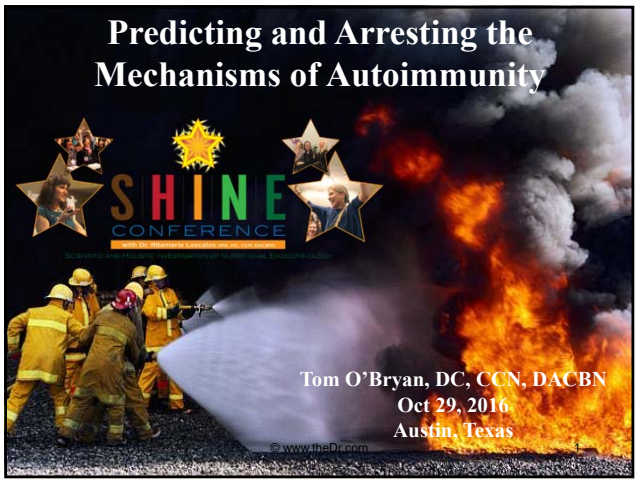


Tom O'Bryan, DC, CCN, DACBN

- Adjunct Faculty, The Institute for Functional Medicine,
- Adjunct Faculty ,The National University of Life Sciences,
- Clinical Consultant on Functional Medicine -NuMedica, Inc.
- Clinical Consultant on Functional Medicine-Vibrant America
- Medical Advisory Board, Functional Medicine University
- Medical Advisory Board, Institute for Functional Nutrition
- Medical Advisory Board National Association of Nutritional Professionals
- Scientific Advisory Board-International and American Association of Clinical Nutritionists
- Editorial Review Board-*Alternative Therapies in Health and Medicine*
- Chief Medical Officer, Sun Horse Energy

 2

What Triggers the Systemic Symptoms Initiating the Autoimmune Mechanism?

Genetic predisposition, environmental insult, hypochlorhydria, pancreatic insufficiency, medications, surgery, etc.

↓

Inadequately digested proteins in GI tract (associated with food sensitivities) → Irritation/inflammation/dysbiosis (activating immune inflammatory response)

↓

Eventually Developing into Pathogenic Intestinal Permeability

↓

Increased load on liver detoxification pathways (food antigens, toxins, endotoxin)
AND
Immune complexes in general circulation to macromolecules, neo-epitopes,…

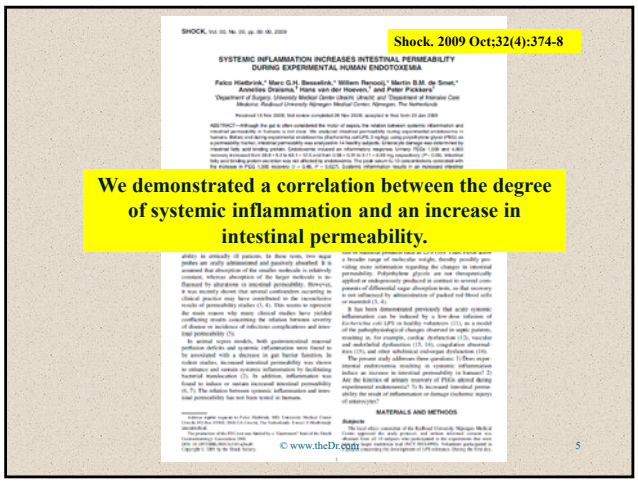
↓

Molecular Mimicry and tissue specific symptoms determined by genetics and antecedents

↓

Initiation of autoimmune mechanisms eventually developing into an AUTOIMMUNE DISEASE

4


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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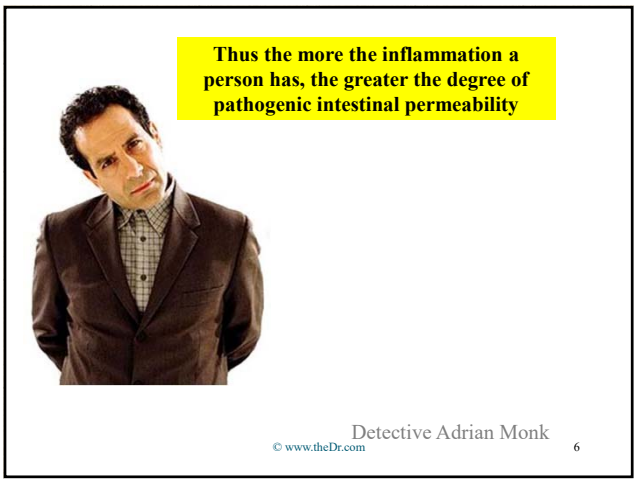
Thus the more the inflammation a person has, the greater the degree of pathogenic intestinal permeability
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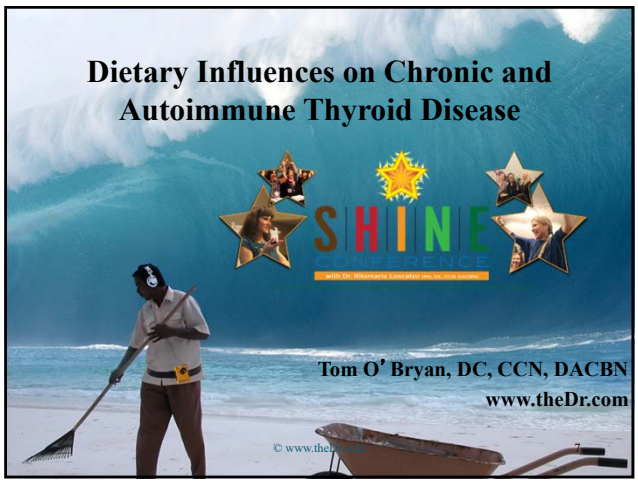
Dietary Influences on Chronic and Autoimmune Thyroid Disease
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'The Neurological UnderBelly of the Gluten-free Lifestyle: Potential Benefits, Devastating Dangers'
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October 30, 2015
Tom O'Bryan, DC, CCN, DACBN
www.theDr.com

Premise #1

Food Sensitivities may have a lasting, significant impact on CNS function

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 9

Premise #2

Gluten Sensitivity is not yet recognized by Practitioners as a <u>Primary Presentation</u> in Their Offices

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Premise #3

Gluten Sensitivity with or without the enteropathy Celiac Disease is a systemic autoimmune disease

Journal of Alzheimer's Disease 45 (2015) 349–362

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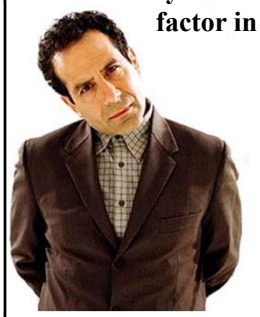
 11

Premise #4

Food selection has a direct impact on dysbiosis and may be an initiating factor in an autoimmune cascade



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Premise #5

Both Parkinson's and Alzheimer's diseases involve the formation of transmissible self-propagating prion-like proteins.

Journal of Alzheimer's Disease 45 (2015) 349–362

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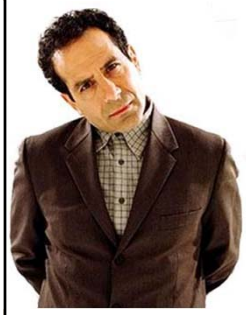
Premise #6

A GFD may contribute to dysbiosis



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Premise #7

y Office benefits from ring SUCCESSFUL, prehensive, Thorough idance for Patients to tion into a Microbiome- ing dietary lifestyle via a l-Trained Nutritionist, tered Dietician, or Staff Specialist

Mechanisms identified in this Presentation

- **Cross-reactivity with purkinje cells**
- **Anti-gliadin Abs strongly react with blood vessel structures in the brain**
- **1 exposure of gluten per month in sensitive individuals increases the SMR to 6:1**
- **Diet changes explained 57% of the total structural variation in gut microbiota, whereas genetic mutation accounted for no more than 12%.**
- **GFD may lead to reductions in beneficial gut bacteria populations and the ability of faecal samples to stimulate the host's immunity**
- **gut microbiota influence the GABAergic, glutaminergic, serotonergic, dopaminergic, histaminergic, and adrenergic systems**

Is Gluten Sensitivity limited to Celiacs?

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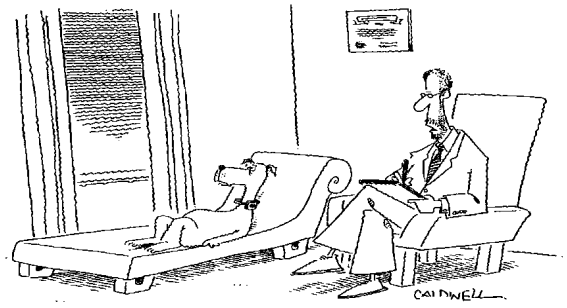
17



"Please…tell me more about this imaginary fence."

Nutrients 2015, 7, 1565-1576

Nutrients 2015, 7, 1565-1576; doi:10.3390/nu7031565

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nutrients

ISSN 2072-6643

www.mdpi.com/journal/nutrients

Article

Effect of Gliadin on Permeability of Intestinal Biopsy Explants from Celiac Disease Patients and Patients with Non-Celiac Gluten Sensitivity

We aimed to study response to gliadin exposure, in terms of barrier function and cytokine secretion, using intestinal biopsies obtained from four groups:
- **celiac patients with active disease (ACD),**
- **celiac patients in remission (RCD),**
- **non-celiac patients with gluten sensitivity (GS) and**
- **non-celiac controls (NC).**

* Author to whom correspondence should be addressed; E-Mail: justin.hollon@med.navy.mil; Tel.: +757-953-4529; Fax: +757-953-3293.

Received: 28 October 2014 / Accepted: 11 February 2015 / Published: 27 February 2015

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Article

Effect of Gliadin on Permeability of Intestinal Biopsy Explants from Celiac Disease Patients and Patients with Non-Celiac Gluten Sensitivity

Justin Hollon [1,*], Elaine Leonard Puppa [2], Bruce Greenwald [2], Eric Goldberg [3], Anthony Guerrerio [4] and Alessio Fasano [5]

[1] Department of Pediatric Gastroenterology, Naval Medical Center Portsmouth, 620 John Paul Jones

egoldber@medicine.umaryland.edu (E.G.)

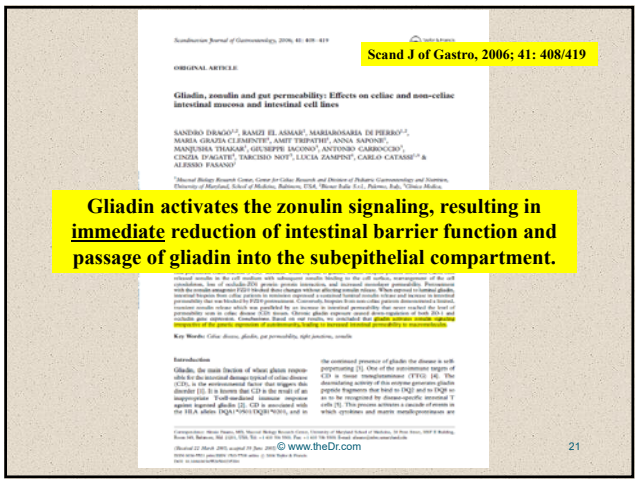
[4] Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; E-Mail: aguerrerio@jhmi.edu

[5] Center for Celiac Research, Massachusetts General Hospital and Division of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, MA 02114, USA; E-Mail: afasano@partners.org

* Author to whom correspondence should be addressed; E-Mail: justin.hollon@med.navy.mil; Tel.: +757-953-4529; Fax: +757-953-3293.

Received: 28 October 2014 / Accepted: 11 February 2015 / Published: 27 February 2015

Conclusions: Increased intestinal permeability after gliadin exposure occurs <u>in all individuals</u>.


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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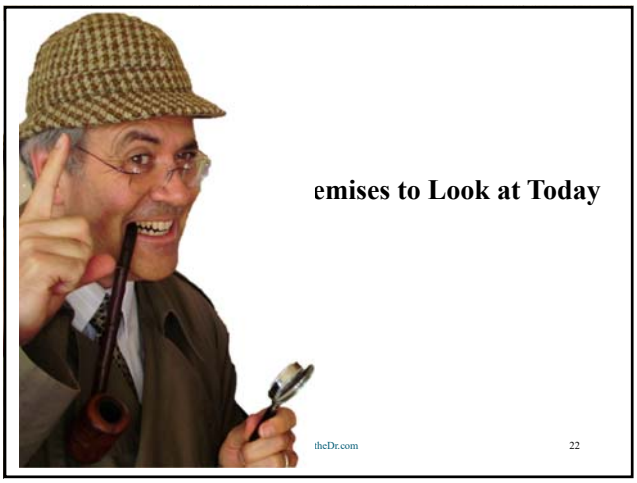
emises to Look at Today
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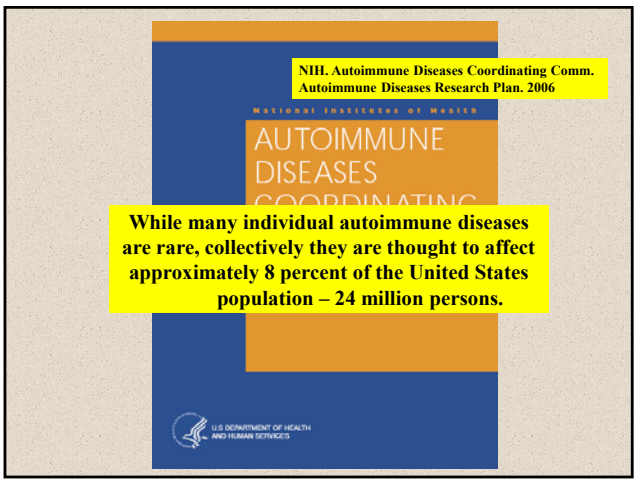
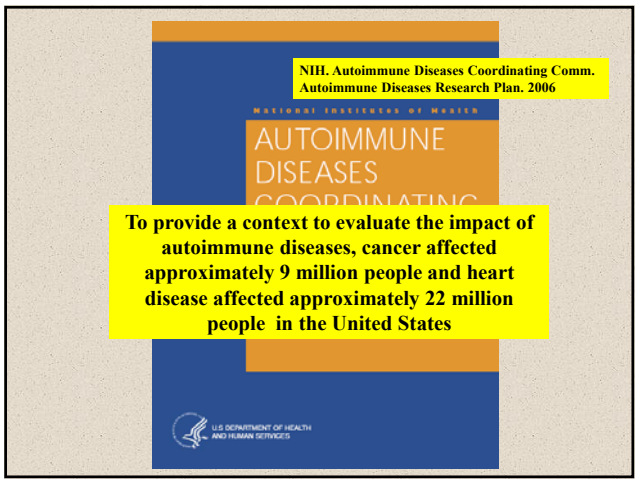
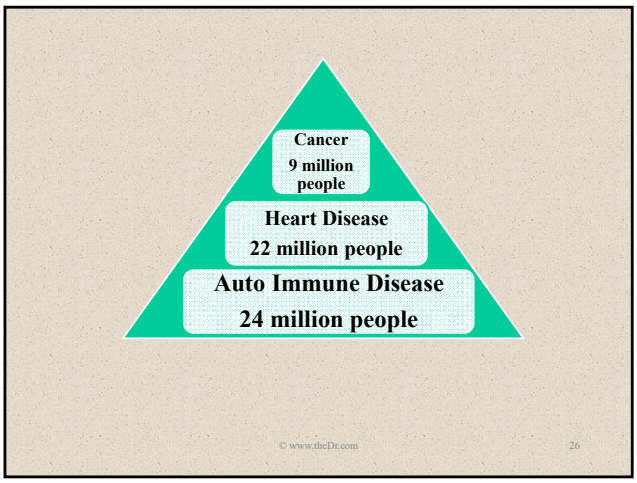
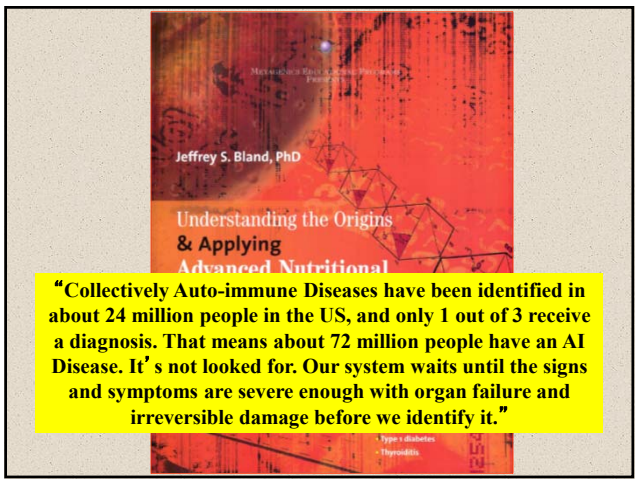
AUTOIMMUNITY


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.


NIH. Autoimmune Diseases Coordinating Comm. Autoimmune Diseases Research Plan. 2006
NATIONAL INSTITUTES OF HEALTH
AUTOIMMUNE
DISEASES
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


Cancer
9 million people
Heart Disease
22 million people
Auto Immune Disease
24 million people
© www.theDr.com
26

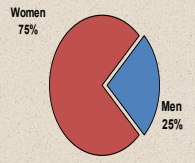

Jeffrey S. Bland, PhD
Understanding the Origins
& Applying
"Collectively Auto-immune Diseases have been identified in about 24 million people in the US, and only 1 out of 3 receive a diagnosis. That means about 72 million people have an AI Disease. It's not looked for. Our system waits until the signs and symptoms are severe enough with organ failure and irreversible damage before we identify it."


REVIEW
Vitamin D and autoimmunity: new aetiological and therapeutic considerations
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.
28

Autoimmunity at a Glance

American Autoimmune Related Disease Association

- Over 100 diseases
- Affecting 50 million Americans
- Costing over $120 billion annually
- 250,000 new diagnoses each year
- A major cause of death in women



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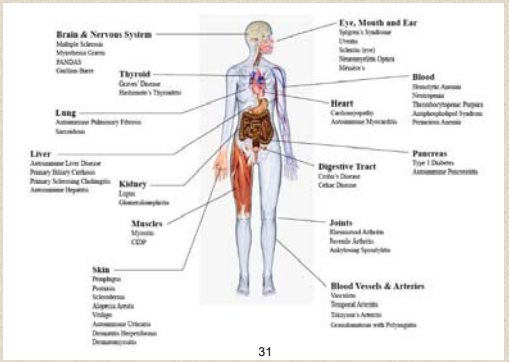
Autoimmune disease can affect any part of the body



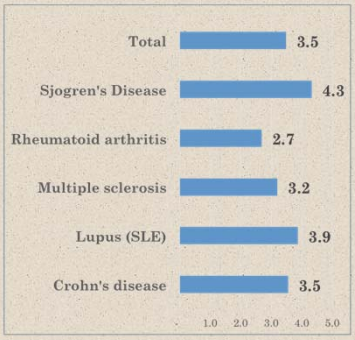
31

AD Diagnosis Takes an Inordinate Amount of Time and Perseverance by the Patient

Survey Issues	1996	2001	2006	2013
Years to Diagnosis	5	4	4	4
No. Physicians Seen	6	4	4	5
Labeled Chronic Complainer	64%	45%	45%	51%

32

Years to Diagnosis



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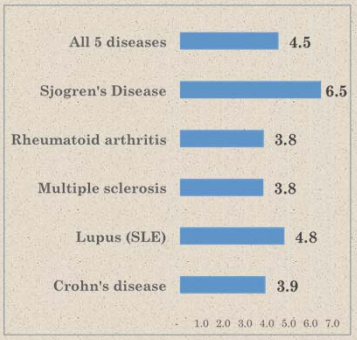
Number of Doctors Seen to get a Diagnosis



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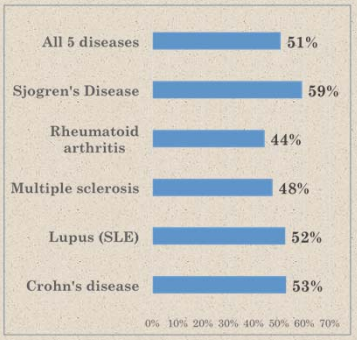
Percent told their disease was imagined or they were overly concerned …



35

Why so Long and Difficult to Get a Correct Diagnosis?

Physician Education was identified as a contributing factor.

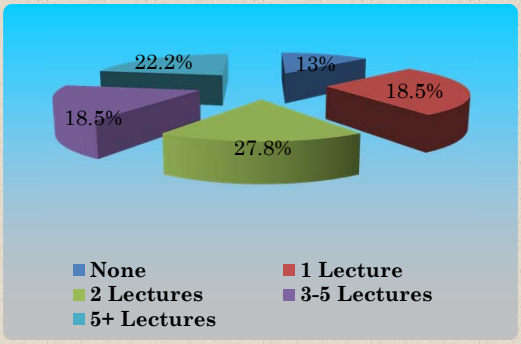
36

AARDA Conducted a Survey of Physicians

- AARDA participated in an educational workshop attended by 130 family physicians.
- Participants were asked to participate in a survey on the extent of their knowledge of autoimmune diseases.
- The survey results prompted a larger ongoing study.

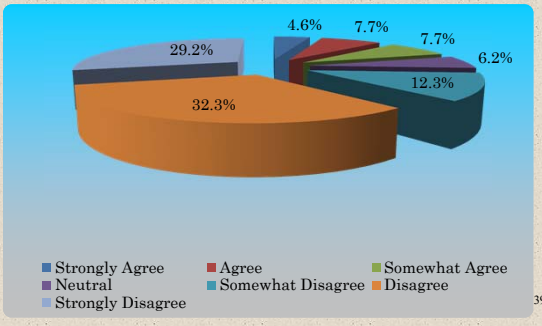
37

In medical school, how much training in autoimmune diseases did you receive?



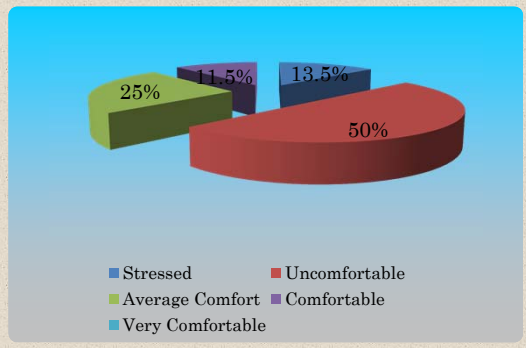
38

Would you agree that you received enough training to diagnose and treat autoimmune disease



39

What is your level of comfort in diagnosing autoimmune disease?



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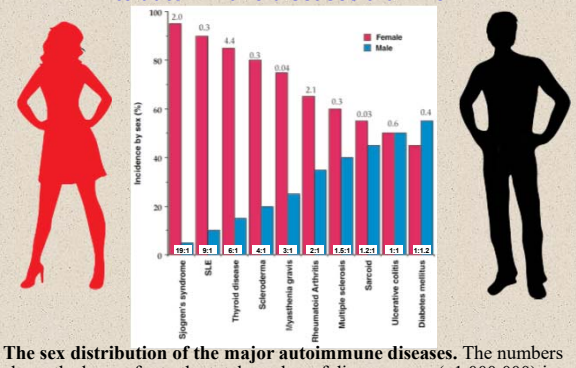
Women are generally more susceptible to autoimmune diseases than men.

