimuli. Tests include evaluation of innate, NK cell function and proliferation panels as well as selected proteins of the complement (C1q, C2, C3, C3c, C4, C4d) cascade and cytokine (IL-1B, IL-2, IL-6, tumor necrosis factor [TNF]) production. Based on test results you may decide to enhance innate and or humoral immunity through lifestyle modification or medicinally with dietary polysaccharides, larch arabinogalactan, Ganoderma, Terminalia bellirica, Salacia chinensis, Zingiber montanum, or Peltophorum pterocarpum.

Group D provides a more detailed evaluation and diagnosis of selected autoimmune conditions such as Sjögren’s syndrome, arthritis (14-3-3 proteins), immune complex disease (myeloperoxidase), or neurologic immune disorders (myelin-associated glycoprotein antibody). Diagnosis of autoimmune conditions should be done in conjunction with an immunologist and every effort put forth to work together for the betterment of the patient.

TESTING ALLERGIES/INTOLERANCES

In addition to the standard metabolic labs described above, patients presenting with conditions such as ongoing or seasonal sinusitis, chronic recurrent rhinitis, postnasal drip, sinus pressure, headaches, cough, allergic asthma, eczema, dermatitis, and psoriasis, or elevation of WBCs, subsets of eosinophils, and/or total IgE may benefit from an allergy and/or sensitivity panel. As summarized in Table 2, some of these panels vary based on the environmental allergens exposed by region. For example, Connecticut is designated as Region I, along with the rest of New England, New Jersey, New York, and Pennsylvania. Therefore, consider this regional variation before ordering. In addition to the traditional IgE-based allergy test profiles (Table 3), many laboratories now provide IgG-based panels to evaluate sensitivity and intolerance in addition to the anaphylactic or immediate type 1 IgE-driven immune hypersensitivity responses.

(continued on page 16)
Because these ingredients support the immune systems ability to adapt and not simply upregulate immune function, those with hyperactive immune responses may also incorporate this formula, under a physician’s supervision, into their daily regimen.*

WELLMUNE® | 250 MG PER SERVING
The researched ingredients in Immuno Benefits™ include the yeast beta 1,3/1,6 glucan derived from the cell wall of a proprietary strain. Wellmune® is clinically proven ingredient to support the functionality of the immune system. It has been studied for its effects on supporting healthy respiratory tract function and immune response after physical stress, such as exercise. This branded version of Beta glucan has also been found to play a support the balance of Th1/Th2 (Kirmaz, Bayrak, Yilmaz, & Yuksel, 2005).

MONOLAURIN | 300 MG PER SERVING
Another ingredient in Immuno Benefits™, Monolaurin, exhibits potent capabilities relative to microbial balance in the body (Lieberman, Enig, & Preuss, 2006). Researchers have found that Monolaurin can provide broad immune support (Lieberman, Enig, & Preuss, 2006), can support the body’s ability to adapt appropriately when in the presence of many gram-positive bacteria (Peterson & Schlievert, 2006), and balance the presence of Candida albicans (Bergsson, Arnfinnsson, Steingrimsson, & Thormar, 2001). Monolaurin achieves this at the cellular level by incorporating itself into the cell membrane of gram-positive bacteria, supporting a healthy level of replication (Tokarskyy & Marshall, 2008).

COLOSTRUM | 500 MG PER SERVING
YIELDING IMMUNOGLOBULINS (IgG) | 200 MG
Finally, Immuno Benefits™ contains colostrum. Colostrum supports immune system health through its content of transfer factors, peptide and protein complexes, that directly support immune capabilities.* Bovine colostrum also contains naturally occurring compounds, such as lactoferrin and immunoglobulin G, which our healthy cells continually recruit and utilize to support the functionality of the immune system.* These compounds also provide support to the immune system by working in the digestive system prior to foreign invaders even making it into the blood (Cesarone MR, et al., 2007).

IMMUNO BENEFITS™ IS AIMED AT PROVIDING IMMUNE SUPPORTIVE NUTRIENTS BOTH ON A DAILY BASIS AS WELL AS DURING ACUTE IMMUNE STRESS.*

