Fire in The Hole
Intestinal Permeability: The Development of Autoimmune Disease, and a Comprehensive Approach to Healing the Gut

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Figure 1: Factors that contribute to autoimmune disease.
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

Alessio Fasano* and Terez Shea-Donohue

The classical paradigm of autoimmune pathogenesis involving a specific genetic makeup and exposure to environmental triggers has been challenged by the addition of a third element: the loss of intestinal barrier function.

It becomes independent or continuous exposure to the environmental trigger and is therefore self-perpetuating and irreversible. Epitope-specific cross-reactivity between microbial antigens and self-antigens has been shown in some animal models to initiate autoimmunity. Conversely, in most human autoimmune diseases, molecular mimicry seems to be a factor in the progression of a pre-existing subclinical autoimmune response, rather than in the initiation of autoimmunity. Another theory suggests that microorganisms expose self-antigens to the immune system by directly damaging tissues during active infection, and that this leads to the development of autoimmunity. This mechanism has been referred to as the 'bystander effect', and it occurs only when the new antigen is presented with the
Figure 1: Factors that contribute to autoimmune disease.

Environmental triggers

Breakdown in oral tolerance

Change in gut microbiota

Enhanced gut permeability to large macromolecules

Immune reactivity

Autoimmunity and neuroautoimmunity

Figure 2: Mechanism for the induction of autoimmunity and neuroautoimmunity by environmental triggers.
Increased intestinal permeability is an early biological change that often precedes the onset of autoimmune diseases. Such increased permeability could be due to environmental factors (such as infection, toxic molecules, allergenic foods) that possibly initiate the (autoimmune) disease.
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

Alessio Fasano* and Terez Shea-Donohue

Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself-antigens, (and suggests that)

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The autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier function.
AUTOIMMUNITY
While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 8 percent of the United States population – 24 million persons.
To provide a context to evaluate the impact of autoimmune diseases, cancer affected approximately 9 million people and heart disease affected approximately 22 million people in the United States.
Cancer
9 million people

Heart Disease
22 million people

Auto Immune Disease
24 million people
Collectively Auto-immune Diseases have been identified in about 24 million people in the US, and only 1 out of 3 receive a diagnosis. That means about 72 million people have an AI Disease. It’s not looked for. Our system waits until the signs and symptoms are severe enough with organ failure and irreversible damage before we identify it.”
Autoimmune diseases are the third leading cause of morbidity and mortality in the industrialized world, surpassed only by cancer and heart disease.
Autoimmunity at a Glance
American Autoimmune Related Disease Association

• Over 100 diseases
• Affecting 50 million Americans
• Costing over $120 billion annually
• 250,000 new diagnoses each year
• A major cause of death in women
Autoimmune disease can affect any part of the body.
AD Diagnosis Takes an Inordinate Amount of Time and Perseverance by the Patient

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<tbody>
<tr>
<td>Years to Diagnosis</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No. Physicians Seen</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Labeled Chronic Complainer</td>
<td>64%</td>
<td>45%</td>
<td>45%</td>
<td>51%</td>
</tr>
</tbody>
</table>
Years to Diagnosis

- Total: 3.5 years
- Sjogren's Disease: 4.3 years
- Rheumatoid arthritis: 2.7 years
- Multiple sclerosis: 3.2 years
- Lupus (SLE): 3.9 years
- Crohn's disease: 3.5 years
Number of Doctors Seen to get a Diagnosis

- All 5 diseases: 4.5
- Sjogren's Disease: 6.5
- Rheumatoid arthritis: 3.8
- Multiple sclerosis: 3.8
- Lupus (SLE): 4.8
- Crohn's disease: 3.9
Percent told their disease was imagined or they were overly concerned ...
Why so Long and Difficult to Get a Correct Diagnosis?

Physician Education was identified as a contributing factor.
AARDA Conducted a Survey of Physicians

• AARDA participated in an educational workshop attended by 130 family physicians.

• Participants were asked to participate in a survey on the extent of their knowledge of autoimmune diseases.

• The survey results prompted a larger ongoing study.
In medical school, how much training in autoimmune diseases did you receive?

- None: 18.5%
- 2 Lectures: 22.2%
- 1 Lecture: 18.5%
- 3-5 Lectures: 18.5%
- 5+ Lectures: 13%

27.8%
Would you agree that you received enough training to diagnose and treat autoimmune disease?
What is your level of comfort in diagnosing autoimmune disease?

- Stressed: 25%
- Uncomfortable: 11.5%
- Average Comfort: 13.5%
- Comfortable: 50%
- Very Comfortable: 27%
Women are generally more susceptible to autoimmune diseases than men.

The sex distribution of the major autoimmune diseases. The numbers above the bars refer to the total number of disease cases (x1,000,000) in the USA. Whitacre CC, *Nature Immunol.*, 2:777-780, 2001
Premise #1
Just How Prevalent is the Development of Autoimmune Disease?
New Concept
True Prevalence of Autoimmunity
Autoimmune diseases are the third leading cause of morbidity and mortality in the industrialized world, surpassed only by cancer and heart disease.
Detective Adrian Monk

AND
In the United States, CVD prevalence in the general population is expected to reach 40%, with direct related costs set to reach 800 billion dollars per year in the next two decades.
In Europe, CVD causes 47% of all deaths accounting for 4 million fatalities each year, and costing 196 billion euros a year.
The first indicator of atherosclerosis for 30%-50% of patients was an acute, and in many cases fatal, myocardial infarction (MI).

How is it possible that our Health Care System could be so Blind? We’re looking in the wrong place. And we keep looking in the wrong place. TOB
Perhaps if We Open to More Current Information…..
Immune-driven inflammation is key to the development of cardiovascular disease (CVD)
Atherosclerosis is increasingly considered an immune system–mediated process of the vascular system.
Autoimmunity plays a major role in the development of dyslipidemia and atherosclerotic plaque formation.
Atherogenesis has been proposed to be considered an autoimmune disease, raising the hope that CVD could be prevented by immunomodulation.
Dyslipidaemia in Rheumatological Autoimmune Diseases

Fig. (5). Common changes in the lipid profile amongst the autoimmune rheumatic diseases have marked impact on athero-atherosclerotic plaque formation. LDL: Low density lipoproteins, TG: Triglycerides, Lp(a): Lipoprotein (a), Anti-LPL: anti-Lipoprotein Lipase, HDL: high density lipoproteins, ApoA1: Apolipoprotein A1, Anti-APL: anti-phospholipid.
Autoimmunity plays a major role in the development of dyslipidemia and atherosclerotic plaque formation.
Thus, If CVD has an Initiating Autoimmune Component, Arguably, What Becomes the #1 Mechanism in the Progression of Morbidity and Mortality?
Antibodies as predictors of autoimmune diseases and cancer

Aristo Vojdani
Immunosciences Lab., Inc., 8693 Wilshire Blvd, Ste. 200, Beverly Hills, CA 90211, USA

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 many autoimmune diseases. 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.

Objective: To provide an overview of antibody arrays that are measured against different human tissue antigens, cross reactive epitopes of infectious agents, dietary proteins, and haptenic chemicals in autoimmune diseases and cancer.