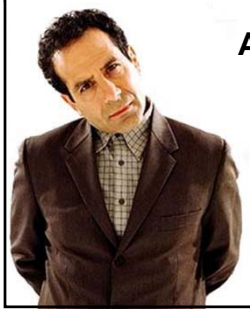


The sex distribution of the major autoimmune diseases. The numbers above the bars refer to the total number of disease cases (x1,000,000) in the USA. Whitacre CC, *Nature Immunol* , **2**:777-780, 2001

41

Premise #1

Just How Prevalent is the Development of Autoimmune Disease?



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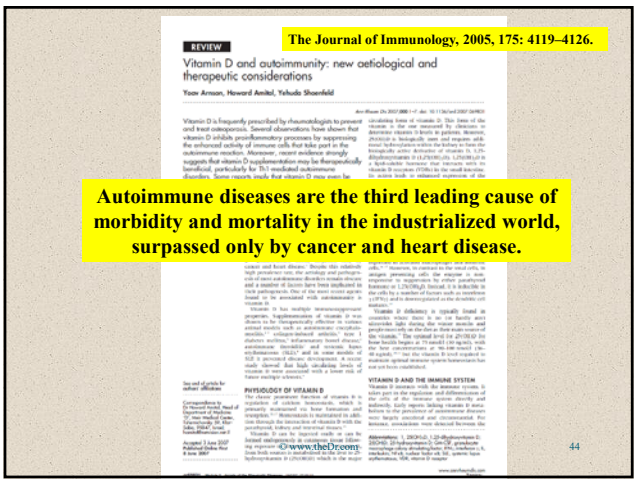

The Journal of Immunology, 2005, 175: 4119–4126.

REVIEW

Vitamin D and autoimmunity: new aetiological and therapeutic considerations

Yoav Arnson, Howard Amital, Yehuda Shoenfeld

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

44

AND

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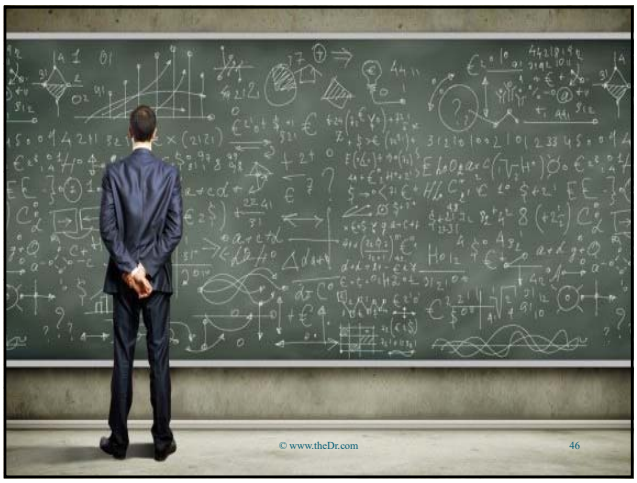
 45



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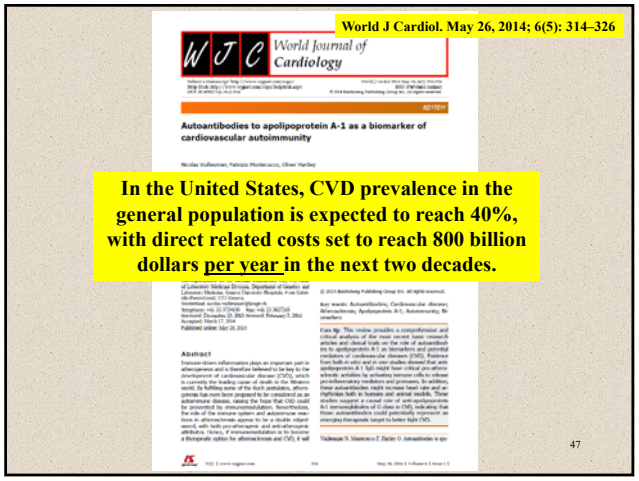


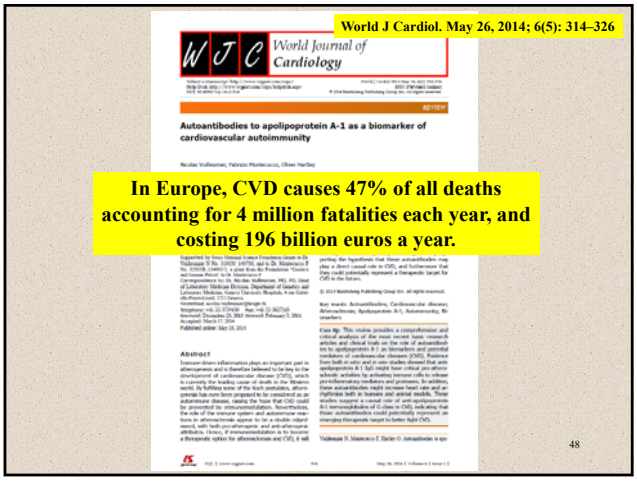
World J Cardiol. May 26, 2014; 6(5): 314–326

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.

47



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

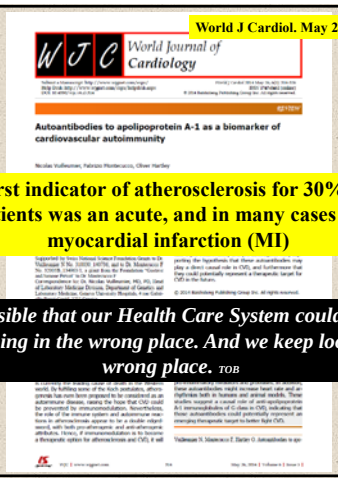
World Journal of Cardiology

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.

48

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)

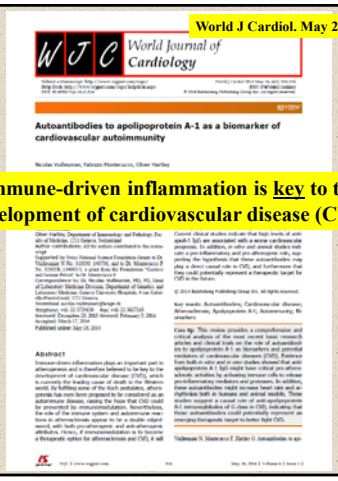
How is it possible that our Health Care System could be so Blind? We're looking in the wrong place. And we keep looking in the wrong place. TOB

49

Perhaps if We Open to More Current Information…..

50

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 <u>key</u> to the development of cardiovascular disease (CVD)

51

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.

52

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

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

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

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

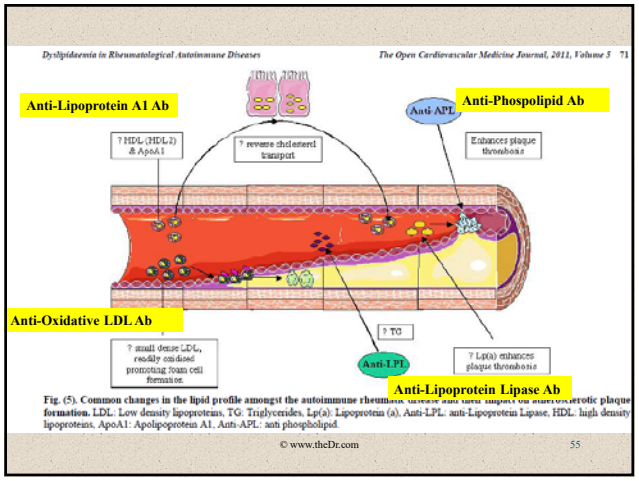


Fig. (5). Common changes in the lipid profile amongst the autoimmune rheumatic disease and their impact on atherosclerotic plaque formation. LDL: Low density lipoproteins, TG: Triglycerides, Lp(a): Lipoprotein (a), Anti-LPL: anti-Lipoprotein Lipase, HDL: high density lipoproteins, ApoA1: Apolipoprotein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

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

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

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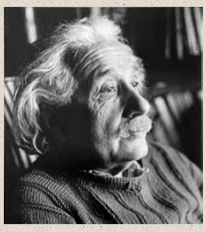
Thus, If CVD has an Initiating Autoimmune Component, Arguably, What Becomes the #1 Mechanism in the Progression of Morbidity and Mortality in the Industrialized World?



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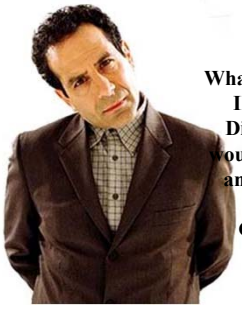

Silently
Point to 2 People
Close By

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

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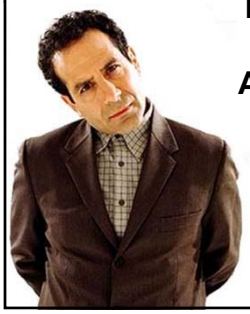
 58

 59



Premise #2

How Can We Identify People At Risk for the Development of Autoimmune Disease?

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 60

National Institutes of Health
THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

Potential of Biomarkers:

- Enable diagnosis before the onset of symptoms
- Predict specific organ involvement
- Predict disease flares
- Identify clinically meaningful disease subsets
- Predict and monitor response to therapy
- Describe organ or tissue damage

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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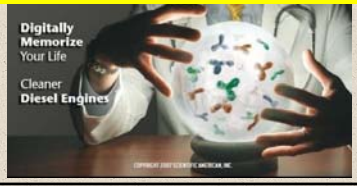
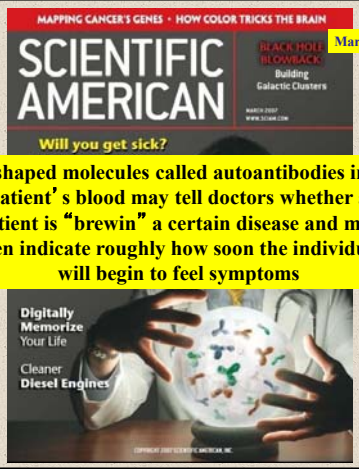
Understanding auto-antibodies

63

March 2007

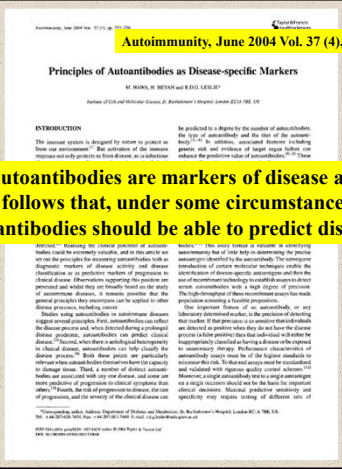
Molecules called predictive autoantibodies appear in the blood years before people show symptoms of various disorders. Tests that detected these molecules could warn of the need to take preventive action





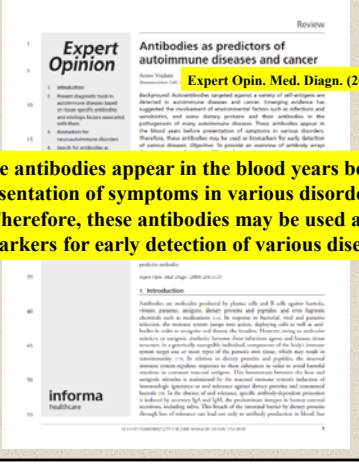
March 2007

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



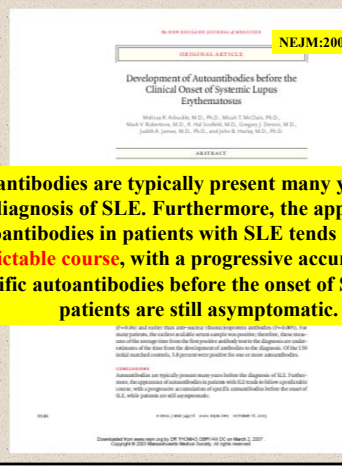
Autoimmunity, June 2004 Vol. 37 (4), pp. 253-256

Since autoantibodies are markers of disease activity, it follows that, under some circumstances, autoantibodies should be able to predict disease.



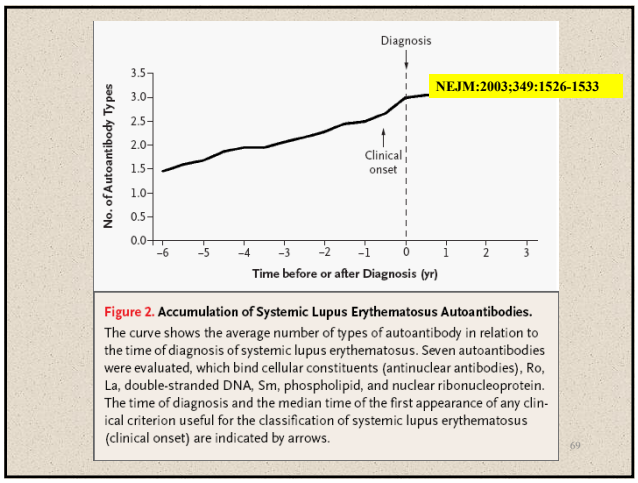
Expert Opin. Med. Diagn. (2008) 2(6):1-13

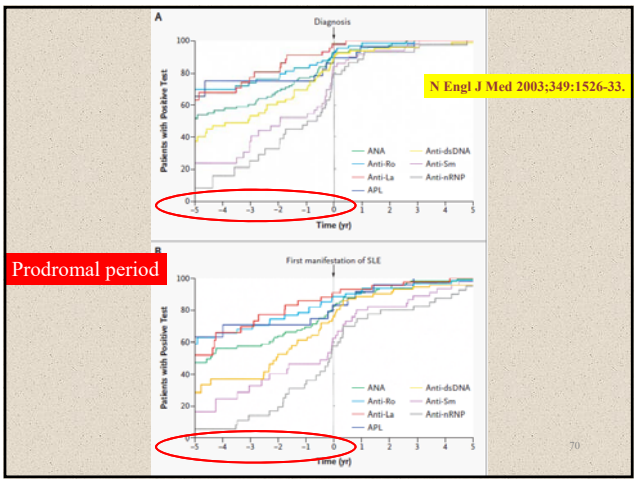
These antibodies appear in the blood years before presentation of symptoms in various disorders. Therefore, these antibodies may be used as biomarkers for early detection of various diseases.

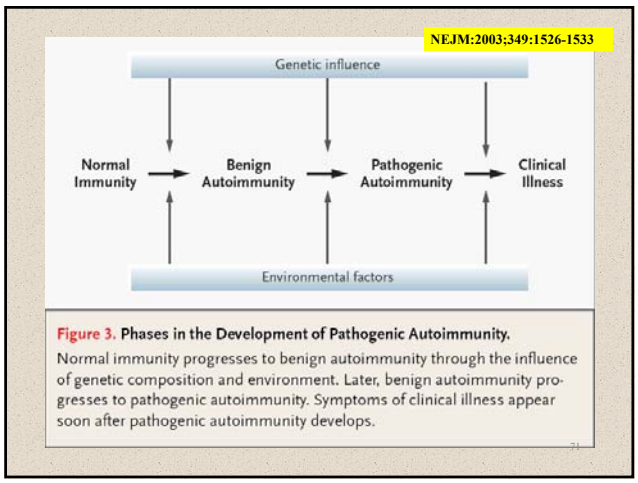


NEJM:2003;349:1526-1533

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.


Diagnosis
Clinical onset
No. of Autoantibody Types
Time before or after Diagnosis (yr)
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.


Diagnosis
Patients with Positive Test
ANA
Anti-dsDNA
Anti-Ro
Anti-Sm
Anti-La
Anti-nRNP
APL
Time (yr)
First manifestation of SLE
N Engl J Med 2003;349:1526-33.
Prodromal period


NEJM:2003;349:1526-1533
Genetic influence
Normal Immunity
Benign Autoimmunity
Pathogenic Autoimmunity
Clinical Illness
Environmental factors
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.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The Gluten Summit
A Grain of Truth

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 who now hold heads of departments and institutes in medical research.**

 73

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?

 74

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 by Dr. Arbuckle in 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.

 75

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."

 76

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.

 77

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

 78

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.

 79

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.

 80

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.

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.

Autoantibodies are messengers from the future

"Individuals who are at risk to developing an autoimmune disease should be advised to refrain from activities and lifestyle which endangers their health and quality of life"

Shepshelovich D and Shoenfeld Y. Prediction and prevention of autoimmune disease: additional aspects of the mosaic of autoimmunity. Lupus 2006;15:183-190

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
1° 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

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

85

Predictivity of Autoimmunity

Organ specific autoimmune diseases

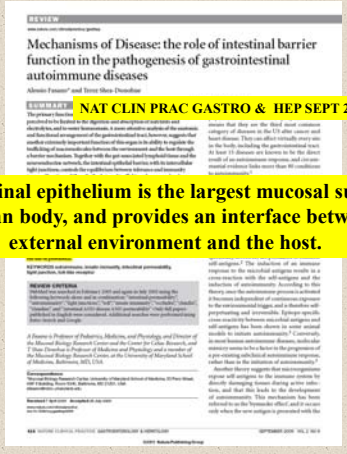
Disease	Antibodies	PPV	Years before Clinical Dx
Addison's disease	Adrenal cortex antibodies	70	10
Crohn's colitis	Anti- *Saccharomyces cerevisae* antibodies	100%	3
Celiac disease	Anti-tissue transglutaminase Anti-endomysial antibodies (HLA-DO2 or DO8 antigens)	50-60% (100%)	7

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

Premise #3
How does Autoimmunity Develop?

Detective Adrian Monk

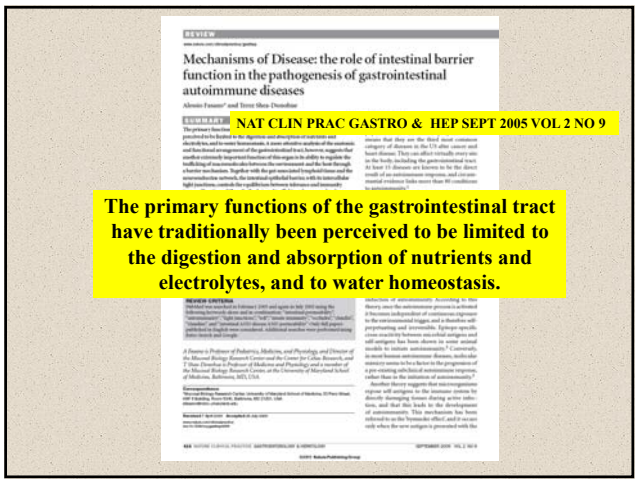
87

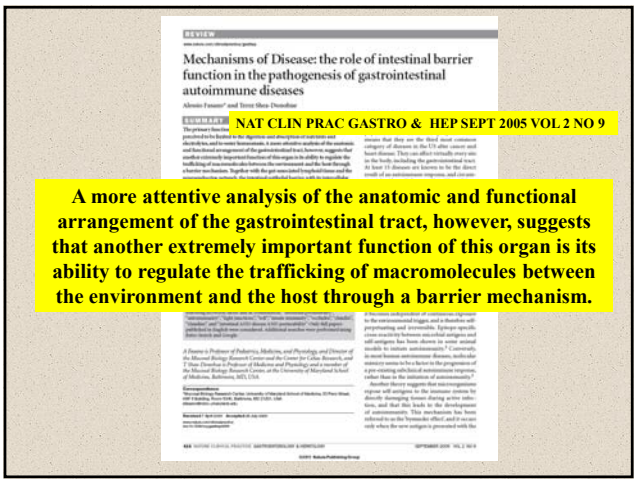


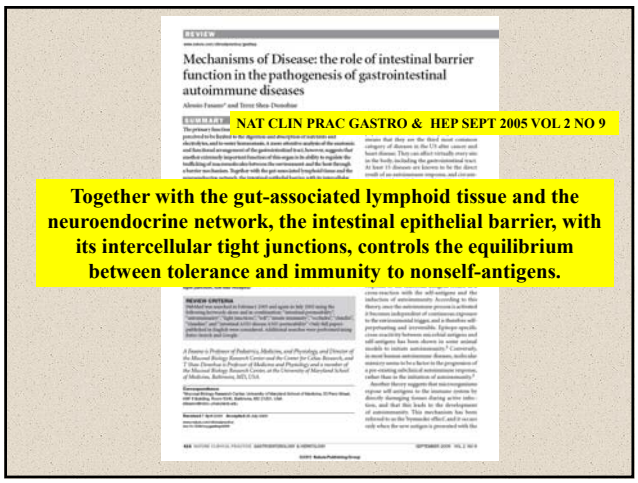
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

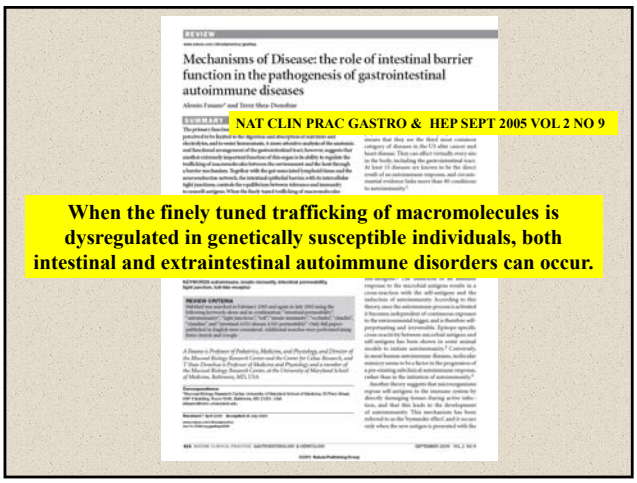
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9

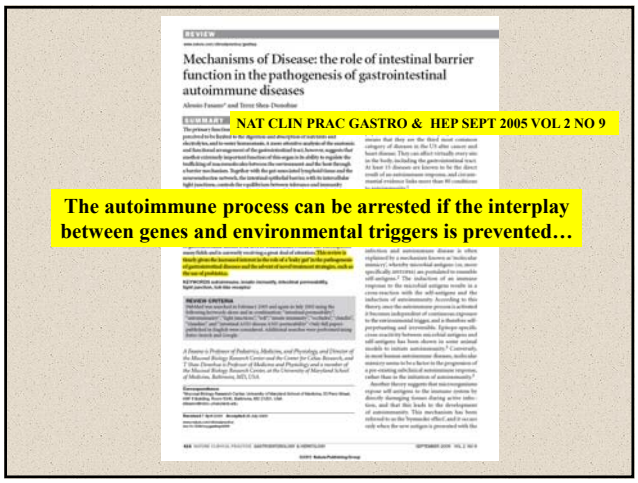
The intestinal epithelium is the largest mucosal surface in the human body, and provides an interface between the external environment and the host.