OUR NEW BENEFITS LINE™ FORMULAS SO POWERFUL YOU HAVE TO SEE TO BELIEVE
Diagnosing intolerances and allergies can be difficult because symptoms often overlap or may be confused with other conditions, such as gas, bloating, abdominal pain, diarrhea, constipation, heartburn, fatigue or loss of energy, headaches and migraines, anxiety, depression, mood swings, poor concentration, and muscle/joint pain. According to the guidelines set by the National Institute of Allergy and Infectious Diseases, food allergy arises from (and is reproduced by) a specific immune response on exposure to a given food. However, an intolerance may cause the same reproducible adverse reaction but may not have an established underlying immune-mediated mechanism. For example, someone who is truly allergic to cow’s milk has an immune system response to milk protein (casein or whey) and therefore has a food allergy. But someone who has difficulty drinking milk due to an inability to digest lactose in milk has food intolerance, which may be due to low lactase production or any number of problems with the digestive system. Similarly, the diagnosis of celiac disease is based on a multigenic immune-mediated enteropathy triggered by dietary gluten, present in wheat, barley, and rye. With celiac disease, human leukocyte antigen (HLA) typing is performed; 90% of celiac patients express the HLA-DQ2 molecules. Gluten peptides presented by these HLA molecules induce an abnormal mucosal immune response and tissue damage.  

### CONCLUSION AND FUTURE DIRECTIONS

The immune system represents a complex network of organs, tissues, and blood products whose role is to balance a state of tolerance with swift and decisive action. As integrative practitioners our focus is to promote lifestyle balance and immune optimization by minimizing the impact of stressors and maximizing therapies that positively modulate the immune response. Fundamental tools include a comprehensive understanding of the immune system, its diagnosis, and its management; proper application of healthy diets, food elimination, and detoxification; exercise; dietary supplements; lifestyle interventions such as stress reduction, sleep, meditation, and energy therapies; and timely diagnosis and management of allergies, autoimmunity, cancer, and inflammatory processes. Communicating findings to both patients and referring doctors can provide novel treatment options for complex immune-mediated diseases that traditionally rely on steroids, immunosuppressants, and chemotherapy agents as first-line treatments. Keeping patients safe and caregivers engaged will ultimately create an environment in which integrative therapies can be used and given the time they need to turn around the most complex immune-mediated conditions.

### TABLE 4. COMMON IgG-BASED ALLERGY TEST PROFILES

<table>
<thead>
<tr>
<th>IgG Allergy Adult</th>
<th>Food IgG Pediatric</th>
<th>IgG Panel 1</th>
<th>IgG Panel 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef, f127</td>
<td>Casein, f78</td>
<td>Casein, f78</td>
<td>Apple, f149</td>
</tr>
<tr>
<td>Cacao (chocolate), f93</td>
<td>Casein, f78</td>
<td>Cacao (chocolate), f93</td>
<td>Banana, f92</td>
</tr>
<tr>
<td>Cod fish, f3</td>
<td>Cod fish, f3</td>
<td>Maize/corn, f8</td>
<td>Beef, f27</td>
</tr>
<tr>
<td>Coffee, f221</td>
<td>Maize/corn, f8</td>
<td>Egg white, f1</td>
<td>Casein, f78</td>
</tr>
<tr>
<td>Maize/corn, f8</td>
<td>Egg white, f1</td>
<td>Wheat, f4</td>
<td>Chicken, f83</td>
</tr>
<tr>
<td>Egg white, f1</td>
<td>Orange, f33</td>
<td>Yeast (bakers/brewers), f45</td>
<td>Cacao (chocolate), f93</td>
</tr>
<tr>
<td>Peanut, f13</td>
<td>Peanut, f13</td>
<td>Cockroach, i6</td>
<td>Maize/corn, f8</td>
</tr>
<tr>
<td>Soybean, f14</td>
<td>Pork, f26</td>
<td>Egg white, f1</td>
<td>Orange, f33</td>
</tr>
<tr>
<td>Tomato, f25</td>
<td>Soybean, f14</td>
<td>Potato, f35</td>
<td>Yeast, f14</td>
</tr>
<tr>
<td>Wheat, f4</td>
<td>Wheat, f4</td>
<td>Tomato, f25</td>
<td>Wheat, f4</td>
</tr>
</tbody>
</table>

Adapted from Quest ImmunoCAP®. d=dust mites (house), e=epidermal, f=food, g=grass, i=insect, m=mold, t=tree, w=weed
REFERENCES

Benefits of Elderberry for Symptoms of Common Cold in Air Travelers

A randomized, placebo-controlled trial

REFERENCE

OBJECTIVE
To determine whether a standardized membrane-filtered elderberry extract (Berry-Pharma; Iprona, Italy) is effective in preventing symptoms of common colds during long-haul air travel

DESIGN
Double-blind, placebo-controlled clinical trial

PARTICIPANTS
All participants were economy class air travelers on at least a 7-hour flight with less than a 12-hour stopover and a minimum of a 4-day stay at their destinations. Three hundred and twenty five adults were enrolled and 312 completed the trial. All participants were 18 years or older in good general health, with an average age of 50; 66% were female. Fifty-four percent had received a vaccine more than 10 days before starting the trial; 96% were nonsmokers; 70% had travel time of more than 16 hours; 82% traveled for holiday. Subjects were recruited from the Gold Coast region of Australia and traveled between April 2013 and December 2014.

