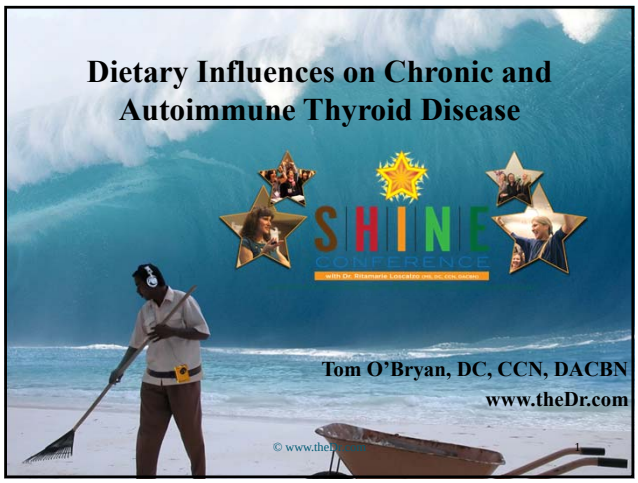
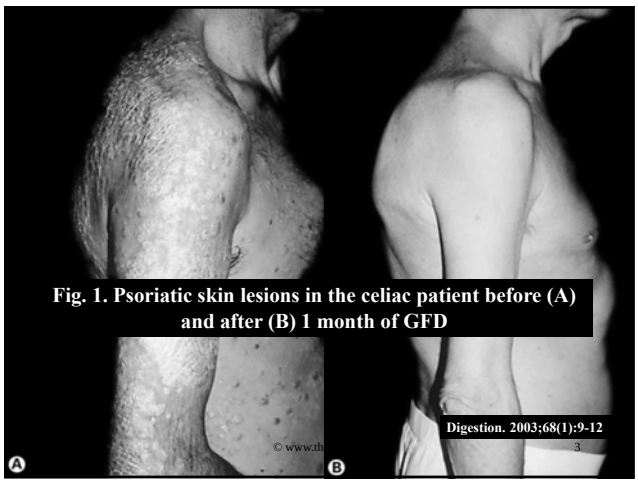


Tom O'Bryan, DC holds:

- Adjunct Faculty, The Institute for Functional Medicine,
- Adjunct Faculty ,The National University of Life Sciences,
- Clinical Consultant on Functional Medicine-BioBotanical Research
- Clinical Consultant on Functional Medicine -NuMedica, Inc.
- Scientific Advisory Board-International and American Association of Clinical Nutritionists
- Medical Advisory Board National Association of Nutritional Professionals

 2



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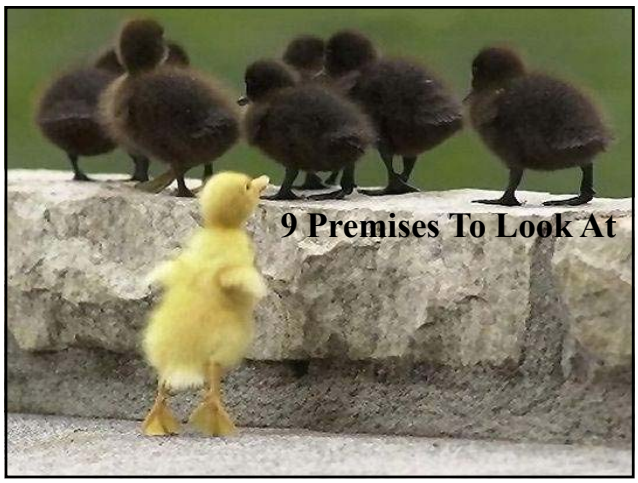


Premise #1

What is the Most Common Cause of Morbidity and Mortality in the Industrialized World?

Detective Adrian Monk

 5

NIH. Autoimmune Diseases Coordinating Comm. Autoimmune Diseases Research Plan. 2006

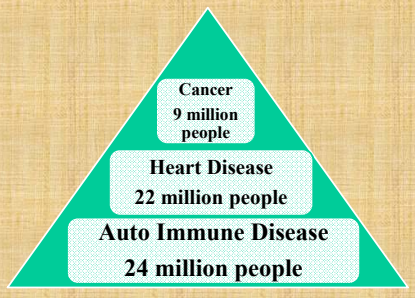
National Institutes of Health

AUTOIMMUNE DISEASES COORDINATING

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

 6



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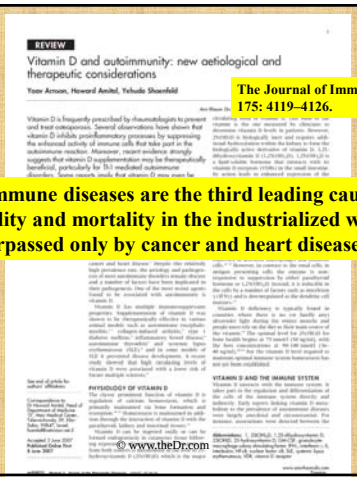


REVIEW

Vitamin D and autoimmunity: new aetiological and therapeutic considerations

Yoav Arnson, Howard Amital, Yehuda Shoenfeld

The Journal of Immunology, 2005, 175: 4119–4126.

Autoimmune diseases are the third leading cause of morbidity and mortality in the industrialized world, surpassed only by cancer and heart disease.

 8

AND

Detective Adrian Monk

 9

World J Cardiol. May 26, 2014; 6(5): 314–326

World Journal of Cardiology

Autoantibodies to apolipoprotein A-1 as a biomarker of cardiovascular autoimmunity

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.

10

World J Cardiol. May 26, 2014; 6(5): 314–326

World Journal of Cardiology

Autoantibodies to apolipoprotein A-1 as a biomarker of cardiovascular autoimmunity

In Europe, CVD causes 47% of all deaths accounting for 4 million fatalities each year, and costing 196 billion euros a year.

11

World J Cardiol. May 26, 2014; 6(5): 314–326

World Journal of Cardiology

Autoantibodies to apolipoprotein A-1 as a biomarker of cardiovascular autoimmunity

The first indicator of atherosclerosis for 30%-50% of patients was an acute, and in many cases fatal, myocardial infarction (MI)

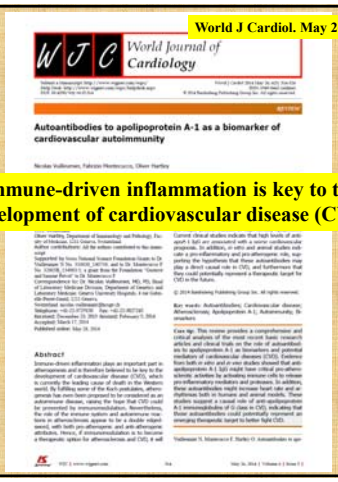
How is it possible that our Health Care System could be so Blind? We're looking in the wrong place. And we keep looking in the wrong place. *TOB*

12

Perhaps if We Open to More Current Information…..

 13

World J Cardiol. May 26, 2014; 6(5): 314–326


World Journal of Cardiology

Autoantibodies to apolipoprotein A-1 as a biomarker of cardiovascular autoimmunity

Immune-driven inflammation is key to the development of cardiovascular disease (CVD)

14


Contemporary Reviews in Cardiovascular Medicine

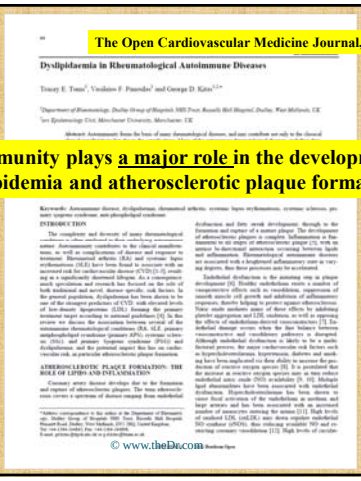
Accelerated Atherosclerosis in Autoimmune Rheumatic Diseases

Circulation. 2005;112:3337-3347

Atherosclerosis is increasingly considered an immune system–mediated process of the vascular system.

 15

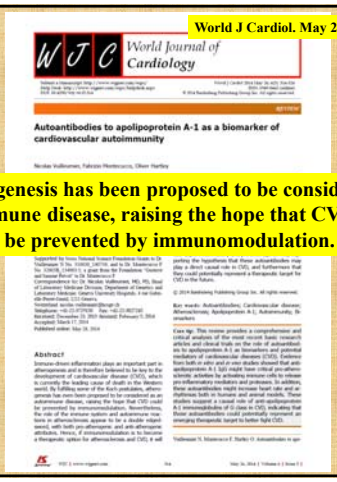
The Open Cardiovascular Medicine Journal, 2011, 5, 64-75


Dyslipidaemia in Rheumatological Autoimmune Diseases

Autoimmunity plays a major role in the development of dyslipidemia and atherosclerotic plaque formation.

 16

World J Cardiol. May 26, 2014; 6(5): 314–326


World Journal of Cardiology

Autoantibodies to apolipoprotein A-1 as a biomarker of cardiovascular autoimmunity

Atherogenesis has been proposed to be considered an autoimmune disease, raising the hope that CVD could be prevented by immunomodulation.

17

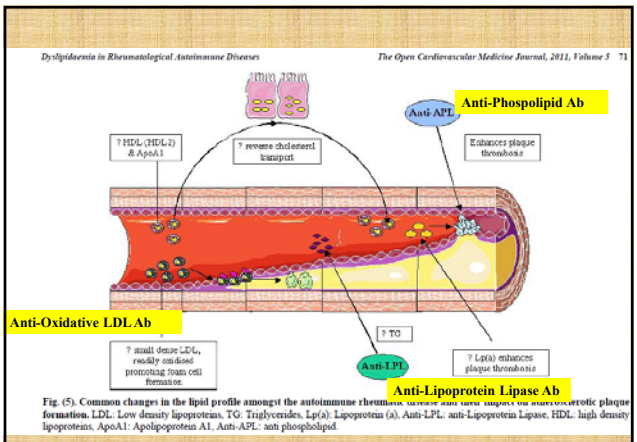


Fig. (5). Common changes in the lipid profile amongst the autoimmune rheumatic disease and their impact on atherosclerotic plaque formation. LDL: Low density lipoproteins, TG: Triglycerides, Lp(a): Lipoprotein (a), Anti-LPL: anti-Lipoprotein Lipase, HDL: high density lipoproteins, ApoA1: Apolipoprotein A1, Anti-APL: anti phospholipid.

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The Open Cardiovascular Medicine Journal, 2011, 5, 64-75


Dyslipidaemia in Rheumatological Autoimmune Diseases

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.

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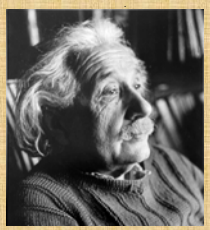
Thus, If CVD has an Initiating Autoimmune Component, Arguably, What Becomes the #1 Mechanism in the Progression of Morbidity and Mortality?



© www.theDr.com 20

Silently
Point to 2 People
Close By

How often do you see Autoimmune Disorders Currently in Your Practice and Given these Numbers, What Would the Impact Be IF You were Recognizing Autoimmune Disorders at this Frequency?

Detective Adrian Monk

 21

National Institutes of Health
THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

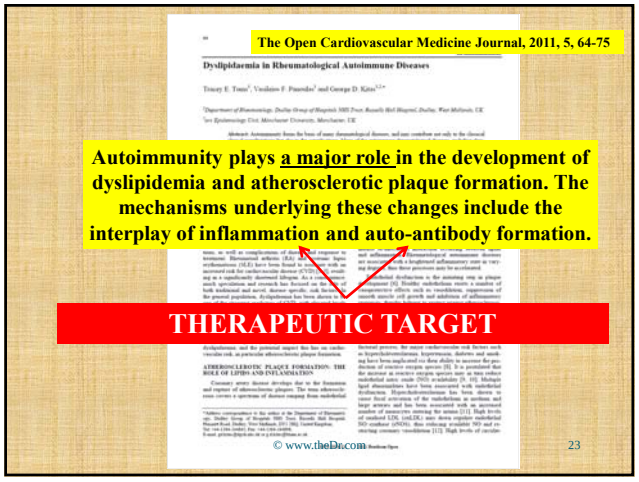
Prevention of Autoimmune Diseases:

- Define genetic make-up of susceptible individuals
- Identify environmental triggers
- Identify autoantibodies
- Develop preventive interventions

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

 22



The Open Cardiovascular Medicine Journal, 2011, 5, 64-75

Dyslipidaemia in Rheumatological Autoimmune Diseases

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.

THERAPEUTIC TARGET

 23

The overexpression of inflammation genes, immune-response genes and genes associated with the lysosomal system J Clin Immunol 29:397405, 2009

 24

Premise #2

Genes Control Function

Detective Adrian Monk

 25

Reproductive Toxicology 23 (2007) 297–307

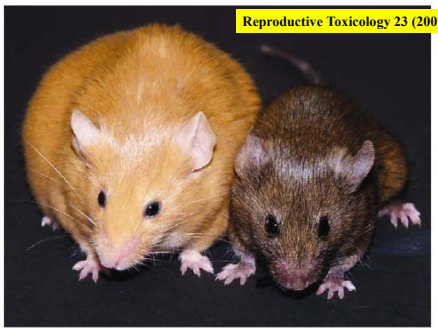
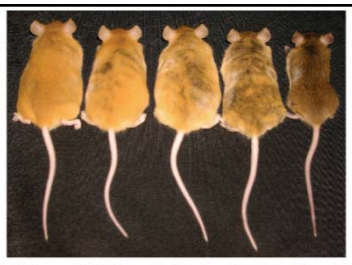


Fig. 1. One-year-old female genetically identical viable yellow agouti mice (A^{vy}). Maternal dietary supplementation with methyl donors such as folic acid, choline, and betaine [34] or the phytoestrogen, genistein [32], shifts the coat color of the offspring from yellow to brown, and reduces the incidence of obesity, diabetes, and cancer.

 26



Yellow | Slightly Mottled | Mottled | Heavily Mottled | Pseudo-agouti

Figure 1. Genetically identical 3-mo-old A^{vy} mice representing the five coat color phenotypes. Yellow mice are hypomethylated at the transposable element upstream of the *Agouti* gene allowing maximal ectopic expression, whereas hypermethylation of this site silences ectopic Agouti expression in the pseudoagouti animals. Mice that are predominately yellow are also clearly more obese than brown mice. Reprinted from Dolinoy DC *et al.* 2006 Environ Health Perspect 114:567–572, with permission.

Pediatr Res. 2007;61:30R–37R.

 27

 28

The Epigenetics Revolution

Which Genes Do YOU Want To Turn On?

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Which Genes Do YOU Want To Turn On?

What Epigenetics Really Means

 31

How are you Feeding Your Genes

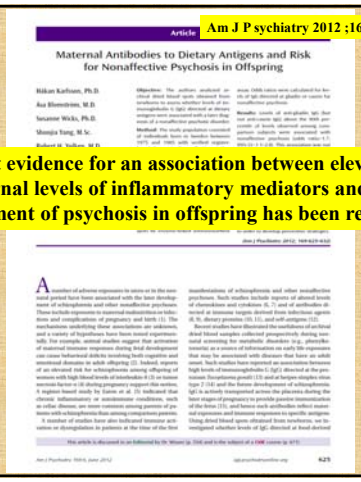
8 months later

 32

POTENTIAL TRIGGER #1

 33

Am J P sychiatry 2012 ;169:625–632


Article

Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring

Direct evidence for an association between elevated maternal levels of inflammatory mediators and the development of psychosis in offspring has been reported.

