Autoimmune Disease: Leaving the Era of Reaction and Entering the New Era of Prediction

David M. Brady, ND, DC, CCN, DACBN

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Director, Human Nutrition Institute
Associate Professor of Clinical Sciences

Autoimmune Disease: Leaving the Era of Reaction and Entering the New Era of Prediction 2013 ~ David M. Brady, N.D.
Autoimmune Disease: Leaving the Era of Reaction and Entering the New Era of Prediction

Increasing Incidence of Immune Regulatory Disorders

- Multiple sclerosis
- Crohn's disease
- Type 1 diabetes
- Asthma


How do we see illness?

Autoimmune Disease
Autoimmune Disease: Leaving the Era of Reaction and Entering the New Era of Prediction

The Importance of Mucosal Immunity

“The dominating part of the immune defense, even if flora is excluded, is localized in the gut—no less than 75% of the immune cells of the body are suggested to be found in the G-I tract.”

Bengmark S. Acute and "chronic" phase reaction—a mother of disease, ClinNutr, Vol. 23, No. 6, pp. 1256-1266, December 2004
“Death begins in the colon”

- E. E. Metchnicoff
  - Russian Pathologist,
  - 6th Ever Nobel Laureate (1908)
  - Father of “orthobiosis” theory and probiotics
A microbial symbiosis factor prevents intestinal inflammatory disease

Sarkis K. Mazmanian1,*, June L. Round1,4 & Dennis L. Kasper2,3

Humans are colonized by multitudes of commensal organisms representing members of five of the six kingdoms of life; however, our gastrointestinal tract provides residence to both beneficial and potentially pathogenic microorganisms. Imbalances in the composition of the bacterial microbiota, known as dysbiosis, are postulated to be a major factor in human disorders such as inflammatory bowel disease. We report here that the 

beneficial activity requires a single microbial molecule (polysaccharide A, PSA). In animals harboring B. fragilis not expressing PSA, H. hepaticus colonization leads to disease and pro-inflammatory cytokine production in colonic tissues. Purified PSA administered to animals is required to suppress pro-inflammatory interleukin-17 production by intestinal immune cells and also inhibits in vitro reactions in cell cultures. Furthermore, PSA protects from inflammatory disease through a functional requirement for interleukin-10-producing CD4+ T cells. These results show that molecules of the bacterial microbiota can mediate the critical balance between health and disease. Harnessing the immunomodulatory capacity of symbiosis factors such as PSA might potentially provide therapeutics for human inflammatory disorders on the basis of entirely novel biological principles.
Disorders Associated with Dysbiosis and Intestinal Hyperpermeability

<table>
<thead>
<tr>
<th>Autoimmune Disease: Leaving the Era of Reaction and Entering the New Era of Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory Bowel Disease</td>
</tr>
<tr>
<td>Dermatitis Herpetiformis</td>
</tr>
<tr>
<td>Irritable Bowel Syndrome</td>
</tr>
<tr>
<td>Celiac Disease</td>
</tr>
<tr>
<td>Infectious Enterocolitis</td>
</tr>
<tr>
<td>Chronic Fatigue Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>Acute Injury</td>
</tr>
<tr>
<td>Childhood Hyperactivity</td>
</tr>
<tr>
<td>Spondylarthropathies</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Dermatitis Herpetiformis</td>
</tr>
<tr>
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<td>Spondylarthropathies</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
</tbody>
</table>


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Real-Time PCR Quantitation of Clostridia in Feces of Autistic Children

Yoli Song,1,2 Chengqin Liu,3 and Selvhey M. Fingar1,4,5

Research Services and Infectious Diseases Section, VA Medical Center West Los Angeles, and Department of Medical and Department of Microbiology, Immunology, and Molecular Genetics, UCLA School of Medicine, Los Angeles, California.

Received 11 February 2004; accepted 27 June 2004.

