For Gut’s Sake: 
Stop the Autoimmune Epidemic

Aristo Vojdani, PhD
Health Extravaganza 2013
Anaheim, CA

By the end of this presentation participants should be able to:

- Identify the structures of the intestinal barrier and understand its protective functions.
- Acknowledge the serious implications of systemic lipopolysaccharides.
- Map pathological cascades (cross-reactivity, inflammation and binding to human tissues) triggered by different environmental triggers that lead to autoimmune reactivity.
- Understand that by removing the environmental triggers and re-establishing barrier integrity, the autoimmune reactivity can be slowed, stopped and sometimes reversed.

The Triad of Autoimmunity

- Genetic Susceptibility
- Gut Dysbiosis and Increased Intestinal Permeability
- Environmental Triggers
  - Dietary components
  - Toxic chemicals
  - Infections

In the past decade, more than 15 top medical journals have reported that in industrialized countries around the world the increasing incidences of many autoimmune and neuroimmune disorders are reaching epidemic proportions.

More recently, the National Institute of Environmental Health Sciences (NIEHS) convened an expert panel workshop to review the body of literature examining the role of the environment in the development of autoimmune disease.

On the whole, the workshop’s findings concluded that genetics and heritability can only account for a portion of the incidence of autoimmune disease, supporting the hypothesis that the etiology of autoimmune disease involves both genetic and environmental factors. More emphasis therefore should be placed on the role of epigenetics and environmental components in the manifestations of autoimmune disease.
Is it the gene or the environment?

Possible maternal influence on neonatal tolerance induction through breast feeding. Before reaching the milk, ingested airborne and dietary antigens are handled by the maternal digestive system, which could contribute to the generation of tolerogenic peptides. Depending on the maternal antigen exposure and mammary gland permeability, various amounts of antigen will be found in breast milk. Maternal sensitization to the ingested allergens will dictate whether the transferred antigens will be found in the milk free or complexed to antigen-specific IgA and IgG.

Gut Dysbiosis and Increased Intestinal Permeability

The Actomyosin Network forms cables across epithelial cells which regulate the opening and closing of tight junctions.

Aristo Vojdani, PhD

Actomyosin Network
**Occludin/Zonulin**

IgG, IgM, IgA

Occludin/Zonulin are proteins that make up the tight junctions between epithelial cells

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**Lipopolysaccharides**

IgG, IgM, IgA

Lipopolysaccharides are endotoxins on gram negative bacteria in the gut

LPS protects gram negative bacteria from being destroyed by gram positive bacteria

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**Gut Microbiota in Health and Disease**

The microbiota is intimately involved in numerous aspects of normal host physiology, from nutritional status to behavior and stress response. Additionally, they can be a central or a contributing cause of many diseases, affecting both near and far organ systems.

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**Gut Microbiota in Health and Disease**

As the gut microbiota appears to contribute to nearly every aspect of the host’s growth and development, it is not surprising that a tremendous array of diseases and dysfunctions have been associated with an imbalance in either composition, numbers, or habitat of the gut microbiota.
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Environmental Triggers

- Toxic Chemicals
- Infections
- Dietary Proteins & Peptides

Change in microbiota

- Eubiosis
- Dysbiosis

Interaction with the host

- Immune homeostasis
  - Healthy, stable state

- Systemic inflammation
  - Asthma, atopic dermatitis, RA, arthritis, multiple sclerosis, Guillain-Barré syndrome, obesity, metabolic syndrome, others

Alteration of gut microbiota by environmental triggers

Bacterial Life on Mucosal Surfaces with Different Characteristics

- Good Bacteria (Lactobacillus, Akkermansia)
- Bad Bacteria (Escherichia coli, Staphylococcus)
- Ugly Bacteria (Fecal bacteria)

- Release of antigens
  - Increase in ratio of immature DCs and Mφs
  - Increase in the ratio of Treg/TTh17

- Tissue inflammation
  - Release of antigens
  - Increase in ratio of immature DCs and Mφs
  - Change in lymphocyte mobility
  - Decrease in the ratio of Treg/TTh17

- Subversion of mucosal immune system

- Further decrease in the ratio of immature DCs and Mφs

- Further decrease in the ratio of Treg/TTh17

The addition of a single bacterial strain can change behavior.