INTERVENTION
Study intervention was elderberry extract, each capsule containing 300 mg of elderberry extract [22% polyphenols (ie, quercetin and its glycosides, rutin); 15% anthocyanins (ie, cyanidin and pelargonidin glycosides), and 150 mg of rice flour]. Placebo contained matched excipients and was identical in appearance.

Participants were randomized into 2 groups, to receive either study medication or placebo, beginning with a priming dose of 2 capsules per day 10 days before air travel (baseline; –10 days), followed by an overseas dose of 3 capsules per day taken before departure (–2 days) until 4 or 5 days after arrival (+4/5 days). A daily diary was kept throughout the study period (from day –10 to days +4/5) to record cold symptoms as well as to note additional health issues and additional medications.

STUDY PARAMETERS ASSESSED
Participants completed a number of surveys during the study period—at baseline (–10 days), before travel (–2 days), and after travel (+4/5 days). The Wisconsin Upper Respiratory Symptom Survey (WURSS-21) was used to assess respiratory symptom-related quality of life, the SF-12 assessed general quality of life, and the Perceived Stress Scale (PSS) was used to measure participants’ perception of stress. Cold diagnosis was assessed by measuring the Jackson Score.

PRIMARY OUTCOME MEASURES
Total number of cold episode days were measured for the 6 days prior to the end of the study (days –2/~1 to days +4/5).

KEY FINDINGS
Twenty-nine of 312 participants (9%) suffered from a well-defined cold (12 on elderberry and 17 on placebo; nonsignificant difference: P=0.4). Collectively, the placebo group had a longer duration of cold symptoms (117 d vs 57 d; P=0.02) and higher symptoms scores (583 vs 247; P=0.05) compared to the elderberry group.

PRACTICE IMPLICATIONS
Black elderberry (Sambucus nigra) extract has been shown, in previous clinical studies (including those discussed below), to lessen duration and symptoms of both influenza and the common cold. This trial aimed to discover whether elderberry was effective at preventing the common cold and reducing its duration and symptoms, specifically in the context of air travel.

Black elderberry extract has been shown to inhibit human influenza A (H1N1) infection in vitro by binding to H1N1 virions, thereby blocking the ability of the viruses to infect host cells. The same study showed elderberry to be effective against 10 strains of influenza virus and compared its effectiveness favorably to the known anti-influenza activities of oseltamivir (Tamiflu) and amantadine.

In a double-blind, placebo-controlled, randomized study, black elderberry extract (Sambucol) reduced the duration of flu symptoms by 3 to 4 days. In addition, during the convalescent phase participants’ blood serum showed a higher antibody level to influenza virus in the Sambucol group than in the control group.

Another study assessed the effect of Sambucol products on the healthy immune system—namely, their effects on cytokine production. The production of inflammatory cytokines was tested using blood-derived monocytes from 12 healthy human donors. Adherent monocytes were separated from peripheral blood lymphocytes and incubated with different Sambucol preparations (ie, Sambucol Elderberry).
Get to the Root Cause of Ill Health

Could it be hidden food and chemical sensitivity?

Sometimes, common foods, chemicals, and medications can overstress the immune system, making it hard for the body to defend and repair as it should.

Prolonged assault by these hidden immune burdens can lead to chronic conditions like asthma, diabetes, and many more.

LRA by ELISA/ACT testing can help identify the reactive items preventing your patients from feeling their best.
Extract, Sambucol Black Elderberry Syrup, Sambucol Immune System, and Sambucol for Kids). Production of inflammatory cytokines [interleukin (IL)-1 beta, tumor necrosis factor (TNF)-alpha, IL-6, IL-8] was significantly increased, mostly by the Sambucol Black Elderberry Extract (from 2-fold to 45-fold), as compared to lipopolysaccharide (LPS), a known monocyte activator (from 3.6-fold to 10.7-fold). The most striking increase was noted in TNF-alpha production (44.9-fold). The authors concluded that, in addition to its antiviral properties, Sambucol Elderberry Extract and its formulations activate the healthy immune system by increasing inflammatory cytokine production.