Based on the hypothesis that intestinal clostridia play a role in late-onset autism, we have been characterizing clostridia from stools of autistic and control children. We applied the TaqMan real-time PCR procedure to detect and quantitate three Clostridium species and one Clostridium perfringens species, C. difficile, in stool samples. Group- and species-specific primers targeting the 16S rRNA gene were designed, and specificity of the primers was confirmed with DNA from related bacterial strains. In this procedure, a linear relationship exists between the threshold cycle (Ct) fluorescent value and the number of bacterial cells (CP). The assay showed high specificity for the three species, with a Ct value of 36.50 for Clostridium difficile, 36.24 for Clostridium perfringens, and 36.40 for Clostridium difficile. There were no significant differences between autistic and control children for C. difficile and the following Clostridium species were statistically significant in controls: C. difficile and Clostridium difficile and Clostridium perfringens. This study indicates that a potential pathogenic role for Clostridium difficile in autistic children, and is consistent with the hypothesis that Clostridium difficile plays a role in late-onset autism.

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Univ. of Bridgeport
Clostridia in Autism by Real Time PCR

<table>
<thead>
<tr>
<th></th>
<th>C. bolteae</th>
<th>Clostridium cluster I</th>
<th>Clostridium cluster XI</th>
<th>Clostridium cluster XIVab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (N=8)</td>
<td>(3.9 ± 0.3) $10^3$</td>
<td>(4.1 ± 0.3) $10^5$</td>
<td>(4.0 ± 0.4) $10^6$</td>
<td>(2.6 ± 0.2) $10^8$</td>
</tr>
<tr>
<td>Autistic (N=15)</td>
<td>(1.8 ± 0.1) $10^5$</td>
<td>(3.7 ± 0.4) $10^6$</td>
<td>(1.4 ± 0.1) $10^7$</td>
<td>(4.8 ± 0.6) $10^8$</td>
</tr>
</tbody>
</table>

- **Group I (Clostridium cluster I)**
  - Forward primer, CI-F1 TACCHRAGGAGGAAGCCAC 54.6
- **Group II (Clostridium cluster XI)**
  - Forward primer, CXI-F1 ACCTACTCCTGAGGAGGA 46.5
- **Group III (Clostridium cluster XIVab)**
  - Forward primer, CXIV-F1 GAWGAAGTATYTCGGTATGT 46.2

Gut Microbes and Systemic Pathology

Examples of epidemiologic associations between GI microbes and systemic autoimmune pathology:

- Klebsiella: Ankylosing Spondylitis
- Citrobacter, Klebsiella, Proteus Rheumatoid Arthritis
- Yersinia: Grave’s Disease & Hashimoto’s Dz.
- S. Pyogenes: Rheumatic Fever
- Campylobacter jejuni: Gullian Barre Syndrome
- E. coli, Proteus: Autoimmunity in general

Modified from: Miyazaki MD. Epidemiologic studies of environmental agents and systemic autoimmune diseases. Environ Health Perspect 1999;107(suppl. 5):743-748
FRIEND OR FOE: T-cells recognize foreign antigens when they are presented by the HLA molecules of the immune system. In some people, especially those who have certain HLA types, a foreign antigen may resemble antigen produced by the body. Such molecular mimicry provokes the T-cells to attack body tissues that contain the self-antigens.

Gut-Autoimmune Connection

- Maldigestion
- Leaky Gut
- GI Infections

Immune Complex Formation
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The Colonization Resistance of the Mucous Membrane of the Large Intestine in Patients with Rheumatoid Arthritis in a Period of Exacerbation

"The mucous membrane of healthy people is colonized by bifidobacteria, lactobacilli, Bacteroides, Escherichia and enterococci. The mucous membrane in RA subjects is mainly colonized by aerobic opportunistic conventionally pathogenic enterobacteria (enteropathogenic Escherichia, Citrobacter, Enterobacter, Klebsiella, etc.), staphylococci, enterococci and anaerobic bacteria (Bacteroides, peptococci, peptostreptococci, etc.). Taking into account significant changes of colonization resistance in the colon mucous membrane in remission period of RA, it is necessary to apply bacteriotherapy, using bacterial drugs containing bifidobacteria and lactobacteria."