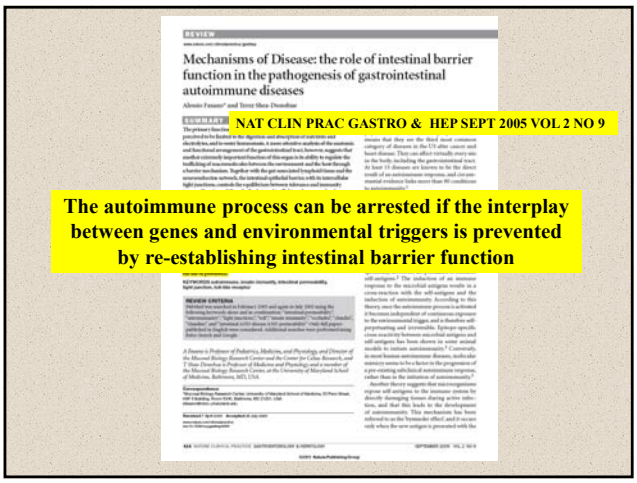

Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
The primary functions of the gastrointestinal tract have traditionally been perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis.

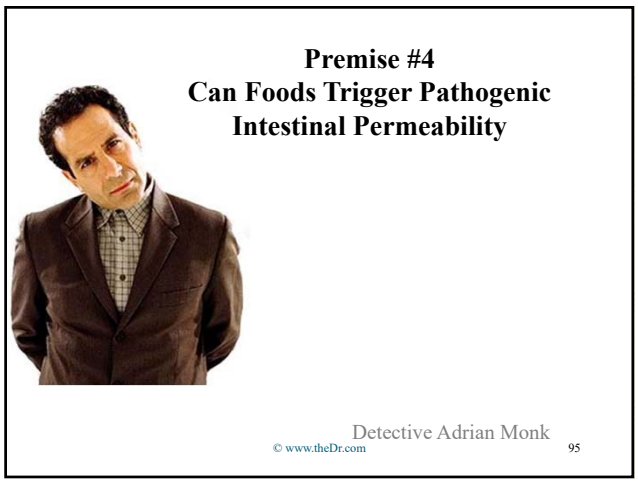

Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that another 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.


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.


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.


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


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


Premise #4
Can Foods Trigger Pathogenic Intestinal Permeability
Detective Adrian Monk
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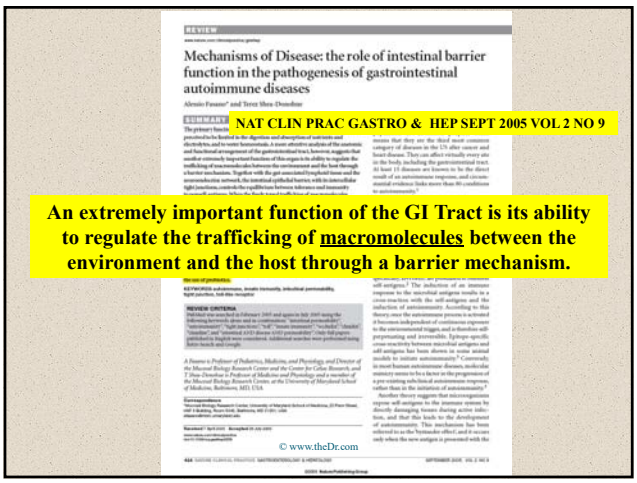
95


REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
SUMMARY
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.
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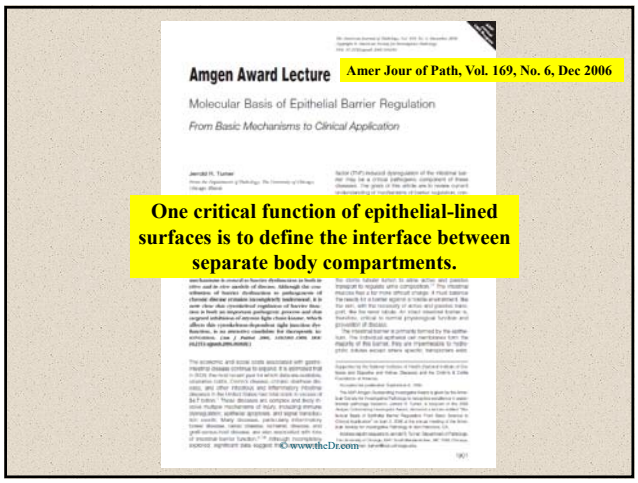
Amgen Award Lecture
Amer Jour of Path, Vol. 169, No. 6, Dec 2006
Molecular Basis of Epithelial Barrier Regulation
From Basic Mechanisms to Clinical Application
One critical function of epithelial-lined surfaces is to define the interface between separate body compartments.
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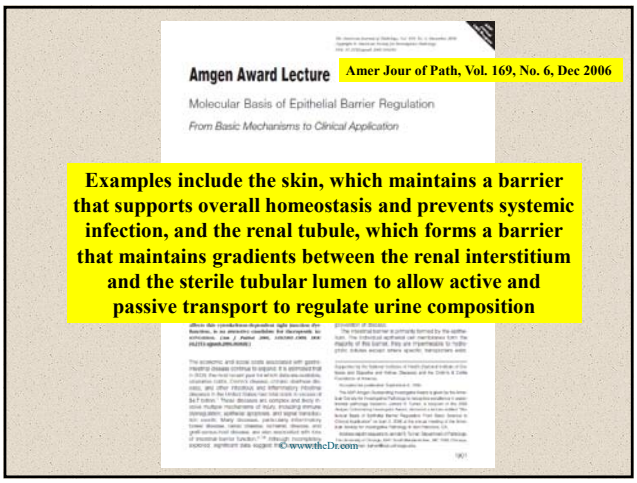
Amgen Award Lecture
Amer Jour of Path, Vol. 169, No. 6, Dec 2006
Molecular Basis of Epithelial Barrier Regulation
From Basic Mechanisms to Clinical Application
Examples include the skin, which maintains a barrier that supports overall homeostasis and prevents systemic infection, and the renal tubule, 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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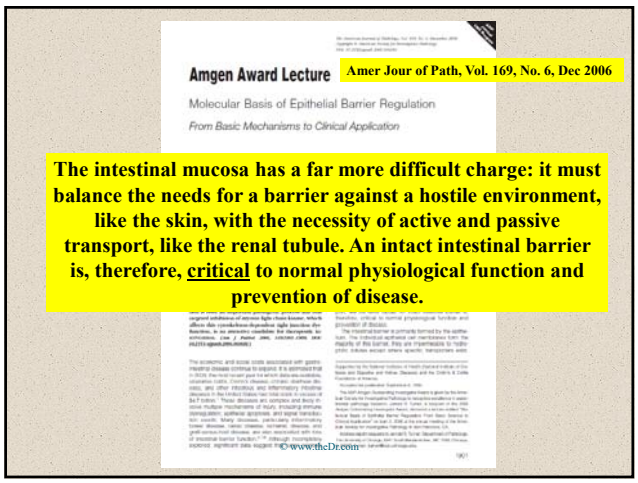
Amgen Award Lecture
Amer Jour of Path, Vol. 169, No. 6, Dec 2006
Molecular Basis of Epithelial Barrier Regulation
From Basic Mechanisms to Clinical Application
The intestinal mucosa has a far more difficult charge: it must balance the needs for a barrier against a hostile environment, like the skin, 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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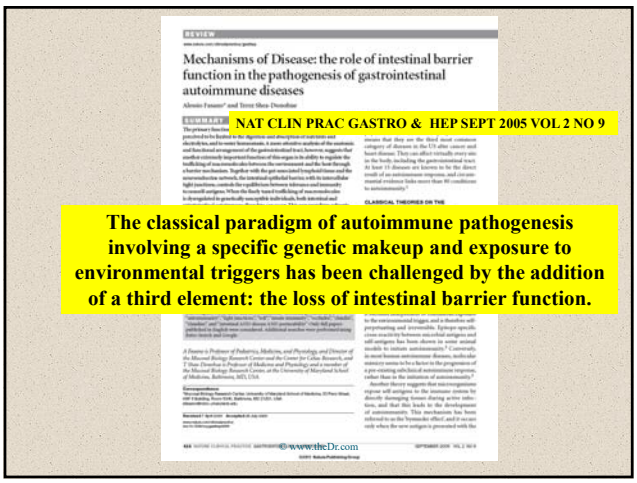
REVIEW
Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases
NAT CLIN PRAC GASTRO & HEP SEPT 2005 VOL 2 NO 9
The classical paradigm of autoimmune pathogenesis involving a specific genetic makeup and exposure to environmental triggers has been challenged by the addition of a third element: the loss of intestinal barrier function.
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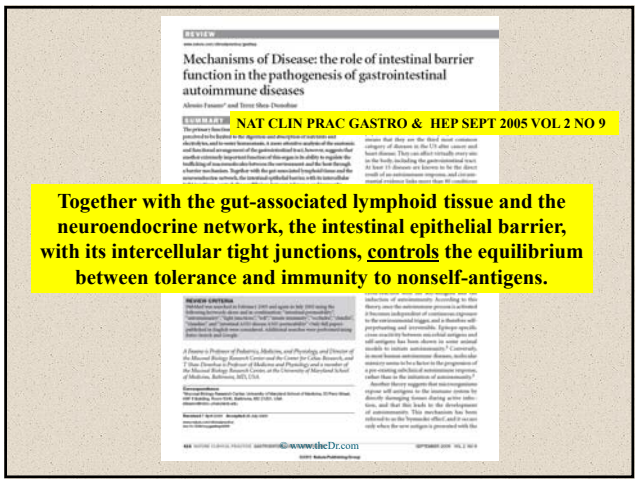
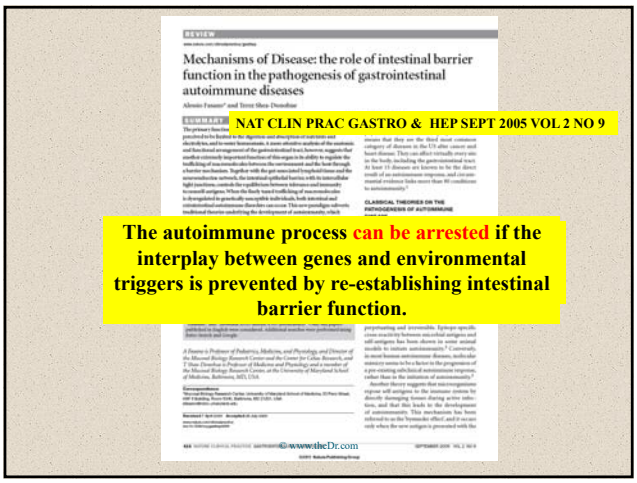


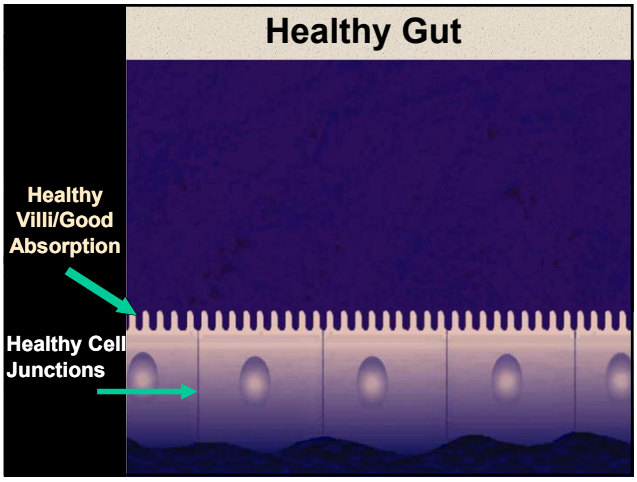


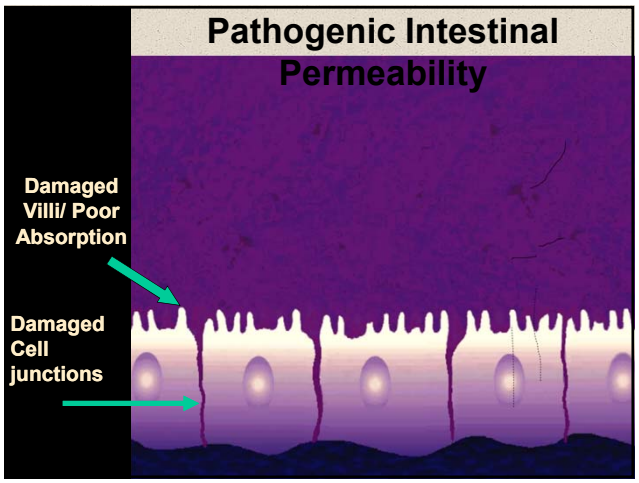
A Common Initial Autoimmune Pathway and Therapeutic Target to Degenerative Disease

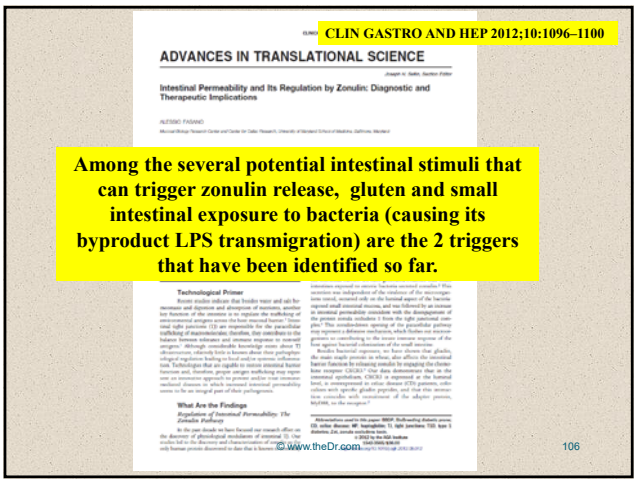
Immune Response to Intestinal Antigen Presentation (Dysbiosis, food sensitivities, LPS, toxic chemicals,…)

→ Intestinal Inflammation from antigen delivery
→ Loosening tight junction barrier proteins
→ Antibody production to Barrier Proteins (zonulin, TG2, Actin, Myosin, Calprotectin,…)
→ Leaky or Leaking Gut, Leaky Brain, Leaky Bladder,…
→ Pathogenic Intestinal Permeability
→ Antigen translocation(foods, LPS, chemical toxins…)
→ Immune Response = Antibody Production
→ Molecular Mimicry
→ Autoimmune Mechanism initiated

Neuroendocrinology Letters Volume 29 No. 1




Pathogenic Intestinal Permeability
Damaged Villi/ Poor Absorption
Damaged Cell junctions


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, gluten and small intestinal exposure to bacteria (causing its byproduct LPS transmigration) are the 2 triggers that have been identified so far.
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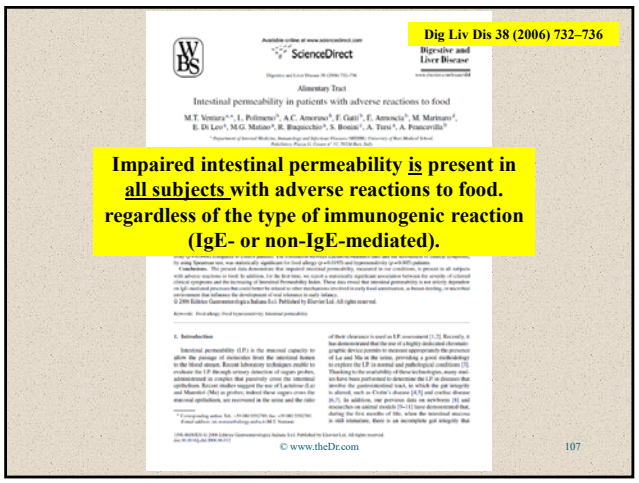
Dig Liv Dis 38 (2006) 732–736
ScienceDirect
Digestive and Liver Disease
Intestinal permeability in patients with adverse reactions to food
Impaired intestinal permeability is present in all subjects with adverse reactions to food. regardless of the type of immunogenic reaction (IgE- or non-IgE-mediated).
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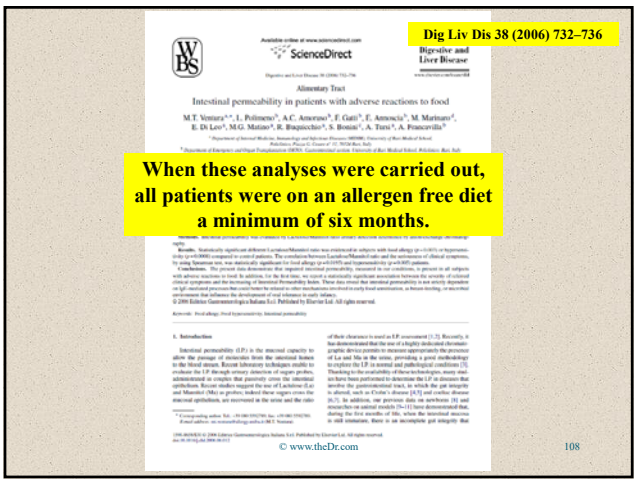
Dig Liv Dis 38 (2006) 732–736
ScienceDirect
Digestive and Liver Disease
Intestinal permeability in patients with adverse reactions to food
When these analyses were carried out, all patients were on an allergen free diet a minimum of six months.
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Gastroenterology 2014;147:1012–1020

CLINICAL—ALIMENTARY TRACT

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

Annette Fritscher-Ravens,[1] Detlef Schuppan,[2,3,4] Mark Ellrichmann,[1] Stefan Schoch,[1] Christoph Röcken,[5] Jochen Brasch,[6] Johannes Bethge,[1] Martina Böttner,[7] Julius Klose,[1] and Peter J. Milla[8]

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

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

an objective diagnosis, and effective therapies are lacking. Some patients recognize that food may trigger symptoms,[3] which may be caused by an allergy or innate immune activation by, for example, food constituents, which could not be proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets.[4]

Gastroenterology 2014;147:1012–1020

CLINICAL—ALIMENTARY TRACT

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Annette Fritscher-Ravens,[1] Detlef Schuppan,[2,3,4] Mark Ellrichmann,[1] Stefan Schoch,[1] Christoph Röcken,[5] Jochen Brasch,[6] Johannes Bethge,[1] Martina Böttner,[7] Julius Klose,[1] and Peter J. Milla[8]

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

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

Keywords: Imaging; FODMAP; Food Allergy; Gluten.

BACKGROUND & AIMS: We investigated suspected food intolerances in patients with irritable bowel syndrome (IBS) using confocal laser endomicroscopy (CLE) for real-time visualization of structural/functional changes in the intestinal mucosa after food challenge. Patients with functional changes after food challenge (CLE+) were placed on personalized exclusion diets and followed up for long-term symptom relief. **METHODS:** Thirty-six IBS patients with suspected food intolerance and 10 patients with Barrett's esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa

Irritable bowel syndrome (IBS) represents a common and economically important gastrointestinal (GI) disorder.[1,2] Because no reliable biomarkers are available, IBS is characterized by chronic or recurrent abdominal pain associated with altered bowel habits when other etiologies have been excluded. Current tests commonly fail to obtain an objective diagnosis, and effective therapies are lacking. Some patients recognize that food may trigger symptoms,[3] which may be caused by an allergy or innate immune activation by, for example, food constituents, which could not be proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets.[4]

Gastroenterology 2014;147:1012–1020

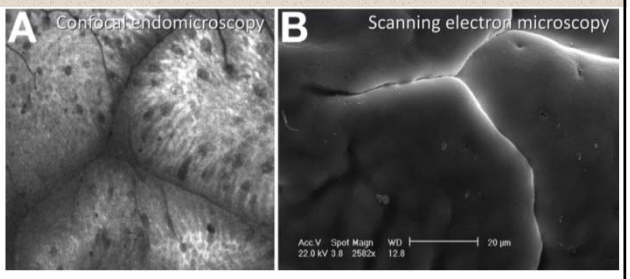

Figure 5. Intervillous space at baseline as visualized with endomicroscopy and scanning electron microscopy.

Gastroenterology 2014;147:1012–1020

CLINICAL—ALIMENTARY TRACT

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

Annette Fritscher-Ravens,[1] Detlef Schuppan,[2,3,4] Mark Ellrichmann,[1] Stefan Schoch,[1] Christoph Röcken,[5] Jochen Brasch,[6] Johannes Bethge,[1] Martina Böttner,[7] Julius Klose,[1] and Peter J. Milla[8]

Four commonly encountered major antigen mixtures and suspensions were applied;

- **cow's milk mixed with 30% sterile water;**
- **wheat, 2 g;**
- **yeast, 1 g;**
- **soy, 2 g**

18 mL sterile water/2 mL simethicone served as a control substance.

without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa

an objective diagnosis, and effective therapies are lacking. Some patients recognize that food may trigger symptoms,[3] which may be caused by an allergy or innate immune activation by, for example, food constituents, which could not be proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets.[4]

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

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

BACKGROUND & AIMS: We investigated suspected food intolerances in patients with irritable bowel syndrome (IBS) using confocal laser endomicroscopy (CLE) for real-time visualization of structural/functional changes in the intestinal mucosa after food challenge. Patients with functional changes after food challenge (CLE+) were placed on personalized exclusion diets and followed up for long-term symptom relief. **METHODS:** Thirty-six IBS patients with suspected food intolerance and 10 patients with Barrett's esophagus (controls) without IBS symptoms were examined by CLE at University Hospital Schleswig-Holstein (Kiel, Germany). Diluted food antigens were administered directly to the duodenal mucosa

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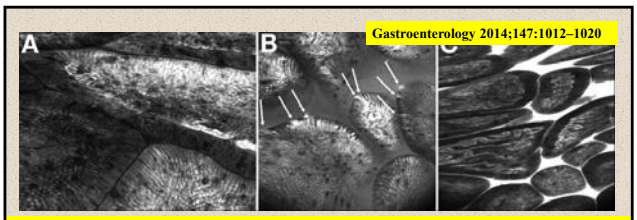


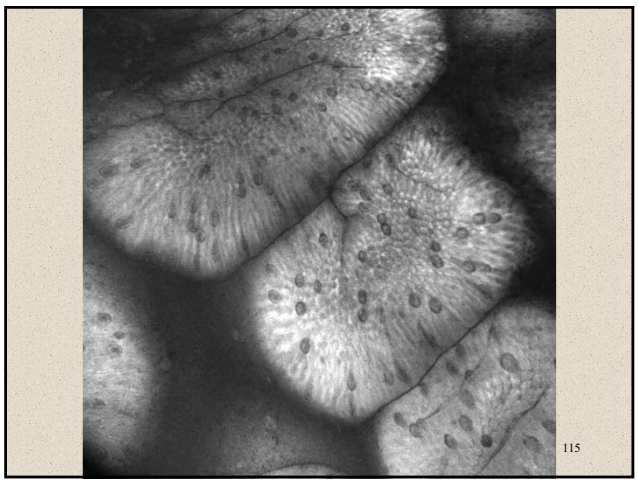
Gastroenterology 2014;147:1012–1020

CLE images of (A) baseline and (B and C) after food challenge

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

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

(C) End stage of the reaction. With an influx of fluorescein the IVS turned white and widened further.