Black elderberries are dark violet in color owing to their anthocyanins, which are considered to be the active constituent of the fruit. The elimination of plasma anthocyanins appears to follow first-order kinetics, and most anthocyanin compounds are excreted in urine within 4 to 5 hours after ingestion. A study by Frank et al found the elimination half-life of total anthocyanins was slightly lower following consumption of 278 mg (1.85 h) than after the consumption of 1,852 mg (2.57 h). The urinary excretion rate of intact anthocyanins was fast and appeared to be monoexponential with high variability. The low dose-normalized area under the concentration curve (AUC) and the fraction of orally administered anthocyanins recovered unchanged in urine indicate a low bioavailability of these compounds.

The product used in the current study under review consisted of 600-900 mg of elderberry extract containing 90-135 mg of anthocyanins daily. This dose was far lower than the doses used in the Zakay-Rones randomized study of Sambucol, which used an extract containing approximately 1,900 mg anthocyanins. Since most of the active ingredients are excreted within 5 hours, it may be necessary to dose elderberry 4 or 5 times daily to even begin to obtain a 24-hour anti-influenza action from the plant. Whether this applies to the rhinoviruses and other viruses causing the common cold is unknown.

In both the elderberry and placebo groups, 50% of the subjects who developed cold symptoms used co-medication to relieve symptoms. This presents a significant confounding factor in interpreting the results. As a group, the participants with cold symptoms used 25 different conventional medications and 1 natural medicine. Some participants took 1 medication, others took up to 4.

The authors of this study previously published a similar trial attempting to show Echinacea root extract to be effective in reducing respiratory symptom score and the number of participants affected by respiratory disease symptoms. The results failed to achieve significance. Similarly, in the present study, many of the outcome measures did not reach significance. Yet in both of these publications the authors repeatedly stretch the limits of statistical significance by reporting “trends” and “marginal” results rather than adhering to the accepted standard of a P value < 0.05, giving the impression that their studies are more conclusive than they actually are.

Given the fact that I have lived in Hawaii for over 30 years and travel frequently, every flight I take (other than to the other Hawaiian islands) is at least 4.5 hours in duration (depending on wind conditions). Whether I travel to the West Coast, East Coast, or Europe, I find the conditions uncomfortable and stressful and I routinely take an herbal formula containing echinacea and elderberry to shore up my immune system. It seems to work. However, we will need to wait for better high-quality, well-powered studies to find out whether these herbal extracts meet the standards of scientific proof for prophylaxis and treatment of respiratory illness associated with air travel. Meanwhile, I find the risk/benefit balance tips firmly in the direction of flu prophylaxis with elderberry extracts.

REFERENCES
1 Roschek B, Fink RC, McMichael MD, Li D, Alberte RS. Elderberry flavonoids bind to and prevent H1N1 infection in vitro. Phytochemistry. 2009;70:1255-1261.
Full spectrum non-GMO vegan enzyme blend, including Glutalytic®, lactase, lipase, alpha-galactosidase, and amylase, to assist breakdown of gluten, gliadin, casein, whey, lactose, protein, fats, and carbohydrates.* It can also degrade other allergens, including salmon, almonds, peanuts, and ovalbumin.*

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.
Treatment of IgE-mediated Food Allergies with Baked Egg Biscuits

Updates on oral immunotherapy for food allergies

REFERENCE

STUDY OBJECTIVE
To develop a home-based oral immunotherapy with baked egg and to find out if it is a safe, practical, and effective treatment for children with egg allergies

DESIGN
Case series design

STUDY PROTOCOL
Immunotherapy protocol was designed in 5 stages, starting with 125 µg of egg protein, increasing it daily over a period of 60 days to a target maximum dose of 6.25 g of egg protein.

The first dose was administered in a hospital and the rest was continued at home.

Baked egg biscuit recipe consisted of 4 ingredients: flour (40 g at stages 1-4 and 80 g at stage 5); sugar (40 g); margarine (25 g at stages 1-3, 15 g at stage 4, and none at stage 5); and egg (0.1 mL at stage 1, 0.5 mL at stage 2, 1.0 mL at stage 3, 10 mL at stage 4, and 50 mL at stage 5). The amount of biscuit eaten was gradually increased on a daily basis.

PARTICIPANTS
Fifteen children with IgE-mediated egg allergy; 9 boys and 6 girls ranging from age 6 to 17, with median age of 11 years and 2 months. Inclusion criteria were age >5 years, persistent IgE-mediated egg allergy with a positive skin prick test (wheal>3 mm) to egg white and egg yolk, and symptoms of allergic reaction to baked egg in the previous 6 months or a positive open food challenge result.

PRIMARY OUTCOME MEASURES
Ability to tolerate whole boiled egg without adverse reactions

KEY FINDINGS
Eight children completed the whole program successfully, 4 children within the target of 60 days and 4 children between 80 and 270 days. Seven children did not complete the study; 2 could not tolerate the first dose without symptoms and 5 achieved partial tolerance at days 10 to 47, allowing them to include trace amounts of egg in their diet. Adverse reactions were minor and could be controlled by antihistamine medications.