"In AS the incidence of gut inflammation was found in 70% of the cases... These findings provide further arguments... joint disease is triggered through the gut."

Reference:
J Rheumatology. 1990; 8:523-524

Author's Reply

In the cited report, Dr. Maican et al. concluded that patients with AS had an increased gut permeability compared to healthy controls. However, further studies are needed to fully understand the mechanism behind this association.

Dr. Brady
There are findings that support the hypothesis that oral infections play a role in RA pathogenesis. Of special importance are the impact of periodontal pathogens, such as Porphyromonas gingivalis on citrullination, and the association of PD in RA patients with seropositivity toward rheumatoid factor and the anti-cyclic citrullinated peptide antibody.
Antibodies to Proteus in RA

Table 1. Worldwide distribution of elevated Proteus antibodies in patients with RA.

<table>
<thead>
<tr>
<th>No.</th>
<th>Location (country)</th>
<th>RA patients</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>London (England)</td>
<td>58</td>
<td>1985</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>Winchester (England)</td>
<td>162</td>
<td>1986, 1997</td>
<td>104, 105</td>
</tr>
<tr>
<td>3</td>
<td>Newcastle (England)</td>
<td>142</td>
<td>1992</td>
<td>106</td>
</tr>
<tr>
<td>4</td>
<td>Epsom (England)</td>
<td>27</td>
<td>1993</td>
<td>107</td>
</tr>
<tr>
<td>6</td>
<td>Dundee (Scotland)</td>
<td>116</td>
<td>1995, 1999</td>
<td>109, 40</td>
</tr>
<tr>
<td>7</td>
<td>Dublin (Ireland)</td>
<td>28</td>
<td>1988</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>Toulouse (France)</td>
<td>15</td>
<td>1994</td>
<td>111</td>
</tr>
<tr>
<td>9</td>
<td>Brest (France)</td>
<td>10</td>
<td>1995</td>
<td>112</td>
</tr>
<tr>
<td>10</td>
<td>Hamilton (Canada)</td>
<td>34</td>
<td>1995</td>
<td>108</td>
</tr>
<tr>
<td>11</td>
<td>Oslo (Norway)</td>
<td>53</td>
<td>1995</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>Osaka (Japan)</td>
<td>96</td>
<td>1997</td>
<td>113</td>
</tr>
<tr>
<td>13</td>
<td>Chandigarh (India)</td>
<td>10</td>
<td>1997</td>
<td>114</td>
</tr>
<tr>
<td>14</td>
<td>Amsterdam (Holland)</td>
<td>25</td>
<td>1998</td>
<td>115</td>
</tr>
<tr>
<td>15</td>
<td>Tachikawa</td>
<td>30</td>
<td>1999</td>
<td>116</td>
</tr>
<tr>
<td>16</td>
<td>Brno (Czech Republic)</td>
<td>34</td>
<td>1999</td>
<td>107</td>
</tr>
<tr>
<td>17</td>
<td>Moscow (Russia)</td>
<td>27</td>
<td>2000</td>
<td>117</td>
</tr>
<tr>
<td>18</td>
<td>Bethesda &amp; Philadelphia (USA)</td>
<td>113</td>
<td>2000</td>
<td>19</td>
</tr>
<tr>
<td>19</td>
<td>Tokyo (Japan)</td>
<td>30</td>
<td>Submitted</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Helsinki (Finland)</td>
<td>90</td>
<td>1979</td>
<td>Submitted</td>
</tr>
</tbody>
</table>

Total number of RA patients: 1205

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Rheumatoid arthritis: proposal for the use of anti-microbial therapy in early cases