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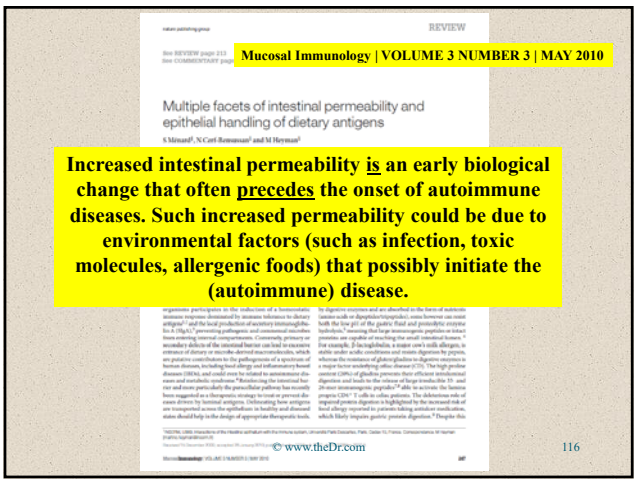

REVIEW

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.

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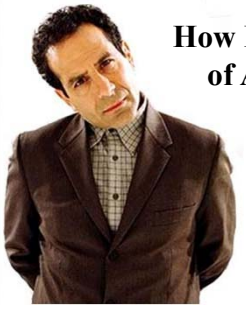
Premise #5



How Frequent is the Production of Antibodies To Dairy and Wheat?

Detective Adrian Monk

 117

Nutrients 2014, 6, 15-36

Nutrients **2014**, *6*, 15-36; doi:10.3390/nu6010015

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Article

The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities

Aristo Vojdani [1,*], Datis Kharrazian [2] and Partha Sarathi Mukherjee [3]

Blood samples from 400 blood donors (181 males and 219 females), cross-spectrum of the population, mixture of Caucasians, Hispanics, and African-Americans, aged 18 and older) were purchased.

Tel.: +1-310-657-1077; Fax: +1-310-657-1053.

Received: 16 October 2013; in revised form: 6 December 2013 / Accepted: 10 December 2013 / Published: 19 December 2013

Nutrients 2014, 6, 15-36

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Prior to shipping, each blood sample was tested according to FDA guidelines for the detection of hepatitis B surface antigen, antibodies to HIV, antibodies to hepatitis C, HIV-1 RNA, hepatitis C RNA, and syphilis. All units yielded non-reactive/negative results for each test performed.

Received: 16 October 2013; in revised form: 6 December 2013 / Accepted: 10 December 2013 / Published: 19 December 2013

Nutrients 2014, 6, 15-36

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Article

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Aristo Vojdani [1,*], Datis Kharrazian [2] and Partha Sarathi Mukherjee [3]

No medical examinations or additional lab tests were conducted to otherwise determine the health status of the donors.

E-Mail: parthamukherjee@boisestate.edu

* Author to whom correspondence should be addressed; E-Mail: drari@msn.com; Tel.: +1-310-657-1077; Fax: +1-310-657-1053.

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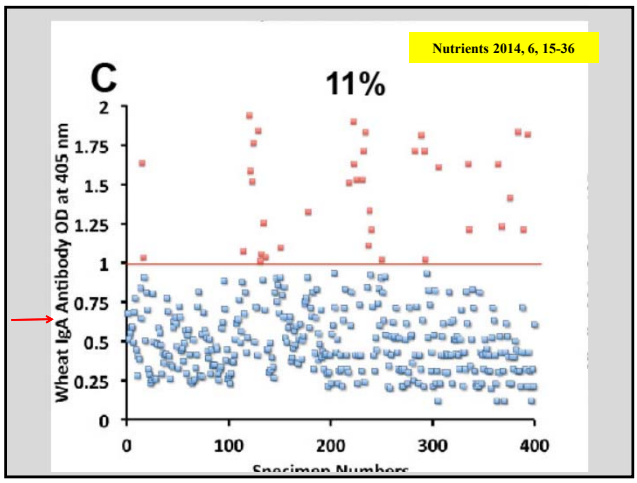
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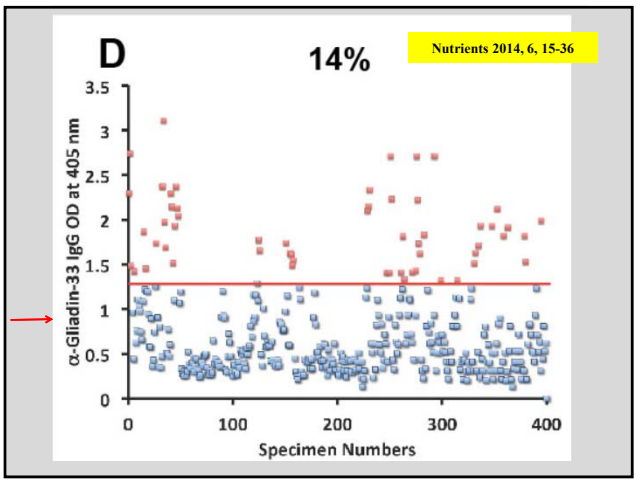
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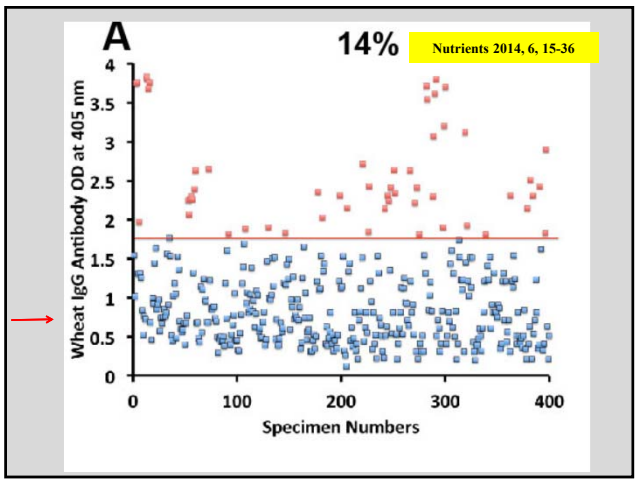
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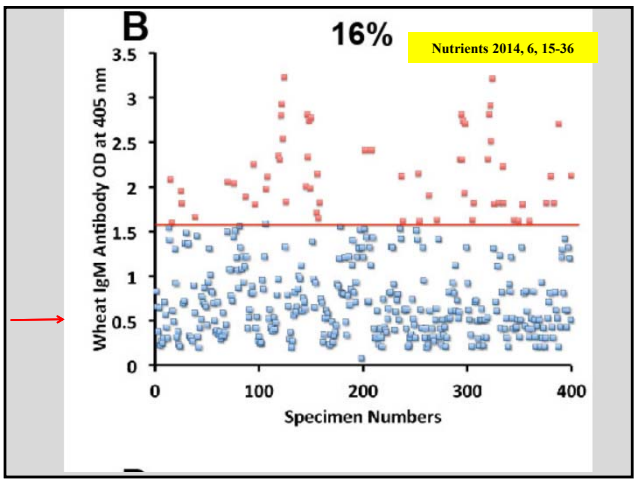
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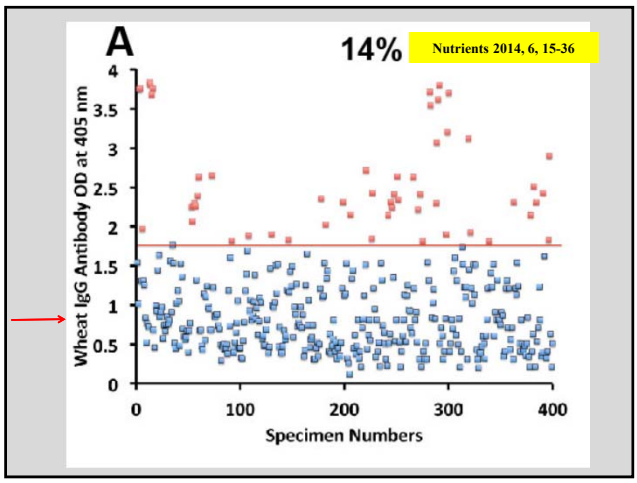
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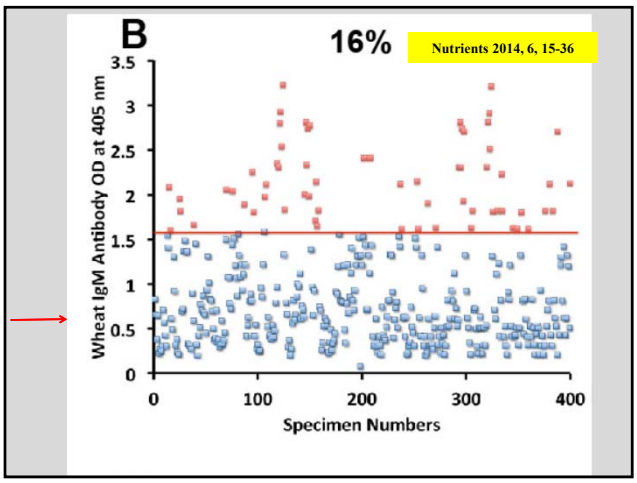
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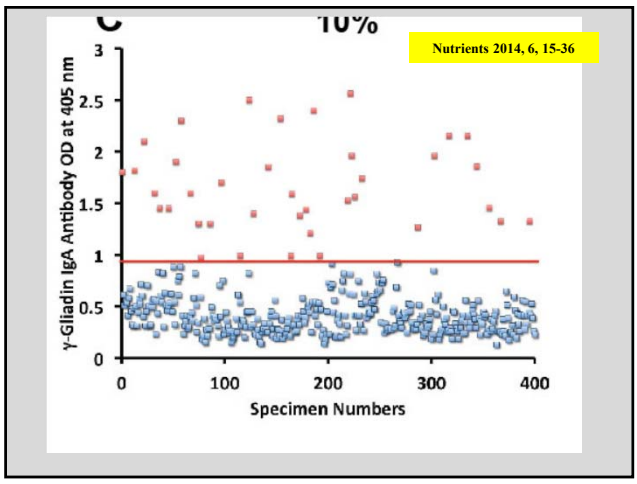
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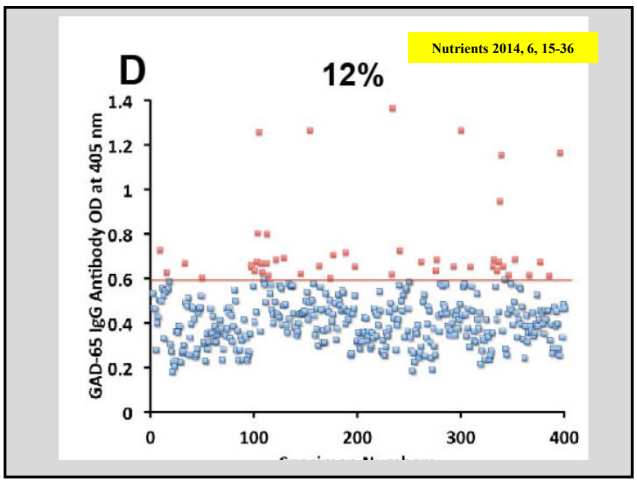
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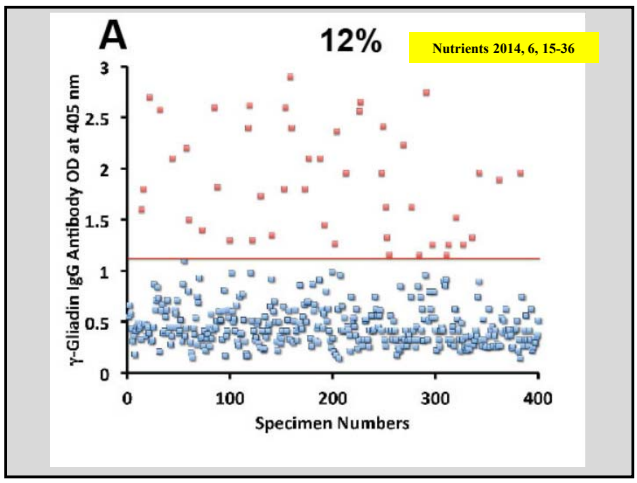
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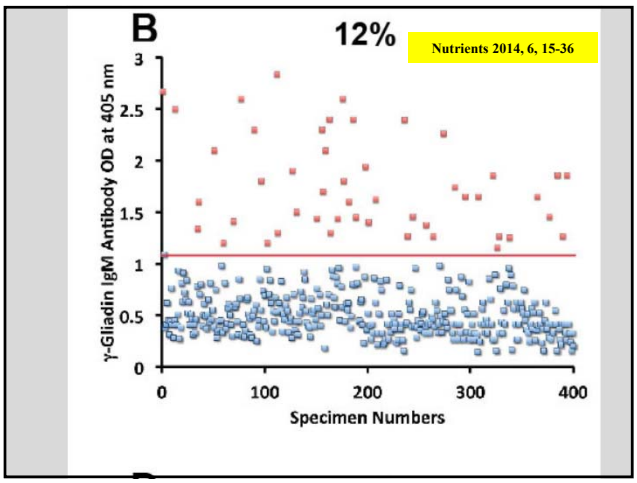
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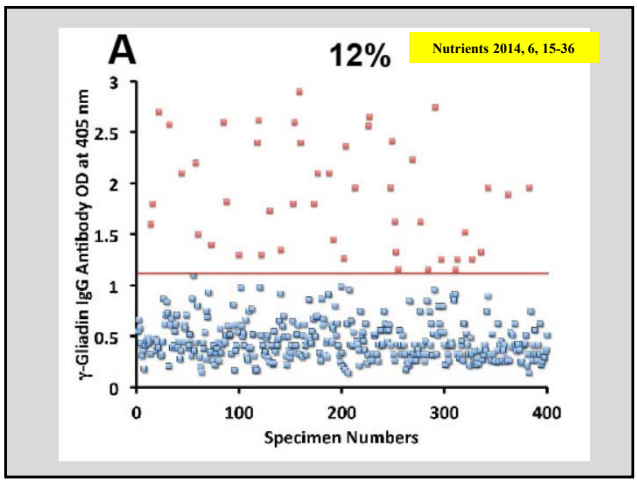
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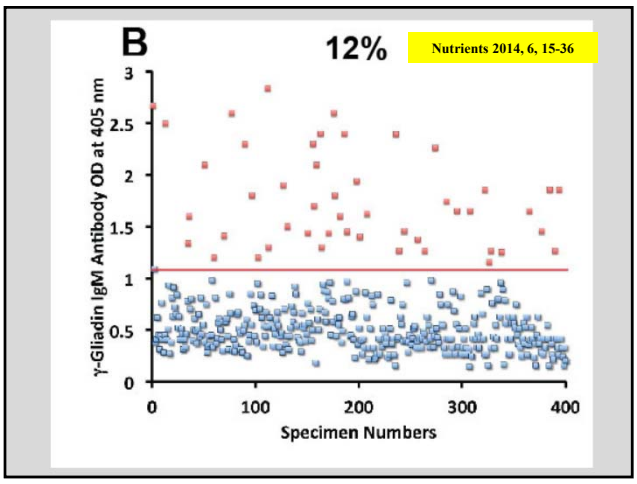
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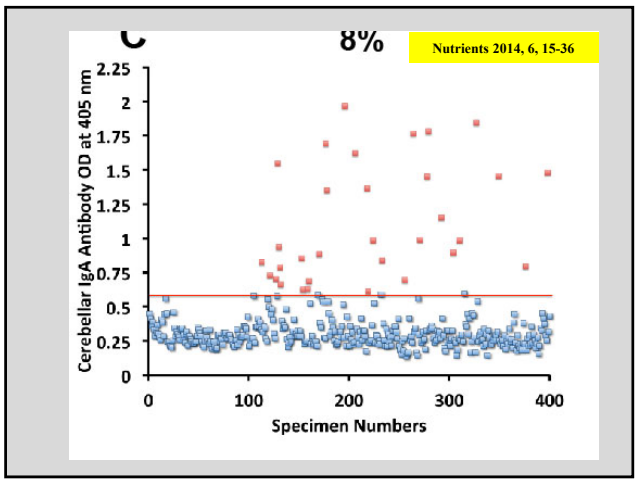
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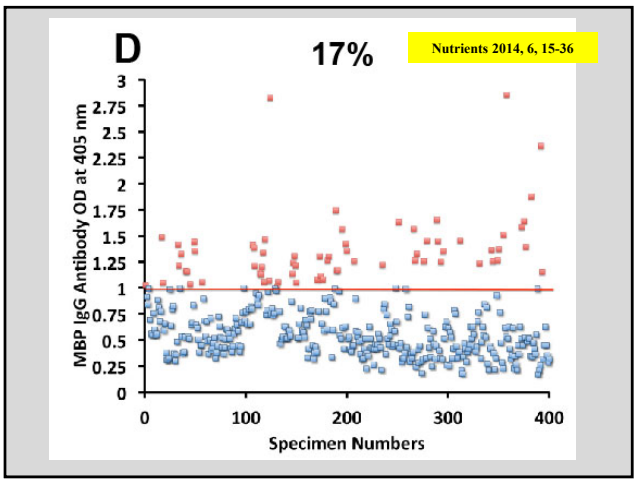
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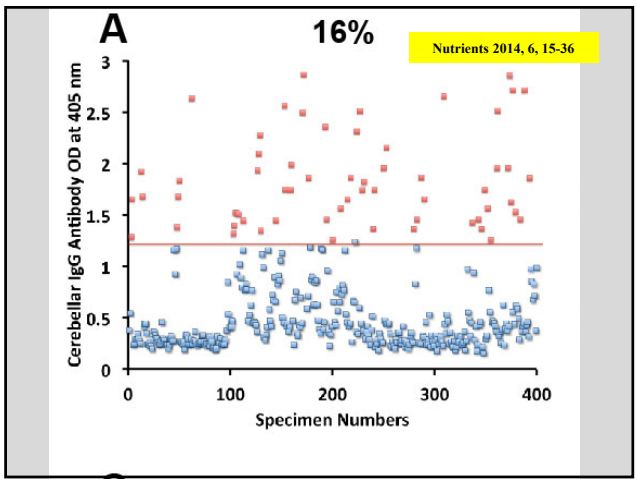
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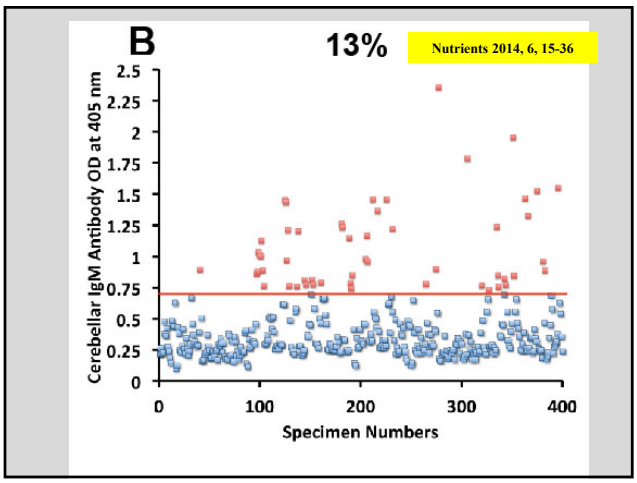
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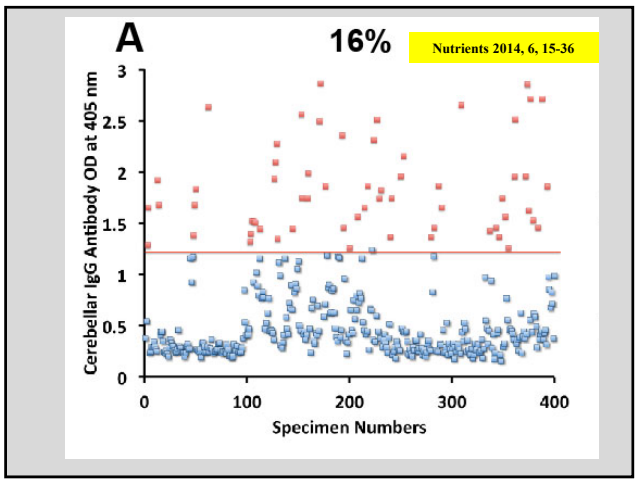
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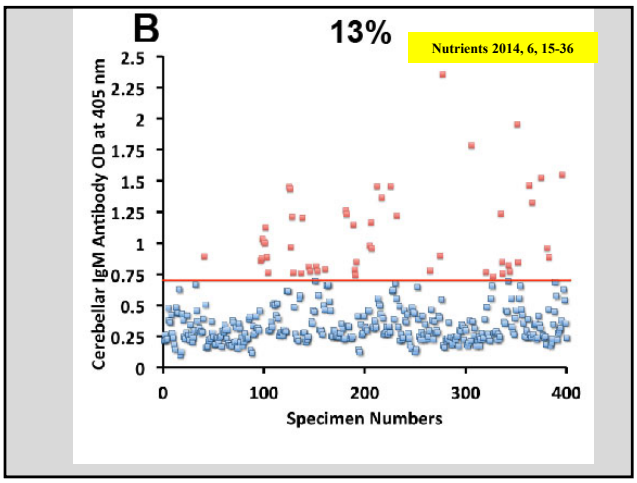
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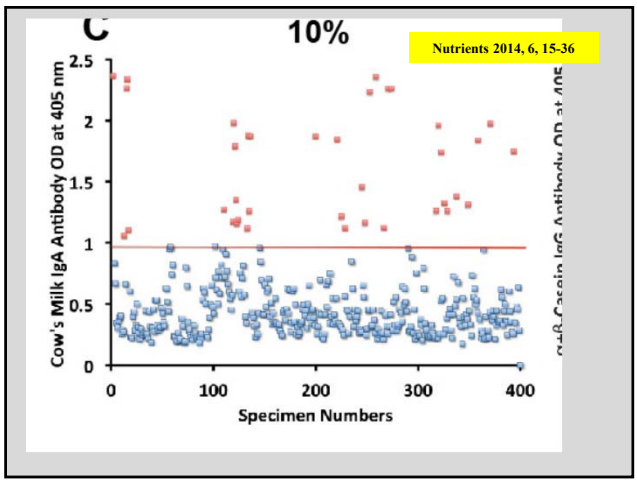
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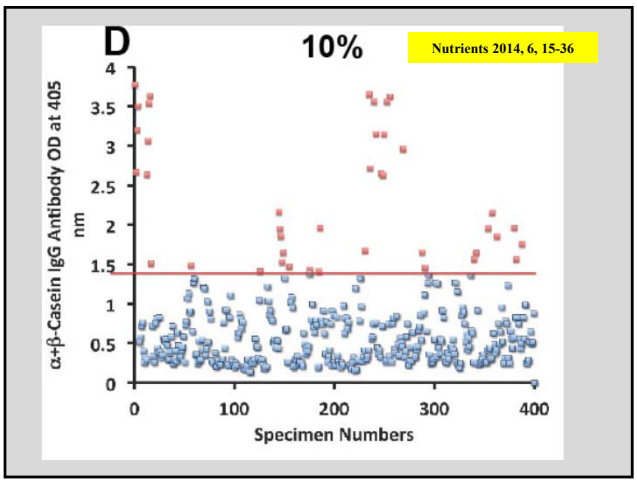
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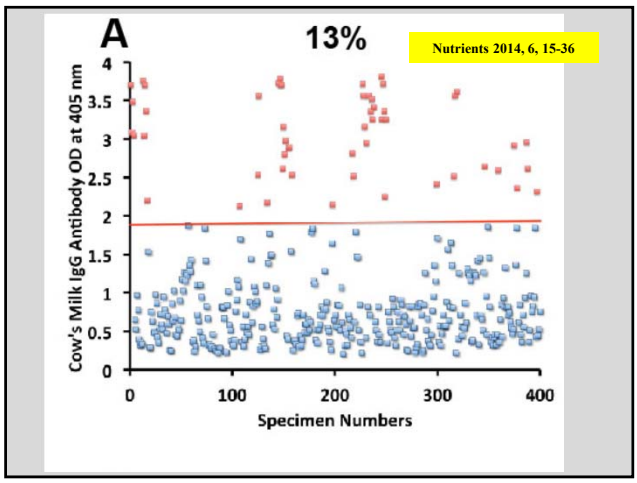
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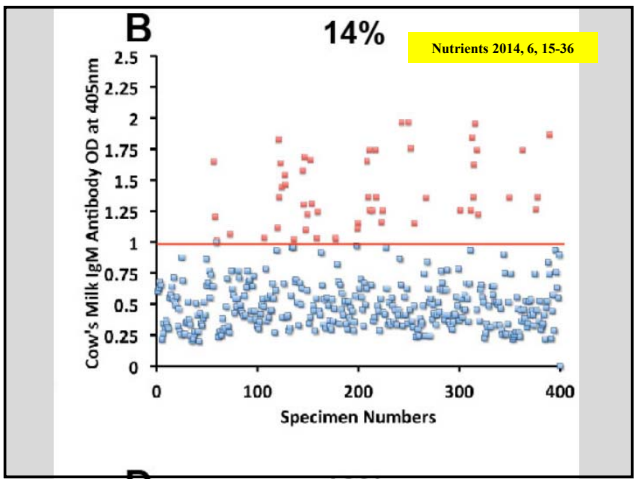
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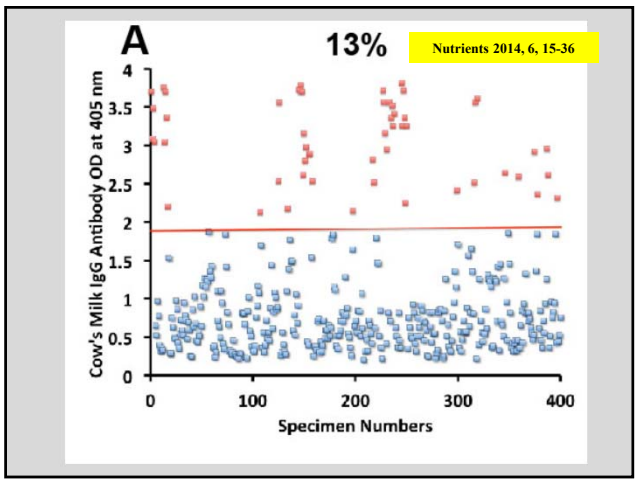
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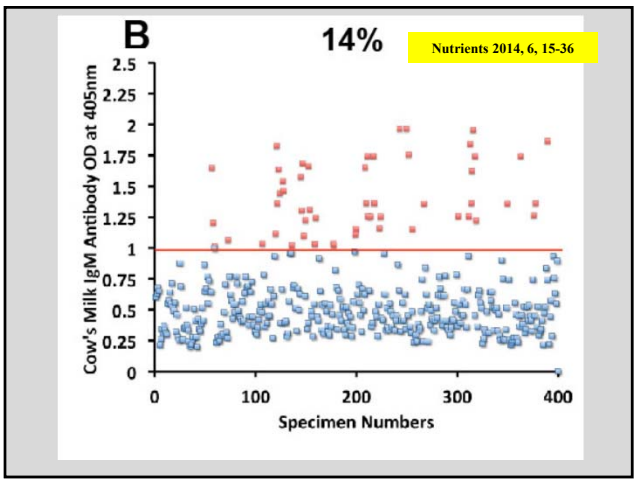
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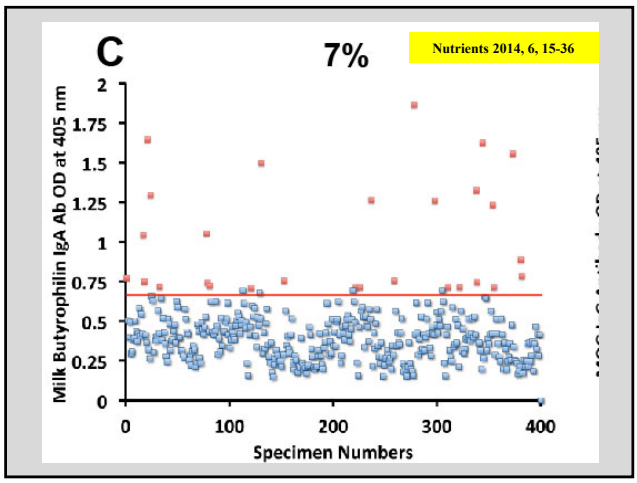
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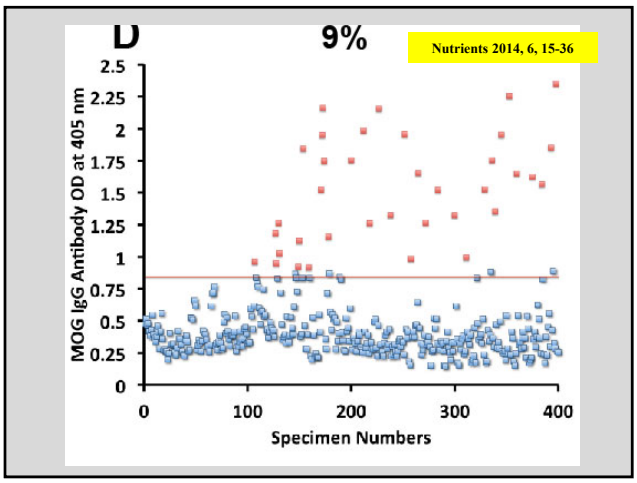
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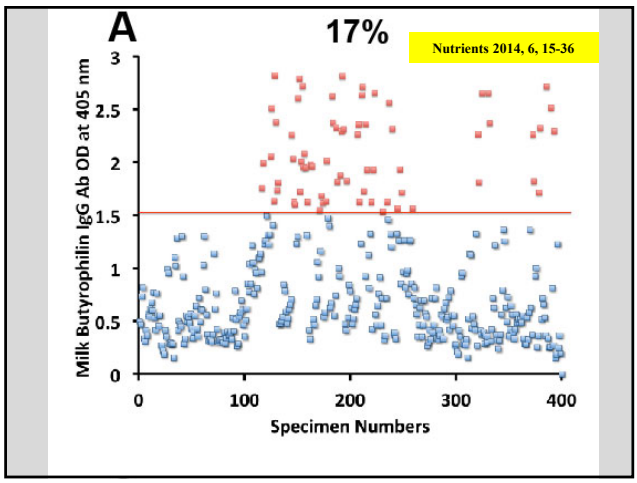
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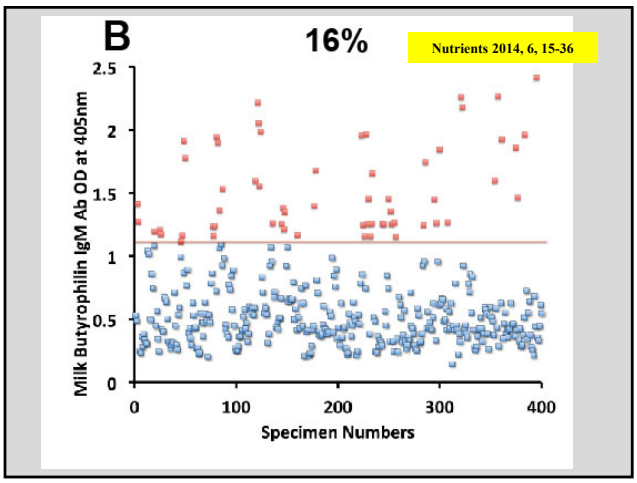
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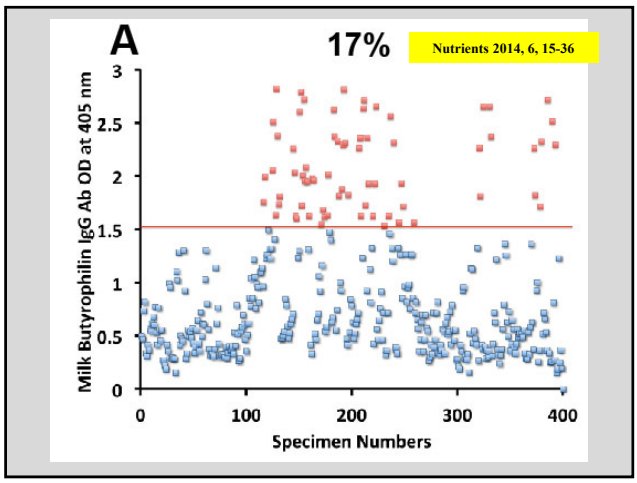