34

Am J P sychiatry 2012 ;169:625–632

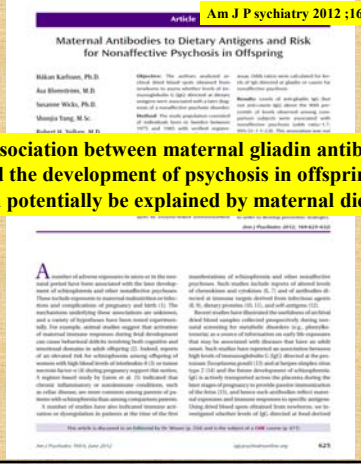

Article

Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring

Activation of maternal immune responses during fetal development can cause behavioral deficits involving both cognitive and emotional domains in adult offspring

35

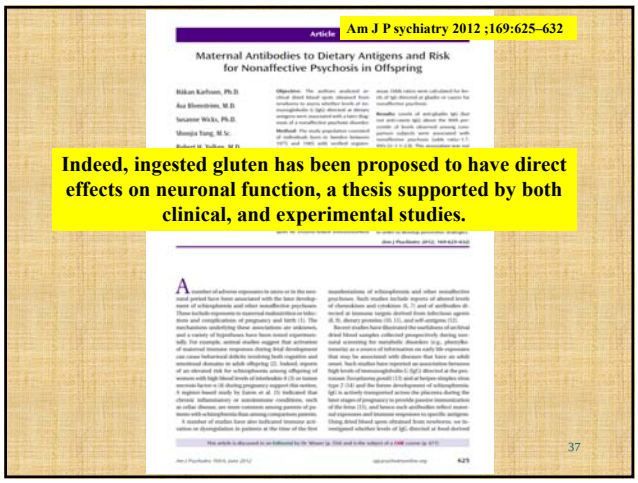
Am J P sychiatry 2012 ;169:625–632

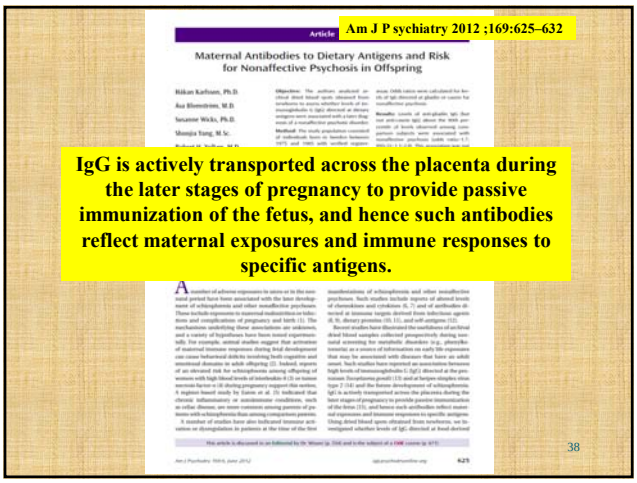

Article

Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring

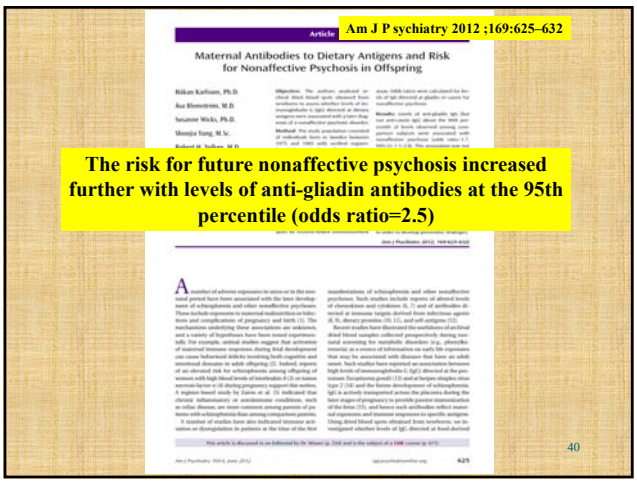
The association between maternal gliadin antibodies and the development of psychosis in offspring can potentially be explained by maternal diet.

36


Article
Am J P sychiatry 2012 ;169:625–632
Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring
Håkan Karlsson, Ph.D.
Ava Bloemstrom, M.D.
Suzanne Wicks, Ph.D.
Shonjia Yang, M.Sc.
Indeed, ingested gluten has been proposed to have direct effects on neuronal function, a thesis supported by both clinical, and experimental studies.
37


Article
Am J P sychiatry 2012 ;169:625–632
Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring
IgG is actively transported across the placenta during the later stages of pregnancy to provide passive immunization of the fetus, and hence such antibodies reflect maternal exposures and immune responses to specific antigens.
38


Article
Am J P sychiatry 2012 ;169:625–632
Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring
A significantly elevated risk for nonaffective psychoses was associated with high levels (90th percentile) of IgG anti-gliadin antibodies (odds ratio=1.7), but not anti-casein antibodies (odds ratio=0.8).
39


Article
Am J P sychiatry 2012 ;169:625–632
Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring
The risk for future nonaffective psychosis increased further with levels of anti-gliadin antibodies at the 95th percentile (odds ratio=2.5)
40

Am J P sychiatry 2012 ;169:625–632

Article

Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring

We did not find an association with antibodies to casein, suggesting that the risk is not associated with an overall increase in antibodies to food antigens.

41

Am J P sychiatry 2012 ;169:625–632

Article

Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring

The risk associated with high levels of IgG anti-gliadin antibodies appears to act independently of maternal age, immigration, and mode of delivery.

42

Am J P sychiatry 2012 ;169:625–632

Article

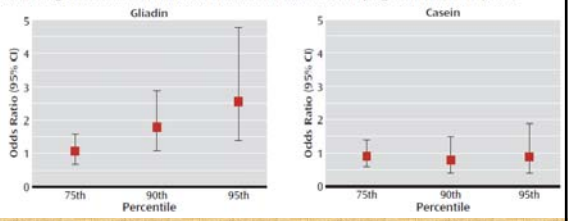
Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring

The bulk of fetal IgG is transferred from the mother during the last 4 weeks of the pregnancy.

43

Am J P sychiatry 2012 ;169:625–632

FIGURE 1. Levels of IgG Directed at Gliadin and Casein and Odds of Developing Nonaffective Psychosis



44

Am J P sychiatry 2012 ;169:625–632

Article

Maternal Antibodies to Dietary Antigens and Risk for Nonaffective Psychosis in Offspring

A mechanism potentially linking maternal antigliadin reactivity with the later development of psychosis in offspring involves maternal inflammation.

45

**So What is the Clinical Relevance of This?
How Do I Use This Information in My Practice?**

46

EVERY PREGNANT WOMAN IS ACCURATELY TESTED FOR A GLUTEN RELATED DISORDER, NOT JUST CELIAC DISEASE

47

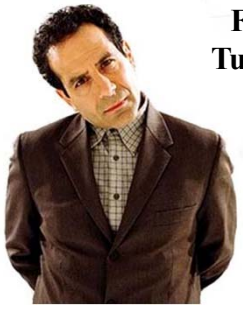
Latent celiac disease in reproductive performance of women

Fertility and Sterility Vol. 95, No. 3, March 1, 2011

The seroprevalence of transglutaminase IgA was 6.70% in the group with recurrent abortion, 5.70% in the group with stillbirth, 5.65% in the group with infertility, 9.33% in the group with intrauterine growth restriction, and 1.30% in the control group.

48

Premise #3



Food Turns On and Turns OFF Our Genes

Detective Adrian Monk

 49

Am J Clin Nutr. 2007;85:1417-1427

Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study[1–4]

Our aim was to test whether carbohydrate dietary modifications improve insulin sensitivity and secretion and glucose tolerance in overweight or obese persons with the metabolic syndrome, even in the absence of weight loss.

 50

Am J Clin Nutr. 2007;85:1417-1427

Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study[1–4]

The subjects were randomly assigned to 12-week diets in which either rye bread and pasta or oat and wheat bread and potato were the main carbohydrate sources (34% and 37% of energy intake, respectively).

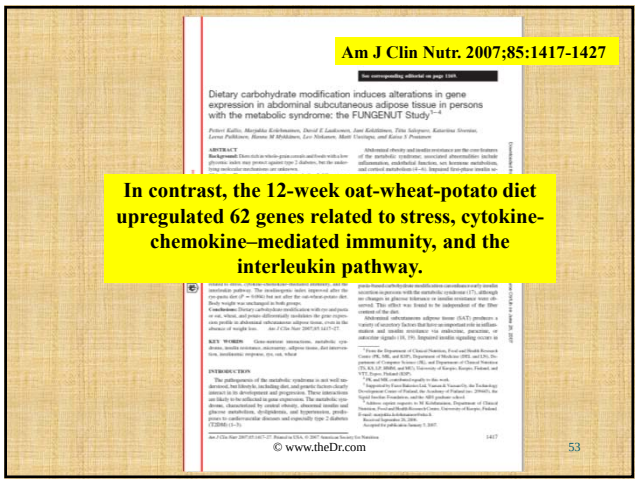
 51

Am J Clin Nutr. 2007;85:1417-1427

Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study[1–4]

We detected 71 down-regulated genes in the rye-pasta group, including genes linked to insulin signaling and apoptosis

 52


Am J Clin Nutr. 2007;85:1417-1427
Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study
In contrast, the 12-week oat-wheat-potato diet upregulated 62 genes related to stress, cytokine-chemokine–mediated immunity, and the interleukin pathway.
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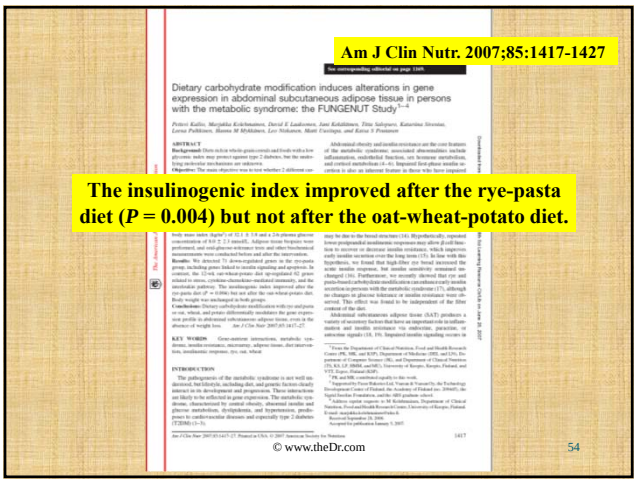
Am J Clin Nutr. 2007;85:1417-1427
Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study
The insulinogenic index improved after the rye-pasta diet (P = 0.004) but not after the oat-wheat-potato diet.
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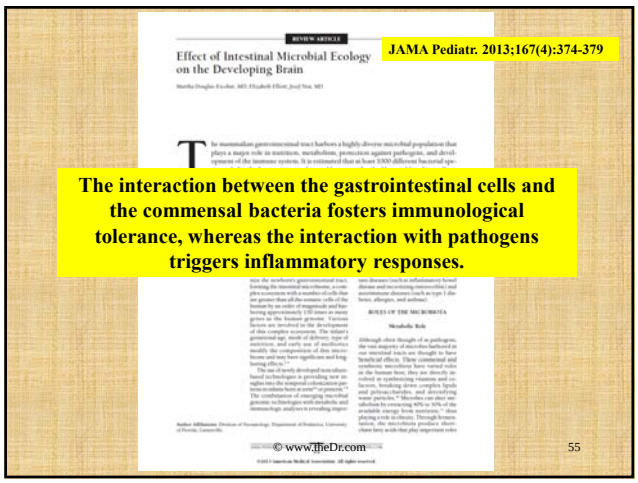
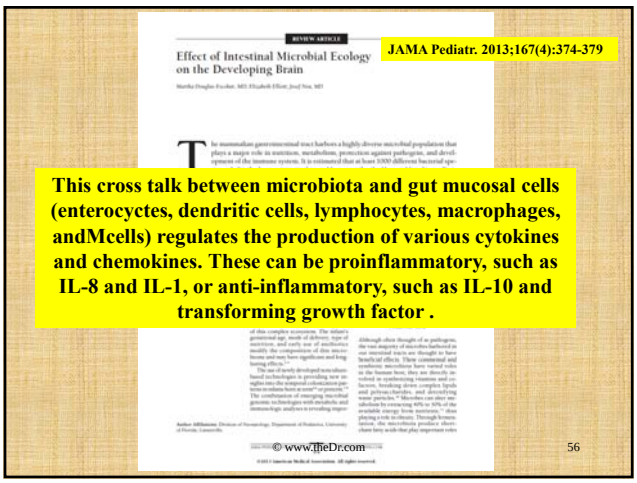

JAMA Pediatr. 2013;167(4):374-379
Effect of Intestinal Microbial Ecology on the Developing Brain
The interaction between the gastrointestinal cells and the commensal bacteria fosters immunological tolerance, whereas the interaction with pathogens triggers inflammatory responses.
© www.theDr.com
55


JAMA Pediatr. 2013;167(4):374-379
Effect of Intestinal Microbial Ecology on the Developing Brain
This cross talk between microbiota and gut mucosal cells (enterocyctes, dendritic cells, lymphocytes, macrophages, andMcells) regulates the production of various cytokines and chemokines. These can be proinflammatory, such as IL-8 and IL-1, or anti-inflammatory, such as IL-10 and transforming growth factor .
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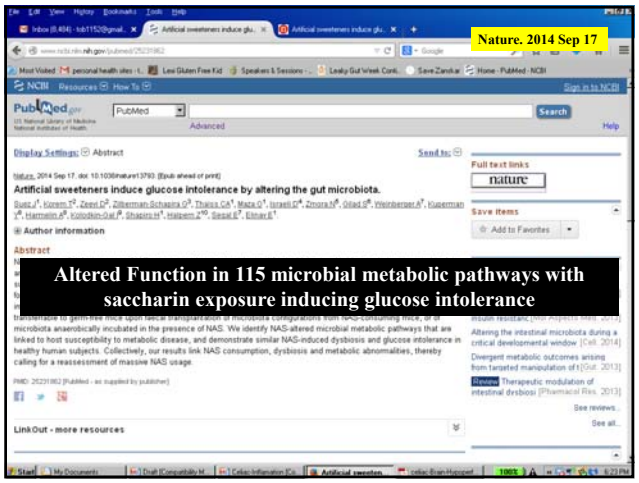


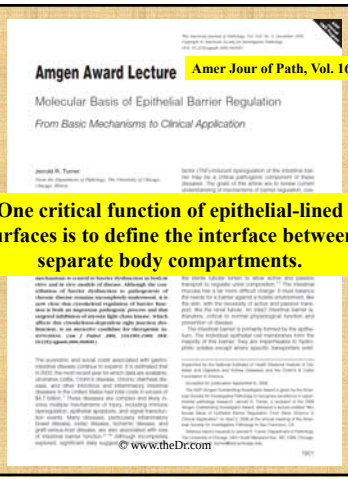
Although there are many contributors to systemic inflammation, there is 1 that is extremely common in most autoimmune diseases

 58

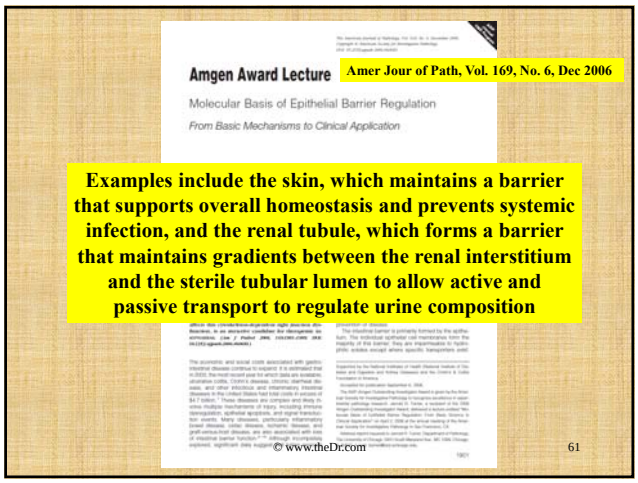
Premise #4

Where Does the Persisting Inflammation Come From?