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. The presence of these antibodies would not necessarily mean that a patient would definitely become sick but may give a percentage of risk for different conditions that may develop over future months or years. Using this high-throughput microarray method, it is possible to screen rapidly for dozens of autoantibodies at low cost. This is an important factor in the implementation of autoantibody testing as a routine part of medical examinations.

Keywords: autoantibodies, autoimmune diseases, ELISA, environmental factors, predictive antibodies

In a review article based on more than 130 papers published in the field of cancer detection, it was demonstrated that p53 antibodies are found predominantly in human cancer patients with a specificity of 96%.
Antibodies as predictors of autoimmune diseases and cancer

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The clinical value of these antibodies remains subject to debate, but consistent results have been observed in breast, colon, oral, uterine, ovarian and gastric cancers, in which they have been associated with high-grade tumors and poor survival.
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The finding of p53-Abs in the sera of individuals who are at high risk of cancer, such as exposed workers or heavy smokers, indicates that they have promising potential in the early detection of cancer.
Silently
Point to 2 People
Close By

What Would the Impact Be in your Practice
IF you were recognizing Autoimmune mechanisms at this frequency? How often would you be considering autoimmunity as an important component of the patients presenting complaint.
Give 2 examples from your Practice.
Premise #2

How Can We Identify People At Risk for the Development of Autoimmune Disease?
Potential of Biomarkers:
• Enable diagnosis before the onset of symptoms
• Predict specific organ involvement
• Predict disease flares
• Identify clinically meaningful disease subsets
• Predict and monitor response to therapy
• Describe organ or tissue damage
Autoimmunity plays a major role in the development of dyslipidemia and atherosclerotic plaque formation.

The mechanisms underlying these changes include the interplay of inflammation and auto-antibody formation.

- Predict specific organ involvement
- Enable diagnosis before the onset of symptoms
- Predict and monitor response to therapy
- Identify clinically meaningful disease subsets
Autoantibodies are typically present many years before the diagnosis of SLE. Furthermore, the appearance of autoantibodies in patients with SLE tends to follow a predictable course, with a progressive accumulation of specific autoantibodies before the onset of SLE, while patients are still asymptomatic.
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 (antinuclear 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.
Prodromal period
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.
### Predictivity of Autoimmunity

#### 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 cardioliptin antibodies</td>
<td>94-100%</td>
<td>7-10</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Anti-centromere antibodies</td>
<td>100%</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Anti-topoisomerase I antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid factor</td>
<td>52-88%</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Anti-cyclic citrullinated peptide</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Sjögren’s</td>
<td>Anti-Ro and anti-La antibodies</td>
<td>73%</td>
<td>5</td>
</tr>
<tr>
<td>1º antiphospholipid syndrome</td>
<td>Anti-nucleosome antibodies</td>
<td>100%</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Anti-cardiolipin antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-β2 glycoprotein 1</td>
<td></td>
<td></td>
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</table>

## 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>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>95%</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>


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## 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- <em>Saccharomyces cerevisae</em> antibodies</td>
<td>100%</td>
<td>3</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Anti-tissue transglutaminase Anti-endomysial antibodies (HLA-DO2 or DO8 antigens)</td>
<td>50-60% (100%)</td>
<td>7</td>
</tr>
</tbody>
</table>

Premise #3

What is the Trigger in the production of Antibodies To Self?
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

Alessio Fasano* and Terez Shea-Donohue

**SUMMARY**

The primary function of the GI Tract is perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis. A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that another extremely important function of this organ is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens. When the finely tuned trafficking of macromolecules means that they are the third most common category of diseases in the US after cancer and heart disease. They can affect virtually every site in the body, including the gastrointestinal tract. At least 15 diseases are known to be the direct result of an autoimmune response, and circumstantial evidence links more than 80 conditions to autoimmunity.

An extremely important function of the GI Tract is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism.

**KEYWORDS**

autoimmune, innate immunity, intestinal permeability, tight junction, toll-like receptor

**REVIEW CRITERIA**

PubMed was searched in February 2005 and again in July 2005 using the following keywords alone and in combinations: "intestinal permeability", "autoimmunity", "tight junction", "toll", "innate immunity", "occludin", "claudin", "macrophage", and "intestinal AND disease AND permeability". Only full papers published in English were considered. Additional searches were performed using RetroSearch and Google.

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The classical paradigm of autoimmune pathogenesis involving a specific genetic makeup and exposure to environmental triggers has been challenged by the addition of a third element: the loss of intestinal barrier function.

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Healthy Gut

Healthy Villi/Good Absorption

Healthy Cell Junctions
Pathogenic Intestinal Permeability

- Damaged Villi/ Poor Absorption
- Damaged Cell junctions
A Common Initial Autoimmune Pathway and Therapeutic Target to Degenerative Disease

Immune Response to Intestinal Antigen Presentation (Dysbiosis, food sensitivities, LPS, toxic chemicals,...)

→ Intestinal Inflammation from antigen delivery
→ Activating tight junction barrier proteins
→ Antibody production to Barrier Proteins (zonulin, TG2, Actin, Myosin, Calprotectin,...)
→ Leaky or Leaking Gut, Leaky Brain, Leaky Bladder,...
→ Pathogenic Intestinal Permeability
→ Antigen & macromolecule translocation
→ Immune Response = Antibody Production
→ Molecular Mimicry (and other pathways)
→ Autoimmune Mechanism initiated
The autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier function.

**KEYWORDS** autoimmune, innate immunity, intestinal permeability, tight junction, toll-like receptor

**REVIEW CRITERIA**

PubMed was searched in February 2005 and again in July 2005 using the following keywords alone and in combination: "intestinal permeability", "autoimmunity", "tight junction", "innate immunity", "occult", "claudin", "intestinal barrier", and "intestinal and disease and permeability". Only full papers published in English were considered. Additional searches were performed using RetroSearch and Google.

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Premise #4
Can Foods Trigger Pathogenic Intestinal Permeability
Confocal Endomicroscopy Shows Food-Associated Changes in the Intestinal Mucosa of Patients With Irritable Bowel Syndrome

Annette Fritscher-Ravens,1 Detlef Schuppan,2,3,4 Mark Ellrichmann,1 Stefan Schoch,1 Christoph Röcken,5 Jochen Brasch,6 Johannes Bethge,1 Martina Böttner,7 Julius Klose,1 and Peter J. Milla8

The present study evaluated whether CLE combined with sequential food challenges in a subgroup of IBS patients with suspected food intolerance can visualize structural and immediate functional mucosal changes and identify those patients in whom exclusion of candidate foods might improve their symptoms.

mucosa after food challenge. Patients with functional changes after food challenge (CLE+) were placed on personalized exclusion diets and followed up for long-term symptom relief.

METHODS: Thirty-six IBS patients with suspected food intolerance and 10 patients with Barrett’s esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa

an objective diagnosis, and effective therapies are lacking. Some patients recognize that food may trigger symptoms,3 which may be caused by an allergy or innate immune activation by, for example, food constituents, which could not be proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets.4
Confocal Endomicroscopy Shows Food-Associated Changes in the Intestinal Mucosa of Patients With Irritable Bowel Syndrome

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At baseline, the villi were closely attached to each other without much visible space between (Figure 5)

See Covering the Cover synopsis on page 945; see editorial on page 952.