Transcellular and Paracellular Pathways

- Transcellular: Maltose size 182 Da
  - Lactulose size 242 Da
  - Epithelial Cells (ECs)

- Paracellular: Different pathways for differently-sized molecules

For the Assessment of Intestinal Permeability, Size Matters

Aristo Vojdani, PhD

ABSTRACT

The permeability of the epithelium to very small sugar molecules such as lactulose/mannitol—used for the past 50 years to gauge intestinal permeability—does not necessarily correlate with epithelial permeability to macromolecules...the article presents evidence indicating that increased intestinal, antigentic permeability plays a key role in the development of various inflammatory and autoimmune disorders.
To avoid False Positives, use large molecules in the assessment of Intestinal Permeability

Food Antigens or Bacterial Toxins

Immune Challenge Zone

Environmental Triggers
- Dietary components
- Toxic chemicals
- Infections

The triggers and mechanisms involved in enhanced (exacerbated) intestinal permeability and how to use the next generation of testing for Intestinal Permeability Identification (IPI).

Bacterial Endotoxin (LPS) IgG, IgM, IgA
Actomyosin Network IgA
Occludin / Zonulin IgG, IgM, IgA

The Characterization of the Repertoire of Wheat Antigens and Peptides Involved in the Humoral Immune Responses in Patients with Gluten Sensitivity and Crohn’s Disease

Intestinal T cells from gluten sensitivity/celiac disease patients respond to a heterogeneous array of peptides. Our study extended this heterogeneity to humoral immune response to various wheat proteins and peptides in patients with gluten sensitivity or Crohn’s disease. IgG and IgA antibodies in sera from those patients and healthy control subjects were measured against an array of wheat antigens and peptides. In gluten-sensitive patients, IgG reacted most against transglutaminase, prodynorphin, wheat extract, and α-, γ-, and ω-gliadin; IgA reacted most against wheat then transglutaminase, glutenin, and other peptides. In the sera of Crohn’s disease patients, IgG reacted most against wheat and wheat germ agglutinin then transglutaminase, prodynorphin, α-gliadin; IgA reacted foremost against prodynorphin then transglutaminase and α-gliadin. These results showed a substantial heterogeneity in the magnitude of IgG and IgA response against various wheat antigens and peptides. Measurements of IgG and IgA antibodies against such an array of wheat peptides and antigens can enhance the sensitivity and specificity of serological assays for gluten sensitivity and celiac disease and may also detect silent celiac disease or its overlap with inflammatory bowel disease.

Measurements of IgG and IgA antibodies against such an array of wheat peptides and antigens can enhance the sensitivity and specificity of serological assays for gluten sensitivity and celiac disease and may also detect silent celiac disease or its overlap with inflammatory bowel disease.
Cross-reaction between gliadin and different food and tissue antigens

We observed significant immune reactivity when these antibodies were applied to cow’s milk, milk chocolate, milk, instant coffee and rice. To investigate whether there was cross-reactivity between α-gliadin antibody and different tissue antigens, we measured the degree to which this antibody bound to these antigens. The most significant binding occurred with asialo-ganglioside, hepatocyte, glutamic acid decarboxylase 65, adrenal 21-hydroxylase, and various neural antigens.

The beneficial effect of amalgam replacement on health in patients with autoimmune

The results show that mercury-containing amalgam may be an important risk factor for patients with autoimmune diseases who are sensitized to mercury. Hence, the removal of amalgam fillings is a useful complementary treatment for such patients. Nickel sensitivity was found to be another risk factor that may negatively affect the chance of regaining health.
Antibodies

- Indicate exposure to chemical
- Indicate body burden of chemical exposure
- Indicate immune reactivity to chemical exposure
- May indicate trigger for autoimmune reactivity

Levels

- Indicate exposure to chemical
- Indicate what is being cleared out of the body
  - Some people can have body burden from “safe” levels of chemical exposures
  - Some people can naturally clear high levels of chemicals

Infection Immune Reactivity

Epidemiological data indicate a link between rheumatoid arthritis (RA) and periodontal disease (PD).

Periodontitis, Porphyromonas, and the pathogenesis of rheumatoid arthritis

This review seeks to provide background on these two diseases in the context of recent discoveries suggesting that their pathogenesis may be related.
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Proposed model for the pathogenesis of RA. In a asymptomatic pre-clinical stage, people with the appropriate genetic background develop ACPAs under the action of P. gingivalis. These antibodies trigger the breakdown of immune tolerance leading to the appearance of RA.

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.


Antibodies as predictors of complex autoimmune diseases.

International Journal of Immunopathology and Pharmacology

Antibodies as predictors of complex autoimmune diseases and cancer.