 59



 60


Amgen Award Lecture
Amer Jour of Path, Vol. 169, No. 6, Dec 2006
Molecular Basis of Epithelial Barrier Regulation
From Basic Mechanisms to Clinical Application
Examples include the skin, which maintains a barrier that supports overall homeostasis and prevents systemic infection, and the renal tubule, which forms a barrier that maintains gradients between the renal interstitium and the sterile tubular lumen to allow active and passive transport to regulate urine composition
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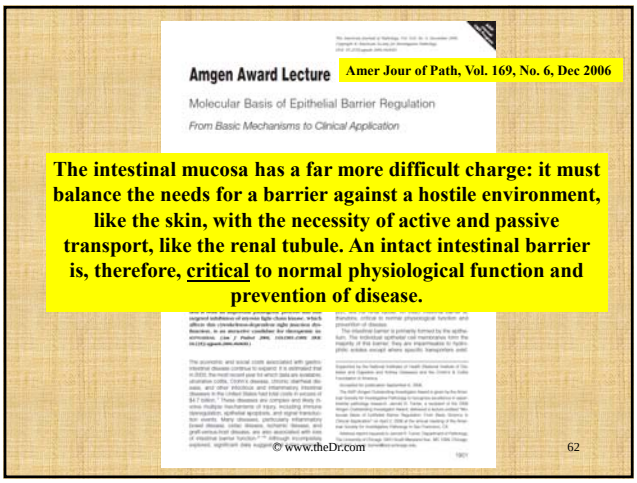
61


Amgen Award Lecture
Amer Jour of Path, Vol. 169, No. 6, Dec 2006
Molecular Basis of Epithelial Barrier Regulation
From Basic Mechanisms to Clinical Application
The intestinal mucosa has a far more difficult charge: it must balance the needs for a barrier against a hostile environment, like the skin, with the necessity of active and passive transport, like the renal tubule. An intact intestinal barrier is, therefore, critical to normal physiological function and prevention of disease.
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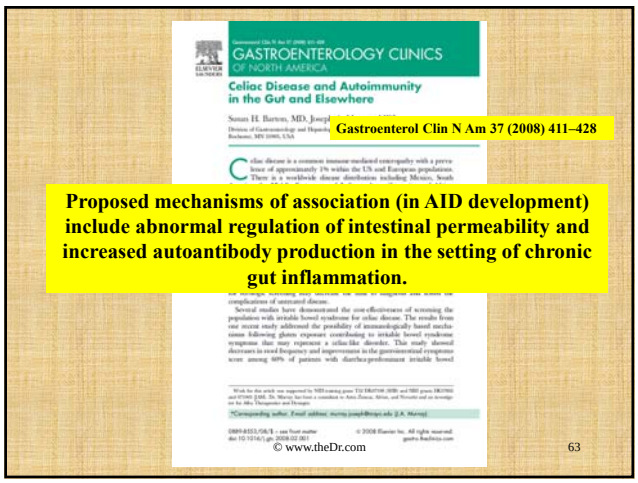
62


GASTROENTEROLOGY CLINICS
OF NORTH AMERICA
Celiac Disease and Autoimmunity in the Gut and Elsewhere
Gastroenterol Clin N Am 37 (2008) 411–428
Proposed mechanisms of association (in AID development) include abnormal regulation of intestinal permeability and increased autoantibody production in the setting of chronic gut inflammation.
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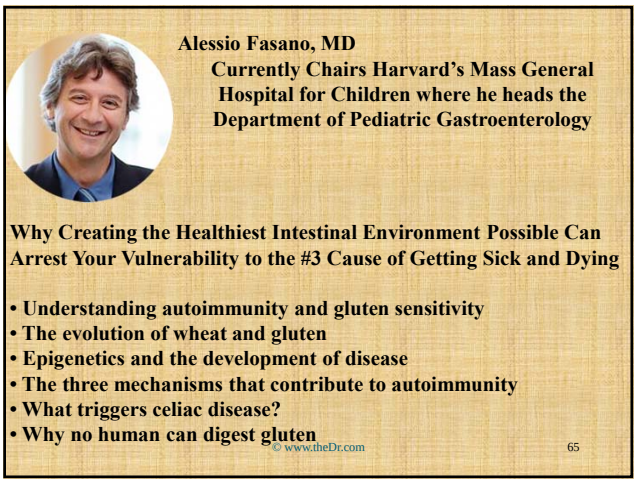
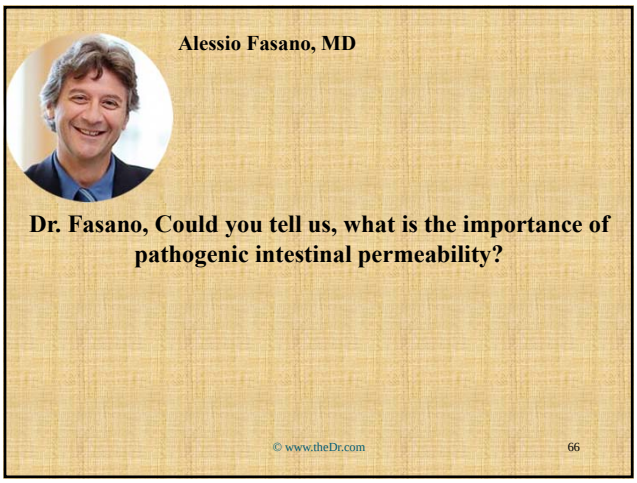
63


Brought to you by theDr.com
The Gluten Summit
A Grain of Truth
64


Alessio Fasano, MD
Currently Chairs Harvard's Mass General Hospital for Children where he heads the Department of Pediatric Gastroenterology
Why Creating the Healthiest Intestinal Environment Possible Can Arrest Your Vulnerability to the #3 Cause of Getting Sick and Dying
• Understanding autoimmunity and gluten sensitivity
• The evolution of wheat and gluten
• Epigenetics and the development of disease
• The three mechanisms that contribute to autoimmunity
• What triggers celiac disease?
• Why no human can digest gluten
© www.theDr.com
65


Alessio Fasano, MD
Dr. Fasano, Could you tell us, what is the importance of pathogenic intestinal permeability?
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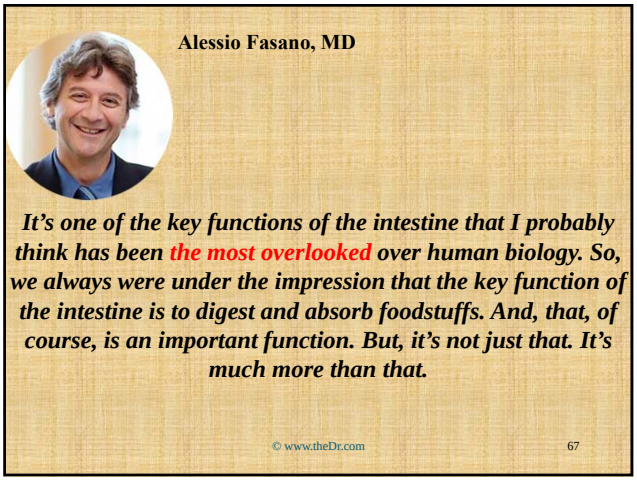
Alessio Fasano, MD
It's one of the key functions of the intestine that I probably think has been the most overlooked over human biology. So, we always were under the impression that the key function of the intestine is to digest and absorb foodstuffs. And, that, of course, is an important function. But, it's not just that. It's much more than that.
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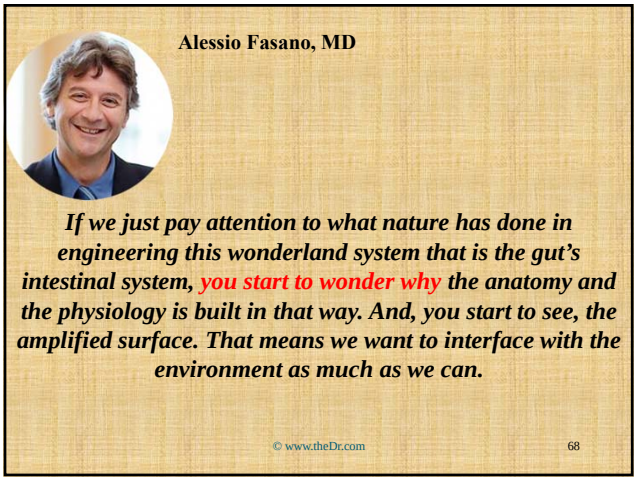
Alessio Fasano, MD
If we just pay attention to what nature has done in engineering this wonderland system that is the gut's intestinal system, you start to wonder why the anatomy and the physiology is built in that way. And, you start to see, the amplified surface. That means we want to interface with the environment as much as we can.
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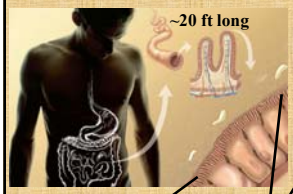
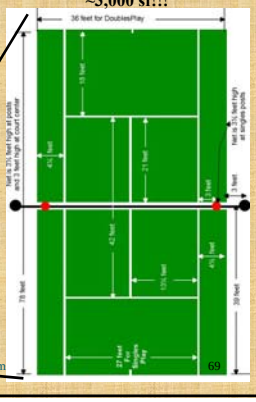
Intestine: Interesting Facts





Alessio Fasano, MD

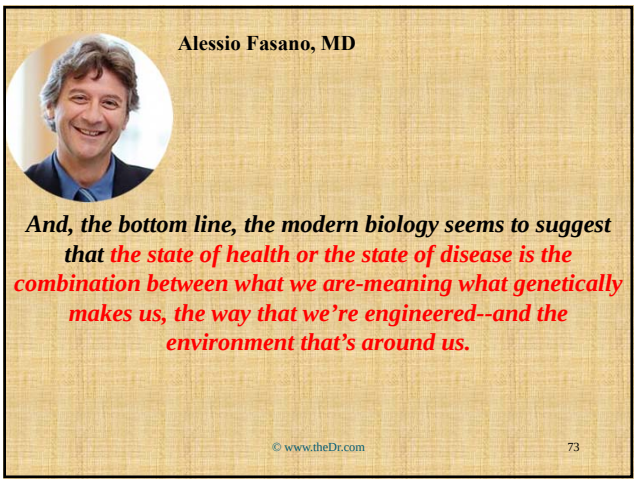
And, again, the simplistic interpretation is that we want to digest and absorb in an efficient way the foodstuff that comes through. But, also, you start to see the fact that it is a single-layer cell, that just underneath that, the most sophisticated and abundant immune component in our body. And, then you start to see there is a very sophisticated neuroendocrine network to control all this.

Alessio Fasano, MD

And, when you put all this together, when you connect the dots, you start to wonder, "Well, what else besides digesting and absorbing foodstuffs is the intestine doing"?

Alessio Fasano, MD

The key function is to interface with the environment and eventually exchange information, including molecules from the environment.


Alessio Fasano, MD
And, the bottom line, the modern biology seems to suggest that the state of health or the state of disease is the combination between what we are-meaning what genetically makes us, the way that we're engineered--and the environment that's around us.
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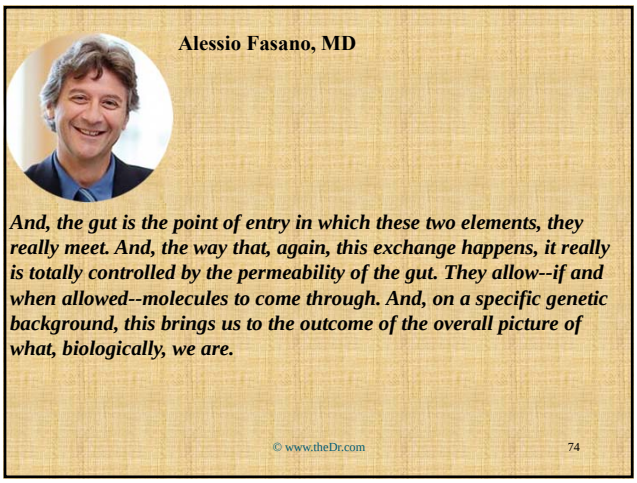
Alessio Fasano, MD
And, the gut is the point of entry in which these two elements, they really meet. And, the way that, again, this exchange happens, it really is totally controlled by the permeability of the gut. They allow--if and when allowed--molecules to come through. And, on a specific genetic background, this brings us to the outcome of the overall picture of what, biologically, we are.
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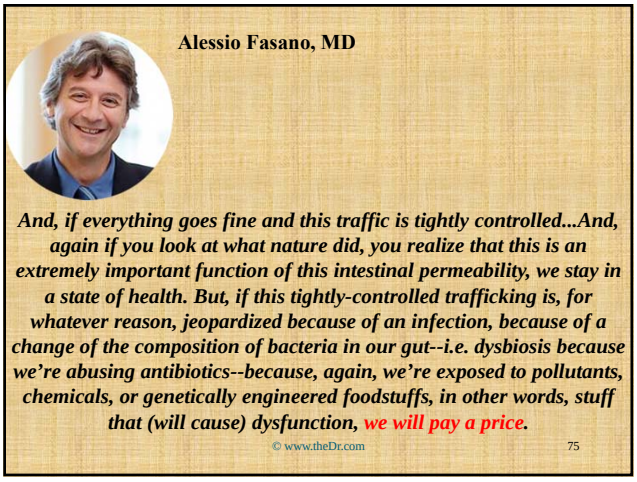
Alessio Fasano, MD
And, if everything goes fine and this traffic is tightly controlled...And, again if you look at what nature did, you realize that this is an extremely important function of this intestinal permeability, we stay in a state of health. But, if this tightly-controlled trafficking is, for whatever reason, jeopardized because of an infection, because of a change of the composition of bacteria in our gut--i.e. dysbiosis because we're abusing antibiotics--because, again, we're exposed to pollutants, chemicals, or genetically engineered foodstuffs, in other words, stuff that (will cause) dysfunction, we will pay a price.
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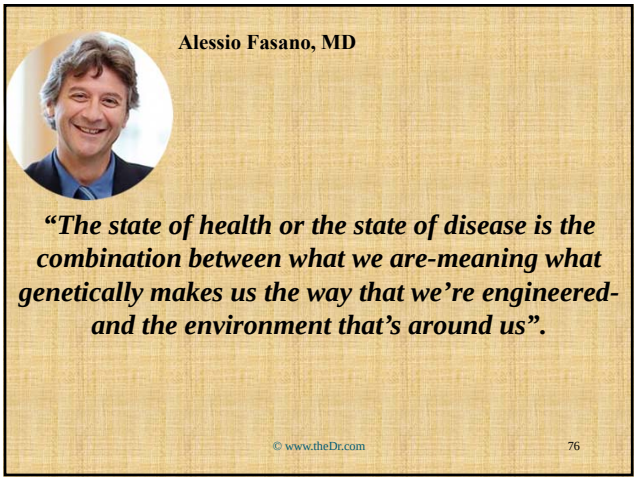
Alessio Fasano, MD
"The state of health or the state of disease is the combination between what we are-meaning what genetically makes us the way that we're engineered-and the environment that's around us".
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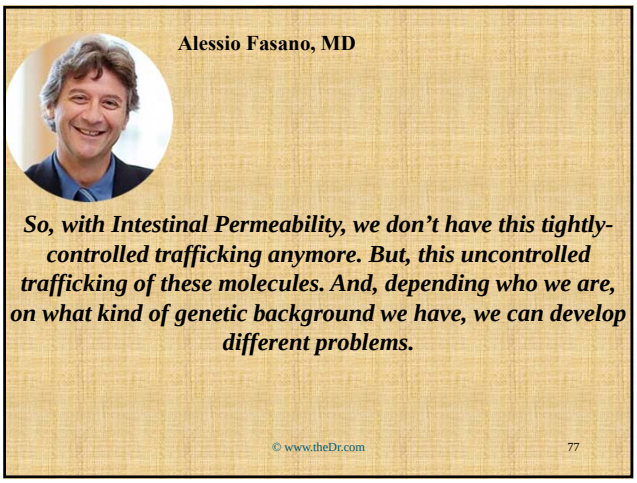
Alessio Fasano, MD
So, with Intestinal Permeability, we don't have this tightly-controlled trafficking anymore. But, this uncontrolled trafficking of these molecules. And, depending who we are, on what kind of genetic background we have, we can develop different problems.
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Alessio Fasano, MD
For example, we can develop food allergies if we are skewed to develop allergies. We can develop autoimmune diseases. We can develop chronic inflammation that can lead to a stroke, Alzheimer's, you name it, cancer. And, all this depends, again, on who we are genetically speaking, and what kind of environment is surrounding us.
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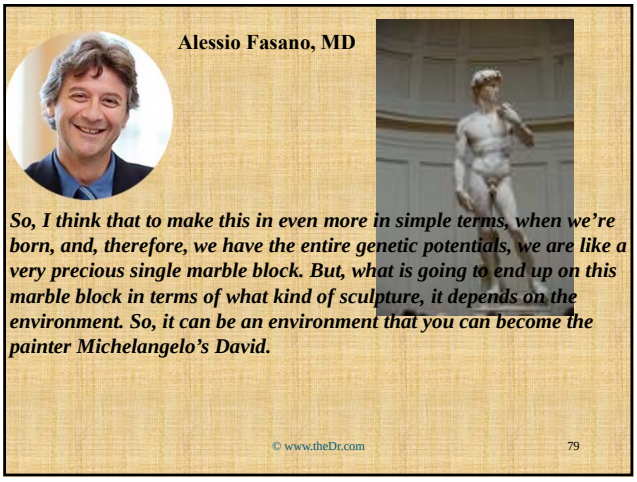
Alessio Fasano, MD
So, I think that to make this in even more in simple terms, when we're born, and, therefore, we have the entire genetic potentials, we are like a very precious single marble block. But, what is going to end up on this marble block in terms of what kind of sculpture, it depends on the environment. So, it can be an environment that you can become the painter Michelangelo's David.
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Alessio Fasano, MD
Or, you can be in a different environment and the outcome will not be so wonderful. And, that's pretty much the story.
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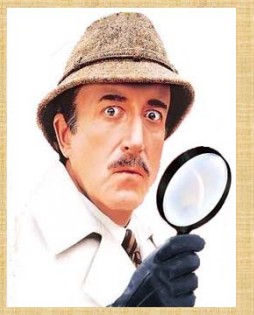
The result of the interface of our environment with our genes

 81

Premise #5

What is the Impact of Intestinal Permeability?