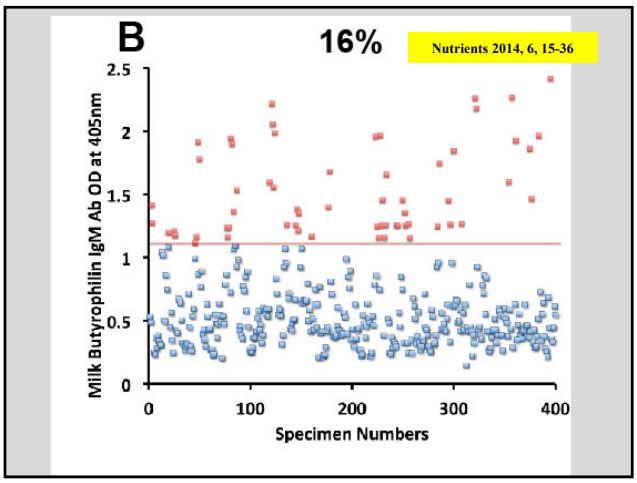

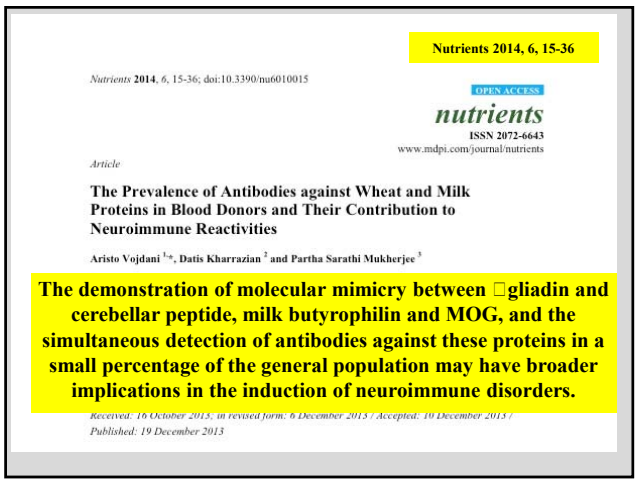
Nutrients 2014, 6, 15-36

Nutrients **2014**, *6*, 15-36; doi:10.3390/nu6010015

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nutrients

ISSN 2072-6643

www.mdpi.com/journal/nutrients

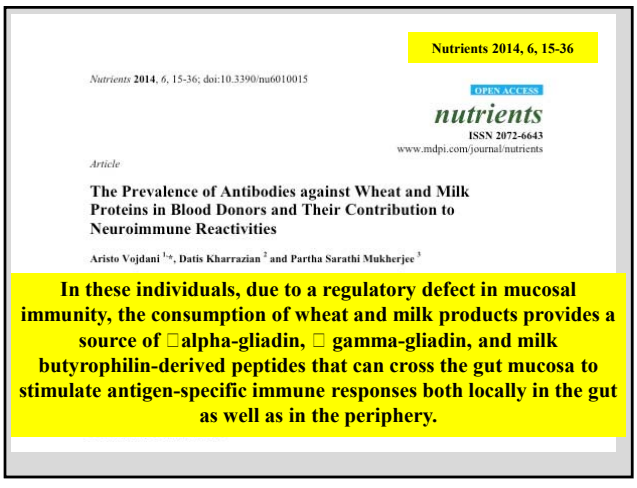
Article

The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities

Aristo Vojdani [1,*], Datis Kharrazian [2] and Partha Sarathi Mukherjee [3]

The demonstration of molecular mimicry between gliadin and cerebellar peptide, milk butyrophilin and MOG, and the simultaneous detection of antibodies against these proteins in a small percentage of the general population may have broader implications in the induction of neuroimmune disorders.

Received: 16 October 2013; in revised form: 6 December 2013 / Accepted: 10 December 2013 / Published: 19 December 2013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Article

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Aristo Vojdani [1,*], Datis Kharrazian [2] and Partha Sarathi Mukherjee [3]

In these individuals, due to a regulatory defect in mucosal immunity, the consumption of wheat and milk products provides a source of alpha-gliadin, gamma-gliadin, and milk butyrophilin-derived peptides that can cross the gut mucosa to stimulate antigen-specific immune responses both locally in the gut as well as in the periphery.

Nutrients 2014, 6, 15-36

Nutrients **2014**, *6*, 15-36; doi:10.3390/nu6010015

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Article

The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities

Aristo Vojdani [1,*], Datis Kharrazian [2] and Partha Sarathi Mukherjee [3]

The pathophysiological consequences of molecular mimicry involving wheat and milk with human tissue antigens are difficult to predict, as is the detection of antibodies against them in human sera.

Tel.: +1-310-657-1077; Fax: +1-310-657-1053.

Received: 16 October 2013; in revised form: 6 December 2013 / Accepted: 10 December 2013 / Published: 19 December 2013

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Article

The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities

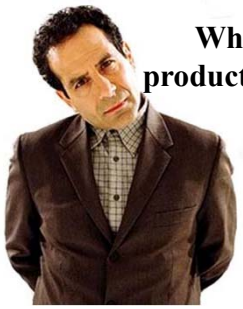
Aristo Vojdani [1,*], Datis Kharrazian [2] and Partha Sarathi Mukherjee [3]

This is because they can be influenced by multiple factors, including an individual's genotype, the timing and level of exposure, and the health of the gut and blood brain barriers, and as such these complex interactions deserve further study.

Received: 16 October 2013; in revised form: 6 December 2013 / Accepted: 10 December 2013 / Published: 19 December 2013

Premise #6

What is the Trigger in the production of Antibodies To Self?



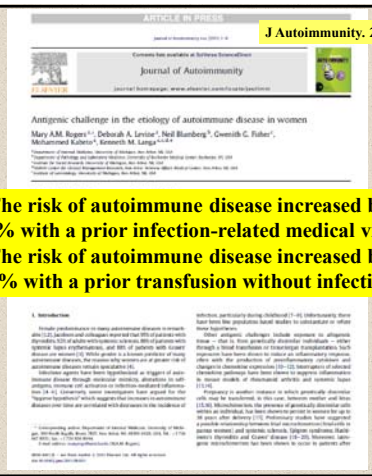
Detective Adrian Monk

155

There are numerous mechanisms that may trigger the production of antibodies to self.

- **Exposure to allergeneic tissue from genetically dissimilar individuals**
  - **-blood transfusion**
  - **-organ transplant**

156


Journal of Autoimmunity

Antigenic challenge in the etiology of autoimmune disease in women

J Autoimmunity. 2012 May;38(2-3)1

The risk of autoimmune disease increased by 41% with a prior infection-related medical visit. The risk of autoimmune disease increased by 90% with a prior transfusion without infection.

There are numerous mechanisms that may trigger the production of antibodies to self.

- **Exposure to allergeneic tissue from genetically dissimilar individuals**
  - **-blood transfusion**
  - **-organ transplant**
- **Pregnancy (Microchimerism, the presence of genetically dissimilar cells within an individual, has been shown to persist in women for up to 38 years after delivery)**
- **Infectious agents via molecular mimicry**
- **Infection mediated inflammation**
- **Molecular Mimicry to Food Antigens**
- **Antibodies to Neoepitopes**

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There are numerous mechanisms that may trigger the production of antibodies to self. Two primary ones are:

- **Molecular Mimicry to Food Antigens**
- **Antibodies to Neoepitopes**

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- **Molecular Mimicry to Food Antigens**

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Nutrients 2014, 6, 15-36

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Article

The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities

(In this study) approximately half of the sera with antibody elevation against gliadin reacted significantly with GAD-65 and cerebellar peptides.

Department of Mathematics, Boise State University, 1910 University Dr., Boise, ID 83725, USA; E-Mail: parthamukherjee@boisestate.edu

* Author to whom correspondence should be addressed; E-Mail: drari@msn.com; Tel.: +1-310-657-1077; Fax: +1-310-657-1053.

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Article

The Prevalence of Antibodies against Wheat and Milk Proteins in Blood Donors and Their Contribution to Neuroimmune Reactivities

Aristo Vojdani [1,*], Datis Kharrazian [2] and Partha Sarathi Mukherjee [3]

About half of the sera with elevated antibodies against □ alpha casein and milk butyrophilin also showed antibody elevation against MBP and MOG.

* Author to whom correspondence should be addressed; E-Mail: drari@msn.com; Tel.: +1-310-657-1077; Fax: +1-310-657-1053.

Received: 16 October 2013; in revised form: 6 December 2013 / Accepted: 10 December 2013 / Published: 19 December 2013

- **Antibodies to Neoepitopes**

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Clinic Rev Allerg Immunol (2010) 38:298–301

Fig. 1 The gliadin processing pathway. Cereal products are digested in the intestine and in this process gliadin is cleaved into peptides which react in the subsequent steps with tissue transglutaminase to form covalently cross-linked complexes

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Journal of Immunological Methods 429 (2016) 15–20

Contents lists available at ScienceDirect

Journal of Immunological Methods

journal homepage: www.elsevier.com/locate/jim

Research paper

Antibodies against neo-epitope tTg complexed to gliadin are different and more reliable then anti-tTg for the diagnosis of pediatric celiac disease

Aaron Lerner [a,b,*], Patricia Ieremias [a], Sandra Neidhöfer [a], Torsten Matthias [a]

There are three possibilities for autoantibody production:

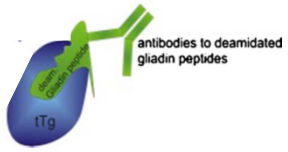
1. **Anti tTg,**
2. **Anti deamidated gliadin peptide, and**
3. **Anti tTg-neo, directed against the neo-complex of tTg cross-linked to the gliadin peptides.**

Keywords:
Celiac disease
Tissue transglutaminase
Neo-epitope tTg
Antibodies
Autoantibodies
Serological markers

Higher OD activity was detected for tTg-neo IgA, IgG and IgA + IgG than for tTg. tTg-neo IgA, IgG correlated better with intestinal damage than tTg. The tTg-neo combined IgA + IgG ELISA kit had higher sensitivity and a comparable specificity for the diagnosis of PCD. The drop in the % competition was much higher with the tTg-neo then the tTg antibodies. The false positivity of the tTg was significantly higher than the tTg-neo one. Serological diagnostic performances, reflection of intestinal damage, diverse epitopes and false positivity were better with the tTg-neo.

Clinic Rev Allerg Immunol (2010) 38:298–301

Fig. 3 The complex of deamidated gliadin peptides cross-linked with tissue transglutaminase (tTG) can detect three different antibodies entities: antibodies to tTg, to deamidated gliadin peptides and to the neo-epitope



Clinic Rev Allerg Immunol (2010) 38:298–301

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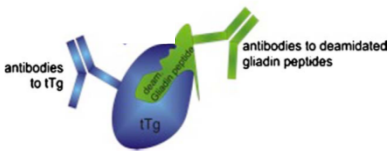

Clinic Rev Allerg Immunol (2010) 38:298–301

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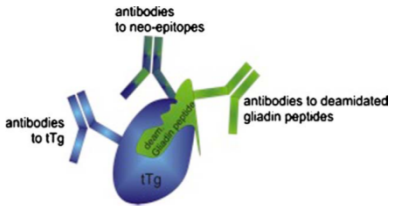