Keywords: Imaging; FODMAP; Food Allergy; Gluten.

BACKGROUND & AIMS: We investigated suspected food intolerances in patients with irritable bowel syndrome (IBS) using confocal laser endomicroscopy (CLE) for real-time visualization of structural/functional changes in the intestinal mucosa after food challenge. Patients with functional changes after food challenge (CLE+) were placed on personalized exclusion diets and followed up for long-term symptom relief.

METHODS: Thirty-six IBS patients with suspected food intolerance and 10 patients with Barrett’s esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa through the working channel of the endoscope. Epithelial lymphocytes (IEL) were measured before and after the food challenge. Patients with functional changes after food challenge (CLE+) were placed on exclusion diets and followed up for long-term symptom relief.

RESULTS: CLE showed a concordance of IELs significantly higher in CLE+ patients to food antigens, IELs increased, epithelial leaks and intervillous spaces also increased significantly and 10 patients with Barrett’s esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa using confocal laser endomicroscopy (CLE) for real-time visualization in vivo at a micron scale, allowing real-time dynamic functional imaging in patients with IBS and/or suspected food intolerance to monitor the onset and evolution of changes. The use of intravenous scans was excluded. Current tests commonly fail to obtain an objective diagnosis, and effective therapies are lacking. Some patients recognize that food may trigger symptoms, which may be caused by an allergy or innate immune activation by, for example, food constituents, which could not be proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets.
gap density was seen in CLE- patients (Table 1 and Figure 4).

Intervillous space. At baseline, the villi were closely attached to each other without much visible space between (N = 31) (Figure 5), although in 5 a minor space was visible; notably, all 5 were later identified as CLE+. Baseline IVS in CLE+ subjects was 8.1 ± 3.5 mm (range, 0 – 58.6; 95% CI, 0.8 – 15.4) (Table 1). After food challenge the IVS widened markedly in CLE+ patients (Figure 2C): 41.1 ± 2.5 mm (range, 21.4 – 60.1; 95% CI, 35.9 – 46.2; P = .0001). There was no change in the IVS in the CLE- group (Table 1).

Nine of 22 CLE+ patients were re-examined outside the study protocol after 1 year. All of them reacted again to the same antigen(s) as before; IELs and break/gap counts did not differ significantly from the initial examination (Supplementary Table 3), although CD3-positive lymphocytes were reduced significantly after a 1-year exclusion diet.

IELs: Histology vs CLE

Conventional histology, performed approximately 2 weeks before and immediately after CLE, showed normal villous/crypt morphology without villous atrophy.

IEL count in histology versus endomicroscopy. Specificity of the lymphocyte population assessed in CLE was proven by immunocytochemistry. By using a cut-off value of > 25 IELs/100 enterocytes to determine a pathologic increase in histologic IELs, when compared with IELs seen on CLE, concordance was only 70.6% with no significant correlation between groups (P = .89; r^2 = 0.027). By using the Marsh classification cut-off value of > 40/100 enterocytes to define pathology, the discordance increased to 58.8% (20 of 34 patients).

Food Exclusion Diet and Follow-up Evaluation

CLE+ patients received detailed instructions for their individualized exclusion diet. After 4 weeks, a clinical review showed that 19 of 22 CLE+ patients had a > 50% reduction of their initial symptom score (Figure 6, Supplementary Table 2); 6 patients had a complete cessation of symptoms. At this first follow-up evaluation many patients were not completely compliant with the diet, indicating that the reduction of symptoms at that stage was an underestimate of the predictive power of the food challenge. After additional instructions the overall symptom score was...
Confocal Endomicroscopy Shows Food-Associated Changes in the Intestinal Mucosa of Patients With Irritable Bowel Syndrome

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Four commonly encountered major antigen mixtures and suspensions were applied;
• cow’s milk mixed with 30% sterile water;
• wheat, 2 g;
• yeast, 1 g;
• soy, 2 g
18 mL sterile water/2 mL simethicone served as a control substance.

without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets. 4

Recent literature has supported the existence of a sub-

culture of IBS patients who improve with exclusion diets such as eliminating fermentable oligosaccharide, disaccharide, monosaccharides polyols (FODMAPs) or gluten—

Changes in the Intestinal Mucosa of Patients With Irritable Bowel Syndrome

Confocal laser endomicroscopy (CLE) is a new endo-

The use of intravenous fluorescein enables high-

Baseline IELs were signi-

First, CLE was performed to evaluate structural/functional changes in the intestinal mucosa. These changes are associated with patient re-

Because no reliable biomarkers are available, IBS is not be-

Irritable Bowel Syndrome (IBS) represents a common
disease (IBS) diagnosis. IBS is a chronic condition with pain

Abbreviations used in this paper:

• Food Allergy; Gluten.
Confocal Endomicroscopy Shows Food-Associated Changes in the Intestinal Mucosa of Patients With Irritable Bowel Syndrome

Annette Fritscher-Ravens,1 Detlef Schuppan,2,3,4 Mark Ellrichmann,1 Stefan Schoch,1 Christoph Röcken,5 Jochen Brasch,6 Johannes Bethge,1 Martina Böttner,7 Julius Klose,1 and Peter J. Milla8

1 Unit of Experimental Endoscopy, Department of Internal Medicine I,2,3,4 Research Unit of Translational Immunology, Department of Medicine I, University College London Institute of Child Health, University College London, London, United Kingdom

Within 5 minutes of exposure to food antigens, IELs increased, epithelial leaks/gaps formed, and intervillous spaces widened.

BACKGROUND & AIMS: We investigated suspected food intolerances in patients with irritable bowel syndrome (IBS) using confocal laser endomicroscopy (CLE) for real-time visualization of structural/functional changes in the intestinal mucosa after food challenge. Patients with functional changes after food challenge (CLE+) were placed on personalized exclusion diets and followed up for long-term symptom relief.

METHODS: Thirty-six IBS patients with suspected food intolerance and 10 patients with Barrett’s esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa.

RESULTS: CLE showed a concordance of IELs and 10 patients with Barrett’s esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa.

CONCLUSIONS: Real-time dynamic functional imaging with CLE may allow for better discrimination of the colonic mucosa. The findings also suggest that CLE may have the potential to become a valuable tool for the diagnosis and treatment of IBS.

Irritable bowel syndrome (IBS) represents a common and economically important gastrointestinal (GI) disorder. Because no reliable biomarkers are available, IBS is characterized by chronic or recurrent abdominal pain associated with altered bowel habits when other etiologies have been excluded. Current tests commonly fail to obtain an objective diagnosis, and effective therapies are lacking. Some patients recognize that food may trigger symptoms, which may be caused by an allergy or innate immune activation by, for example, food constituents, which could not be proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets.
CLE images of (A) baseline and (B and C) after food challenge

A) Confocal image at baseline shows closely attached villi and vascularity, representing the deepest level of mucosal imaging with CLE.

B) Confocal image after mucosal reaction to food. Multiple eruptions represent breaks in the wall (white arrows), through which fluorescein is secreted into the lumen. The IVS widened and is turning grey instead of the initial black.