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Gastroenterol Clin N Am 37 (2008) 411–428

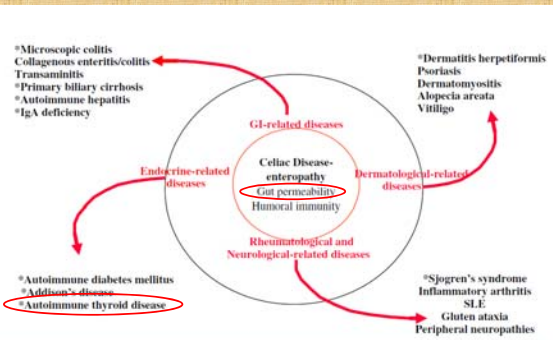


Fig. 1. Autoimmune and inflammatory diseases in relation to celiac disease. *Strongest associations.

 83

A Special Gift For You!

I'm going to send you
3 take-aways to help you implement this information!

Access to the 49 research articles used to create this presentation! plus

"The Conundrum of Gluten Sensitivity"

"Differentiating Gluten Related Disorders"

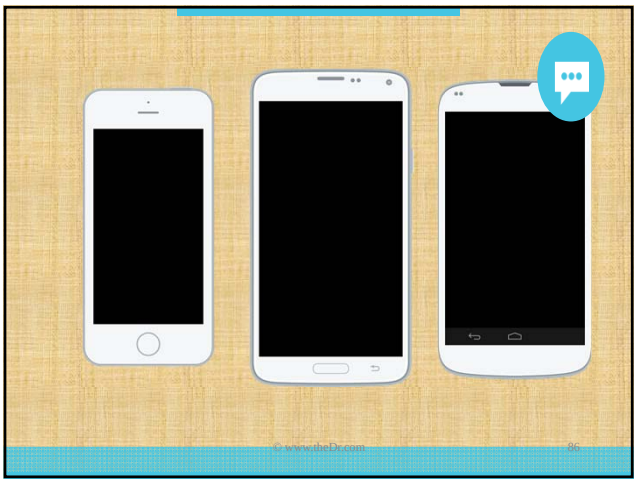
"US Perspective on gluten-related diseases"

Top two written by Dr. Thomas O'Bryan DC, CCN, DACBN

And 1 written by the Center for Celiac Research at Harvard

 84

Get Out Your Phones



- **Use the references:**
  - **For your personal review to increase your knowledge about the connection between food sensitivities and autoimmunity**
  - **Share them with your patients, family, friends and Loved Ones**
  - **Share with your peers, your Study Groups, and begin the discussion with them as to how these research topics may relate to your Practices**

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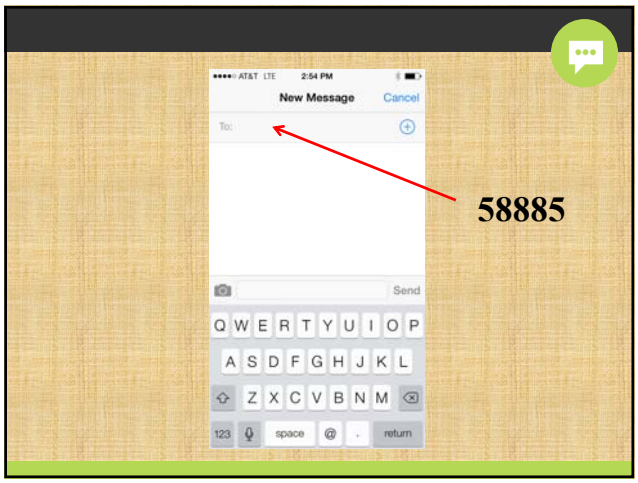
58885

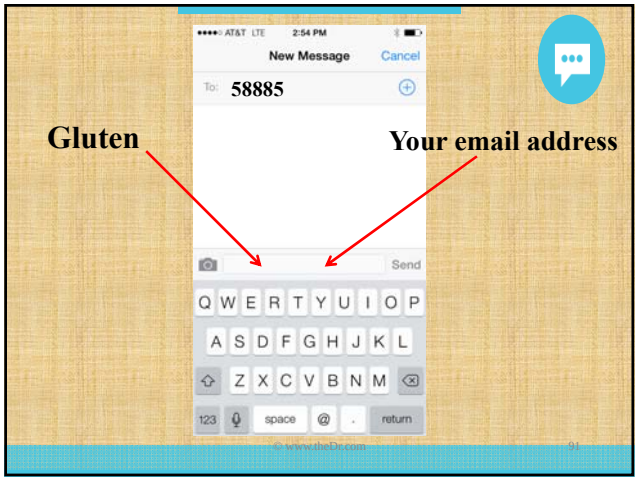


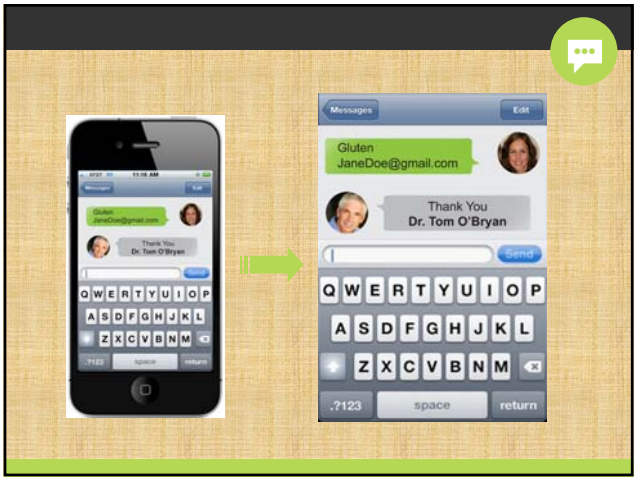
Text the message

Gluten

and your

Email Address





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to receive your
the References and Articles from me!

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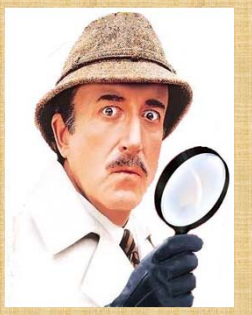
Premise #5
What is the Impact of Intestinal Permeability?



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Gastroenterol Clin N Am 37 (2008) 411–428

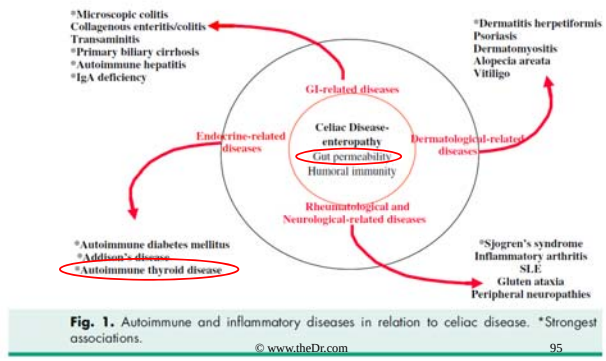
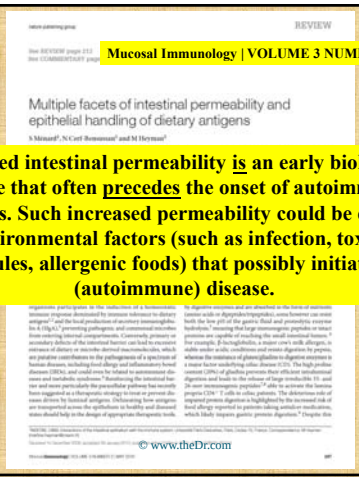


Fig. 1. Autoimmune and inflammatory diseases in relation to celiac disease. *Strongest associations.

 95



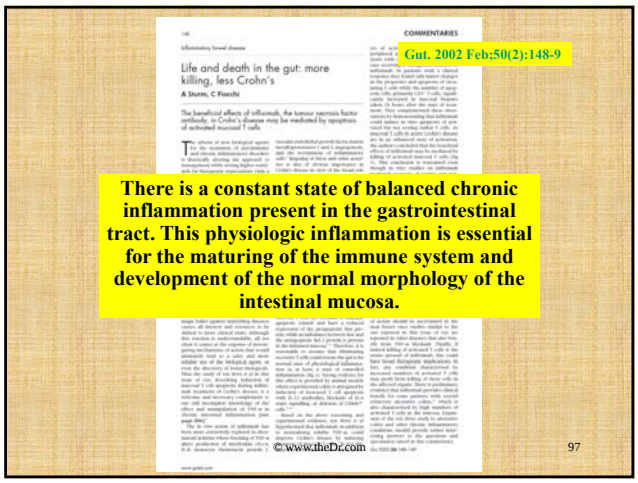
REVIEW

Mucosal Immunology | VOLUME 3 NUMBER 3 | MAY 2010

Multiple facets of intestinal permeability and epithelial handling of dietary antigens

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.

 96


COMMENTARIES
Life and death in the gut: more killing, less Crohn's
A Sturm, C Fiocchi
Gut. 2002 Feb;50(2):148-9
There is a constant state of balanced chronic inflammation present in the gastrointestinal tract. This physiologic inflammation is essential for the maturing of the immune system and development of the normal morphology of the intestinal mucosa.
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REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
The primary functions of the gastrointestinal tract have traditionally been perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis.
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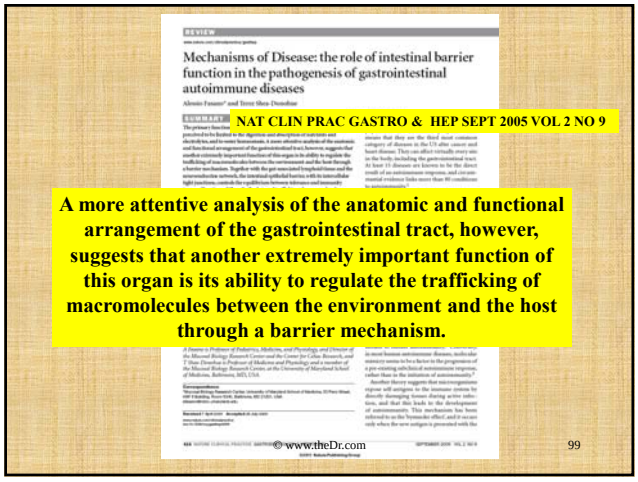
REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that 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.
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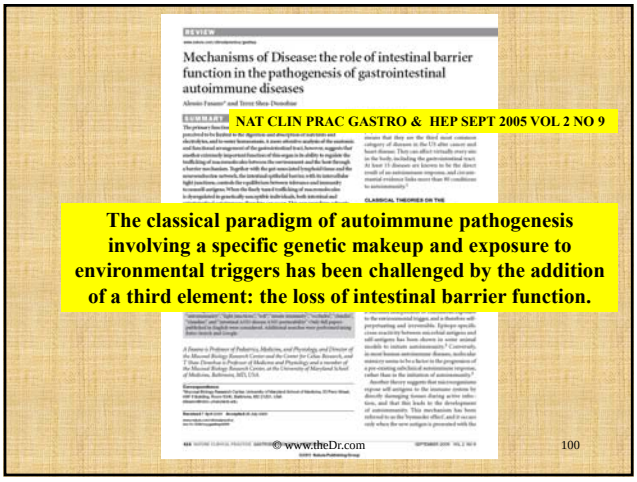
REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
The classical paradigm of autoimmune pathogenesis involving a specific genetic makeup and exposure to environmental triggers has been challenged by the addition of a third element: the loss of intestinal barrier function.
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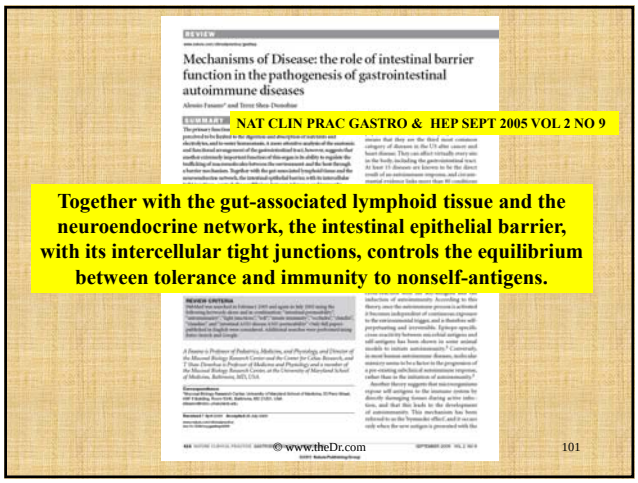
REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself-antigens.
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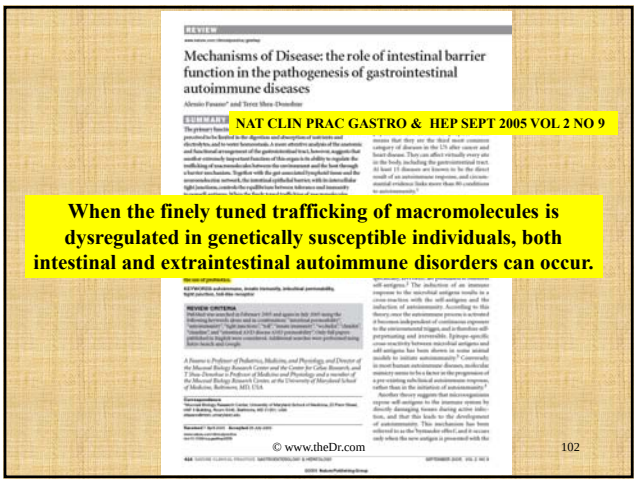
REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur.
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REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
The autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier function.
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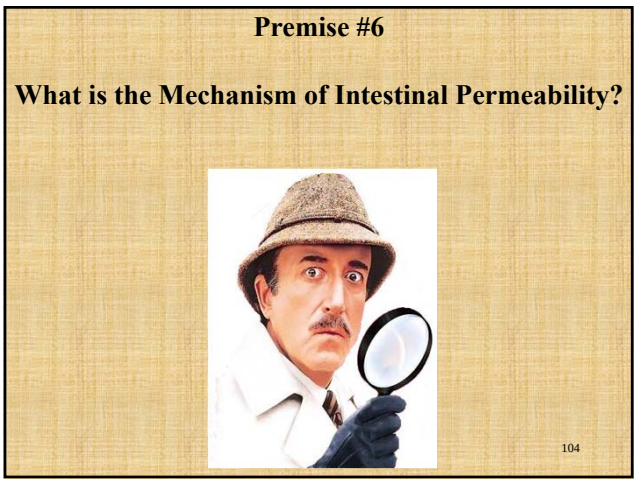

Premise #6
What is the Mechanism of Intestinal Permeability?
104

CLIN GASTRO AND HEP 2012;10:1096–1100

ADVANCES IN TRANSLATIONAL SCIENCE

Intestinal Permeability and Its Regulation by Zonulin: Diagnostic and Therapeutic Implications

Among the several potential intestinal stimuli that can trigger zonulin release, small intestinal exposure to bacteria (its byproduct LPS) and gluten are the 2 triggers that have been identified so far.

 105

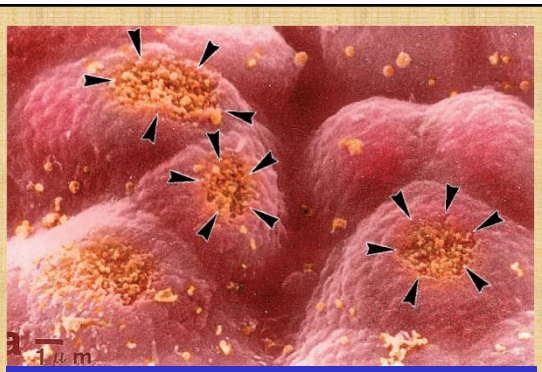
REVIEW

Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9

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.