Alan Ebringer, MD

In 1966, we found antibodies to Proteus in the sera of patients with RA. These were reactive with a common antigen associated with Proteus species. We also found that these antibodies are present in the sera of patients with RA, even in the absence of infection. The presence of these antibodies is associated with a higher incidence of joint destruction, which is a hallmark of RA. These findings suggest that the Proteus antigen may be a trigger for the development of RA.
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Molecular Mimicry: Proteus and HLA-DR1/DR4

A: ESRRAL sequence of *Proteus mirabilis* haemolysin
B: EQRRAA sequence within DRB1*0101 (HLA-DR1)
C: EDERRAA sequence of DRB1*0402 (HLA-DR4/Dw10) (predicted from known crystallographic structure)
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Table II. Possible explanation for some commonly encountered features in RA.

<table>
<thead>
<tr>
<th>Associated RA Features</th>
<th>Suggested Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female preponderance 3:1</td>
<td>Increased incidence of UBTs in females</td>
</tr>
<tr>
<td>Disease onset in 30-50 years</td>
<td>Increased incidence of UBTs among middle and older age groups</td>
</tr>
<tr>
<td>Exacerbation after pregnancy</td>
<td>Involvement of non-genetic environmental factors in the pathogenesis of the disease</td>
</tr>
<tr>
<td>Low concordance rate in identical twins and fluctuating course of the disease</td>
<td>A secondary phenomenon due to B cell stimulation and presence of antigen-antibody complexes</td>
</tr>
<tr>
<td>Presence of rheumatoid factors in high proportions of RA patients</td>
<td>Cross-reactivity with &quot;ESRAL&quot; amino acid sequences present in the Proteus hemolyticus</td>
</tr>
<tr>
<td>Presence of &quot;ESRAG&quot; amino acid motif in over 90% of patients possessing the RA-associated HLA-DR molecules</td>
<td>Cross-reactivity with &quot;LUMB&quot; amino acid motif present in the Proteus urease enzyme</td>
</tr>
<tr>
<td>High proportion of small joints involvement, having hyaline cartilage which contains type XI collagen, possessing the &quot;HSF&quot; amino acid sequence</td>
<td></td>
</tr>
</tbody>
</table>

“We show that a microbial peptide, common to several major classes of bacteria, can induce MS-like disease in humanized mice by crossreacting with a T cell receptor (TCR) that also recognizes a peptide from myelin basic protein, a candidate MS autoantigen. Structural analysis demonstrates this crossreactivity is due to structural mimicry of a binding hotspot shared by self and microbial antigens, rather than to a degenerate TCR recognition. Thus, these data suggest a possible explanation for the difficulty in incriminating individual infections in the development of MS.”
Infection, Thyroid Disease, and Autoimmunity*


david tatem and tom van hasselt


department of medicine, mount sinai school of medicine,
new york, new york 10029

1. introduction
2. role of the thyroid in infections
3. role of infection in the development of thyroid disease
4. infection and the role of the immune system
5. infection and the role of the thyroid
6. infection and the role of the immune system
7. infection and the role of the thyroid
8. infection and the role of the immune system
9. infection and the role of the thyroid
10. infection and the role of the immune system


david m. brady, nd, dc, ccn, dacbn

university of bridgeport


tomer et al, endocrine review 1993 vol 14, no 1

molecular mimicry has long been implicated as a mechanism by which microbes can induce autoimmunity.

virology journal

review: viruses and thyroiditis: an update

rachel delcan and daniel holder

abstract

viral infections are frequently cited as a major environmental factor involved in subacute thyroiditis and autoimmune thyroid diseases. this review examines the data related to the role of viruses in the development of thyroiditis.

our research has been focused on human data. we have reviewed virological data for each type of thyroiditis at different levels of evidence: epidemiological data, serological data or research on circulating viruses, direct evidence of thyroid tissue infection. interpretation of epidemiological and serological data must be cautious as they don't prove that this pathogen is responsible for the disease. however, direct evidence of the presence of viruses or their components in the organ are available for retroviruses (hiv) and murine mammary tumor viruses, for retroviruses (htlv-1, hiv, and sy40) in graves's disease and for htlv-1, enteroviruses, rubella, mumps virus, hsv, ebv, and sarcoma virus in histidinum's thyroids. however, it remains to determine whether they are responsible for thyroid diseases or whether they are just innocent bystanders. further studies are needed to clarify the relationship between viruses and thyroid diseases, in order to develop new strategies for prevention and/or treatment.