C) End stage of the reaction. With an influx of fluorescein the IVS turned white and widened further.
CLINICAL—ALIMENTARY TRACT

Confocal Endomicroscopy Shows Food-Associated Changes in the Intestinal Mucosa of Patients With Irritable Bowel Syndrome

Annette Fritscher-Ravens, Detlef Schuppan, Mark Ellrichmann, Stefan Schoch, Christoph Röcken, Jochen Brasch, Johannes Bethge, Martina Böttner, Julius Klose, and Peter J. Milla

After food challenge, 22 of 36 patients showed immediate and dramatic mucosal responses to antigen(s)

• to milk: n = 9;
• to wheat: n = 13;
• to yeast: n = 6;
• to soy: n = 4

The mucosa after food challenge (CLE+) were placed on personalized exclusion diets and followed up for long-term symptom relief.

METHODS: Thirty-six IBS patients with suspected food intolerance and 10 patients with Barrett's esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa.
Increased intestinal permeability is an early biological change that often precedes the onset of autoimmune diseases. Such increased permeability could be due to environmental factors (such as infection, toxic molecules, allergenic foods) that possibly initiate the (autoimmune) disease.
Premise #4
The more LPS or wheat peptides that pass through a permeable intestine, the stronger the inflammatory response
We demonstrated a correlation between the degree of systemic inflammation and an increase in intestinal permeability.
All 39 studies are available to you at www.theDr.com/NTA
24 of the 39 are the full articles and are free
Premise #6
How do we Arrest Pathogenic Intestinal Permeability
In Healing the Gut, Consider a Pleiotropic Approach

we stand a greater chance of success by considering pleiotropic approaches or gut cocktails consisting of natural pleiotropic agents. Pleiotropic (Greek *pleio*, meaning “many,” and *trepein*, meaning “to turn, to convert”) substances are those that invoke multiple mechanisms, and provide multiple effects. Some nutrients are pleiotrophic by their very nature impacting on several systems of the body.
A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

• Avoid inflammatory triggers
Is Gluten Sensitivity limited to Celiacs?
“Please...tell me more about this imaginary fence.”
We aimed to study response to gliadin exposure, in terms of barrier function and cytokine secretion, using intestinal biopsies obtained from four groups:

- celiac patients with active disease (ACD),
- celiac patients in remission (RCD),
- non-celiac patients with gluten sensitivity (GS) and
- non-celiac controls (NC).
Conclusions: Increased intestinal permeability after gliadin exposure occurs in all individuals.
Wheat
Dairy
Sugar
A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

• Avoid inflammatory triggers
• Include Foods That Heal Intestinal Permeability
  - Vegetables (esp for their insoluble fiber = SCFA production)
    Terry Wahls, MD = 12 cups vegetables/day
A prebiotic was originally defined as “a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, that can improve the host health.”

Prebiotics use live microbial feed additions, whereas probiotics target indigenous flora components. As gastrointestinal disorders are prevalent in terms of human health, both probiotics and prebiotics serve an important role in the prophylactic management of various acute and chronic gut derived conditions. Examples include protection from gastroenteritis and some inflammatory conditions.

**Key Words:** gut disorder, diet, microbiota, probiotics, prebiotics

(J Clin Gastroenterol 2008;42:S75–S79)
Prebiotics as Gut Microflora Management Tools

Glenn R. Gibson, PhD

Any dietary component that reaches the colon intact is a potential prebiotic; however, 3 criteria are required for success, in that the ingredient should:

1. resist host digestion, absorption, and adsorption processes
2. be fermented by the microflora colonizing the gastrointestinal system
3. selectively stimulate the growth and/or the activity of one or a limited number of bacteria within the gastrointestinal system.
A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

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  - Vegetables (esp for their insoluble fiber = SCFA production)
    Terry Wahls, MD = 12 cups vegetables/day
  - Bone Broth
    Terry Wahls, MD 1 quart bone broth/day
Gelatin tannate reduces the proinflammatory effects of lipopolysaccharide in human intestinal epithelial cells

These results suggest that gelatin tannate exerts anti-inflammatory effects by inhibiting the specific cytokines and adhesion molecules involved in several inflammatory disorders.

- strong ability to inhibit inflammatory biomarkers such as LPS-induced ICAM-1, IL-8, and TNF-x.

Caco-2 cells. IL-8 and TNF-α are important inflammatory mediators, recruiting neutrophils and T-lymphocytes. Together with LPS, adding gelatin tannate at different concentrations induced a dose-dependent inhibition of IL-8 and TNF-α released by Caco-2 cells.

Conclusion: These results suggest that gelatin tannate exerts anti-inflammatory effects by inhibiting the specific cytokines and adhesion molecules involved in several inflammatory disorders.

Keywords: Caco-2, ICAM-1, IL-8, TNF-α
A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

• Avoiding inflammatory triggers
• Include Pre-biotic Foods That Heal Intestinal Permeability
  - Vegetables (esp for their insoluble fiber = SCFA production)
    Terry Wahls, MD = 12 cups vegetables/day
  - Bone Broth
    Terry Wahls, MD 1 quart bone broth/day
  - Fermented Vegetables (focus on diversity)
Health benefits of fermented foods: microbiota and beyond

Maria L Marco¹, Dustin Heeney¹, Sylvie Binda², Christopher J Cifelli³, Paul D Cotter⁴, Benoit Foligné⁵, Michael Gänzle⁶, Remco Kort⁷, Gonca Pasin⁸, Anne Pihlanto⁹, Eddy J Smid¹⁰ and Robert Hutkins¹¹

Fermented foods and beverages were among the first processed food products consumed by humans. The production of foods such as yogurt and cultured milk, wine and beer, sauerkraut and kimchi, and fermented sausage were initially valued because of their improved shelf life, safety, and organoleptic properties.

Introduction

Fermented foods and beverages were among the first processed food products consumed by humans. The production of foods such as yogurt and cultured milk, wine and beer, sauerkraut and kimchi, and fermented sausage were initially valued because of their improved shelf life, safety, and organoleptic properties.

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6 University of Alberta, Department of Agricultural, Food and Nutritional
Health benefits of fermented foods: microbiota and beyond

Maria L Marco¹, Dustin Heeney¹, Sylvie Binda², Christopher J Cifelli³, Paul D Cotter⁴, Benoit Foligné⁵, Michael Gänzle⁶, Remco Kort⁷, Gonca Pasin⁸, Anne Pihlanto⁹, Eddy J Smid¹⁰ and Robert Hutkins¹¹

Introduction

The ingestion of fermented foods potentially increases the numbers of microbes in the diet by up to 10,000-fold

Fermented foods and beverages were among the first foods that have been associated with health benefits. Fermented foods can also have enhanced nutritional and functional properties due to transformation of substrates and formation of bioactive or bioavailable end-products. Many fermented foods also contain living microorganisms of which some are genetically similar to strains used as probiotics. Although only a limited number of clinical studies on fermented foods have been performed, there is evidence that these foods provide health benefits well-beyond the starting food materials.

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Health benefits of fermented foods: microbiota and beyond

María L Marco¹, Dustin Heeney¹, Sylvie Binda², Christopher J Cifelli³, Paul D Cotter⁴, Benoît Foligné⁵, Michael Gänzle⁶, Remco Kort⁷, Gonçalo Pasin⁸, Anne Pihlanto⁹, Eddy J Smid¹⁰ and Robert Hutkins¹¹

Consumption of fermented foods may provide an indirect means of counteracting the hygienic, sanitized Western diet and lifestyle.