LIMITATIONS
Study design and small number of participants

ABSTRACT & COMMENTARY

PRACTICE IMPLICATIONS

Food allergies are very common, and the prevalence is growing globally. Up to 15 million Americans have food allergies, including 1 in every 13 children under age 18. According to a 2013 study by the Centers for Disease Control and Prevention, incidence of food allergies among American children has increased. Other countries also are experiencing more cases of food allergies.

Kids at risk for food allergies are more likely to have parents with allergic disorders, and the children themselves are more likely to have related conditions, such as asthma and other allergic reactions. Food allergies can actually trigger many allergic disorders, such as food-induced anaphylaxis, gastrointestinal (GI) food allergies (eg, eosinophilic GI disorders), skin reactions (eg, urticaria, eczema), respiratory manifestations, and Heiner’s syndrome, a rare milk-induced pulmonary disease.

Each year, food allergies in children are responsible for over 300,000 doctor visits and 200,000 emergency department visits. They are the leading cause of anaphylaxis occurring outside of a hospital setting. Current treatment guidelines recommend identification and strict avoidance of allergenic foods. However, diet and unintentional exposures to allergens have significant impact on the quality of life. Better treatment options are needed, and the latest efforts have been concentrated on oral immunotherapy (or OIT, which was used in this study) and sublingual immunotherapy (or SLIT, which employs liquid sublingual preparations of allergenic extracts).

Oral immunotherapy is a great way to introduce allergens in the form of food, as they are encountered in real life.
The most common culprits that account for 90% of immunoglobulin (Ig) E-related food allergies are known as the big 8: milk, eggs, peanuts, tree nuts, wheat, soy, fish, and shellfish. About 18% of children don’t outgrow egg allergies. Reaction to eggs is commonly triggered by the proteins in egg whites, although egg yolk proteins can cause allergies as well.

Oral immunotherapy is a great way to introduce allergens in the form of food, as they are encountered in real life. Cooking processes (heating, acid, mixing) can change allergenicity of the food proteins. Heating egg protein with wheat can form a matrix with the wheat protein, which changes digestibility of the egg protein, making egg biscuits a good choice for the study.

Are we ready to apply oral immunotherapy to our clinical practice? While it is a very promising approach to treat egg allergies, as well as other food reactions, there are a number of issues that make it difficult. Safety is a big factor since the severity of a reaction cannot be predicted by past responses, IgE level, or the size of the prick test wheal. The most common known factor associated with severe reaction is a concurrent diagnosis of asthma. Additionally, the search for optimal doses and duration of treatment is ongoing, and the ease of use outside of the research environment is questionable. Nevertheless, it is very encouraging to see the desensitization of allergic reactions in subjects participating in studies. Oral immunotherapy seems to work faster but has higher rates of systemic reactions. Sublingual immunotherapy reactions are more frequent but are typically milder and confined to the oropharynx, therefore showing a better safety profile at this time.

Meanwhile, as providers we need to counsel our patients regarding hidden sources of food allergens to prevent unintended exposures and remind them to check expiration dates on their EpiPen prescriptions. We also want to consider additional factors related to the development of allergies. Interestingly, introduction of cooked egg earlier on, at 4 to 6 months of age, might protect against egg allergy. Vitamin D deficiency is associated with increased risk of sensitization to food allergens. Encouraging our patients to eat unprocessed foods can help decrease inflammation, because there is some association between food allergies and increased intestinal permeability. Glutamine and curcumin, as well as flavonoids, are helpful in maintenance of good GI function. The gut microbiome, which plays an important role in the development of allergies, is another potential area of research.

REFERENCES
REFERENCE

STUDY OBJECTIVE
To determine whether oral supplementation with vitamin D3 affects T cell activation in those with existing vitamin D deficiency

DESIGN
This was a single-center ancillary study within a study looking at vitamin D therapy in individuals at high risk of hypertension. It was a double-blind, multicenter, randomized controlled trial.

PARTICIPANTS
Participants (n=38) were derived from the Vitamin D Therapy in Individuals at High Risk of Hypertension Study. The original study included 534 men and women ages 18-50 years old with 25(OH)D lower than 25 ng/mL and untreated prehypertension or stage I hypertension. Participants were randomized to receive low-dose vitamin D (400 IU) or high-dose vitamin D (4,000 IU) daily for 6 months.

The current publication involved a subset of 38 randomly selected men and women who had T-cell function in whole blood measured.