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“Yersinia shows on its surface saturable binding sites for TSH. TSH receptor antibodies could be produced in selected individuals having been infected with bacteria showing TSH receptors.”

“It may, therefore, be assumed that the gram-negative bacterium Yersinia enterocolitica may have an active part in triggering immunogenic thyroid diseases…”
Prevalence of Yersinia Antibodies in Thyroid Disorder Patients

![Graph showing the prevalence of Yersinia antibodies in healthy and thyroid disorder patients.](image)

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Sample Natural GI Antimicrobial

<table>
<thead>
<tr>
<th>Serving size</th>
<th>Amounts per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of servings per container</td>
<td>2 caps</td>
</tr>
<tr>
<td>Number of capsules per container</td>
<td>30</td>
</tr>
<tr>
<td>Tribulus terrestris</td>
<td>60</td>
</tr>
<tr>
<td>(standardized to 40% furostanolsaponins)</td>
<td>400 mg</td>
</tr>
<tr>
<td>Chinese Wormwood (Artemisia annua/apiacea)</td>
<td>300 mg</td>
</tr>
<tr>
<td>(standardized to &gt;10% artemisinin)</td>
<td></td>
</tr>
<tr>
<td>Berberine sulfate (from Berberus aquifolius)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Barberry (Berberis vulgaris) (standardized to 6% berberine)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Bearberry</td>
<td>100 mg</td>
</tr>
<tr>
<td>Arctostaphylos uva ursi)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Grapefruit/Citrus Seed Extract</td>
<td>300 mg</td>
</tr>
<tr>
<td>Magnesium Caprylate *(Yielding 267 mg of Caprylic Acid)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Black Walnut (Juglans nigra)</td>
<td></td>
</tr>
</tbody>
</table>

Suggested Dose: Take 2 capsules, one to three times daily, in between meals as directed by your health care practitioner.
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Thyroid Disorders, Autoimmunity and The GI Environment
("Food Antigens")
Autoimmune Thyroid Disease and Celiac Disease

- Celiac patients have approximately 10 times the rate of auto-immune thyroid diseases, such as Hashimoto’s thyroiditis and Grave’s disease, as non-celiac individuals.


GI Parasites
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IBD was unheard of before the 20th century. Beginning of 20th century incidence thought to be about 1:10,000 and now 1:250 (Environmental factors at play). Similar data exists with asthma, hay fever, DM, MS, etc.

Weinstock J: IFM Annual Symposium (2011)
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H. Pylori and Asthma

DC-derived IL-18 drives Treg differentiation, murine Helicobacter pylori--specific immune tolerance, and asthma protection

Persistent colonization with the gastric bacterial pathogen Helicobacter pylori causes gastritis and predisposes infected individuals to gastric cancer. Conversely, it is also linked to protection from allergic, chronic inflammatory, and autoimmune diseases.
Parasites In Your Gut Actually Help Protect You From Allergies

by David Gutierrez, staff writer

Researchers believe that over the course of millions of years, gastrointestinal parasites have evolved an ability to suppress the human immune system as a survival mechanism. Because parasitic infection has been so common throughout human evolutionary history, the human immune system has in turn evolved to compensate for this effect. This means that if the parasites are removed, the immune system may actually function too strongly, resulting in maladaptive immune responses such as asthma, eczema and other allergies.

To test this hypothesis, researchers used drugs to eliminate hookworm infection in 1,500 children between the ages of six and 17 who were living in a rural village in central Vietnam. This region was selected for its very low rates of allergies and high parasitic infection rates. Two-thirds of all children in the area are infected with hookworm or other gastrointestinal parasites.