 106



Identifying Antigenic Intestinal Permeability

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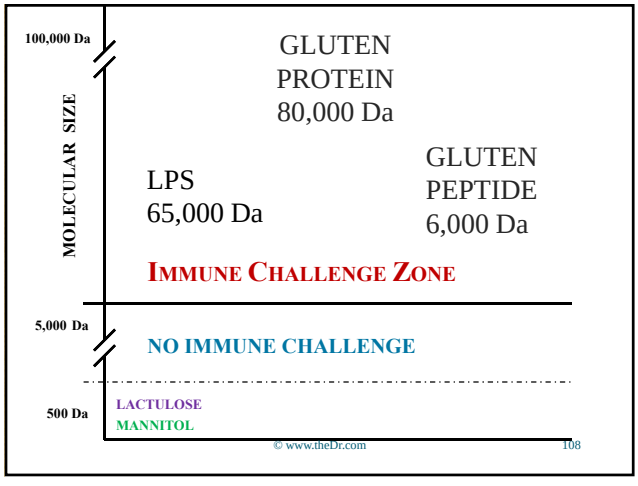

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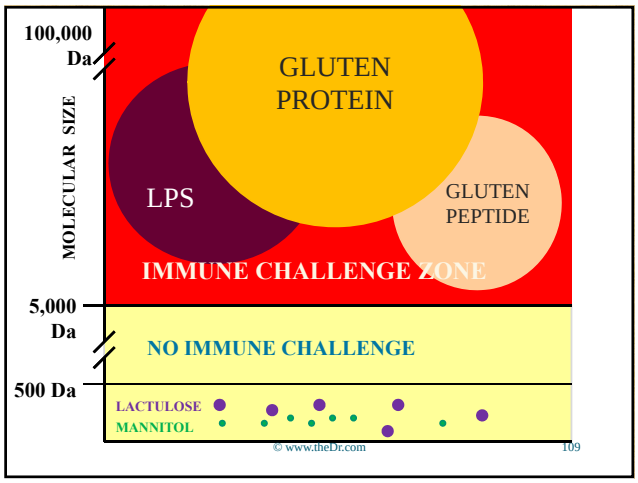
100,000 Da
MOLECULAR SIZE
GLUTEN PROTEIN
LPS
GLUTEN PEPTIDE
IMMUNE CHALLENGE ZONE
5,000 Da
NO IMMUNE CHALLENGE
500 Da
LACTULOSE
MANNITOL
© www.theDr.com
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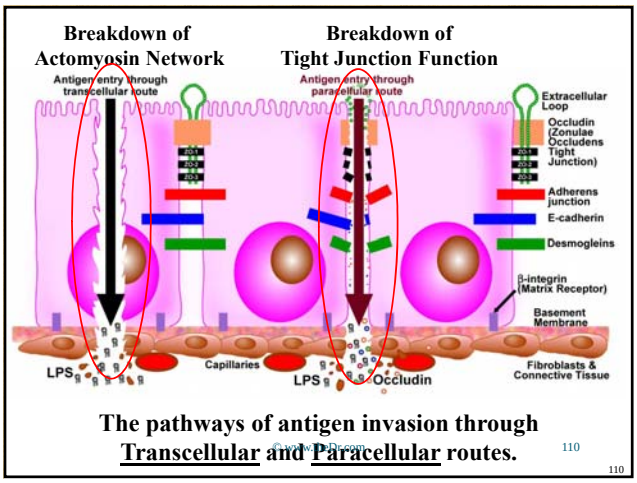
Breakdown of Actomyosin Network
Breakdown of Tight Junction Function
Antigen entry through transcellular route
Antigen entry through paracellular route
Extracellular Loop
Occludin (Zonulae Occludens Tight Junction)
Adherens junction
E-cadherin
Desmogleins
β-integrin (Matrix Receptor)
Basement Membrane
LPS
Capillaries
LPS
Occludin
Fibroblasts & Connective Tissue
The pathways of antigen invasion through Transcellular and Paracellular routes.
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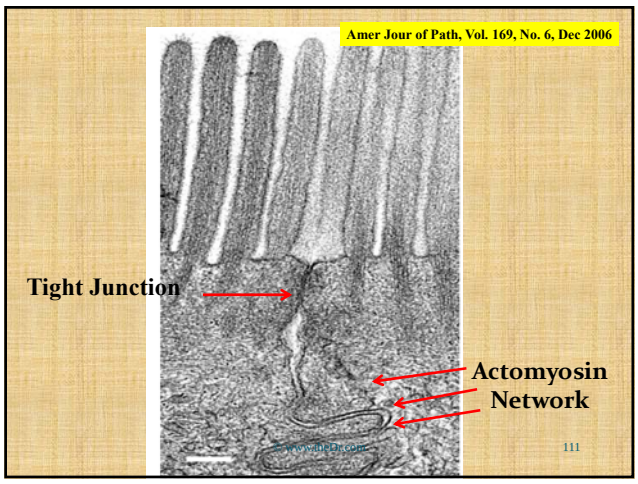
110


Amer Jour of Path, Vol. 169, No. 6, Dec 2006
Tight Junction
Actomyosin Network
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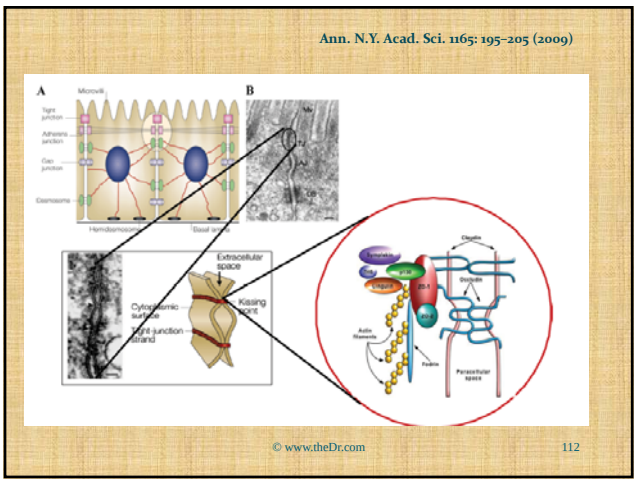
Ann. N.Y. Acad. Sci. 1165: 195–205 (2009)
A
B
Extracellular space
Kissing point
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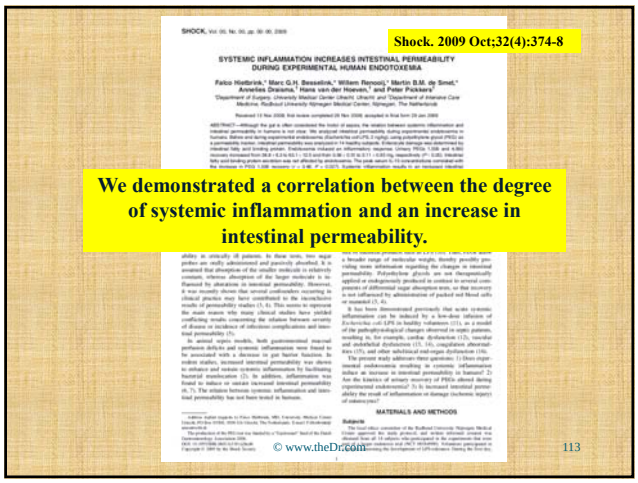
SHOCK, Vol. 00, No. 00, pp. 00–00, 2009
SYSTEMIC INFLAMMATION INCREASES INTESTINAL PERMEABILITY DURING EXPERIMENTAL HUMAN ENDOTOXEMIA
Shock. 2009 Oct;32(4):374-8
We demonstrated a correlation between the degree of systemic inflammation and an increase in intestinal permeability.
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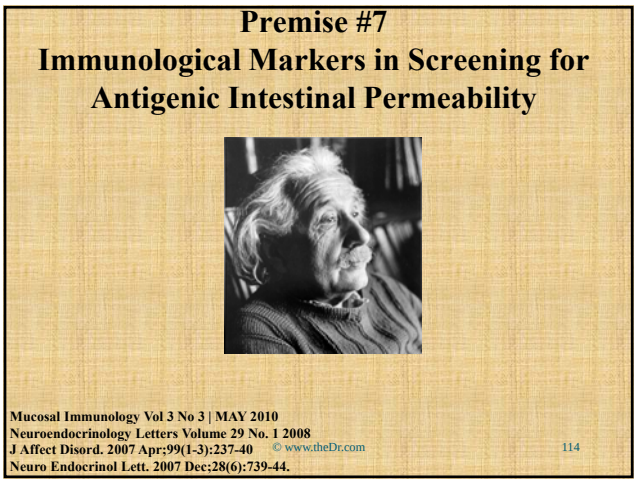
Premise #7
Immunological Markers in Screening for Antigenic Intestinal Permeability
Mucosal Immunology Vol 3 No 3 | MAY 2010
Neuroendocrinology Letters Volume 29 No. 1 2008
J Affect Disord. 2007 Apr;99(1-3):237-40
Neuro Endocrinol Lett. 2007 Dec;28(6):739-44.
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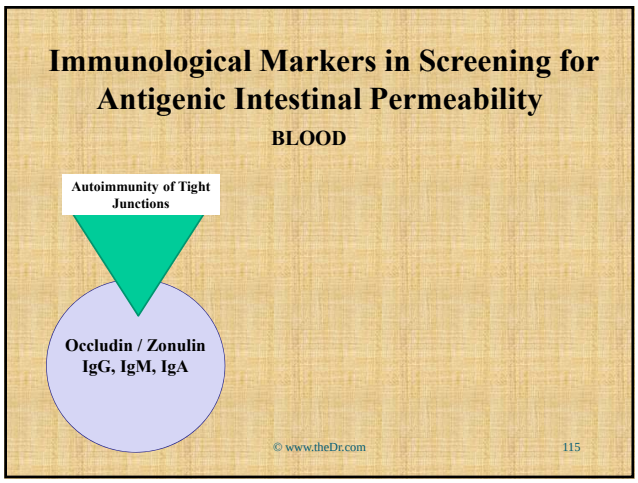
Immunological Markers in Screening for Antigenic Intestinal Permeability
BLOOD
Autoimmunity of Tight Junctions
Occludin / Zonulin
IgG, IgM, IgA
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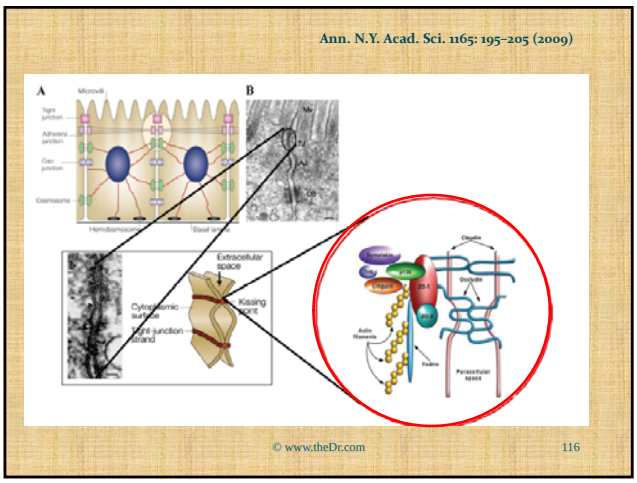
Ann. N.Y. Acad. Sci. 1165: 195–205 (2009)
A
B
Extracellular space
Kissing point
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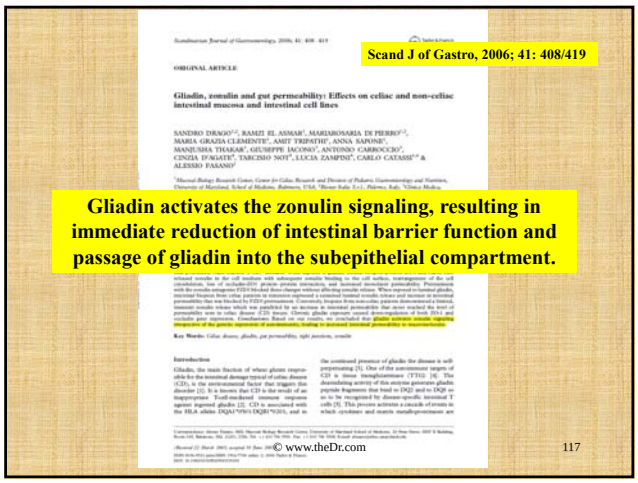
Scand J of Gastro, 2006; 41: 408/419
ORIGINAL ARTICLE
Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines
Gliadin activates the zonulin signaling, resulting in immediate reduction of intestinal barrier function and passage of gliadin into the subepithelial compartment.
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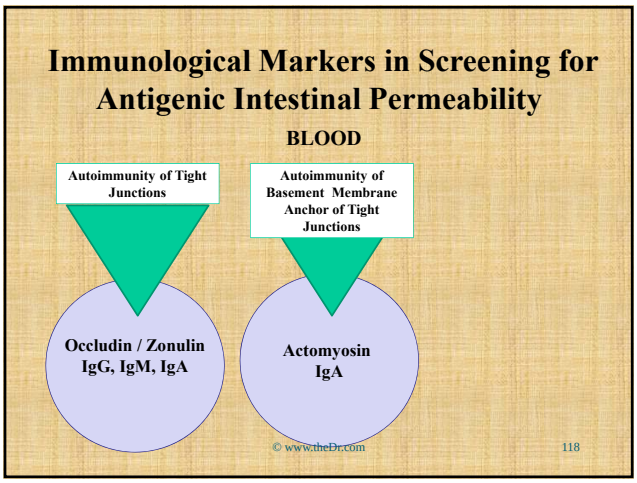
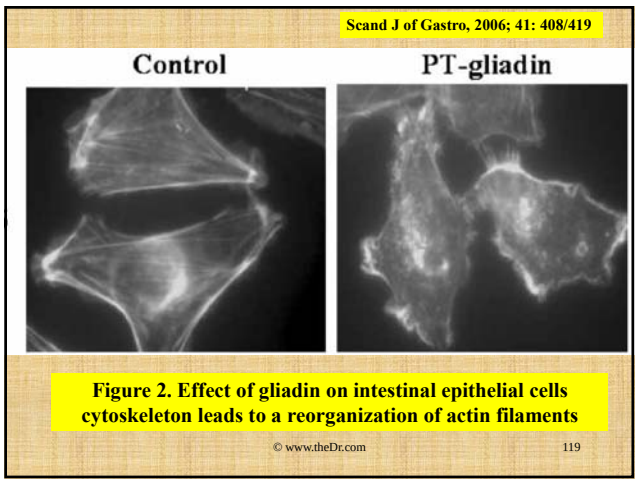

Immunological Markers in Screening for Antigenic Intestinal Permeability
BLOOD
Autoimmunity of Tight Junctions
Autoimmunity of Basement Membrane Anchor of Tight Junctions
Occludin / Zonulin IgG, IgM, IgA
Actomyosin IgA
© www.theDr.com
118


Scand J of Gastro, 2006; 41: 408/419
Control
PT-gliadin
Figure 2. Effect of gliadin on intestinal epithelial cells cytoskeleton leads to a reorganization of actin filaments
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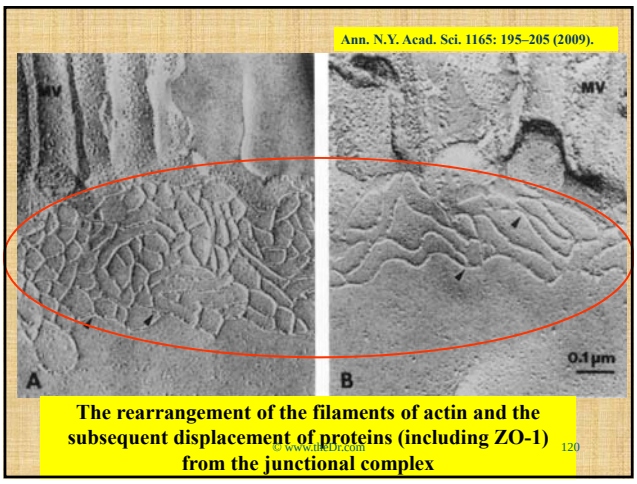
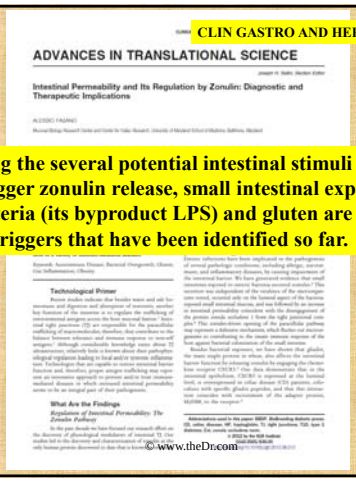
119


Ann. N.Y. Acad. Sci. 1165: 195–205 (2009).
MV
MV
A
B
0.1 µm
The rearrangement of the filaments of actin and the subsequent displacement of proteins (including ZO-1) from the junctional complex
© www.theDr.com
120

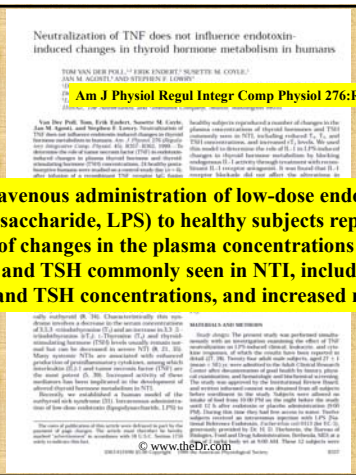
CLIN GASTRO AND HEP 2012;10:1096–1100


ADVANCES IN TRANSLATIONAL SCIENCE

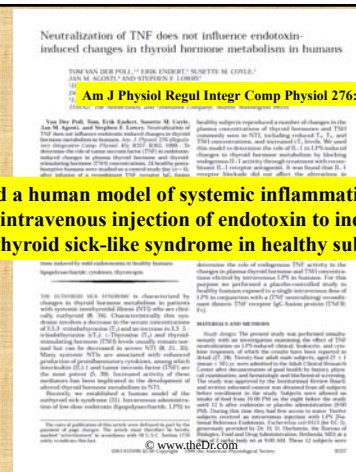
Intestinal Permeability and Its Regulation by Zonulin: Diagnostic and Therapeutic Implications

Among the several potential intestinal stimuli that can trigger zonulin release, small intestinal exposure to bacteria (its byproduct LPS) and gluten are the 2 triggers that have been identified so far.