Among the cohort of 38 patients for whom T-cell function was assessed, 20 participants were randomized to low-dose vitamin D and 18 participants were randomized to high-dose vitamin D. The median age was 45 years (interquartile range, 39-47 years); 9 were women (24%); 8 (21%) were white, 29 (76%) were black, and 1 (3%) was of other or unknown race. Patients were treated with vitamin D for a mean of 117 days (SD: 52 days). Per protocol, both groups were vitamin D–deficient, with similarly low baseline 25(OH)D levels (mean, 16.2 ng/mL; SD, 6.8 ng/mL).

Exclusion criteria included use of an antihypertensive medication within the preceding 3 months; vitamin D supplementation (defined as vitamin D found in a multivitamin or supplement) totaling 400 IU/d within the 3 months before enrollment; and known cardiovascular disease (defined as prior myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass, or stroke).

Other exclusion criteria included history of ulcerative colitis, Crohn’s disease, celiac disease, colostomy, pancreatic enzyme deficiency, short bowel syndrome, gastric bypass, cystic fibrosis, or dumping syndrome.

STUDY PARAMETERS ASSESSED
Activation of T cells was measured by estimating release of intracellular ATP in vitro using plant lectin phytohemagglutinin on whole blood samples of participants. Measurements were taken at baseline and after 2 months of treatment with vitamin D.

PRIMARY OUTCOME MEASURES
Whether ATP level changes were significantly different between treatment groups

KEY FINDINGS
After 2 months of treatment, 25(OH)D levels significantly increased by 5.77 ng/mL among those assigned low-dose vitamin D3 and 9.77 ng/mL among those assigned high-dose vitamin D3.

Treatment with high-dose vitamin D significantly decreased intracellular CD4+ATP release (difference=95.5 ng/ml; interquartile range [IQR], –219.5 to –105.8; P<.026). In contrast, treatment with low-dose vitamin D3 did not significantly influence intracellular CD4+ ATP release (difference=0.5 ng/mL; IQR, –69.2 to –148.5; P=0.538). The difference in follow-up ATP levels at 2 months was significantly different between the low- and high-dose vitamin D3 groups.

In a proportional odds model, treatment with high-dose vitamin D3 was more likely to decrease ATP after antigen stimulation compared to low-dose vitamin D3 (odds ratio [OR]: 3.43; 95% confidence interval [CI]: 1.06-1.11).

Eleven of the 20 patients (45%) treated with high-dose vitamin D3 were considered “responders” with significant decreases in ATP levels. Among those treated with high-dose vitamin D3, 63.5% (7/16) of men, 25% (1/4) of women, 52.9% (9/17) of white, and 48.1% (8/17) of black participants were responders.

This study did not observe a significant difference in results according to race. It did, however, find a significant difference according to sex (P, interaction<0.02). Men were more likely to have decreased ATP antigen stimulation compared to women.

ABSTRACT & COMMENTARY
Vitamin D Effective for Suppressing Immune Reactions
Trial looks at vitamin D in patients at high risk of hypertension

Heather Paulson, ND, FABNO
PRACTICE IMPLICATIONS

This study examined the function of CD4+T cells. As a quick immunology reminder, the CD4+T cells have multiple immune functions and include TH1, TH2, TH17, and T regulator (Treg) cells. The diverse functions of T cells include activation of the innate immune system, B lymphocytes, cytotoxic T cells, and nonimmune cells. In addition Tregs can inhibit the action of other T cells, acting as a balance to the inflammatory immune response. Unfortunately, this study did not differentiate the subtypes of CD4+T cells. So it is impossible to know which subsets of CD4+T cells were influenced by vitamin D3 supplementation.

In clinical practice we often get the question, “How long until my vitamin D levels will increase?” This study confirms that in just 2 months of therapy, significant changes were made in serum vitamin D levels.

In this study, vitamin D was associated with changes in cell-mediated immunity through reduction in activation (less ATP produced). This reduction in activation was significantly different in the low-dose and high-dose groups, with greater suppression of activation in the high-dose group. This suggests that high doses may provide greater immune modulation than low doses.

This study is in keeping with animal studies that have demonstrated vitamin D’s modulation of autoimmunity. Quelling overactive immune-mediated conditions may have far-reaching clinical implications. The story, however, is complicated. Vitamin D receptors (VDRs) are found on a variety of immune cells. These VDRs have high variability themselves, with many genotypes possible. There are also vitamin D binding proteins (VDBPs) that influence the availability of vitamin D. In short, the interplay of vitamin D on immune function is complex, and confusing the data is the influence of VDRs, VDBPs, other nutrients (eg, calcium), and hormonal influences.