Fermented foods and beverages were among the first

Introduction

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Consumption of fermented foods may provide an indirect means of counteracting the hygienic, sanitized Western diet and lifestyle. Food fermentation processes can be categorized by the primary metabolites and microorganisms involved: alcohol and carbon dioxide (yeast), acetic acid (Acetobacter), lactic acid (lactic acid bacteria (LAB) belonging to genera such as Leuconostoc, Lactobacillus, and Streptococcus), propionic acid (Propionibacterium freudenreichii), and ammonia and fatty acids (Bacillus, molds). Fermentations can also be described based on the food substrates, which include meats and fish, dairy, vegetables, soy beans and other legumes, cereals, starchy roots, and grapes and other fruits. Raw materials that contain high concentrations of monosaccharides and disaccharides, or in some cases starch, are fermented by yeasts or lactic acid bacteria. Molds and Bacillus are generally employed for starch saccharification or proteolysis or as secondary ripening microbiota after a primary fermentation.
Many of the species found in fermented foods are either identical to or share physiological traits with species relevant to promoting GI tract health.
A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

- Avoiding inflammatory triggers
- Include Pre-biotic Foods That Heal Intestinal Permeability
  - Vegetables (esp for their insoluble fiber = SCFA production)
    Terry Wahls, MD = 12 cups vegetables/day
  - Bone Broth
    Terry Wahls, MD 1 quart bone broth/day
  - Fermented Vegetables (focus on diversity)

- Nutrient Supplementation to:
  - Address Inflammation
  - Rebuild the Microbiome
  - Healing of the Intestinal Epithelial Lining
Vitamin D plays a role in the etiology of autoimmunity.
Vitamin D down-regulates nuclear factor-kB (NF-kB) activity, increases IL-10 production and decreases IL-6, IL-12, IFN-c, and TNF-a production, leading to a cytokine profile which favors less inflammation.
We investigated whether 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] was able to stimulate the assembly of adherens junctions and/or desmosomes.
1,25-Dihydroxyvitamin D₃ Stimulates the Assembly of Adherens Junctions in Keratinocytes: Involvement of Protein Kinase C

ROBERT GNIEDECKI, BARBARA GAJKOWSKA, AND MICHAEL HANSEN

Department of Dermatological Research, Leo Pharmaceutical Products (R.G.), Ballerup, the Department of Dermatology, University of Copenhagen, Bispebjerg Hospital (R.G.), Copenhagen; and the Microbiology Section, Department of Ecology and Molecular Biology, The Royal Veterinary and Agricultural University (M.R.), Frederiksberg, Denmark; and the Electron Microscopy Laboratory, Polish Academy of Sciences (R.G.), Warsaw, Poland

1,25-(OH)₂D₃ caused assembly of adherens junctions

Received November 22, 1996.
Address all correspondence and requests for reprints to Robert Gniedecki, M.D., Ph.D., Department of Dermatology, University of Copenhagen, Bispebjerg Hospital, Bispebjerg Bakke 25, 2400 Copenhagen NV, Denmark.

Materials and Methods

Chemicals

1,25-(OH)₂D₃ was obtained from the Chemical Research Department, Leo Pharmaceutical Products (Ballerup, Denmark), as a 4× stock solution

© www.theDr.com
VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of tight junction complexes and the healing capacity of the colonic epithelium.
1,25(OH)2D3 markedly enhanced tight junctions by increasing junction protein expression (at the kissing joints) and preserved the structural integrity of tight junctions (tight junction strands).
The critical functions of the commensal flora are:

- **Metabolic processes:**
  - fermentation,
  - vitamin synthesis,
  - energy production;
- **Trophic stimulation:**
  - epithelial cell differentiation,
  - immunomodulation;
- **Pathogen protection:**
  - competing for nutrients, space, adherence;
  - producing bacteriocidins.
There are three main mechanisms, how probiotics contribute to human health, and any single probiotic bacterium could possess more than one of them:

Probiotics shape the ecosystem,
• by competition for limited resources and adhesion sites,
• by decreasing the local pH via the production of organic acids, and
• by production of specific antibacterial substances.
Probiotics as Complementary Treatment for Metabolic Disorders

Mélanie Le Barz¹,²,³, Fernando F. Anhê¹,², Thibaut V. Varin², Yves Desjardins², Emile Levy²,⁴,⁵, Denis Roy², Maria C. Urdaci³, André Marette¹,²

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Over the past decade, growing evidence has established the gut microbiota as one of the most important determinants of metabolic disorders such as obesity and type 2 diabetes. Indeed, obesogenic diet can drastically alter bacterial populations (i.e., dysbiosis) leading to activation of pro-inflammatory mechanisms and metabolic endotoxemia, therefore promoting insulin resistance and cardiometabolic disorders. To counteract these deleterious effects, probiotic strains have been developed with the aim of reshaping the microbiome to improve gut health. In this review, we focus on benefits of widely used probiotics describing their potential mechanisms of action, especially their ability to decrease metabolic endotoxemia by restoring the disrupted intestinal mucosal barrier. We also discuss the perspective of using new bacterial strains such as butyrate-producing bacteria and the mucolytic Akkermansia muciniphila, as well as the use of prebiotics to enhance the functionality of probiotics. Finally, this review introduces the notion of genetically engineered bacterial strains specifically developed to deliver anti-inflammatory molecules to the gut.

Keywords: Gut permeability; Insulin resistance; Metabolic disorders; Mucosal barrier; Obesity; Probiotics
Probiotics as Complementary Treatment for Metabolic Disorders

Mélanie Le Barz1,2,3, Fernando F. Anhe1,2, Thibaut V. Varin3, Yves Desjardins2, Emile Levy2,4,5, Denis Roy2, Maria C. Urdaci3, André Marette1,2

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Keywords: Gut permeability; Insulin resistance; Metabolic disorders; Mucosal barrier; Obesity; Probiotics
Gluten induces coeliac-like disease in sensitised mice involving IgA, CD71 and transglutaminase 2 interactions that are prevented by probiotics

Christina Papista1,2,3, Vassilis Gerakopoulos1, Andreas Kourelis1, Maria Sounidaki1, Anastasia Kontana1, Laureline Berthelot2,3, Ivan C Moura2,3, Renato C Monteiro2,3,4 and Minas Yiangou1

Oral delivery of the S. boulardii KK1 strain reduced epithelial cell CD71 expression and Th1 immune responses and ameliorated the histopathological features of gluten-induced enteropathy, potentially indicating a new therapeutic approach for CD.

enterocytes and an increase of plasma cells producing IgA, which colocalised with the CD71. Moreover, IgA colocalised with the transglutaminase 2 (TG2), the production of which was increased in the lamina propria of G+ mice. These mice displayed increased production of cyclooxygenase-2 (COX-2), pro-inflammatory cytokines and IL-15, as well as anti-gliadin and anti-TG2 autoantibodies. The commensal flora-isolated presumptive probiotic Saccharomyces boulardii KK1 strain hydrolysed the 28-kDa α-gliadin fraction, and its oral delivery in G+ mice improved enteropathy development in association with decrease of epithelial cell CD71 expression and local cytokine production. In conclusion, the G+ BALB/c mouse represents a new mouse model for human CD based on histopathological features and expression of common biomarkers. The selected probiotic treatment reversing disease development will allow the study of the role of probiotics as a new therapeutic approach of CD.