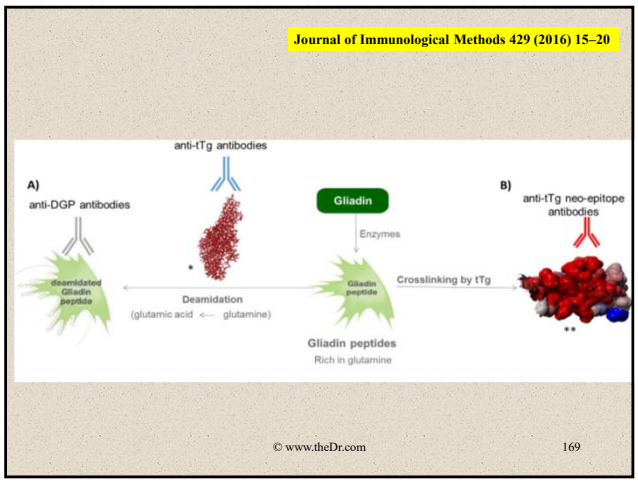
Journal of Immunological Methods 429 (2016) 15–20
anti-tTg antibodies
A)
anti-DGP antibodies
Gliadin
Enzymes
B)
anti-tTg neo-epitope antibodies
deamidated Gliadin peptide
Deamidation
(glutamic acid ← glutamine)
Gliadin peptide
Crosslinking by tTg
Gliadin peptides
Rich in glutamine
© www.theDr.com
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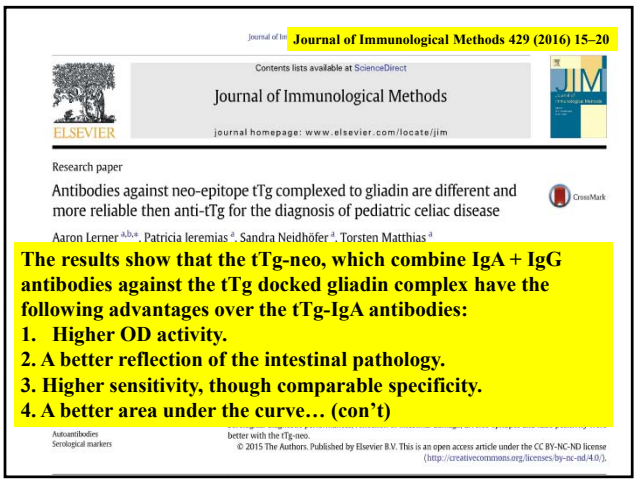
Journal of Immunological Methods 429 (2016) 15–20
Contents lists available at ScienceDirect
Journal of Immunological Methods
journal homepage: www.elsevier.com/locate/jim
Research paper
Antibodies against neo-epitope tTg complexed to gliadin are different and more reliable then anti-tTg for the diagnosis of pediatric celiac disease
Aaron Lerner, Patricia Ieremias, Sandra Neidhöfer, Torsten Matthias
The results show that the tTg-neo, which combine IgA + IgG antibodies against the tTg docked gliadin complex have the following advantages over the tTg-IgA antibodies:
1. Higher OD activity.
2. A better reflection of the intestinal pathology.
3. Higher sensitivity, though comparable specificity.
4. A better area under the curve… (con't)
Autoantibodies
Serological markers
better with the tTg-neo.
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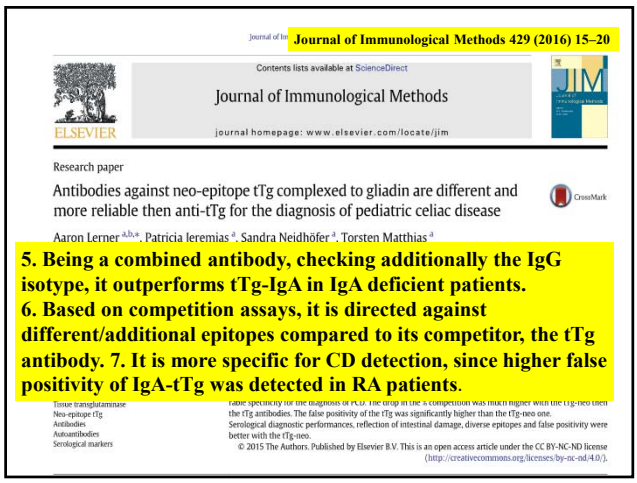
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Research paper
Antibodies against neo-epitope tTg complexed to gliadin are different and more reliable then anti-tTg for the diagnosis of pediatric celiac disease
Aaron Lerner, Patricia Ieremias, Sandra Neidhöfer, Torsten Matthias
5. Being a combined antibody, checking additionally the IgG isotype, it outperforms tTg-IgA in IgA deficient patients.
6. Based on competition assays, it is directed against different/additional epitopes compared to its competitor, the tTg antibody. 7. It is more specific for CD detection, since higher false positivity of IgA-tTg was detected in RA patients.
Tissue transglutaminase
Neo-epitope tTg
Antibodies
Autoantibodies
Serological markers
the tTg antibodies. The false positivity of the tTg was significantly higher than the tTg-neo one.
Serological diagnostic performances, reflection of intestinal damage, diverse epitopes and false positivity were better with the tTg-neo.
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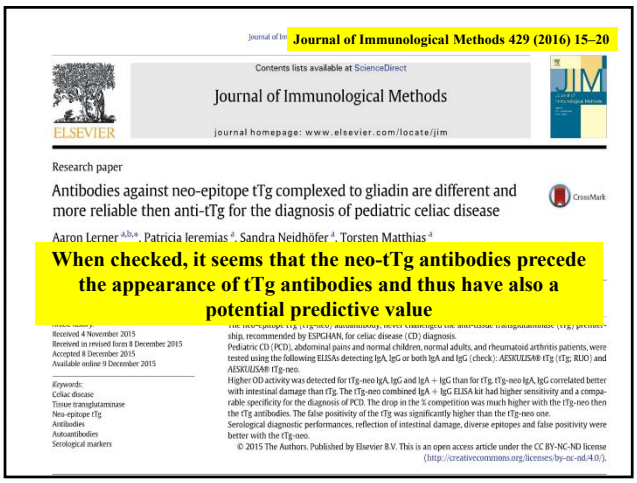
Journal of Immunological Methods 429 (2016) 15–20
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journal homepage: www.elsevier.com/locate/jim
Research paper
Antibodies against neo-epitope tTg complexed to gliadin are different and more reliable then anti-tTg for the diagnosis of pediatric celiac disease
Aaron Lerner, Patricia Ieremias, Sandra Neidhöfer, Torsten Matthias
When checked, it seems that the neo-tTg antibodies precede the appearance of tTg antibodies and thus have also a potential predictive value
Received 4 November 2015
Received in revised form 8 December 2015
Accepted 8 December 2015
Available online 9 December 2015
Keywords:
Celiac disease
Tissue transglutaminase
Neo-epitope tTg
Antibodies
Autoantibodies
Serological markers
ship, recommended by ESPGHAN, for celiac disease (CD) diagnosis.
Pediatric CD (PCD), abdominal pains and normal children, normal adults, and rheumatoid arthritis patients, were tested using the following ELISAs detecting IgA, IgG or both IgA and IgG (check): AESKULISA® tTg (tTg; RUO) and AESKULISA® tTg-neo.
Higher OD activity was detected for tTg-neo IgA, IgG and IgA + IgG than for tTg. tTg-neo IgA, IgG correlated better with intestinal damage than tTg. The tTg-neo combined IgA + IgG ELISA kit had higher sensitivity and a comparable specificity for the diagnosis of PCD. The drop in the % competition was much higher with the tTg-neo then the tTg antibodies. The false positivity of the tTg was significantly higher than the tTg-neo one.
Serological diagnostic performances, reflection of intestinal damage, diverse epitopes and false positivity were better with the tTg-neo.
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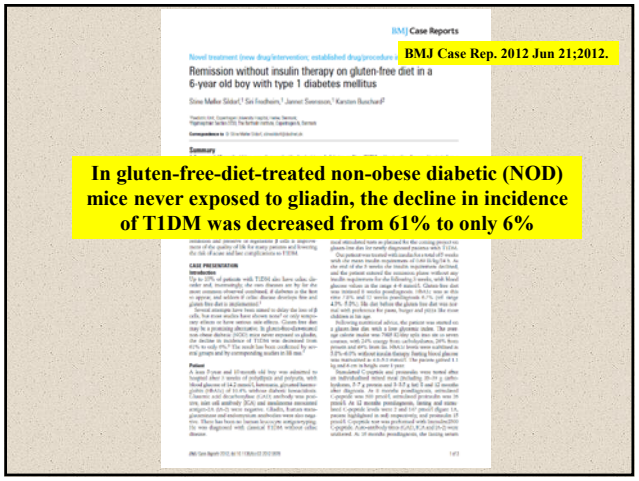
CASE STUDY #1

Reversal of Type 1 Diabetes by eliminating an environmental trigger

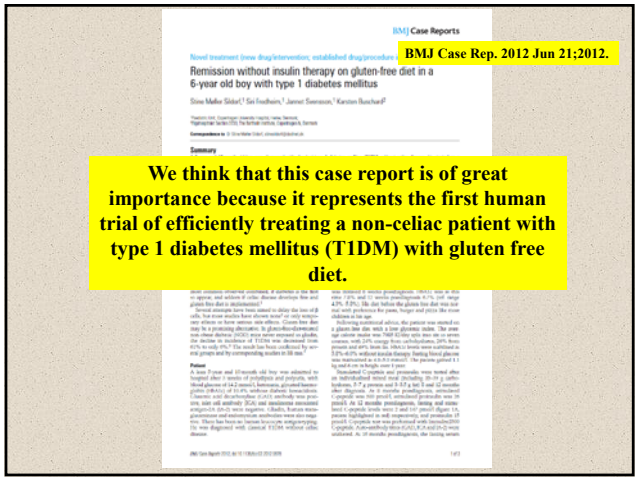


BMJ Case Reports

BMJ Case Rep. 2012 Jun 21;2012.

Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus

In gluten-free-diet-treated non-obese diabetic (NOD) mice never exposed to gliadin, the decline in incidence of T1DM was decreased from 61% to only 6%

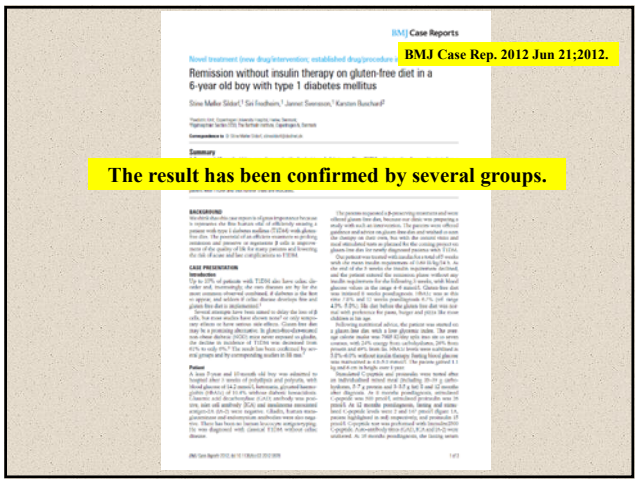


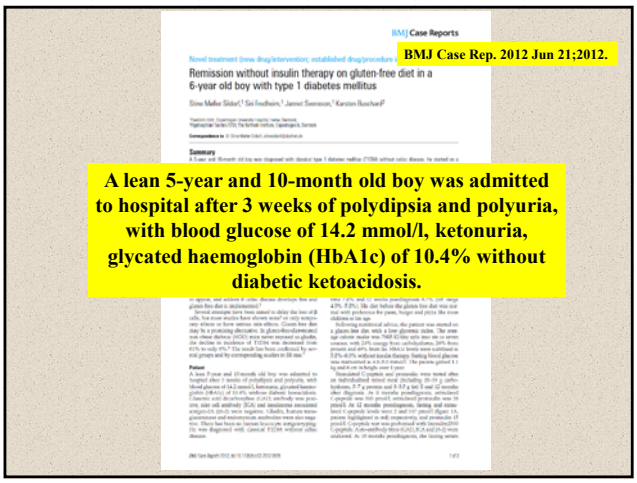
BMJ Case Reports

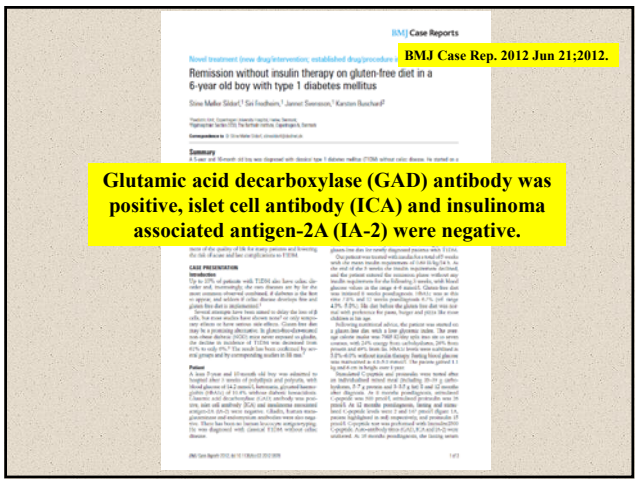
BMJ Case Rep. 2012 Jun 21;2012.

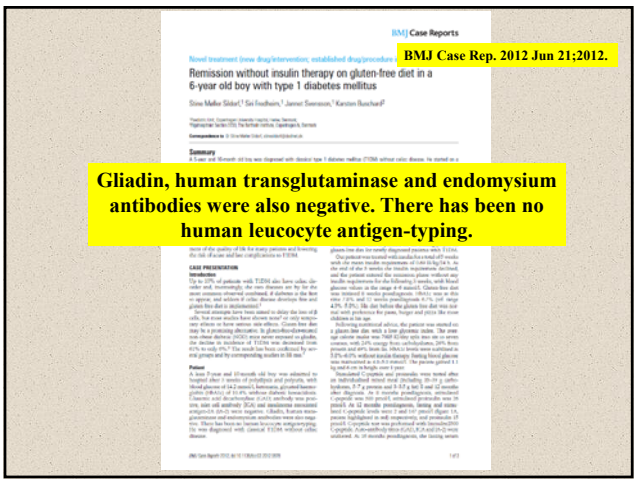
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus

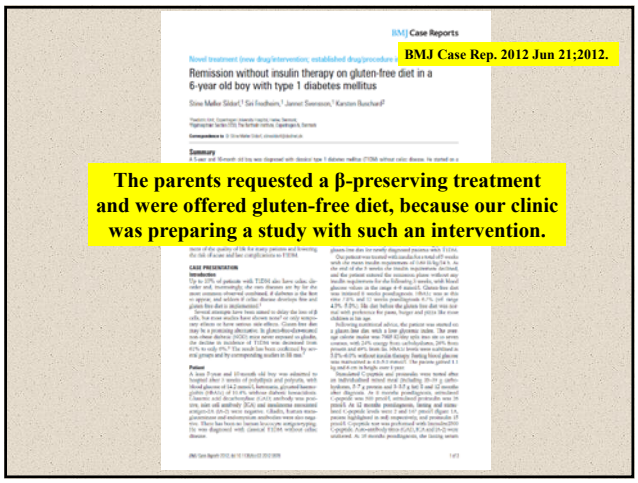
We think that this case report is of great importance because it represents the first human trial of efficiently treating a non-celiac patient with type 1 diabetes mellitus (T1DM) with gluten free diet.

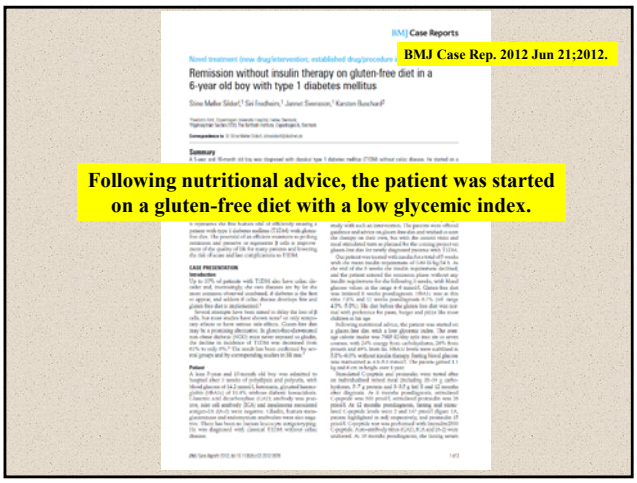

BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
The result has been confirmed by several groups.

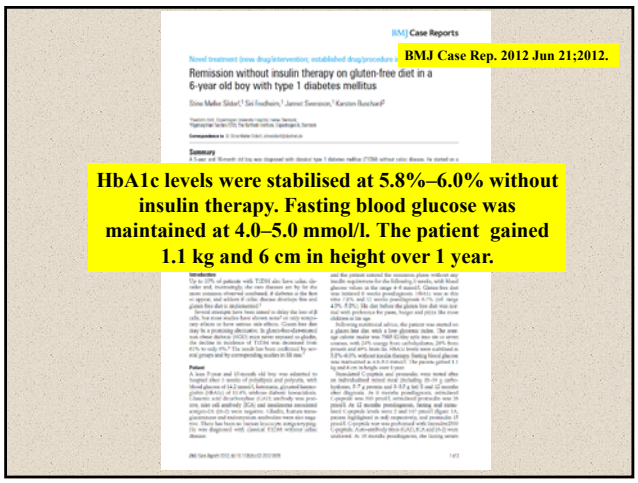

BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
A lean 5-year and 10-month old boy was admitted to hospital after 3 weeks of polydipsia and polyuria, with blood glucose of 14.2 mmol/l, ketonuria, glycated haemoglobin (HbA1c) of 10.4% without diabetic ketoacidosis.

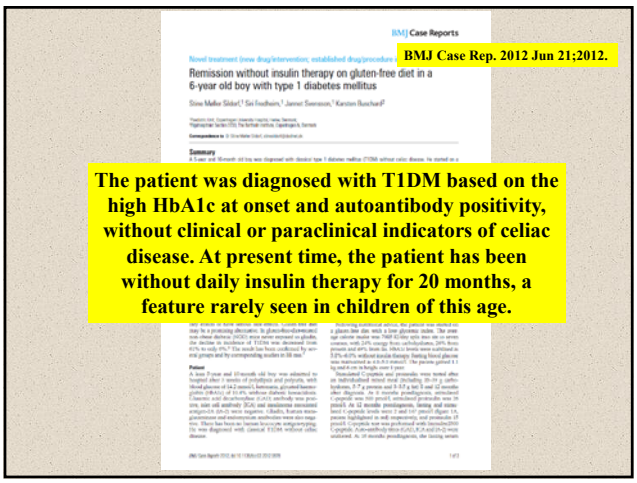

BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
Glutamic acid decarboxylase (GAD) antibody was positive, islet cell antibody (ICA) and insulinoma associated antigen-2A (IA-2) were negative.


BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
Gliadin, human transglutaminase and endomysium antibodies were also negative. There has been no human leucocyte antigen-typing.


BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
The parents requested a β-preserving treatment and were offered gluten-free diet, because our clinic was preparing a study with such an intervention.


BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
Following nutritional advice, the patient was started on a gluten-free diet with a low glycemic index.


BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
HbA1c levels were stabilised at 5.8%–6.0% without insulin therapy. Fasting blood glucose was maintained at 4.0–5.0 mmol/l. The patient gained 1.1 kg and 6 cm in height over 1 year.


BMJ Case Reports
BMJ Case Rep. 2012 Jun 21;2012.
Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus
The patient was diagnosed with T1DM based on the high HbA1c at onset and autoantibody positivity, without clinical or paraclinical indicators of celiac disease. At present time, the patient has been without daily insulin therapy for 20 months, a feature rarely seen in children of this age.

BMJ Case Reports

Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus

BMJ Case Rep. 2012 Jun 21;2012.

CONCLUSION
A child with classical newly diagnosed T1DM started on a gluten-free diet, remains without the need for exogenous insulin after 20 months. The gluten-free diet is safe and without side effects. We propose that the gluten-free diet prolonged remission in this patient with T1DM and that further trials are indicated.

Springerplus. 2016 Jul 7;5(1):994

SpringerPlus

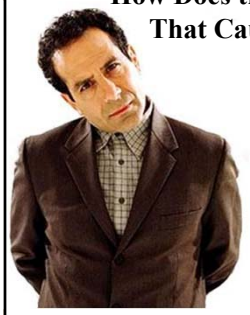
RESEARCH Open Access

Potential beneficial effects of a gluten-free diet in newly diagnosed children with type 1 diabetes: a pilot study

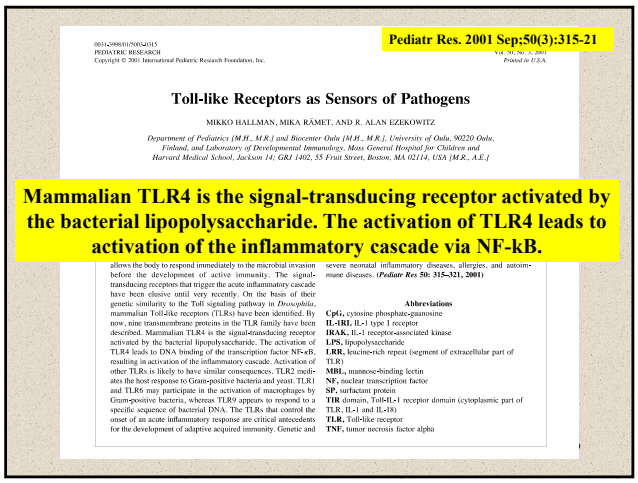
Gluten-free diet is is associated with a significantly better out-come as assessed by HbA1c and IDAA1c.
Three times as many children were still in PR based on IDAA1c ($p < 0.05$). Twelve months after onset HbA1c were 21 % lower and Insulin Dose Adjusted A1c >1 unit lower in the cohort on a gluten-free diet compared to the two previous cohorts ($p < 0.001$).

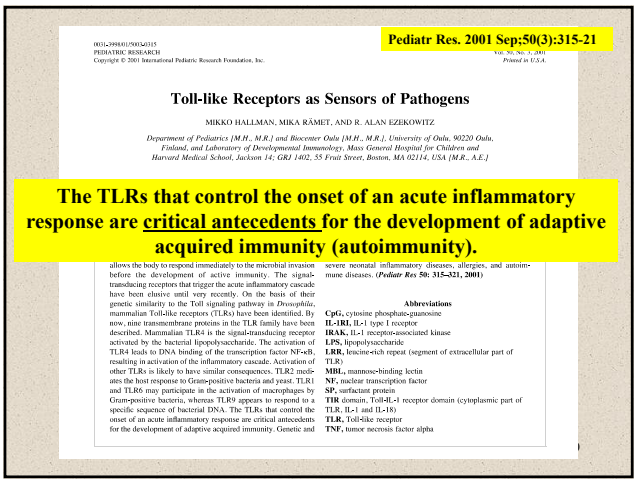
Premise #7

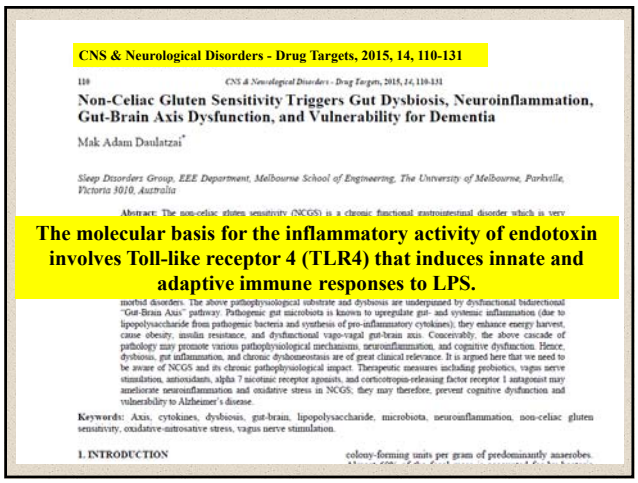
How Does the Inflammatory Cascade Begin That Causes Intestinal Permeability?

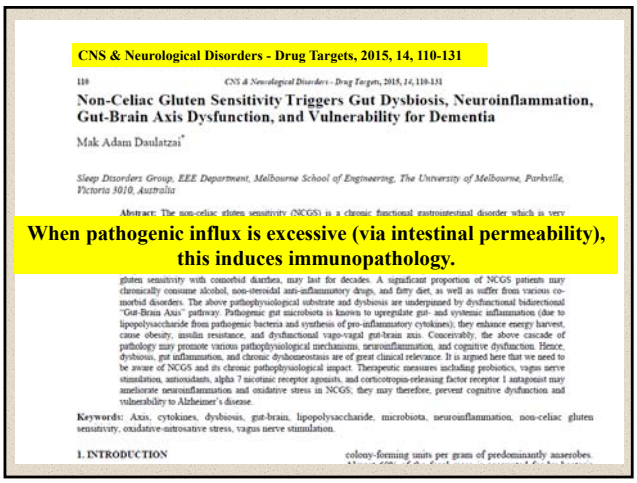


Detective Adrian Monk


Pediatr Res. 2001 Sep;50(3):315-21
Toll-like Receptors as Sensors of Pathogens
MIKKO HALLMAN, MIKA RÄMET, AND R. ALAN EZEKOWITZ
Mammalian TLR4 is the signal-transducing receptor activated by the bacterial lipopolysaccharide. The activation of TLR4 leads to activation of the inflammatory cascade via NF-kB.


Pediatr Res. 2001 Sep;50(3):315-21
Toll-like Receptors as Sensors of Pathogens
MIKKO HALLMAN, MIKA RÄMET, AND R. ALAN EZEKOWITZ
The TLRs that control the onset of an acute inflammatory response are critical antecedents for the development of adaptive acquired immunity (autoimmunity).


CNS & Neurological Disorders - Drug Targets, 2015, 14, 110-131
Non-Celiac Gluten Sensitivity Triggers Gut Dysbiosis, Neuroinflammation, Gut-Brain Axis Dysfunction, and Vulnerability for Dementia
Mak Adam Daulatzai
The molecular basis for the inflammatory activity of endotoxin involves Toll-like receptor 4 (TLR4) that induces innate and adaptive immune responses to LPS.