Am J Physiol Regul Integr Comp Physiol 276:R357-R362, 1999.

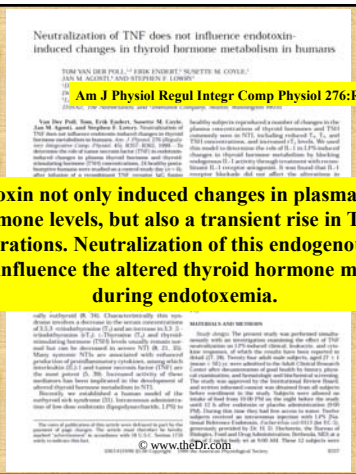

Neutralization of TNF does not influence endotoxin-induced changes in thyroid hormone metabolism in humans

Intravenous administration of low-dose endotoxin (lipopolysaccharide, LPS) to healthy subjects reproduced a number of changes in the plasma concentrations of thyroid hormones and TSH commonly seen in NTI, including reduced T4, T3, and TSH concentrations, and increased rT3 levels.


Neutralization of TNF does not influence endotoxin-induced changes in thyroid hormone metabolism in humans

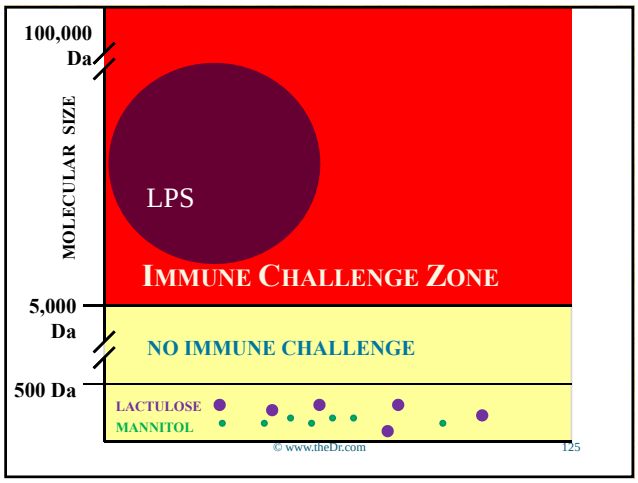
Am J Physiol Regul Integr Comp Physiol 276:R357-R362, 1999.

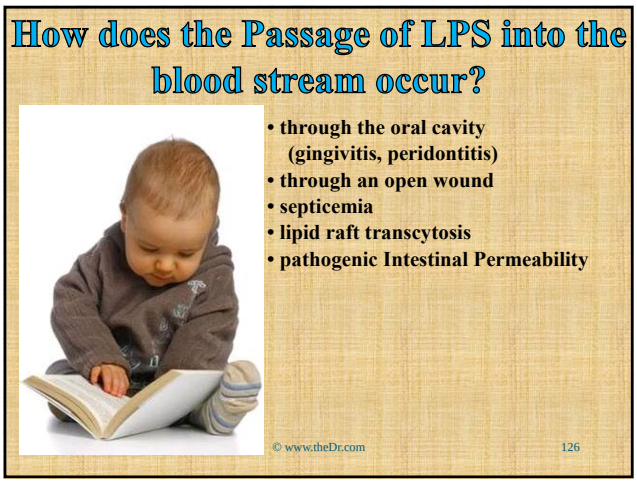
We used a human model of systemic inflammation elicited by intravenous injection of endotoxin to induce a euthyroid sick-like syndrome in healthy subjects.


Neutralization of TNF does not influence endotoxin-induced changes in thyroid hormone metabolism in humans

Am J Physiol Regul Integr Comp Physiol 276:R357-R362, 1999.

Endotoxin not only induced changes in plasma thyroid hormone levels, but also a transient rise in TNF-a concentrations. Neutralization of this endogenous TNF-a did not influence the altered thyroid hormone metabolism during endotoxemia.


100,000 Da
MOLECULAR SIZE
LPS
IMMUNE CHALLENGE ZONE
5,000 Da
NO IMMUNE CHALLENGE
500 Da
LACTULOSE
MANNITOL
© www.theDr.com
125


How does the Passage of LPS into the blood stream occur?
• through the oral cavity (gingivitis, peridontitis)
• through an open wound
• septicemia
• lipid raft transcytosis
• pathogenic Intestinal Permeability
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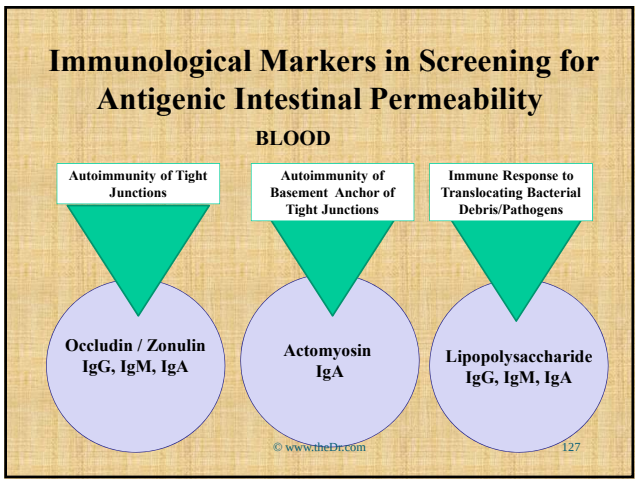
126


Immunological Markers in Screening for Antigenic Intestinal Permeability
BLOOD
Autoimmunity of Tight Junctions
Autoimmunity of Basement Anchor of Tight Junctions
Immune Response to Translocating Bacterial Debris/Pathogens
Occludin / Zonulin IgG, IgM, IgA
Actomyosin IgA
Lipopolysaccharide IgG, IgM, IgA
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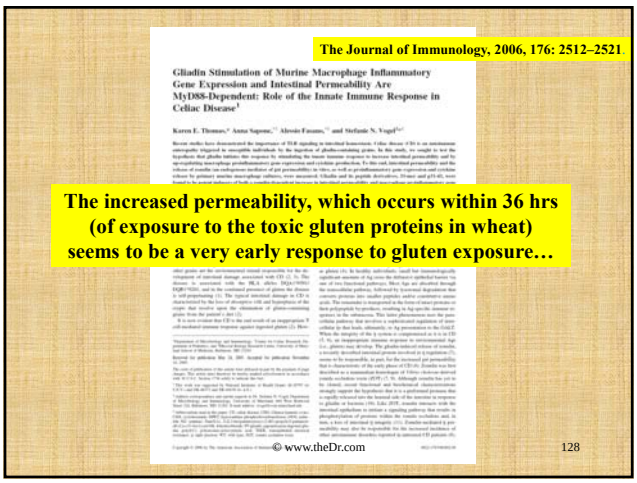
127


The Journal of Immunology, 2006, 176: 2512–2521.
Gliadin Stimulation of Murine Macrophage Inflammatory Gene Expression and Intestinal Permeability Are MyD88-Dependent: Role of the Innate Immune Response in Celiac Disease
The increased permeability, which occurs within 36 hrs (of exposure to the toxic gluten proteins in wheat) seems to be a very early response to gluten exposure…
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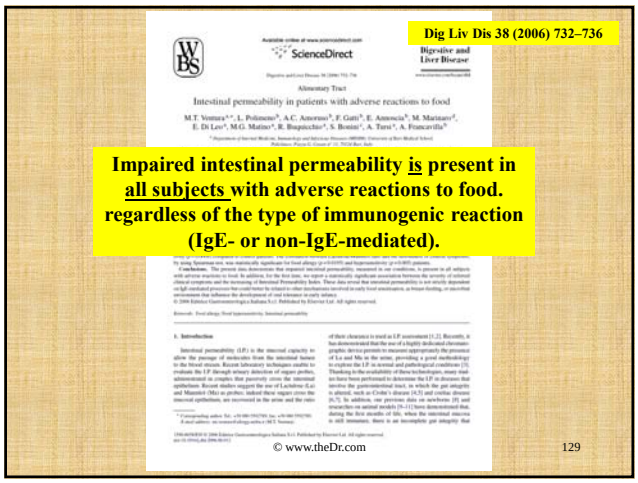
Dig Liv Dis 38 (2006) 732–736
ScienceDirect
Digestive and Liver Disease
Intestinal permeability in patients with adverse reactions to food
Impaired intestinal permeability is present in all subjects with adverse reactions to food. regardless of the type of immunogenic reaction (IgE- or non-IgE-mediated).
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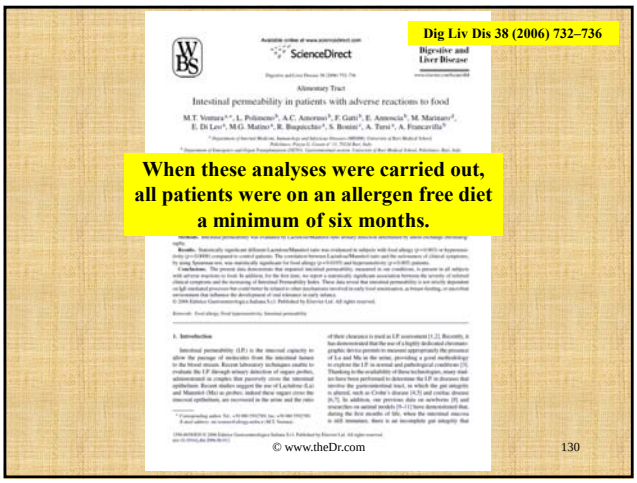
129


Dig Liv Dis 38 (2006) 732–736
ScienceDirect
Digestive and Liver Disease
Intestinal permeability in patients with adverse reactions to food
When these analyses were carried out, all patients were on an allergen free diet a minimum of six months.
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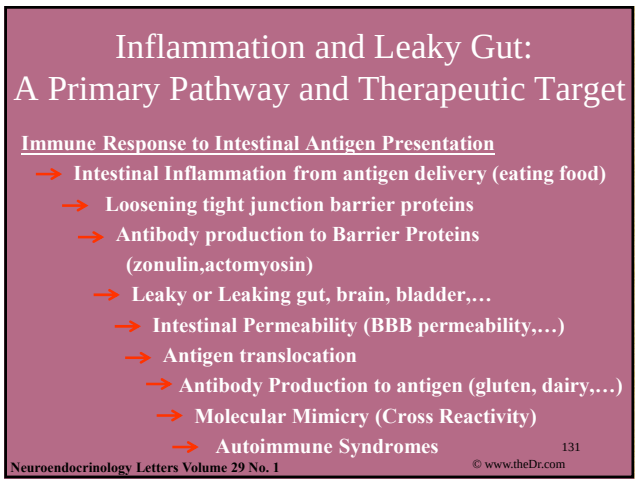
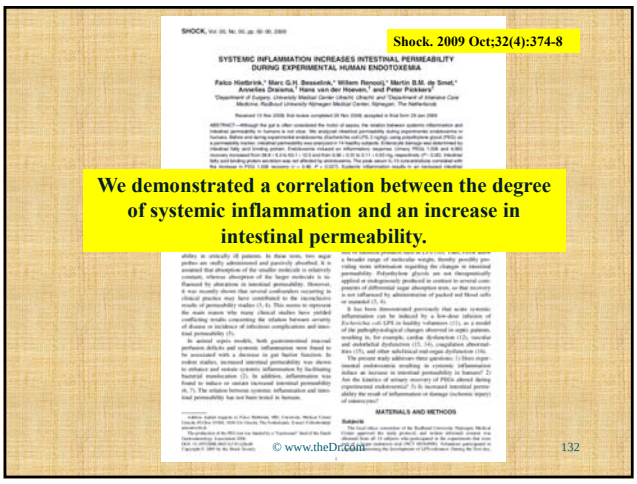
130


Inflammation and Leaky Gut:
A Primary Pathway and Therapeutic Target
Immune Response to Intestinal Antigen Presentation
Intestinal Inflammation from antigen delivery (eating food)
Loosening tight junction barrier proteins
Antibody production to Barrier Proteins (zonulin,actomyosin)
Leaky or Leaking gut, brain, bladder,…
Intestinal Permeability (BBB permeability,…)
Antigen translocation
Antibody Production to antigen (gluten, dairy,…)
Molecular Mimicry (Cross Reactivity)
Autoimmune Syndromes
131
Neuroendocrinology Letters Volume 29 No. 1
© www.theDr.com


Shock. 2009 Oct;32(4):374-8
SYSTEMIC INFLAMMATION INCREASES INTESTINAL PERMEABILITY DURING EXPERIMENTAL HUMAN ENDOTOXEMIA
We demonstrated a correlation between the degree of systemic inflammation and an increase in intestinal permeability.
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132

Physiol Rev 91: 151–175, 2011

Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer

ALESSIO FASANO

Once gluten is removed from the diet, serum zonulin levels decrease, the intestine resumes its baseline barrier function, the autoantibody titers are normalized, the autoimmune process shuts off and, consequently, the intestinal damage (that represents the biological outcome of the autoimmune process) heals completely.

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Premise #7
How Might The Impact of Intestinal Permeability Present?