Laboratory Investigation (2012) 92, 625–635; doi:10.1038/labinvest.2012.13; published online 13 February 2012

KEYWORDS: coeliac disease; gluten; IgA; IgA receptors; inflammatory mediators; probiotic yeast; transglutaminase
VSL#3 Probiotic Stimulates T-cell Protein Tyrosine Phosphatase–mediated Recovery of IFN-γ-induced Intestinal Epithelial Barrier Defects

Moorthy Krishnan, PhD,* Harrison M. Penrose, MS,† Nilay N. Shah, MS,† Ronald R. Marchelletta, PhD,† and Declan F. McCole, PhD*

VSL#3 reduces IFN-g signaling and IFN-g-induced epithelial barrier defects in a dose-dependent manner. These data point to a key role as a therapeutic target for restoration of barrier function using probiotics.

Results: VSL#3 increased TCPTP protein levels and enzymatic activity, correlating with a VSL#3-induced decrease in IFN-γ signaling. VSL#3 corrected the decrease in transepithelial electrical resistance and the increase in epithelial permeability induced by IFN-γ. Moreover, the restorative effect of VSL#3 against IFN-γ signaling, epithelial permeability defects, altered expression and localization of the tight junction proteins claudin-2, occludin, and zonula occludens-1, were not realized in stable TCPTP/(PTPN2)-deficient HT-29 intestinal epithelial cells.

Conclusions: VSL#3 reduces IFN-γ signaling and IFN-γ-induced epithelial barrier defects in a TCPTP-dependent manner. These data point to a key role for TCPTP as a therapeutic target for restoration of barrier function using probiotics.

(Inflamm Bowel Dis 2016;0:1–13)

Key Words: claudin-2, inflammation, IFN-γ, PTPN2, STAT-1
**LETTER**

**Diet rapidly and reproducibly alters the human gut microbiome**

Lawrence A. David1,2,†, Corinne F. Maurice1, Rachel N. Carmody1, David B. Gootenberg1, Julie E. Button1, Benjamin E. Wolfe1, Alisha V. Ling3, A. Sloan Devlin4, Yug Varma4, Michael A. Fischbach4, Sudha B. Biddinger3, Rachel J. Dutton1 & Peter J. Turnbaugh1

Our findings that the human gut microbiome can rapidly switch between herbivorous and carnivorous functional profiles may reflect past selective pressures during human evolution. Consumption of animal foods by our ancestors was probably volatile, depending on season and stochastic foraging success, with readily available plant foods offering a fall-back source of calories and nutrient...
Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David¹,²†, Corinne F. Maurice¹, Rachel N. Carmody¹, David B. Gootenberg¹, Julie E. Button¹, Benjamin E. Wolfe¹, Alisha V. Ling³, A. Sloan Devlin⁴, Yug Varma⁴, Michael A. Fischbach⁴, Sudha B. Biddinger³, Rachel J. Dutton⁴ & Peter J. Turnbaugh¹

We found that microbiota changes on the animal-based diet could be linked to altered faecal bile acid profiles and the potential for human enteric disease.

overwhelms inter-individual differences in microbial gene expression. The animal-based diet increased the abundance of bile-tolerant microorganisms (Alistipes, Bilophila and Bacteroides) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (Roseburia, Eubacterium rectale and Ruminococcus bromii). Microbial activity mirrored differences between herbivorous and lysis of his diet and gut microbiota).

Each diet arm significantly shifted subjects’ macronutrient intake (Fig. 1a–c). On the animal-based diet, dietary fat increased from 32.5 ± 2.2% to 69.5 ± 0.4% kcal and dietary protein increased from 16.2 ± 1.3% to 30.1 ± 0.5% kcal (P < 0.01 for both comparisons, Wilcoxon signed-rank test; Supplementary Table 5). Fibre intake was nearly...
Probiotics
(treatment time – indefinitely)

• *Lactobacillus* (various species): 10–100 billion live organisms daily or higher
• *Saccharomyces boulardii*: 500 mg–3 g daily
• *Bifidobacterium* (various species): 10–100 billion live organisms daily
• *Probiotic mixtures*: 10 billion-3.6 trillion live organisms daily

Prebiotics
(treatment time – indefinitely)

• FOS: 500–5,000 mg QD-TID
• Inulin: 500–5,000 mg QD-TID
• Fiber (high soluble)
• Larch (arabinogalactans): 500–5,000 mg QD-TID
EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation and thus reducing elaboration of proinflammatory mediators.
The safety of fatty acid supplementation is high and has been well established in numerous clinical studies. Drug interactions are extremely rare with fatty acids.
Invited Review

A Review of Complementary and Alternative Approaches to Immunomodulation

John O. Clarke, MD; and Gerard E. Mullin, MD
Division of Gastroenterology, The Johns Hopkins Hospital

ABSTRACT: Current Western therapies for inflammatory diseases are suboptimal; increasingly, patients are turning to complementary and alternative medicine for symptom relief and improved quality of life. There is emerging evidence that many of these therapies have the ability to modulate the immune system and disrupt the proinflammatory cascade through a variety of mechanisms, including antioxidant effects, alterations in cell signaling (in particular the nuclear factor kappa B pathway), cytokines, proinflammatory mediators, and disrupter of cell signaling.

A dose of up to 3 g per day of EPA plus DHA has been determined to be safe for general consumption. In fact, there were already 30,000–40,000 books regarding these practices already in existence.

With all the focus on drug development and marketing, it is easy to forget that nutrition represents the world’s earliest medicinal therapy. In the words of Hippocrates (obviously translated) “He who does not know food—how can he cure the disease of man?” Many of the medicinal agents used for therapy today are directly derived from food sources. The role of functional foods in health and disease per-

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Treatment Protocols
(personal recommendations-EPA/DHA)

Therapeutic dosages:
30-75 lbs = at least 1 g/d (Total Omega 3’s)
76-125 lbs = at least 2g/d (Total Omega 3’s)
> 125 lbs = 3+ g/d (Total Omega 3’s)

Note: Numerous studies regarding the impact of Omega 3’s on CardioVascular and Cognitive function show beneficial results with dosages of 3 g/d up to 20 g/d. Caution is recommended regarding hypocoagubility
The gastrointestinal tract is by far the greatest user of glutamine in the body, as enterocytes in the intestinal epithelium use glutamine as their principal metabolic fuel.

Biochemistry
L-glutamine accounts for 30-35 percent of the amino acid nitrogen in the plasma. It contains two ammonia groups, one from its precursor, glutamate, and the other from free ammonia in the bloodstream. One of glutamine’s roles is to protect the body from high levels of ammonia by acting as a “nitrogen shuttle.” Thus, glutamine can act as a buffer, accepting, then releasing excess ammonia when needed to form other amino acids, amino sugars, nucleotides, and urea. This capacity to accept and donate nitrogen makes glutamine the major vehicle for nitrogen transfer among tissues. Glutamine is one of the three amino acids involved in glutathione synthesis. Glutathione, an important intracellular antioxidant and hepatic detoxifier, is comprised of glutamic acid, cysteine, and glycine.