CNS & Neurological Disorders - Drug Targets, 2015, 14, 110-131
Non-Celiac Gluten Sensitivity Triggers Gut Dysbiosis, Neuroinflammation, Gut-Brain Axis Dysfunction, and Vulnerability for Dementia
Mak Adam Daulatzai
When pathogenic influx is excessive (via intestinal permeability), this induces immunopathology.

CNS & Neurological Disorders - Drug Targets, 2015, 14, 110-131

110 *CNS & Neurological Disorders - Drug Targets, 2015, 14, 110-131*

Non-Celiac Gluten Sensitivity Triggers Gut Dysbiosis, Neuroinflammation, Gut-Brain Axis Dysfunction, and Vulnerability for Dementia

Mak Adam Daulatzai*

Sleep Disorders Group, EEE Department, Melbourne School of Engineering, The University of Melbourne, Parkville, Victoria 3010, Australia

Abstract: The non-celiac gluten sensitivity (NCGS) is a chronic functional gastrointestinal disorder which is very

TLR4 acts as a co-receptor for LPS (along with gluten).

inflammation, diarrhea, constipation, visceral hypersensitivity, abdominal pain, dysfunctional metabolic state, and peripheral immune and neuro-immune communication. Thus, immune-mediated gut and extra-gut dysfunctions, due to gluten sensitivity with comorbid diarrhea, may last for decades. A significant proportion of NCGS patients may chronically consume alcohol, non-steroidal anti-inflammatory drugs, and fatty diet, as well as suffer from various co-morbid disorders. The above pathophysiological substrate and dysbiosis are underpinned by dysfunctional bidirectional "Gut-Brain Axis" pathway. Pathogenic gut microbiota is known to upregulate gut- and systemic inflammation (due to lipopolysaccharide from pathogenic bacteria and synthesis of pro-inflammatory cytokines); they enhance energy harvest, cause obesity, insulin resistance, and dysfunctional vago-vagal gut-brain axis. Conceivably, the above cascade of pathology may promote various pathophysiological mechanisms, neuroinflammation, and cognitive dysfunction. Hence, dysbiosis, gut inflammation, and chronic dyshomeostasis are of great clinical relevance. It is argued here that we need to be aware of NCGS and its chronic pathophysiological impact. Therapeutic measures including probiotics, vagus nerve stimulation, antioxidants, alpha 7 nicotinic receptor agonists, and corticotropin-releasing factor receptor 1 antagonist may ameliorate neuroinflammation and oxidative stress in NCGS; they may therefore, prevent cognitive dysfunction and vulnerability to Alzheimer's disease.

Keywords: Axis, cytokines, dysbiosis, gut-brain, lipopolysaccharide, microbiota, neuroinflammation, non-celiac gluten sensitivity, oxidative-nitrosative stress, vagus nerve stimulation.

1. INTRODUCTION

colony-forming units per gram of predominantly anaerobes.

Best Practice & Research Clinical Gastroenterology 29 (2015) 469e476

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

ELSEVIER

9

Non-celiac wheat sensitivity: Differential diagnosis, triggers and implications

Detlef Schuppan, MD,PhD [a, b, *], Geethanjali Pickert, PhD [a], Muhammad Ashfaq-Khan, BSci [a], Victor Zevallos, PhD [a]

Wheat amylase-trypsin inhibitors …are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa.

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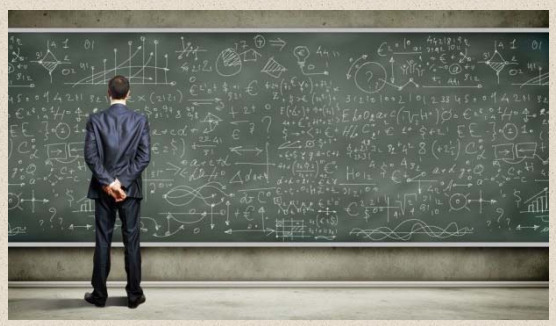
All 39 studies are available to you at www.theDr.com/Shine
24 of the 39 are the full articles and are free



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Premise #8
How do we Arrest Pathogenic Intestinal Permeability

Detective Adrian Monk

 198

In Healing the Gut, Consider a Pleiotropic Approach

we stand a greater chance of success by considering *pleiotropic drugs* or *gut cocktails* consisting of natural pleiotropic agents. Pleiotropic (Greek *pleio,* meaning "many," and *trepein,* meaning "to turn, to convert") substances are those that invoke multiple mechanisms, and provide multiple effects. Some nutrients are pleiotrophic.

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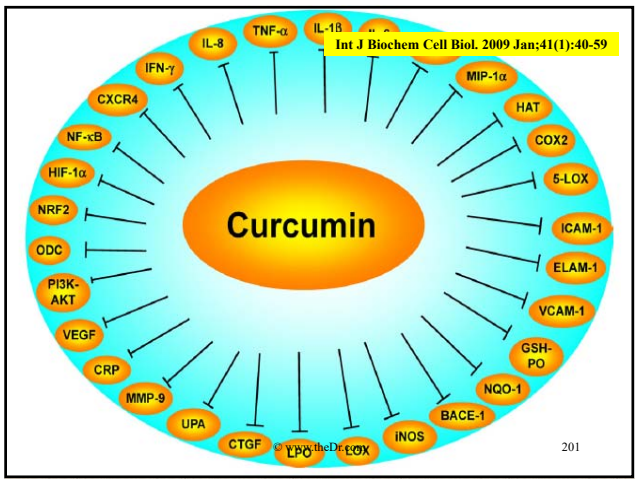
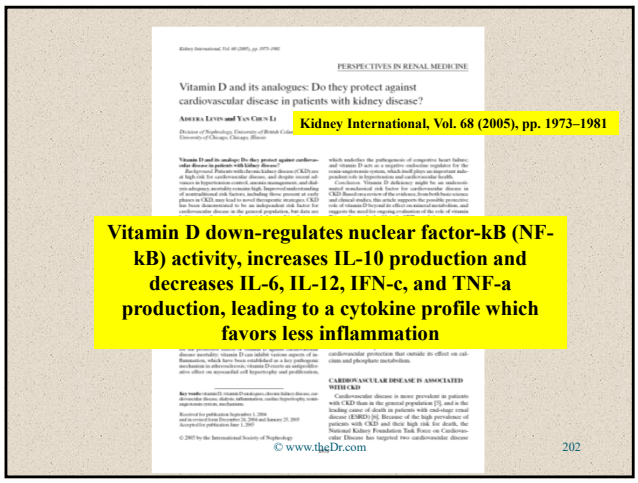


Int J Biochem Cell Biol. 2009 Jan;41(1):40-59

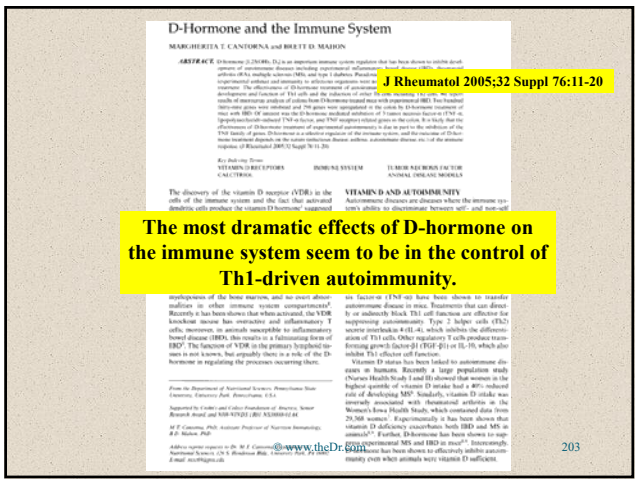


PERSPECTIVES IN RENAL MEDICINE

Vitamin D and its analogues: Do they protect against cardiovascular disease in patients with kidney disease?

Kidney International, Vol. 68 (2005), pp. 1973–1981

Vitamin D down-regulates nuclear factor-kB (NF-kB) activity, increases IL-10 production and decreases IL-6, IL-12, IFN-c, and TNF-a production, leading to a cytokine profile which favors less inflammation

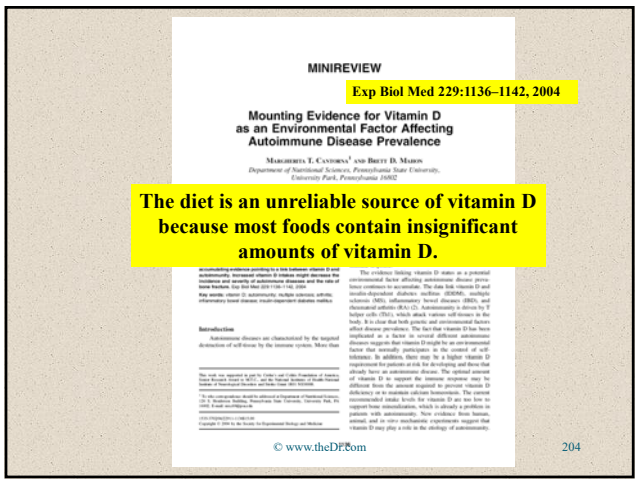


D-Hormone and the Immune System

MARGHERITA T. CANTORNA and BRETT D. MAHON

J Rheumatol 2005;32 Suppl 76:11-20

The most dramatic effects of D-hormone on the immune system seem to be in the control of Th1-driven autoimmunity.

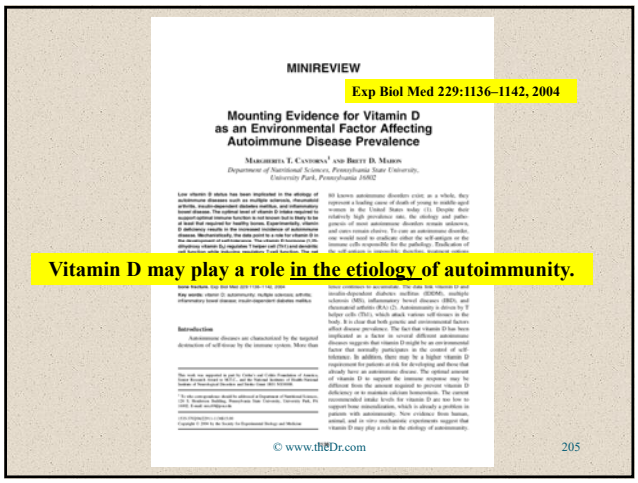


MINIREVIEW

Mounting Evidence for Vitamin D as an Environmental Factor Affecting Autoimmune Disease Prevalence

Exp Biol Med 229:1136–1142, 2004

The diet is an unreliable source of vitamin D because most foods contain insignificant amounts of vitamin D.


MINIREVIEW
Exp Biol Med 229:1136–1142, 2004
Mounting Evidence for Vitamin D as an Environmental Factor Affecting Autoimmune Disease Prevalence
Vitamin D may play a role in the etiology of autoimmunity.
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Endocrinology. 1997 Jun;138(6):2241-8
1,25-Dihydroxyvitamin D3 Stimulates the Assembly of Adherens Junctions in Keratinocytes: Involvement of Protein Kinase C
We investigated whether 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] was able to stimulate the assembly of adherens junctions and/or desmosomes.
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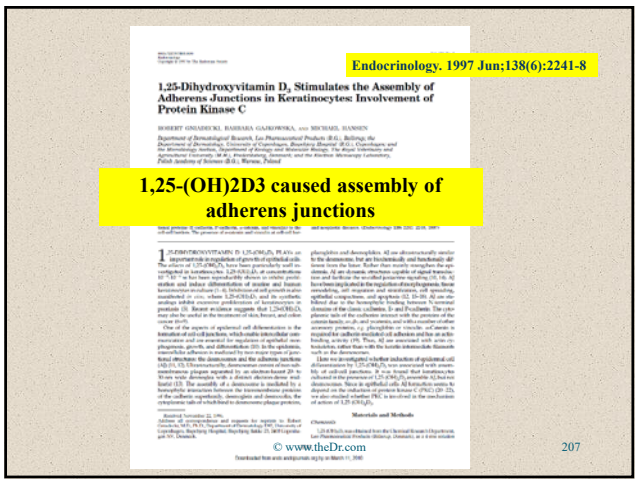
Endocrinology. 1997 Jun;138(6):2241-8
1,25-Dihydroxyvitamin D3 Stimulates the Assembly of Adherens Junctions in Keratinocytes: Involvement of Protein Kinase C
1,25-(OH)2D3 caused assembly of adherens junctions
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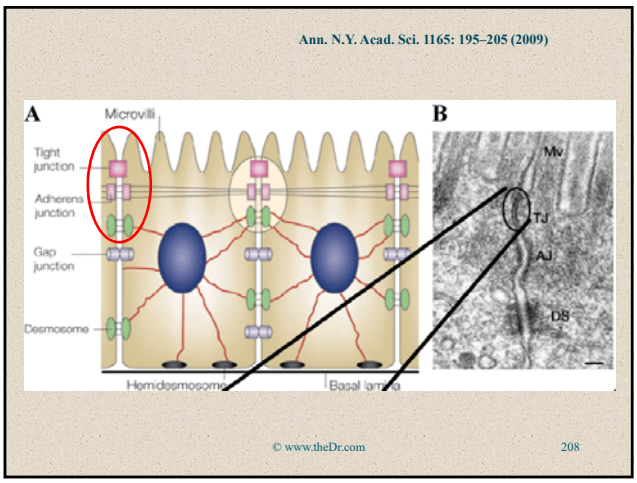
Ann. N.Y. Acad. Sci. 1165: 195–205 (2009)
A
Microvilli
Tight junction
Adherens junction
Gap junction
Desmosome
Hemidesmosome
Basal lamina
B
Mv
TJ
AJ
DS
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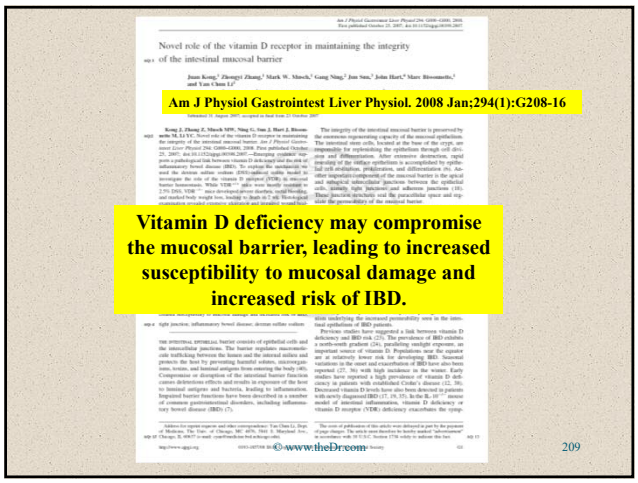
Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier
Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294(1):G208-16
Vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.
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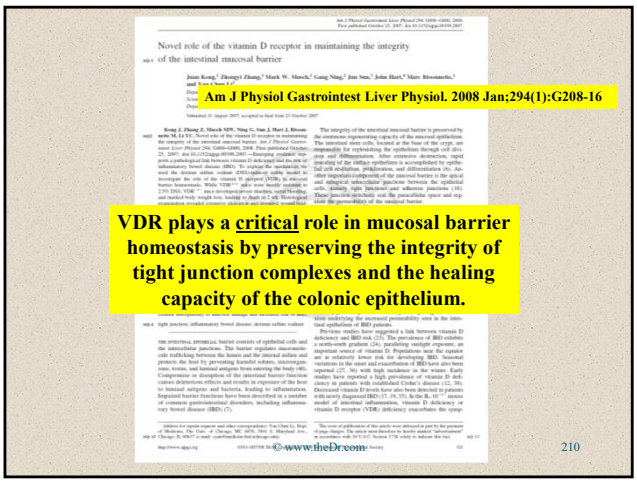
Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier
Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294(1):G208-16
VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of tight junction complexes and the healing capacity of the colonic epithelium.
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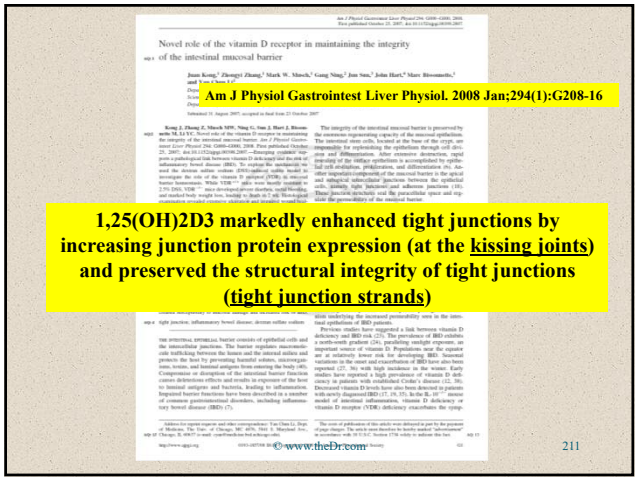
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1,25(OH)2D3 markedly enhanced tight junctions by increasing junction protein expression (at the kissing joints) and preserved the structural integrity of tight junctions (tight junction strands)
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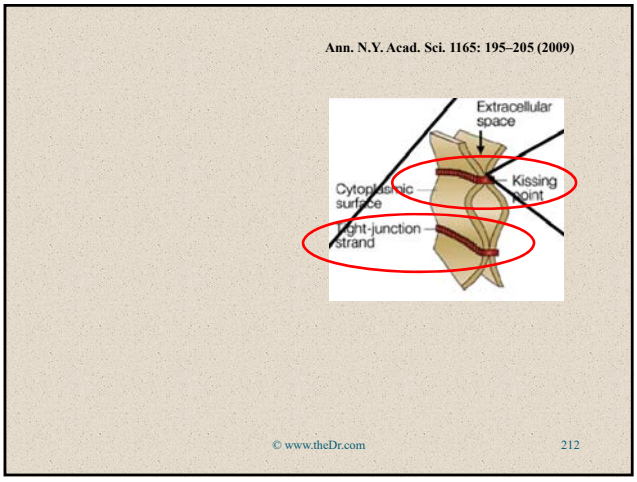
Ann. N.Y. Acad. Sci. 1165: 195–205 (2009)
Extracellular space
Kissing point
Cytoplasmic surface
Tight-junction strand
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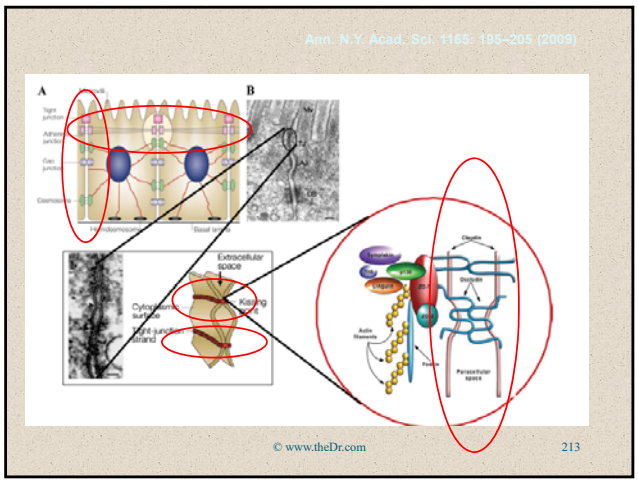
Ann. N.Y. Acad. Sci. 1165: 195–205 (2009)
A
B
Extracellular space
Cytoplasmic surface
Kissing
Tight-junction strand
Claudin
Occludin
Actin filaments
Paracellular space
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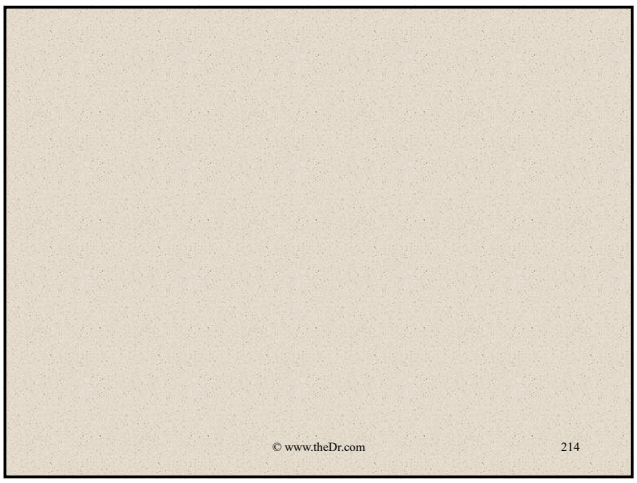
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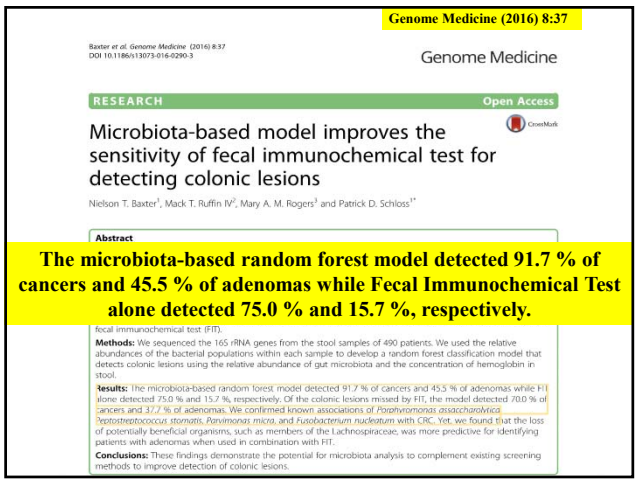
Genome Medicine (2016) 8:37
Baxter et al. Genome Medicine (2016) 8:37
DOI 10.1186/s13073-016-0290-3
Genome Medicine
RESEARCH
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Microbiota-based model improves the sensitivity of fecal immunochemical test for detecting colonic lesions
Nielson T. Baxter[1], Mack T. Ruffin IV[2], Mary A. M. Rogers[3] and Patrick D. Schloss[1*]
Abstract
The microbiota-based random forest model detected 91.7 % of cancers and 45.5 % of adenomas while Fecal Immunochemical Test alone detected 75.0 % and 15.7 %, respectively.
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Methods: We sequenced the 16S rRNA genes from the stool samples of 490 patients. We used the relative abundances of the bacterial populations within each sample to develop a random forest classification model that detects colonic lesions using the relative abundance of gut microbiota and the concentration of hemoglobin in stool.
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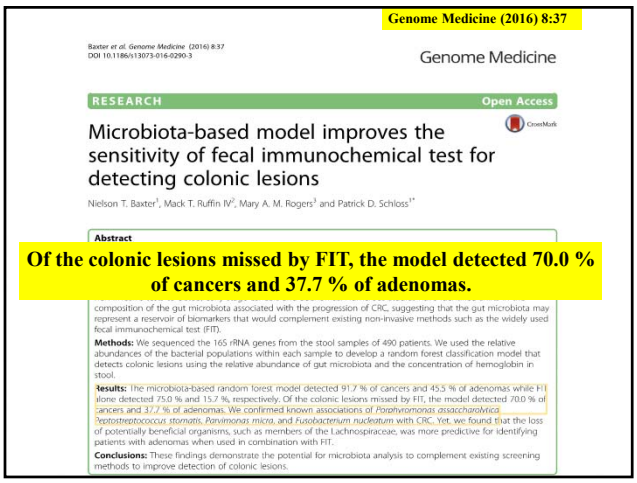
Conclusions: These findings demonstrate the potential for microbiota analysis to complement existing screening methods to improve detection of colonic lesions.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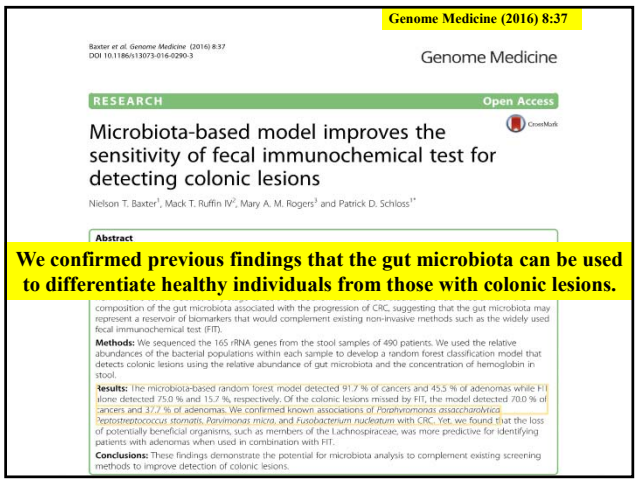
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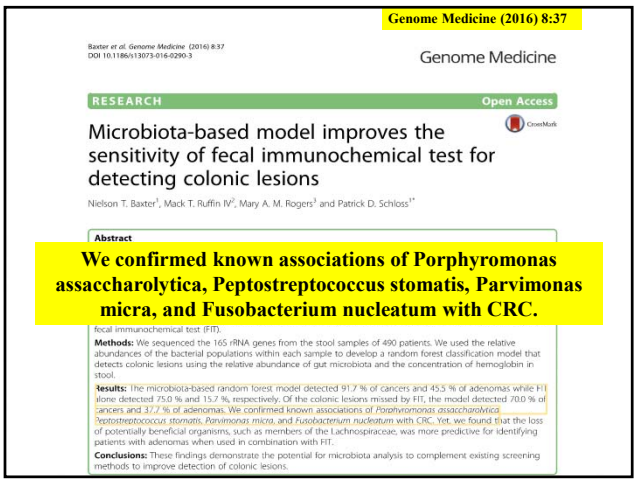
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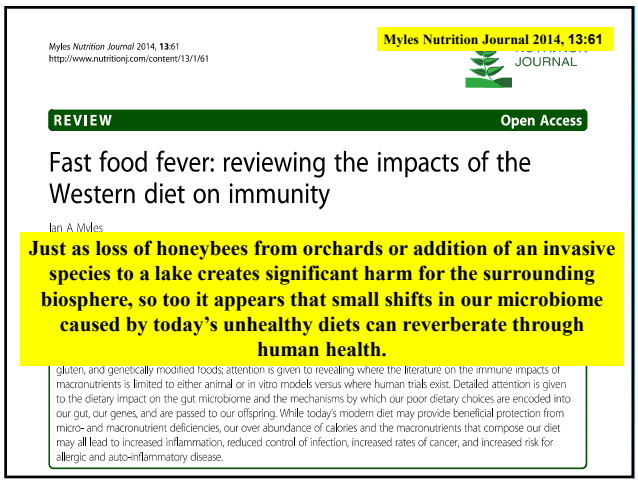
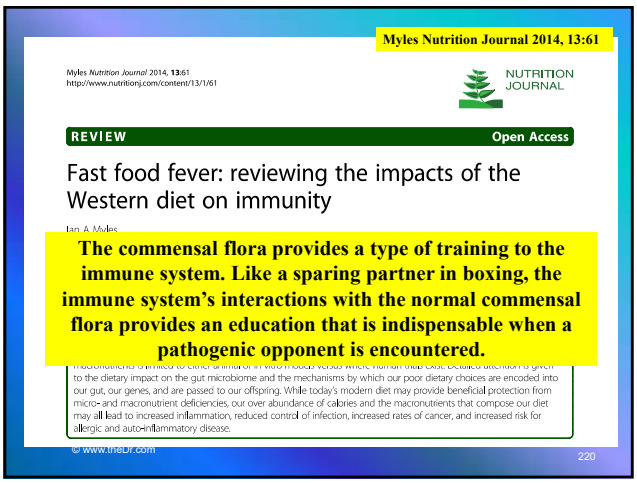