The researchers found that once the children were no longer infected with parasites, their rates of dust mite allergies significantly increased. This supports the hypothesis that parasitic help regulate immune responses.

"The next step is to understand exactly how and when gut parasites program the human immune system in a way that protects against allergies, and for such studies, follow-up from birth will be essential," said researcher Carsten Fehr.

Researchers hope that understanding the relationship between parasites and the human immune system could lead to a better overall understanding of allergies.

"The prospects for further studies in this area are very exciting, as we could see groundbreaking treatments for asthma and other allergies developed as a result," said Elaine Hyers of Asthma UK, which funded the study.
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Healthy Gut

Healthy Villi – Good Absorption

Healthy Cell junctions
Leaky Gut & Malabsorption

- Damaged Villi – Poor Absorption
- Damaged Cell junctions

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**Test**

- **Lactobacilli**: 0.1
- **WBCs**: Neg
- **Mucus**: Neg

**Reference Range**

- **Lactobacilli**: ~ 7.3 x 10^7 /mL

**Inflammation**

- **Fecal sigA**: 19 L
- **Anti-gluten sigA**: 5

**Benefits**

- **SCFA**: short-chain fatty acids
  - **Butyrate**: 40 - 204 mg/dL
  - **Acetate**: 6 - 36 mg/dL
  - **Propionate**: 15 - 30 mg/dL

**Pathology**

- **Nystagmus**: abnormal involuntary eye movements
- **Obstructive jaundice**: accumulation of bile in the bloodstream

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Fasano A. Surprises from Celiac Disease. Scientific American, August 2009

Increased Prevalence Over Time in U.S.A. (in Line with Other Autoimmune Diseases)

During the past 35 years the true prevalence of CD in USA doubled every 15 years.

C. Catassi et al, Annal Med 2011
A TRIO OF CAUSES

- triggers: autoimmune response, environmental triggers, genetic susceptibility
- autoimmune response: tissue damage, autoantibodies, organ dysfunction
- environmental triggers: dietary, chemical, physical, infectious
- genetic susceptibility: HLA, genetics, lifestyle factors

THE INSIDE STORY

- intestinal lining: normal vs. autoimmune response
- immune cells: proliferation, infiltration, cytokine release
- cytokines: interleukin, tumor necrosis factor, interferon
- autoantibodies: identification, function, treatment
- genetic markers: identification, relevance, treatment options
Zonulin Signaling Working Hypothesis

Proposed mechanisms through which zonulin activates EGFR. Zonulin can activate EGFR through direct binding (1) and/or through PAR2 transactivation (2). This second mechanism can be mediated by either Src signaling (2a) or by the release of MMPs and/or ADAMS that in turn will activate Pro-HB-EGF. When cell trypsin IV cleaves zonulin in its two subunits (so eliminating one of the three required disulfide bridges necessary for EGR activity), the molecule is not able to bind to EGFR (3), while will acquire a different function (HB binding) and becomes an inflammatory marker.


AT1001, the Zonulin Inhibitor

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**Example GI Mucosal Repair Formulation**

<table>
<thead>
<tr>
<th>Serving size</th>
<th>Amounts per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tsp. (6 g)</td>
<td></td>
</tr>
<tr>
<td>Number of servings per container</td>
<td>40</td>
</tr>
<tr>
<td>L-Glutamine</td>
<td>1500 mg</td>
</tr>
<tr>
<td>N-Acetyl Glucosamine</td>
<td>1000 mg</td>
</tr>
<tr>
<td>PepZin GI (Zinc-Carnosine)</td>
<td>75 mg</td>
</tr>
<tr>
<td>Deglycyrrhizinated Licorice (DGL; Glycyrrhiza glabra)</td>
<td>400 mg</td>
</tr>
<tr>
<td>Aloe vera (Aloe barbadensis)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Slippery Elm (Ulmus fulva)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Marshmallow (Althaea officinalis)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Chamomile (Matricaria chamomilla)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Okra (Hibiscus esculenta)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Cat’s Claw (Uncaria tomentosa-TOA free)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Mucin</td>
<td>200 mg</td>
</tr>
<tr>
<td>MSM</td>
<td>100 mg</td>
</tr>
<tr>
<td>Quercitin</td>
<td>100 mg</td>
</tr>
<tr>
<td>Prunus (cranberry)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Citrus pectin</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Stevia</td>
<td>Natural Flavors</td>
</tr>
</tbody>
</table>