Clinical Indications
Gastrointestinal Disease
The gastrointestinal tract is by far the greatest user of glutamine in the body, as enterocytes in the intestinal epithelium use glutamine as their principal metabolic fuel. Most of the research on glutamine...
A clinical study of ulcerative colitis patients

- 30 g daily of glutamine four weeks
- significant clinical and endoscopic improvement, independent of disease state.
- Disease exacerbation returned when treatment was discontinued.
L-glutamine is a very useful clinical tool, but it is also a substrate for lymphocytes and macrophages, in addition to being a precursor of nitric oxide. Thus, it is necessary to ensure that inflammation is resolved before treating with this powerful trophic factor. Glutamine has also been noted to be a substrate for *Candida synthesis*, so this should be evaluated before initiating therapy.
Treatment Protocols
(personal recommendations-Glutamine)

Therapeutic dosages:
Dosages vary greatly depending on the clinical situation
• 2-4 g/d in divided dosages for wound healing and general intestinal support
• 10-40 g/d in divided dosages for critically ill and advanced disease
Turmeric, an approved food additive, or its component curcumin, has shown surprisingly beneficial effects in experimental studies of acute and chronic diseases characterized by an exaggerated inflammatory reaction. There is ample evidence to support its clinical use, both as a prevention and a treatment.
The cell signaling effects of curcumin seem to be pleiotropic as administration of curcumin has been reported to modulate a host of other cytokines and signaling pathways, including inducible nitric oxide synthase (iNOS), matrix metalloproteinase-9 (MMP-9), TNF, c-Jun N-terminal kinase (JNK), p38, Akt, Janus kinase (JAK), extracellular signal regulated protein kinase (ERK), and protein kinase C (PKC).
Potential clinical value of curcumin

**Anti-amyloidogenic**

- Inhibits BACE1 up-regulation
  - Salt bridge disruption
  - Caps APP height
  - Inhibits GSK-3β, activates Wnt signalling
- Binds Aβ
- Inhibits Aβ aggregation and deposition

**Neuroprotection**

- Reduces oxidative stress
- Promotes neuroplasticity and cell growth
- Lowers cholesterol levels
- Inhibits acetylcholinesterase activities

**Antioxidant**

- Enhances Aβ phagocytosis by microglia/macrophages

**Ant-inflammatory**

- Inhibits inflammation

**Cognition**

- Flourochrome

**Diagnostic marker**

---

**Fig. 1.** Curcumin: reported mechanisms of action. BACE1, β-APP-cleaving enzyme-1; Aβ, β amyloid; APP, amyloid precursor protein.
Table 1. Studies using curcumin in Alzheimer’s disease (AD): diagnosis, prevention and treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Cohort</th>
<th>Dose</th>
<th>Duration</th>
<th>End points and brief summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baum et al. (NCT00164749)</td>
<td>Curcumin and ginkgo</td>
<td>Probable AD; 50 years+; n 30</td>
<td>1, 4 g daily</td>
<td>6 months</td>
<td>Safety and effects, biochemical and cognitive measures; No differences detected between treatment groups in Aβ levels or MMSE scores</td>
</tr>
<tr>
<td>Ringman et al. (ACT00099710)</td>
<td>Curcumin C3 complex®</td>
<td>Mild/moderate AD; age 49 years+; n 30</td>
<td>2, 4 g daily</td>
<td>24 weeks plus</td>
<td>Side effects, blood biomarkers and cognition; No differences detected between treatment groups in clinical or biomarker efficacy measures; results also indicated low bioavailability</td>
</tr>
<tr>
<td>Hishikawa et al. (150)</td>
<td>Turmeric capsules</td>
<td>Severe AD; n 3</td>
<td>100 mg curcumin daily</td>
<td>12 months, tested after 12 weeks</td>
<td>MMSE and NPIQ; score on NPIQ decreased significantly, MMSE increased in 1/3</td>
</tr>
<tr>
<td>Poncha (NCT01001637)</td>
<td>Longvida™</td>
<td>Moderate – severe AD; 50–80 years; n 160</td>
<td>2, 3 g twice daily</td>
<td>2 months</td>
<td>Efficacy and safety; blood and cognition</td>
</tr>
<tr>
<td>Martins &amp; Goozee (ACTRN12613000681752)</td>
<td>Biocurcumax™ BCM-95</td>
<td>Retirement living, healthy 65–90 years; n 100</td>
<td>500 mg, thrice daily</td>
<td>12 months</td>
<td>Cognition, blood biomarkers/chemistry; lifestyle questionnaires; brain imaging (MRI, PET FDG and amyloid), retinal imaging</td>
</tr>
<tr>
<td>Martins (ACTRN12611000437965)</td>
<td>Biocurcumax™ BCM-95</td>
<td>Community living, healthy 55–75 years; n 100</td>
<td>500 mg, thrice daily</td>
<td>12 months</td>
<td>Cognition, blood biomarkers/chemistry; lifestyle brain imaging</td>
</tr>
<tr>
<td>Small (NCT01383161)</td>
<td>Theracurmin CR-031P™</td>
<td>MCI/normal ageing n 132</td>
<td>90 mg/d twice daily</td>
<td>18 months</td>
<td>Cognition; blood; genetic profile</td>
</tr>
<tr>
<td>Frautschy (NCT018811381)</td>
<td>Longvida and yoga</td>
<td>Subjective cognitive complainers 55–90 years; n 80</td>
<td>400 mg, twice daily</td>
<td>6 months</td>
<td>Biochemistry, cognition and FDG PET</td>
</tr>
<tr>
<td>Cox et al. (ACTRN12612001027808)</td>
<td>Longvida™</td>
<td>Healthy and cognitive decline 65–80 years; n 60</td>
<td>400, 800 mg daily</td>
<td>Phase 1: acute 1–3 h/ 4 weeks Phase 2: 8 weeks</td>
<td>Cognition, mood and anxiety; blood biomarkers fMRI; cognition</td>
</tr>
<tr>
<td>Patterson (NCT00595582 early termination)</td>
<td>Curcumin bioperine</td>
<td>MCI 55–85 years; n 10</td>
<td>900 mg twice daily</td>
<td>24 months</td>
<td>Cognition and size of metabolic lesions on the PET scan</td>
</tr>
<tr>
<td>Martins &amp; Goozee (ACTRN12614001024639)</td>
<td>Biocurcumax™ BCM-95</td>
<td>Healthy and MCI 65–90 years; n 48</td>
<td>500 mg twice daily</td>
<td>3 months</td>
<td>Gene regulation and expression; and cognition</td>
</tr>
<tr>
<td>Verdooner &amp; Martins (ACTRN12613000367741)</td>
<td>Longvida™</td>
<td>Healthy, MCI, mild/moderate AD 50 years+; n 200</td>
<td>20 g daily (shake)</td>
<td>7 d</td>
<td>Diagnostics; curcumin fluorescence retinal imaging of Aβ plaques</td>
</tr>
</tbody>
</table>

Aβ, β amyloid; MMSE, Mini Mental State Examination; PET, positron emission tomography; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; NPIQ, Neuro-Psychiatric Inventory-Brief Questionnaire; fMRI, functional MRI.
Fig. 2. Effect of curcumin on various proinflammatory diseases.
Treatment Protocols
(personal recommendations-Curcumin)