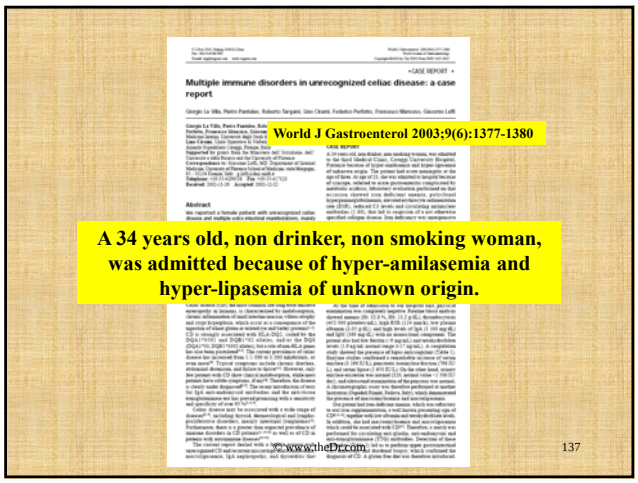
135

CASE STUDY #1

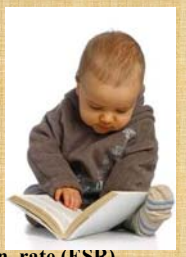
Recurrent Miscarriages and Autoimmune Diseases

World J Gastroenterol 2003;9(6):1377-1380

136
136



Health History (since age 3)



- acute meningitis
- syncope, due to acute gastroenteritis complicated by metabolic acidosis
- recurrent iron deficient anemia,
- polyclonal hypergammaglobulinemia,
- recurrent elevated erythrocyte sedimentation rate (ESR),
- reduced C3 levels and circulating antinuclear antibodies (1:80) that led to suspicion of a not otherwise specified collagen disease

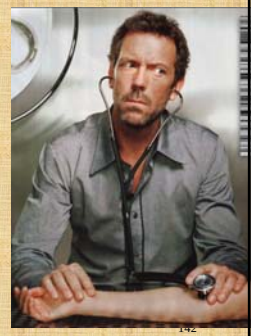
World J Gastroenterol 2003;9(6):1377-1380

During admission because of the second abortion, a thorough investigation was performed that was negative for potential causes of fetal demise, including:

- fasting glucose,
- basal FSH, LH and estradiol levels on day 3 of a natural cycle,
- TSH and prolactin levels,
- antinuclear antibodies,
- antibodies against infectious agents,
- hysterosalpingography and genetic karyotyping of the couple

On that occasion, she was found to have:

- hyperamilasemia and hyperlipasemia,
- anemia,
- thrombocytosis,
- high ESR,
- low plasma albumin
- high levels of IgA and IgM.
- low ferritin and tetrahydrofolate levels
- A coagulation study = + presence of lupus anticoagulant
- elevated anti-thyroglobulin and anti-b2-glicoprotein-1 antibodies



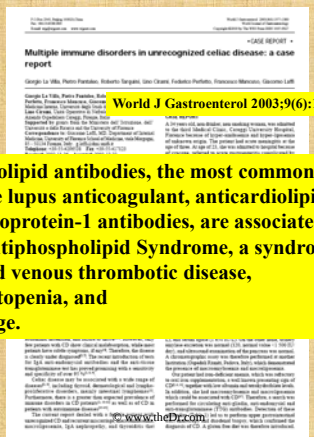
142

World J Gastroenterol

On that occasion, she also was found to have:

- Urinalysis showed glomerular proteinuria,
- microscopic hematuria,
- hyaline and granular casts
- An IgA Nephropathy

World J Ga
2003;9(6):13

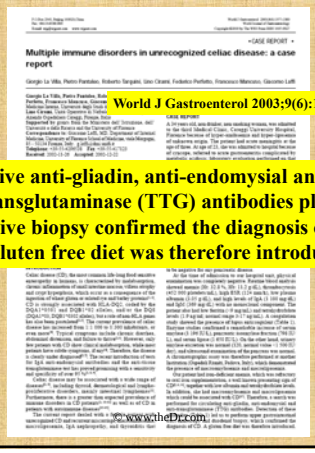


Multiple immune disorders in unrecognized celiac disease: a case report

World J Gastroenterol 2003;9(6):1377-1380

Antiphospholipid antibodies, the most commonly detected of which are lupus anticoagulant, anticardiolipin and anti-b2-glycoprotein-1 antibodies, are associated with the so-called Antiphospholipid Syndrome, a syndrome of:
-arterial and venous thrombotic disease,
-thrombocytopenia, and
-fetal wastage.

144


Multiple immune disorders in unrecognized celiac disease: a case report

World J Gastroenterol 2003;9(6):1377-1380

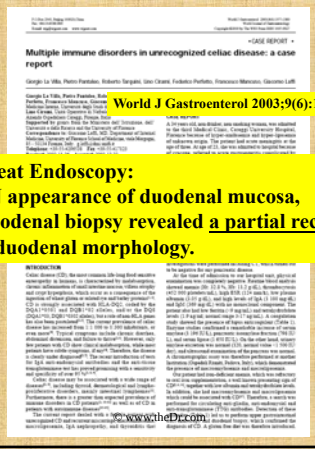
Positive anti-gliadin, anti-endomysial and anti-transglutaminase (TTG) antibodies plus a positive biopsy confirmed the diagnosis of CD. A gluten free diet was therefore introduced.


Multiple immune disorders in unrecognized celiac disease: a case report

World J Gastroenterol 2003;9(6):1377-1380

After <u>six months</u> of controlled gluten free diet:

- body weight increased 12 kg
- laboratory rechecks demonstrated normalization of serum amylase, serum lipase and all immunoglobulin levels antigliadin, anti-b2-glicoprotein-1, anti-thyroglobulin antibodies were no longer detectable but <u>antiendomysial antibodies were still present</u>.
-Due to the persistence of proteinuria (2.3 g/day), microscopic hematuria and hyaline and granular casts, a kidney biopsy was positive for IgA nephropathy


Multiple immune disorders in unrecognized celiac disease: a case report

World J Gastroenterol 2003;9(6):1377-1380

Repeat Endoscopy:
- EN appearance of duodenal mucosa,
- Duodenal biopsy revealed <u>a partial recovery</u> of duodenal morphology.

Recommendation to the patient???
"You're improving. Stay the course"
"But Dr. It's been SIX MONTHS"
"STAY THE COURSE"


Multiple immune disorders in unrecognized celiac disease: a case report

World J Gastroenterol 2003;9(6):1377-1380

After 24 months of gluten-free diet:
-complete recovery of villous architecture.
-Renal function further improved and proteinuria markedly decreased.
-Amylase, lipase, and immunoglobulin levels were within the normal range.
Anti-b2-glicoprotein-1 undetectable,
-anti-thyroglobulin undetectable
-antigliadin, antiendomysial and anti-TTG undetectable
-coagulation study was normal

 149

Syncope
Acute gastroenteritis
Metabolic Acidosis
Anemia
Hypergammaglobulinemia
Elevated ESR
Positive ANA, Positive RF, Positive Thyroid Abs
Positive Liver Enzymes
Low Ferritin, Low Tetrahydrofolate
Total Villous Atrophy and Celiac Disease
Positive Pancreatic Hypersecretion
Positive Thyroid Antibodies
IgA Nephropathy
Loss of 2 pregnancies

CAN SUPPOSEDLY GOOD FOODS REALLY DO THIS TO ME???
WITHIN 2 YEARS!

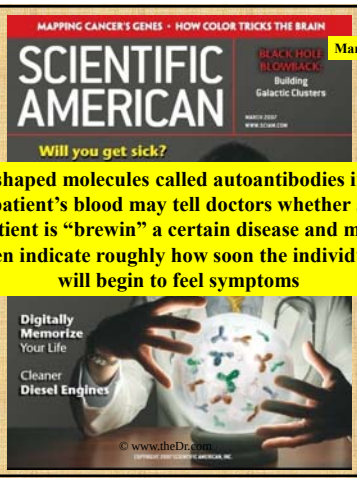
150

Premise #8
When Does Autoimmune Disease Begin?

 151

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

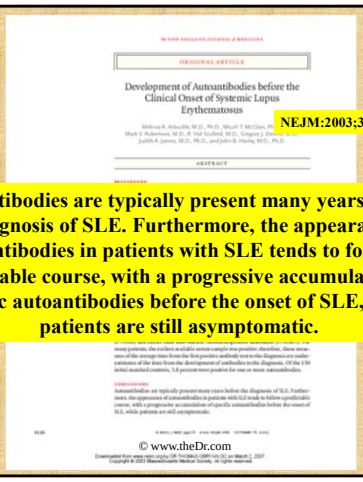
 152



March 2007

Y-shaped molecules called autoantibodies in a patient's blood may tell doctors whether a patient is "brewin" a certain disease and may even indicate roughly how soon the individual will begin to feel symptoms

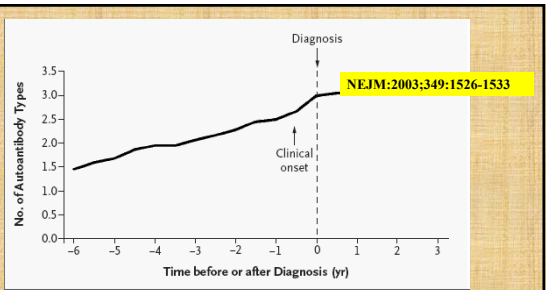
153



NEJM:2003;349:1526-1533

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.

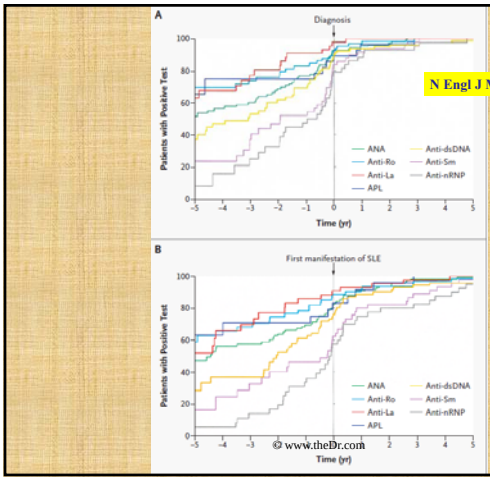
154



NEJM:2003;349:1526-1533

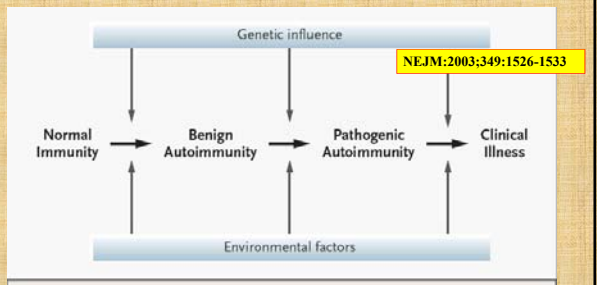
Figure 2. Accumulation of Systemic Lupus Erythematosus Autoantibodies.
The curve shows the average number of types of autoantibody in relation to the time of diagnosis of systemic lupus erythematosus. Seven autoantibodies were evaluated, which bind cellular constituents (antinuclear antibodies), Ro, 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.

155



N Engl J Med 2003;349:1526-33.

156



NEJM:2003;349:1526-1533

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.

 157

Are You Developing an Autoimmune Disease Years Before Symptoms?

Prof. Yehuda Shoenfeld, MD, FRCP

- **published more than 1,700 papers in journals such as the New England Journal of Medicine, Nature, The Lancet, the Proceedings of the National Academy of Sciences of the United States, the Journal of Clinical Investigation, the Journal of Immunology, the Journal Blood…**
- **written more than 350 chapters in books, and has authored and edited 25 books**
- **organized over 20 international congresses in autoimmunity**
- **He has educated a long list of students, over 25 students, who now hold heads of departments and institutes in medical research.**

 158

Dr. O'Bryan: So, Professor, the question is, "When did they get lupus?" And our position has been as clinicians, the mechanism began many, many years before the symptoms ever showed.

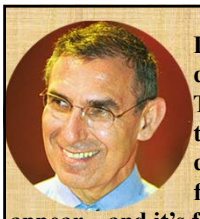
Is that the rationale for this world of predictive autoimmunity, to begin to identify these antibodies long before there are symptoms that have developed?

 159

Dr. Shoenfeld: You have summarized it precisely. What you said has several consequences and take-home messages.

Number one is that autoimmune diseases have a long incubation time. There was this wonderful article in the well-known journal called the *New England Journal of Medicine* in which it has been found that the markers, as well as those missiles—the autoantibodies—have been detected in the blood of the patients years before the disease becomes overt clinically, the patient had, indeed, symptoms of either pains in their joints, fever, or increase in the organs due to inflammation and so forth. Sometimes the incubation time may take even 40 years.

 160



Dr. Shoenfeld: We have an autoimmune disease called primary biliary cirrhosis. The disease affects women 20 times more than men, like many of the autoimmune diseases which are more prevalent among females. However, the diseases do appear—and it's frequent—at the sixth and even seventh decade. Yet the marker, the same autoantibody, the missile, that is so specific that if you detect it incidentally, even 20 or 30 years ago, you can assure the younger woman that when she will reach the age of 60 or 70, she will develop this devastating condition called primary biliary cirrhosis.

 161

Dr. Shoenfeld: So it means that you need to have the missiles, the autoantibodies, in the blood for a long time before the damage accumulates in such a way that the disease becomes overt. This is called prediction of autoimmunity.

In the past, when students have asked me, "What would you do with a completely healthy subject in which you found such antibodies or autoantibodies like anti-DNA antibodies?" Or let's say for the sake of primary biliary cirrhosis, what is called anti-PBH antibodies. I would have said, "Leave the healthy subject alone. We treat patients. But we don't treat inflammation of the lab, laboratoritis."

 162

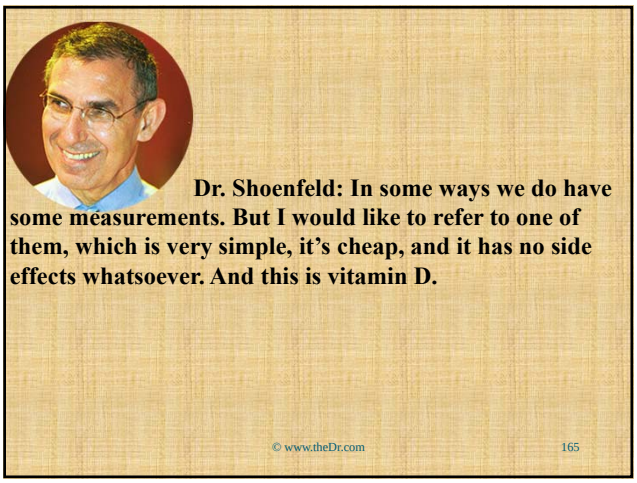
Dr. Shoenfeld: Yet what we have learned today is that we should not neglect this incidental finding. And we should follow the patient for a long time because those who have this marker in their blood, they have a greater chance to develop a clinical disease.

Prediction is important, but it has meaning only if you can help the patient. The question is even ethical. What would you gain by just saying to the patient, "Listen, in 20 years you will develop the disease." It's unethical.

 163

Dr. Shoenfeld: So we are entering into the era, not only of prediction, but we have to think about prevention. This means that we need to have drugs, research, or means by which we can clean, suppress the production of those deleterious autoantibodies before the damage will accumulate so that the patient will be clinically overt

 164


Dr. Shoenfeld: In some ways we do have some measurements. But I would like to refer to one of them, which is very simple, it's cheap, and it has no side effects whatsoever. And this is vitamin D.
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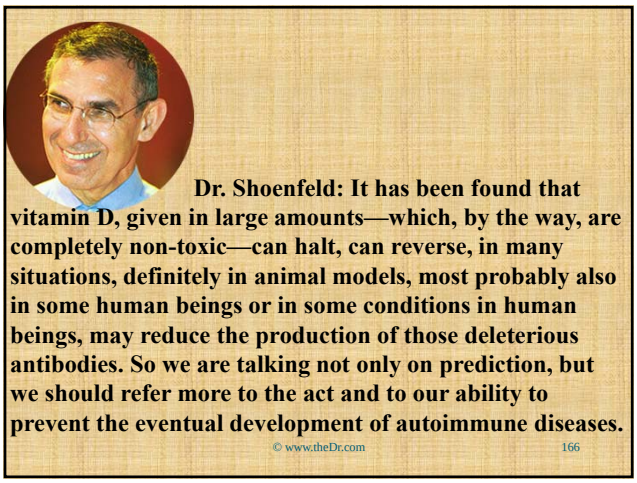
Dr. Shoenfeld: It has been found that vitamin D, given in large amounts—which, by the way, are completely non-toxic—can halt, can reverse, in many situations, definitely in animal models, most probably also in some human beings or in some conditions in human beings, may reduce the production of those deleterious antibodies. So we are talking not only on prediction, but we should refer more to the act and to our ability to prevent the eventual development of autoimmune diseases.
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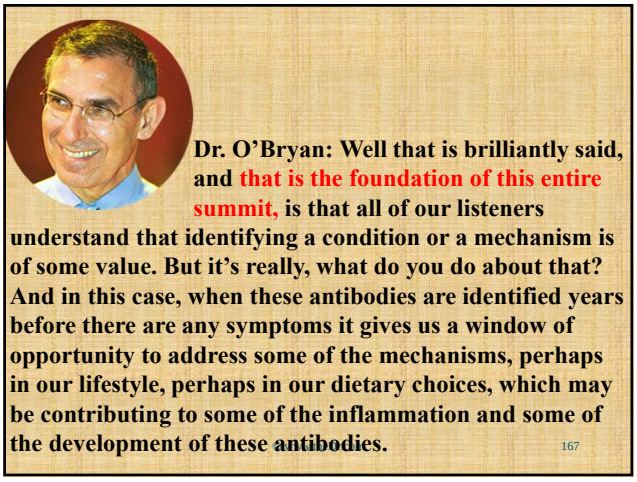
Dr. O'Bryan: Well that is brilliantly said, and that is the foundation of this entire summit, is that all of our listeners understand that identifying a condition or a mechanism is of some value. But it's really, what do you do about that? And in this case, when these antibodies are identified years before there are any symptoms it gives us a window of opportunity to address some of the mechanisms, perhaps in our lifestyle, perhaps in our dietary choices, which may be contributing to some of the inflammation and some of the development of these antibodies.
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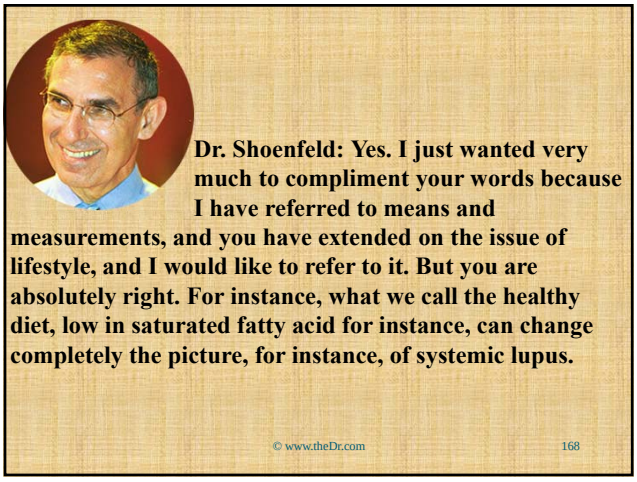
Dr. Shoenfeld: Yes. I just wanted very much to compliment your words because I have referred to means and measurements, and you have extended on the issue of lifestyle, and I would like to refer to it. But you are absolutely right. For instance, what we call the healthy diet, low in saturated fatty acid for instance, can change completely the picture, for instance, of systemic lupus.
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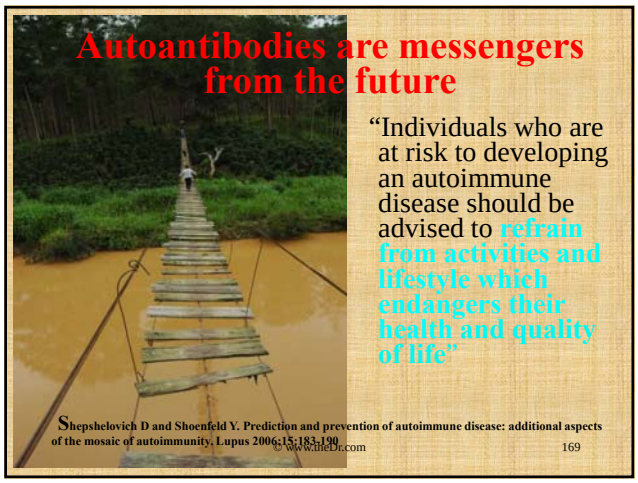