Vitamin D may also be used as a complement to drugs established for overactive immune diseases. One study combining high-dose vitamin D with interferon β-1b in patients with multiple sclerosis showed an improvement in function and a reduction in relapse compared to patients treated with the drug alone.

The role of vitamin D3 supplementation on immune function requires clinical trial outcomes to definitively determine if, and how much, oral vitamin D3 influences disease states. Meanwhile, it can be considered not harmful to bring our patients into the normal range of 25-hydroxycholecalciferol in an effort to optimize their health while clinical studies continue to inform us.

REFERENCES
SPONSORED PODCAST

Getting to the Root of Food Sensitivities
An interview with Todd Born, ND

Sponsored by Allergy Research Group, Producers of Innovative Nutritional Supplements

ABOUT THE EXPERT

TODD A. BORN, ND, is in private practice with his wife, Lindsay Jones-Born, ND, at Born Naturopathic Associates, Inc., in Alameda, CA, where he is co-owner and medical director. Born is product manager, director of new product development, and scientific advisor for Allergy Research Group, LLC, and is editor-in-chief of their Focus Newsletter. He is also a thought leader for the UK-based Clinical Education, a free peer-to-peer service that offers clinicians a closed forum to ask clinical questions and receive evidence-based responses from experts in their fields. Born graduated from Bastyr University in Seattle and completed his residency at the Bastyr Center for Natural Health and its 13 teaching clinics, with rotations at Seattle-area hospitals. He may be reached at dr.born@bornnaturopathic.com.

Born’s clinical focus is using integrative medicine to treat chronic disease. He has a strong interest in difficult and refractory cases, gastrointestinal issues, neurological and neurodegenerative disorders, endocrinology, cardiovascular disease, diabetes, autoimmune disease, ADHD, autism, HIV/AIDS, and geriatrics. He has extensive knowledge and training in the basic medical sciences, physical medicine (osseous manipulation, craniosacral therapy, hydrotherapy and physiotherapy), botanical medicine, homeopathy, biotherapeutic drainage, Ayurveda, counseling, and diet and nutrient therapies.

ABOUT THE SPONSOR

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Periodontitis and Alzheimer’s Disease

Improving dental hygiene may slow cognitive decline

Jacob Schor, ND, FABNO

REFERENCE

DESIGN
Observational cohort study

PARTICIPANTS
Investigators recruited 60 nonsmoking adults with mild to moderate dementia from referrals to community memory assessment services in the United Kingdom. All participants had a minimum of 10 teeth and had not been treated for periodontitis in the 6 months prior to the study. Fifty-two participants completed the study.

OBJECTIVE
To observe any associations between periodontitis and dementia severity, rate of cognitive decline, or chronic inflammation in adults with mild to moderate Alzheimer’s disease.

OUTCOME MEASURES
Cognitive status of participants was tested using both the Alzheimer’s Disease Assessment Scale (ADAS-cog) as the primary cognitive outcome and the standardized Mini-Mental State Examination (sMMSE) as a secondary cognitive outcome. At baseline, venous blood was tested for C-reactive protein (CRP), the pro-inflammatory cytokine tumor necrosis factor (TNF) α, the anti-inflammatory cytokine interleukin (IL)-10 and immunoglobulin G (IgG) antibodies to P. gingivalis. Dental health was assessed by a dental hygienist, blind to cognitive testing outcomes, to determine the presence or absence of periodontitis following established Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) case definitions. All assessments were performed at baseline and repeated at 6 months.

KEY FINDINGS
The presence of periodontitis at baseline was not related to baseline cognitive state but was associated with a 6-fold increase in the rate of cognitive decline (P=0.005). There was no correlation between carriers and noncarriers of apolipoprotein E (ApoE) allele and baseline periodontitis or cognitive decline. Baseline antibody levels to P gingivalis were not statistically associated with cognitive outcomes. Periodontitis at baseline was associated with a relative increase in the pro-inflammatory state (CRP, TNF-α) and decrease in the anti-inflammatory state (IL10) over the 6-month follow-up period. Periodontitis was associated with an increase in cognitive decline in Alzheimer’s disease (AD), independent of baseline cognitive state, which may be related to systemic inflammation.

PRACTICE IMPLICATIONS
First, these data hold out the possibility that improving dental hygiene might slow the rate of cognitive decline in AD. Second, these data support a new theory that AD is in part an immune response to infection.