Therapeutic dosages:

**Turmeric** (*Curcuma longa*) standardized to curcuminoids 500mg TID up to 4g daily
High intestinal permeability is a normal feature of newborn gut ecology. Colostrum functions to reduce inflammation protect against irritation from toxins and check any potential infection, while promote epithelial growth and repair.
Colostrum also promotes re-colonization of the bowel by the friendly flora.
Colostrum is the best remedy known for all-around gut health. Colostrum restores leaky gut to normal permeability levels. It contains growth factors and hormones to help repair damage to the intestinal lining, and restore gut integrity.
Colostrum is unmatched as an immune system stimulant and modulator. There are numerous “one note” products lining the shelves of natural food stores that claim to stimulate the immune system. Only colostrum, however, plays the whole symphony.
Chapter 4

Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry

Elizabeth M. Sajdel-Sulkowska and Romuald Zabielski

Additional information is available at the end of the chapter

1. Introduction

The function of the gut microbiome and the bidirectional communication between the gastrointestinal tract (GIT) and the brain is increasingly recognized in health and disease and disruption in its composition is not unique to the autistic pathology. However, the bidirectional communication between the gut and the brain, “the gut-brain/brain-gut axis” in autism has been relatively understudied. In general, this communication between gut and brain occurs through a direct neuronal pathway via the vagus nerve, the hormonal pathway of several hormones involved in the regulation of food intake, such as cholecystokinin (CCK), ghrelin, leptin and insulin, and by the immunological signaling pathway involving cytokines. Recent studies indicate that the vagus nerve is involved in immunomodulation as suggested by its ability to attenuate the production of proinflammatory cytokines in experimental models of inflammation (de Jonge and Ullola, 2007). Furthermore, the gut microbiome emerges as a major player not only in the maturation of GIT tissue and the gut brain axis but also in brain maturation, through its effect on both the immune and endocrine systems. Many toxins, toxicants, infectious agents, diet or stress, affect an individual’s gut microbiome, which may be especially sensitive during the critical developmental period. Disruption of the developing microbiome may have profound consequences on the developing gut-brain axis including the brain as well as long-term effects on both the physical and psychological development.

This chapter attempts to bridge basic animal studies with clinical findings pertaining to the brain-gut and gut microbiome in autism, and includes a discussion of various strategies in managing autistic symptoms. The discussion also includes possible changes in the reward system.

The two key developmental time-points in the regulation of the GIT both occur postnatally, the first few days after birth when all gut digestive functions are launched by first colostrum ingestion and the second at weaning when the digestive system has to modify its function following a switch from mother’s milk to solid food.
The first time-point is particularly relevant for all mammalian species since it is associated with a complex of dynamic changes in the GIT structure and function leading to a temporary drop in the gut permeability barrier.
Gut on FIRE!

Body on Fire

- Eliminate Inflammatory Foods
- Prebiotics
- Fermented Foods
- Probiotics
- Vitamin D
- Glutamine
- EPA/DHA
- Curcumin
- Colostrum

Note: There are many other beneficial anti-inflammatories that can be used. These are foundational recommendations.
Premise #1

Just How Prevalent is the Development of Autoimmune Disease?
Thus, If CVD has an Initiating Autoimmune Component, Arguably, What Becomes the #1 Mechanism in the Progression of Morbidity and Mortality?
Premise #2

How Can We Identify People At Risk for the Development of Autoimmune Disease?
<table>
<thead>
<tr>
<th>Parietal Cell + ATPase</th>
<th>Intrinsic Factor</th>
<th>ASCA + ANCA</th>
<th>Tropomyosin</th>
<th>Thyroglobulin</th>
<th>Thyroid Peroxidase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial peptide</td>
<td>α-Myosin</td>
<td>Phospholipid</td>
<td>Platelet Glycoprotein</td>
<td>Ovary + Testis</td>
<td></td>
</tr>
<tr>
<td>21 Hydroxylase (Adrenal Cortex)</td>
<td>α + β Tubulin</td>
<td>Osteocyte</td>
<td>Cytochrome P450 Hepatocyte</td>
<td>Insulin + Islet Cell Antigen</td>
<td></td>
</tr>
<tr>
<td>Collagen complex</td>
<td>Arthritic peptide</td>
<td>Asialoanglioside GM1</td>
<td>Cerebellar</td>
<td>Synapsin</td>
<td></td>
</tr>
<tr>
<td>Fibulin</td>
<td>Ovary + Testis</td>
<td>Ovary + Testis</td>
<td>Insulin + Islet Cell Antigen</td>
<td>Synapsin</td>
<td></td>
</tr>
<tr>
<td>Glutamic-Acid Decarboxylase</td>
<td>Myelin Basic Protein</td>
<td>Asialoanglioside GM1</td>
<td>Cerebellar</td>
<td>Synapsin</td>
<td></td>
</tr>
</tbody>
</table>
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Premise #3

What is the Trigger in the production of Antibodies To Self?
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

Alessio Fasano* and Terez Shea-Donohue

The classical paradigm of autoimmune pathogenesis involving a specific genetic makeup and exposure to environmental triggers has been challenged by the addition of a third element: the loss of intestinal barrier function.
Premise #4
Can Foods Trigger Pathogenic Intestinal Permeability
CLE images of (A) baseline and (B and C) after food challenge

A) Confocal image at baseline shows closely attached villi and vascularity, representing the deepest level of mucosal imaging with CLE.

B) Confocal image after mucosal reaction to food. Multiple eruptions represent breaks in the wall (white arrows), through which fluorescein is secreted into the lumen. The IVS widened and is turning grey instead of the initial black.

(C) End stage of the reaction. With an influx of fluorescein the IVS turned white and widened further.
Premise #5
The more LPS or wheat peptides that pass through a permeable intestine, the stronger the inflammatory response.
We demonstrated a correlation between the degree of systemic inflammation and an increase in intestinal permeability.
Premise #6

How do We Arrest Pathogenic Intestinal Permeability?
Gut on FIRE!
Body on Fire

• Eliminate Inflammatory Foods
• Prebiotics
• Fermented Foods
• Probiotics
• Vitamin D
• Glutamine
• EPA/DHA
• Curcumin
• Colostrum

Note: There are many other beneficial anti-inflammatories that can be used. These are foundational recommendations.
Revolutionize Your Practice and Change the Lives of Your Patients

By Becoming a Certified Gluten Practitioner

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BETRAYAL
THE SERIES
THE AUTOIMMUNE DISEASE SOLUTION THEY'RE NOT TELLING YOU
Take Care of Yourself

© www.theDr.com
Make Sure to Tell those Important to You How Much You Love them
Throughout your life the most profound influences on your health, vitality and function are not the Doctors you have visited or the drugs, surgery, or other therapies you have undertaken. The most profound influences are the cumulative effects of the decisions you make about your diet and lifestyle on the expression of your genes.
“Thank You for Your Kind Attention”
Wishing you Sunrises of Beauty throughout your life
Premise #9

Every Office benefits from offering SUCCESSFUL, Comprehensive, Thorough Guidance for Patients to Transition into a GF Lifestyle via a Well-Trained Nutritionist, Registered Dietician, or Staff Specialist