**Suggested Dose:** Take 1/2-1 tsp., one to two times daily or as directed by your health care practitioner.

**CONCLUSIONS:** GlcNAc shows promise as an inexpensive and nontoxic treatment in chronic inflammatory bowel disease, with a mode of action which is distinct from conventional treatments. It may have the potential to be helpful in stricturing disease.
The researchers found that naturally occurring GlcNAc molecules attach to T-cell receptors and these GlcNAc "branches" form a lattice on the cell surface that prevents the receptors from clustering near where the antigens are located... less clustering means less antigen binding, and less activation of Th1 cells, reducing the autoimmune reaction.

The Journal of Biological Chemistry, DOI: 10.1074/jbc.M701890200).
In vitro experiments demonstrate that VDR mediates the activity of 1,25(OH)2D3 that induces junction protein expression and strengthens the tight junction complex. These data are consistent with, and explain at least in part, the observation reported in the literature that vitamin D deficiency is linked to increased incidence of IBD in human population.
NEW PREDICTORS of DISEASE

Molecules called predictive autoantibodies appear in the blood years before people show symptoms of various disorders. Tests that detected these molecules could warn of the need to take preventive action.


**Figure 3. Phases in the Development of Pathogenic Autoimmunity.**

Normal immunity progresses to benign autoimmunity through the influence of genetic composition and environment. Later, benign autoimmunity progresses to pathogenic autoimmunity. Symptoms of clinical illness appear soon after pathogenic autoimmunity develops.
Autoimmune Disease: Leaving the Era of Reaction and Entering the New Era of Prediction

**Figure 2. Accumulation of Systemic Lupus Erythematosus Autoantibodies.**
The curve shows the average number of types of autoantibody in relation to the time of diagnosis of systemic lupus erythematosus. Seven autoantibodies were evaluated, which bind cellular constituents (anti-nuclear antibodies, Ro, La, double-stranded DNA, Sm, phospholipid, and nuclear ribonucleoprotein). The time of diagnosis and the median time of the first appearance of any clinical criterion useful for the classification of systemic lupus erythematosus (clinical onset) are indicated by arrows.

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**Expert Opinion on Medical Diagnostics**

**Antibodies as predictors of autoimmune diseases and cancer**

**Background**: Autoantibodies targeted against a variety of self-antigens are detected in autoimmune diseases and cancer. Emerging evidence has suggested the involvement of environmental factors such as infections and xenobiotics, and some dietary proteins and their antibodies in the pathogenesis of these disorders. The association of various antibodies with different diseases has been demonstrated.

**These antibodies appear in the blood years before presentation of symptoms in various disorders.** Therefore, these antibodies may be used as biomarkers for early detection of various diseases.

**Method**: Microarray analysis of antigen–antibody reaction.

**Conclusion**: The application of these antibody arrays to human autoimmune disease is expanding and is allowing for the identification of patterns or antibody signatures, thus establishing the premises for increased sensitivity and specificity of prediction, as well as positive predictive values.

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David M. Brady, ND, DC, CCN, DACBN
Univ. of Bridgeport
The risk of diabetes increases with the number of diabetes-related autoantibodies in the blood.