National Institutes of Health
THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

Potential of Biomarkers:
Predictive Antibodies for Autoimmune Reactivity
• 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

Multiple Autoimmune Reactivity

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Antibodies as predictors of complex autoimmune diseases.

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Antibodies as predictors of complex autoimmune diseases and cancer.
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A GUT FEELING FOR AUTOIMMUNITY

CASE STUDY

Female with Healthy Gut

- Under chronic stress over root canal and dental implant
- Antibiotic after dental surgery
- Severe allergic reaction to the combination of anesthetic and antibiotic
- Pain medication after dental surgery
- Antacid prescribed for acid reflux
- Continued regular diet regimen

When to use Predictive Antibody Screens

- For a patient with any idiopathic conditions caused by environmental triggers
  - Infections
  - Chemicals
  - Dietary Proteins
- Follow up with a patient who has chronic increased intestinal permeability, which is the gateway for environmentally-induced disorders
- Follow up with an autoimmune patient to monitor treatment and to screen for additional autoimmune disease

40 Days After Dental Implant and Medication Use

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Normal Ranges</th>
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<tbody>
<tr>
<td>Secretory IgA</td>
<td>32</td>
<td>117</td>
<td>16 – 48 mg/mL</td>
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<tr>
<td>Gliadin IgA + IgM</td>
<td>21</td>
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<td>7 – 18 EU</td>
</tr>
<tr>
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A GUT FEELING FOR AUTOIMMUNITY

Chronic stress ➔ Abnormal Mucosal Immunity from root canal

Antibiotic after ➔ Gut Dysbiosis
dental implant

Pain medication ➔ Inhibition of Aminopeptidases

Antacid for ➔ Inhibition of Digestive acid reflux  

Normal diet ➔ Accumulation of Undigested Proteins and Peptides

Accumulation of Undigested Proteins and Peptides

High Level of Proteases and Endotoxins

Breakdown of Epithelial Tight Junction

Production of Antibodies Against:

Lipopolysaccharides (endotoxins) ➔ Tight Junction Proteins (occludin/zonulin) ➔ Dietary Proteins and Peptides

AUTOIMMUNITY

Case Conclusion

Stress combined with medications contributed to mucosal immune abnormality, which resulted in "leaky gut."

If "leaky gut" is not repaired quickly, the patient may develop autoimmunity.

Anytime the mucosal membrane is compromised, the gut barrier is at risk for increased permeability.

An acute allergic reaction through this mechanism may result in a cascade of additional immune reactions.

Multiple Autoimmune Reactivity

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<th>4 wks after dental procedure</th>
<th>6 mos after treatment with probiotics, enzymes</th>
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<tbody>
<tr>
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Health Extravaganza 2013

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**For Gut’s Sake:**
Stop the Autoimmune Epidemic

**Diet and Environmental Factors**
- Imbalanced Microbiota
- Release of endotoxins
- Gut inflammation
- Loss of immune tolerance
- Loss of gut integrity
- Entry of LPS, undigested dietary components in circulation
- Loss of blood-brain barrier integrity
- Humoral and cell-mediated immune response
- Cross-reaction with various tissue antigens
- Multi-organ tissue inflammation and autoimmunity (Liver, Brain, Muscle, Joint, Kidney, Pancreas) and systemic insulin resistance

**Detect**
- Mucosal immune screening
- Intestinal antigenic permeability screening
- Dietary components screening
- Predictive antibody screening
  - Multiple autoimmune reactivity
  - Diabetes autoimmune reactivity
  - Neurological autoimmune reactivity
  - Joint autoimmune reactivity
- Chemical immune reactivity screening
- Infections immune reactivity screening

**Remove Triggers**
- Detoxify the body
- Treat infection
- Exercise
- Minimize medication
- Drink pure water
- Remove offending foods from diet
- Eat pure foods
- Minimize lectins & agglutinins

**Repair the Barriers**
- Regulatory T cells (Treg) → Pathogenic TH17 cells
- Artemisinin
- Glutamine
- Vitamin A (retinoic acid)
- Vitamin D
- Probiotics
- Short chain fructooligosaccharides (Onions, garlic, asparagus, artichoke)
- EPA/DHA
- Green tea extract
- Resveratrol
- Curcumin
- Boswellic acid
- Cruciferous vegetables (broccoli, kale, cabbage, cauliflower)
- Lipoic acid
- Minoycline
- Nutrition for your healthy microbiota