Several earlier studies have reported that AD patients have worse dental health than control subjects of similar ages and that the worse the dementia, the worse the dental health.1,2 The obvious assumption was that this was due to poorer self-care with advancing dementia (ie, people were forgetting to brush their teeth).3

This study did not find a clear relationship between the dementia severity and periodontitis, but that may be because patients with severe dementia were not included in the cohort. This is the first study that correlates rates of declining cognitive function with poor dental health. Knowing that periodontitis was associated with faster cognitive decline during this study’s 6-month follow-up period suggests that we should be far more proactive with patients showing early signs of AD and insist on aggressive dental care.

While we may look for other explanations for this association, the most obvious one, that periodontitis drives Alzheimer’s disease progression, makes the most sense in light of other recent research and the newer hypothesis that suggests AD is an immune reaction to infection.

In May 2016, Science Translational Medicine published a paper by Harvard researcher Deepak Kumar and colleagues that suggested that the amyloid proteins that are the hallmark of AD normally serve an antimicrobial function, protecting the brain against infection. Their theory is that infections, in particular mild infections, combined with increased permeability of the blood brain barrier (BBB), elicit an over-response by the brain’s defensive mechanism that in its enthusiasm generates an overabundance of amyloid plaque. Amyloid beta, the substance that forms the plaque of Alzheimer’s disease, may in fact have a purpose in the brain. It is a defense mechanism against...
infection and is now described as “primary effector molecules of innate immunity, antimicrobial peptides (AMPs), also called host defense peptides.”

When a virus, fungus or bacteria slips across the BBB, the brain generates amyloid material that surrounds and traps the invader. The amyloid cocoons the interloper into a cage. Even after the invader dies, the trap remains in place, forming permanent plaque deposits in the brain. The Harvard team has demonstrated this process occurring in vitro, to date. The study currently under review lends support to this theory, with its preliminary finding of an association between periodontitis and AD in humans.

These data support a new theory that AD is in part an immune response to infection.

There are several other examples of chronic infections associated with AD. In September 2016, Shim et al reported that elevated Epstein-Barr Virus (EBV) antibody levels are associated with cognitive decline, and went so far as to suggest EBV antibody levels might be used as a biomarker for assessing rate of disease progression. Herpes simplex virus-1 antibody titers also share a similar association with cognitive impairment.

A similar association has been seen with bacterial infections in numerous studies. A meta-analysis of 25 separate studies, published in August 2016, found significant associations between both Chlamydia pneumoniae and spirochetal bacteria with AD. Spirochetal infections were associated with a 10-fold increased occurrence of AD (OR: 10.61; 95% CI: 3.38-33.29). A greater than 5-fold increase in risk of AD was seen with Chlamydia infection (OR: 5.66; 95% CI: 1.83-17.51).

It may not be the type of infectious agent as much as the chronicity or persistence of the infection that provokes the AD triggering response in the brain. It may take continuous antigen exposure to trigger the amyloid response.

Another paper published in August 2016 expands this hypothesis, suggesting that the chain of events that leads to AD starts in the gut with intestinal microbiota increasing intestinal permeability and in turn increasing permeability of the BBB. This in turn presents more antigenic material to the brain that triggers the amyloid beta producing reaction.

Noting the many studies that have associated herpes antibody levels with AD, Ruth Itzhaki, writing in August 2016 in the *Journal of Alzheimer’s Disease*, suggested we consider “the usage of antiviral treatment to slow or halt the progression of AD.”

Thus we could be fast entering a new era in how we view Alzheimer’s disease, one in which we both understand the underlying mechanisms and also have some simple interventions to offer our patients, starting with reminding them to brush their teeth.

**REFERENCES**

10. Itzhaki RF. Herpes and Alzheimer’s Disease: Subversion in the central nervous system and how it might be halted [published online ahead of print August 1, 2016]. *J Alzheimers Dis*.
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Immune Processes and Brain Health
An Interview with Heather Zwickey, PhD

In this interview with Natural Medicine Journal’s Editor-in-Chief, Tina Kaczor, ND, FABNO, Zwickey explains how immune processes can influence brain health—including in Parkinson’s, Alzheimer’s, and depressive disorders. She discusses nutrition, supplements, and the complicated ways gut health and immunity interact with cognitive function.

ABOUT THE EXPERT
HEATHER ZWICKEY, PhD, is dean of research and graduate studies and a professor of immunology at the National College of Natural Medicine, Portland, Oregon, as well as director of Helfgott Research Institute. Currently, she heads several pilot studies looking at the effects of botanicals, hydrotherapy, energy medicine, and diet on immunological parameters. Zwickey trained at the National Jewish Medical and Research Center in Denver, Colorado. She received her doctorate in immunology and microbiology from the University of Colorado Health Sciences Center and completed a postdoctoral fellowship at Yale University.

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