Risk Projection

- GAD-65
- Tyrosine Phosphatase IA-2
- Insulin

Number of Autoantibody Types in Blood

- 1
- 2
- 3

Percent Who Will Become Diabetic within Five Years

- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

Source: Aristo Vojdani, PhD

Predictivity of Autoimmunity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibodies</th>
<th>PPV</th>
<th>Years before Clinical Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto’s thyroiditis *</td>
<td>Anti-thyroid peroxidase antibodies (postpartum)</td>
<td>92%</td>
<td>7–10</td>
</tr>
<tr>
<td>Primary biliary cirrhosis*</td>
<td>Anti-mitochondrial antibodies</td>
<td>96%</td>
<td>25</td>
</tr>
<tr>
<td>Type I diabetes**</td>
<td>Pancreatic islet cell, insulin, 65 kD glutamic acid decarboxylase, tyrosine phosphatase-like protein</td>
<td>43, 55, 42, and 29%</td>
<td>14</td>
</tr>
</tbody>
</table>


Source: Thomas O’Brien, DC, CCN
Autoimmune Disease: Leaving the Era of Reaction and Entering the New Proactive Era of Prediction

**Predictivity of Autoimmunity**

### Organ Specific Autoimmune Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibodies</th>
<th>PPV</th>
<th>Years before Clinical Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>Adrenal cortex antibodies</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>Crohn’s colitis</td>
<td>Anti–Saccharomyces cerevisiae antibodies</td>
<td>100%</td>
<td>3</td>
</tr>
</tbody>
</table>
| Celiac disease  | Anti–tissue transglutaminase
                | Anti–endomysial antibodies
                | (HLA–DR2 or DQ8 antigens) | 50–60% (100%) | 7 |


**Systemic Autoimmune Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibodies</th>
<th>PPV</th>
<th>Years before Clinical Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>RNP, Sm, dsDNA, Ro, La, and cardiolipin antibodies</td>
<td>94–100%</td>
<td>7–10</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Anti–centromere antibodies Anti–topoisomerase 1 antibodies</td>
<td>100%</td>
<td>11</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid factor Anti–cyclic citrullinated peptide</td>
<td>52–88% (97%)</td>
<td>14</td>
</tr>
<tr>
<td>Sjögren’s</td>
<td>Anti–Ro and anti–La antibodies</td>
<td>73%</td>
<td>5</td>
</tr>
</tbody>
</table>
POTENTIAL USES OF AUTOANTIBODIES

Autoantibodies could:
- Predict the risk of falling ill
- Project the probability of contracting a particular disease so that the potential patient could consider preventive therapy:
  - Primary prevention – Remove environmental factors that trigger the disease
  - Secondary prevention – Modulate the destructive process before the onset of clinical symptoms
- Anticipate the timing of a disorder, revealing how soon a disease is likely to cause symptoms
- Project the course of a disease
- Predict the severity and probable rate of progression of a disease
- Classify the disease

In a patient with an established disease autoantibodies can help define the nature of the markers to classify the disease as autoimmune or not autoimmune

If inexpensive tests for predictive antibodies can be developed, they could become a standard part of a routine checkup.
Autoimmune Disease: Leaving the Era of Reaction and Entering the New Era of Prediction

Slide source: Aristo Vojdani, PhD

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Assessments & Interventions for Autoimmune Disease

- Detect and remove opportunistic and pathogenic GI bugs
- Detect and eliminate food sensitivities
- Predictive autoantibody testing
- Check for toxins & support detoxification
- Vitamin D status optimization
- Quench excess inflammation & oxidative stress
- Nutritional interventions (anti-inflammatory diet, Low AA)
- Gastrointestinal restoration (4R program)
- Stress Reduction

Special Thank You!

- Todd LePine, MD
- Aristo Vojdani, PhD
- Tom O’ Bryan, DC, CCN, DACBN
- Vera Stejskal, PhD
- Joel Weinstock, MD
- David Perlmutter, MD
- Alessio Fasano, MD
- Alan Ebringer, MD
Autoimmune Disease: Leaving the Era of Reaction and Entering the New Proactive Era of Prediction

“Dr. Brady, may I be excused?
My brain is full.”