Predictivity of Autoimmunity

Systemic autoimmune diseases

Disease	Antibodies	PPV	Years before Clinical Dx
SLE	RNP, Sm, dsDNA, Ro, La, and cardioliptin antibodies	94-100%	7-10
Scleroderma	Anti-centromere antibodies Anti-topoisomerase I antibodies	100%	11
RA	Rheumatoid factor Anti-cyclic citrullinated peptide	52-88% 97%	14
Sjögren's	Anti-Ro and anti-La antibodies	73%	5
1º antiphospholipid syndrome	Anti-nucleosome antibodies Anti-cardiolipin antibodies Anti-β2 gylcoprotien 1	100%	11

Shoenfeld Y, Blank M, Abu-Shakra M, et al. The Mosaic of autoimmunity: prediction, autoantibodies, and therapy in autoimmune disease – 2008. *IMAJ* 2008;10:13-19

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Predictivity of Autoimmunity

Organ specific autoimmune diseases

Disease	Antibodies	PPV	Years before Clinical Dx
Hashimoto's thyroiditis *	Anti-thyroid peroxidase antibodies (postpartum)	92%	7-10
Primary biliary cirrhosis *	Anti-mitochondrial antibodies	95%	25
Type I diabetes**	Pancreatic islet cell, insulin, 65 kD glutamic acid decarboxylase, tyrosine phosphatase-like protein	43, 55, 42, and 29%	14

* Shoenfeld Y, Blank M, Abu-Shakra M, et al. The Mosaic of autoimmunity: prediction, autoantibodies, and therapy in autoimmune disease – 2008. *IMAJ* 2008;10:13-19

** Lindberg B, Ivarsson SA, et al. Islet autoantibodies in cord blood from children who developed Type I (insulin-dependent) diabetes mellitus before 15 years of age *Diabetologia* 1999 42: 181–187

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Predictivity of Autoimmunity

Organ specific autoimmune diseases

Disease	Antibodies	PPV	Years before Clinical Dx
Addison's disease	Adrenal cortex antibodies	70	10
Crohn's colitis	Anti- *Saccharomyces cerevisae* antibodies	100%	3
Celiac disease	Anti-tissue transglutaminase Anti-endomysial antibodies (HLA-DO2 or DO8 antigens)	50-60% (100%)	7

Shoenfeld Y, Blank M, Abu-Shakra M, et al. The Mosaic of autoimmunity: prediction, autoantibodies, and therapy in autoimmune disease – 2008. *IMAJ* 2008;10:13-19

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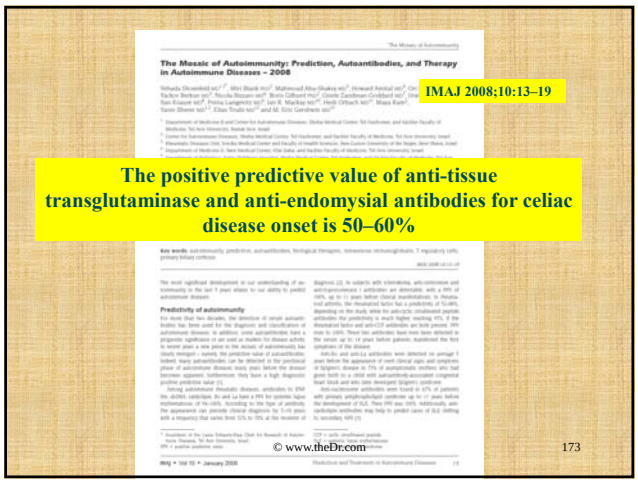
The Mosaic of Autoimmunity: Prediction, Autoantibodies, and Therapy in Autoimmune Diseases – 2008
IMAJ 2008;10:13–19
The positive predictive value of anti-tissue transglutaminase and anti-endomysial antibodies for celiac disease onset is 50–60%
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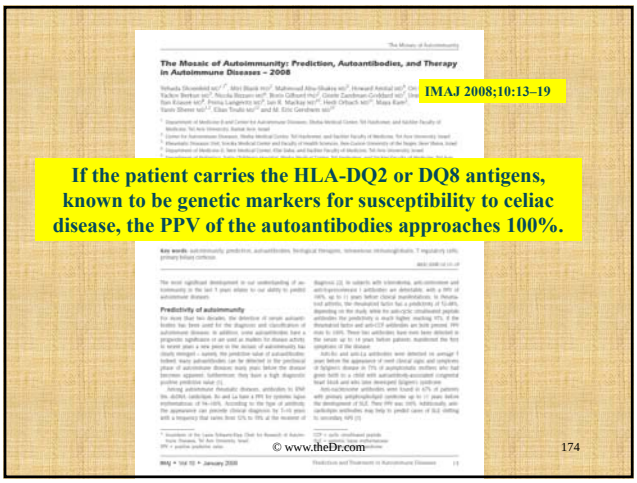
The Mosaic of Autoimmunity: Prediction, Autoantibodies, and Therapy in Autoimmune Diseases – 2008
IMAJ 2008;10:13–19
If the patient carries the HLA-DQ2 or DQ8 antigens, known to be genetic markers for susceptibility to celiac disease, the PPV of the autoantibodies approaches 100%.
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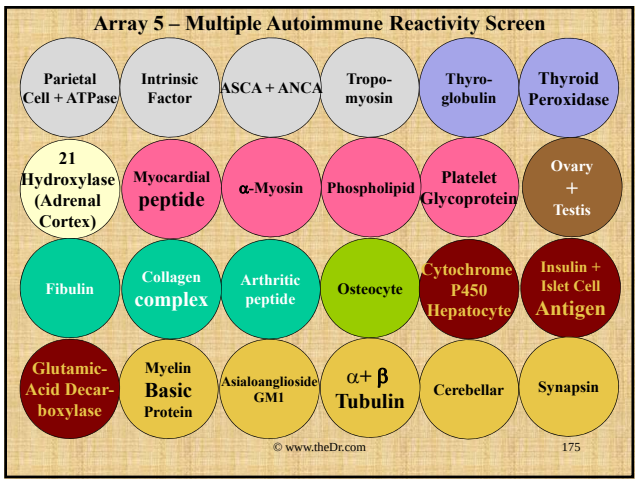
Array 5 – Multiple Autoimmune Reactivity Screen
Parietal Cell + ATPase
Intrinsic Factor
ASCA + ANCA
Tropo-myosin
Thyro-globulin
Thyroid Peroxidase
21 Hydroxylase (Adrenal Cortex)
Myocardial peptide
α-Myosin
Phospholipid
Platelet Glycoprotein
Ovary + Testis
Fibulin
Collagen complex
Arthritic peptide
Osteocyte
Cytochrome P450 Hepatocyte
Insulin + Islet Cell Antigen
Glutamic-Acid Decar-boxylase
Myelin Basic Protein
Asialoanglioside GM1
α+ β Tubulin
Cerebellar
Synapsin
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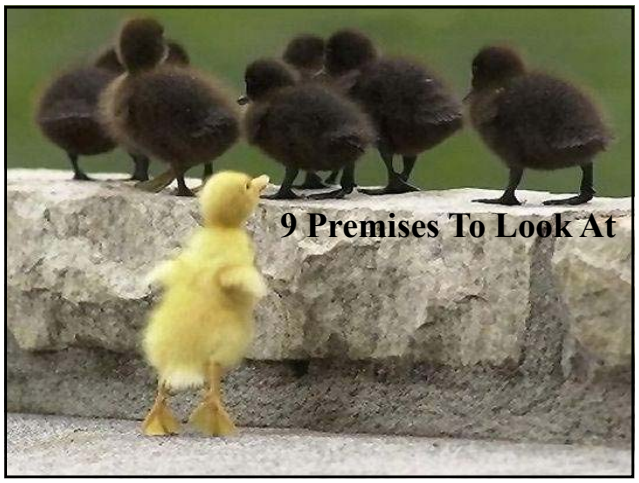

Premise #1

What is the Most Common Cause of Morbidity and Mortality in the Industrialized World?

Detective Adrian Monk

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NIH. Autoimmune Diseases Coordinating Comm. Autoimmune Diseases Research Plan. 2006

AUTOIMMUNE DISEASES

While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 8 percent of the United States population – 24 million persons.

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Premise #2

Genes Control Function

Detective Adrian Monk

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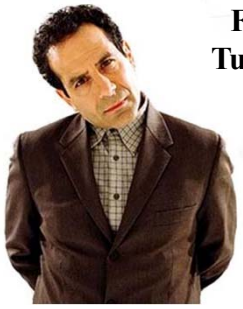
Premise #3

Food Turns On and Turns OFF Our Genes



Detective Adrian Monk

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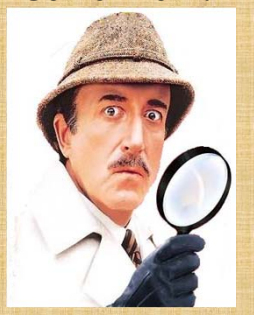
Premise #4

Where Does the Persisting Inflammation Come From?



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Premise #5

What is the Impact of Intestinal Permeability?

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Gastroenterol Clin N Am 37 (2008) 411–428

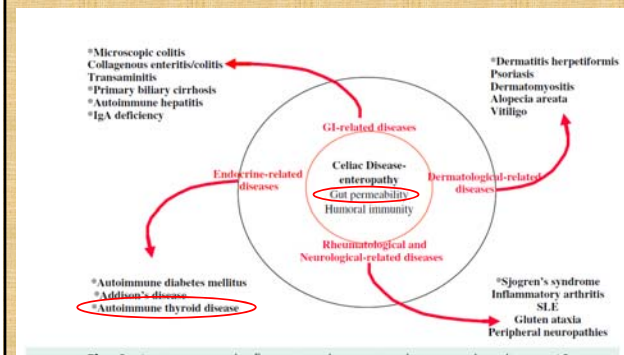

Fig. 1. Autoimmune and inflammatory diseases in relation to celiac disease. *Strongest associations.

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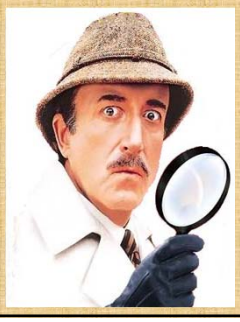
Premise #6

What is the Mechanism of Intestinal Permeability?



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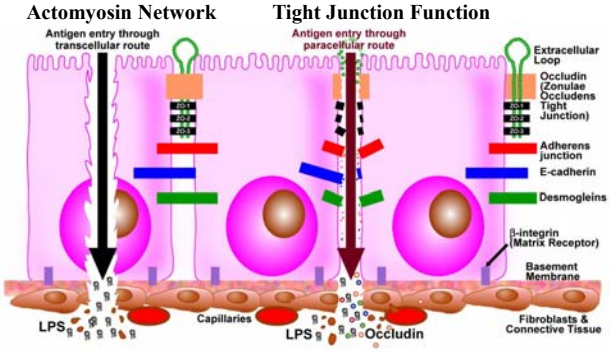

The pathways of antigen invasion through Transcellular and Paracellular routes.

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Premise #7

How Might The Impact of Intestinal Permeability Present?

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Premise #8

Immunological Markers in Screening for Antigenic Intestinal Permeability

Mucosal Immunology Vol 3 No 3 | MAY 2010
Neuroendocrinology Letters Volume 29 No. 1 2008
J Affect Disord. 2007 Apr;99(1-3):237-40
Neuro Endocrinol Lett. 2007 Dec;28(6):739-44.

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Immunological Markers in Screening for Antigenic Intestinal Permeability

BLOOD

Autoimmunity of Tight Junctions	Autoimmunity of Basement Anchor of Tight Junctions	Immune Response to Translocating Bacterial Debris/Pathogens
Occludin / Zonulin IgG, IgM, IgA	Actomyosin IgA	Lipopolysaccharide IgG, IgM, IgA

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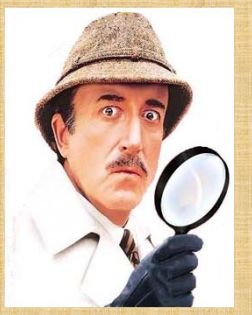
Premise #9
When Does Autoimmune Disease Begin?



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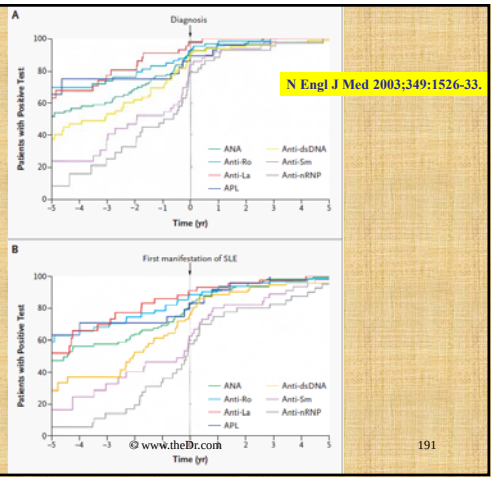

N Engl J Med 2003;349:1526-33.

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Premise #7
Immunological Markers in Screening for Antigenic Intestinal Permeability

Mucosal Immunology Vol 3 No 3 | MAY 2010
Neuroendocrinology Letters Volume 29 No. 1 2008
J Affect Disord. 2007 Apr;99(1-3):237-40
Neuro Endocrinol Lett. 2007 Dec;28(6):739-44.

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Premise #10
How Might The Impact of Intestinal Permeability Present?

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CASE STUDY #1

Recurrent Miscarriages and Autoimmune Diseases

J Neurochem. 2011 Nov;119(4):826-38

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Take Care of Yourself

 196

Make Sure to Tell those Important to You How Much You Love them

 197

GENETIC NUTRITIONEERING

How You Can Modify Inherited Traits and Live a Longer, Healthier Life

"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."

JEFFREY S. BLAND, PH.D.
WITH SARA H. BENUM, M.A.

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"Thank You for Your Kind Attention"

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Wishing you Sunrises of Beauty throughout your life

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