Myles Nutrition Journal 2014, 13:61
Myles Nutrition Journal 2014, 13:61
http://www.nutritionj.com/content/13/1/61
JOURNAL
REVIEW
Open Access
Fast food fever: reviewing the impacts of the Western diet on immunity
Ian A Myles
Just as loss of honeybees from orchards or addition of an invasive species to a lake creates significant harm for the surrounding biosphere, so too it appears that small shifts in our microbiome caused by today's unhealthy diets can reverberate through human health.
gluten, and genetically modified foods; attention is given to revealing where the literature on the immune impacts of macronutrients is limited to either animal or in vitro models versus where human trials exist. Detailed attention is given to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.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NUTRITION JOURNAL
REVIEW
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Ian A Myles
The commensal flora provides a type of training to the immune system. Like a sparing partner in boxing, the immune system's interactions with the normal commensal flora provides an education that is indispensable when a pathogenic opponent is encountered.
to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.
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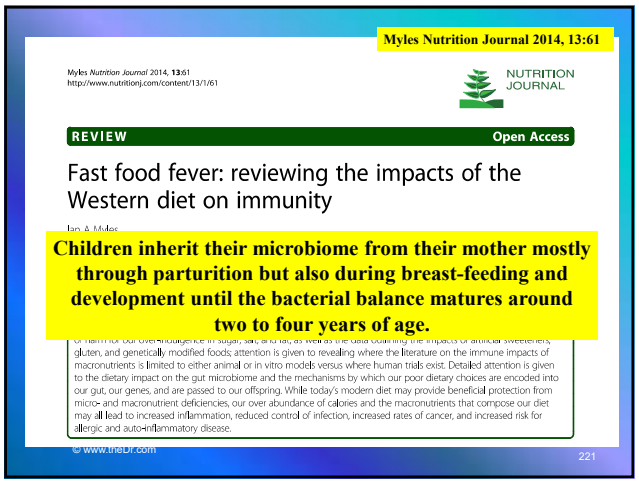
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REVIEW
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Fast food fever: reviewing the impacts of the Western diet on immunity
Children inherit their microbiome from their mother mostly through parturition but also during breast-feeding and development until the bacterial balance matures around two to four years of age.
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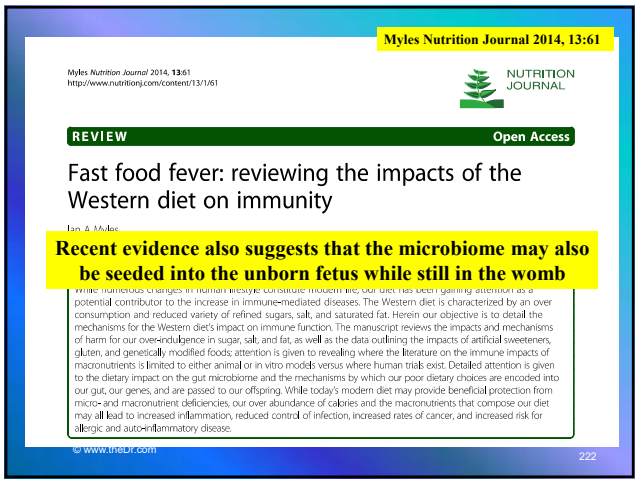
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Recent evidence also suggests that the microbiome may also be seeded into the unborn fetus while still in the womb
potential contributor to the increase in immune-mediated diseases. The Western diet is characterized by an over consumption and reduced variety of refined sugars, salt, and saturated fat. Herein our objective is to detail the mechanisms for the Western diet's impact on immune function. The manuscript reviews the impacts and mechanisms of harm for our over-indulgence in sugar, salt, and fat, as well as the data outlining the impacts of artificial sweeteners, gluten, and genetically modified foods; attention is given to revealing where the literature on the immune impacts of macronutrients is limited to either animal or in vitro models versus where human trials exist. Detailed attention is given to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.
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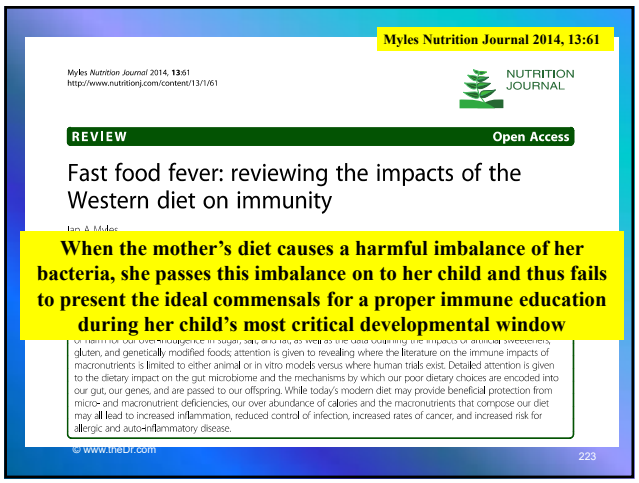
Myles Nutrition Journal 2014, 13:61
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http://www.nutritionj.com/content/13/1/61
NUTRITION JOURNAL
REVIEW
Open Access
Fast food fever: reviewing the impacts of the Western diet on immunity
When the mother's diet causes a harmful imbalance of her bacteria, she passes this imbalance on to her child and thus fails to present the ideal commensals for a proper immune education during her child's most critical developmental window
gluten, and genetically modified foods; attention is given to revealing where the literature on the immune impacts of macronutrients is limited to either animal or in vitro models versus where human trials exist. Detailed attention is given to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.
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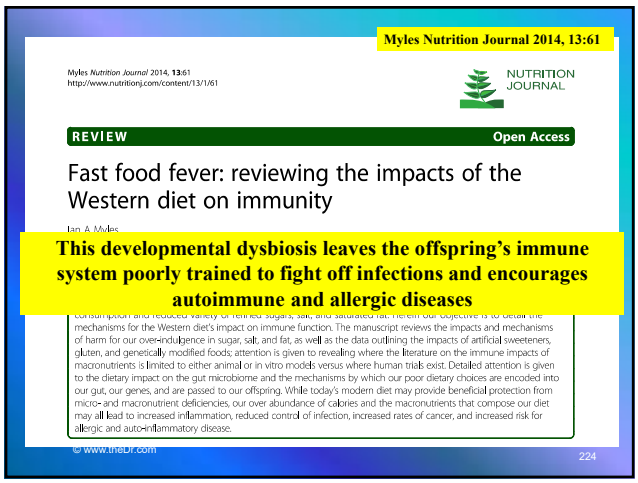
Myles Nutrition Journal 2014, 13:61
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http://www.nutritionj.com/content/13/1/61
NUTRITION JOURNAL
REVIEW
Open Access
Fast food fever: reviewing the impacts of the Western diet on immunity
This developmental dysbiosis leaves the offspring's immune system poorly trained to fight off infections and encourages autoimmune and allergic diseases
mechanisms for the Western diet's impact on immune function. The manuscript reviews the impacts and mechanisms of harm for our over-indulgence in sugar, salt, and fat, as well as the data outlining the impacts of artificial sweeteners, gluten, and genetically modified foods; attention is given to revealing where the literature on the immune impacts of macronutrients is limited to either animal or in vitro models versus where human trials exist. Detailed attention is given to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.
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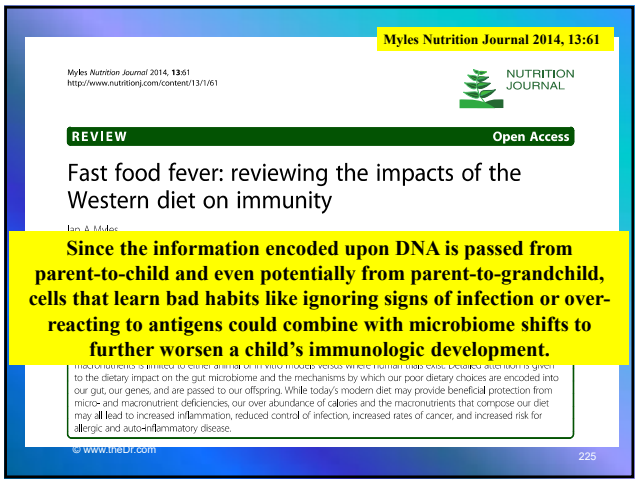
Myles Nutrition Journal 2014, 13:61
Myles Nutrition Journal 2014, 13:61
http://www.nutritionj.com/content/13/1/61
NUTRITION JOURNAL
REVIEW
Open Access
Fast food fever: reviewing the impacts of the Western diet on immunity
Since the information encoded upon DNA is passed from parent-to-child and even potentially from parent-to-grandchild, cells that learn bad habits like ignoring signs of infection or over-reacting to antigens could combine with microbiome shifts to further worsen a child's immunologic development.
to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.
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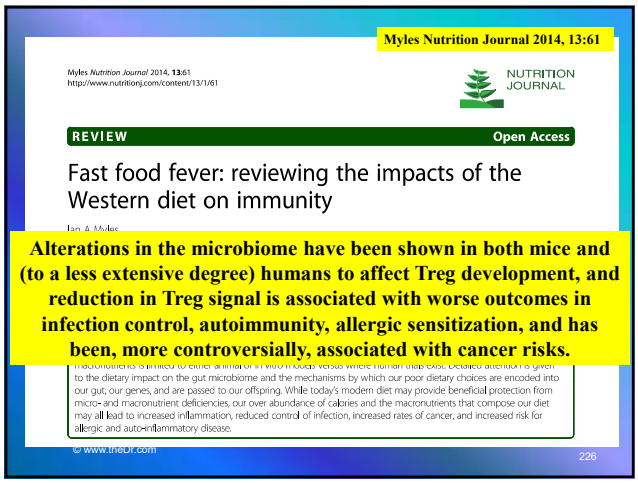
Myles Nutrition Journal 2014, 13:61
Myles Nutrition Journal 2014, 13:61
http://www.nutritionj.com/content/13/1/61
NUTRITION JOURNAL
REVIEW
Open Access
Fast food fever: reviewing the impacts of the Western diet on immunity
Alterations in the microbiome have been shown in both mice and (to a less extensive degree) humans to affect Treg development, and reduction in Treg signal is associated with worse outcomes in infection control, autoimmunity, allergic sensitization, and has been, more controversially, associated with cancer risks.
to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into our gut, our genes, and are passed to our offspring. While today's modern diet may provide beneficial protection from micro- and macronutrient deficiencies, our over abundance of calories and the macronutrients that compose our diet may all lead to increased inflammation, reduced control of infection, increased rates of cancer, and increased risk for allergic and auto-inflammatory disease.
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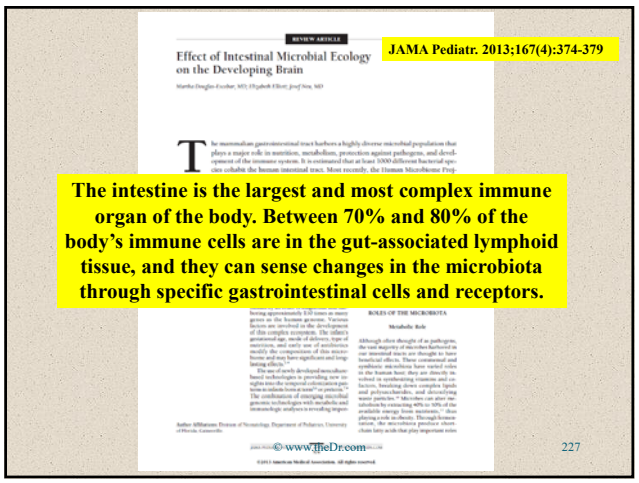
Effect of Intestinal Microbial Ecology on the Developing Brain
JAMA Pediatr. 2013;167(4):374-379
The intestine is the largest and most complex immune organ of the body. Between 70% and 80% of the body's immune cells are in the gut-associated lymphoid tissue, and they can sense changes in the microbiota through specific gastrointestinal cells and receptors.
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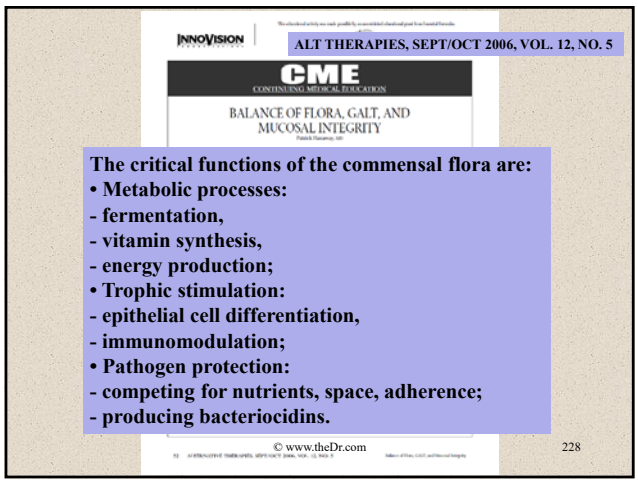
INNOVISION
ALT THERAPIES, SEPT/OCT 2006, VOL. 12, NO. 5
CME
CONTINUING MEDICAL EDUCATION
BALANCE OF FLORA, GALT, AND MUCOSAL INTEGRITY
The critical functions of the commensal flora are:
• Metabolic processes:
- fermentation,
- vitamin synthesis,
- energy production;
• Trophic stimulation:
- epithelial cell differentiation,
- immunomodulation;
• Pathogen protection:
- competing for nutrients, space, adherence;
- producing bacteriocidins.
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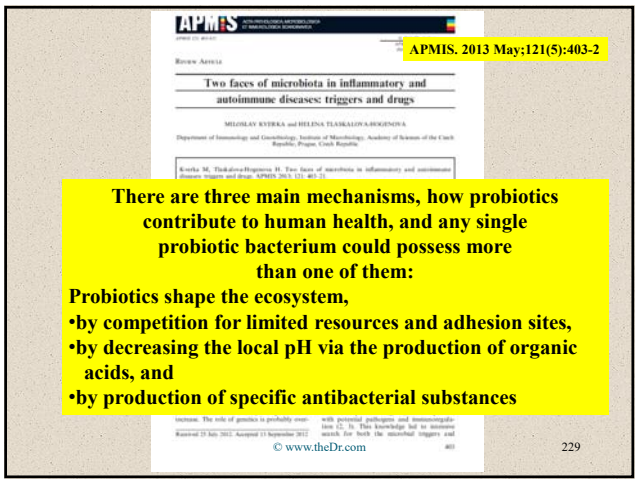
APMIS. 2013 May;121(5):403-2
Two faces of microbiota in inflammatory and autoimmune diseases: triggers and drugs
There are three main mechanisms, how probiotics contribute to human health, and any single probiotic bacterium could possess more than one of them:
Probiotics shape the ecosystem,
•by competition for limited resources and adhesion sites,
•by decreasing the local pH via the production of organic acids, and
•by production of specific antibacterial substances
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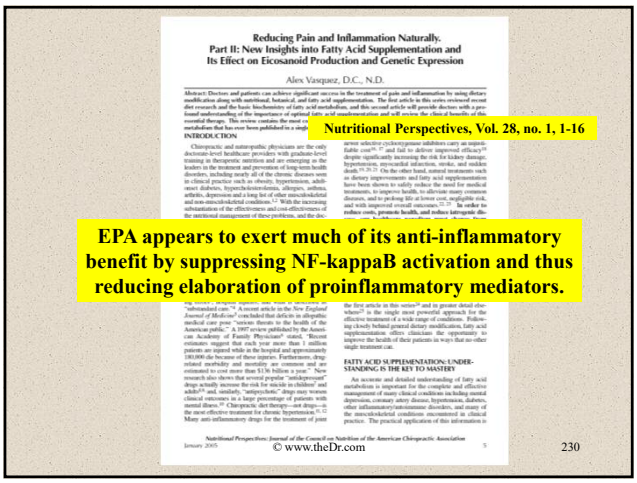
Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression
Nutritional Perspectives, Vol. 28, no. 1, 1-16
EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation and thus reducing elaboration of proinflammatory mediators.
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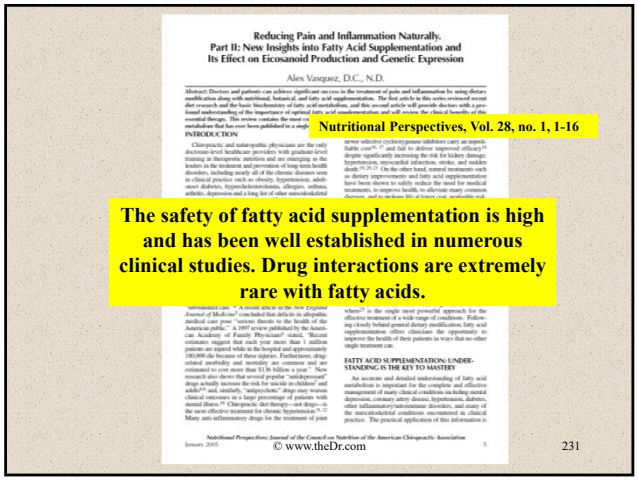
Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression
Nutritional Perspectives, Vol. 28, no. 1, 1-16
The safety of fatty acid supplementation is high and has been well established in numerous clinical studies. Drug interactions are extremely rare with fatty acids.
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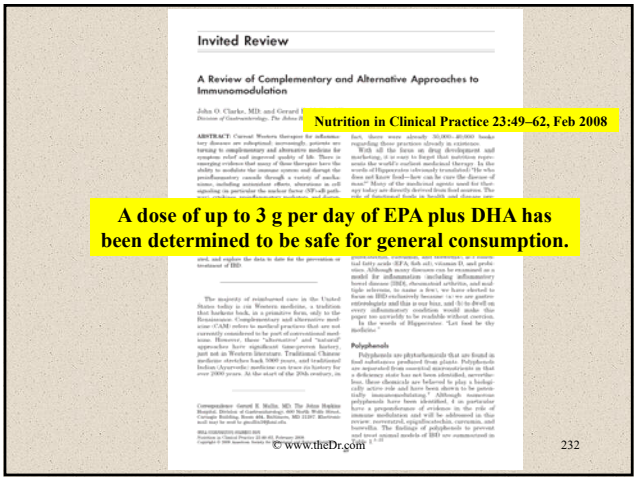
Invited Review
A Review of Complementary and Alternative Approaches to Immunomodulation
Nutrition in Clinical Practice 23:49–62, Feb 2008
A dose of up to 3 g per day of EPA plus DHA has been determined to be safe for general consumption.
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Treatment Protocols
(personal recommendations-EPA/DHA)

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

Note: Numerous studies regarding the impact of Omega 3's on CardioVascular and Cognitive function show beneficial results with dosages of 3 g/d up to 20 g/d. Caution is recommended regarding hypocoagubility

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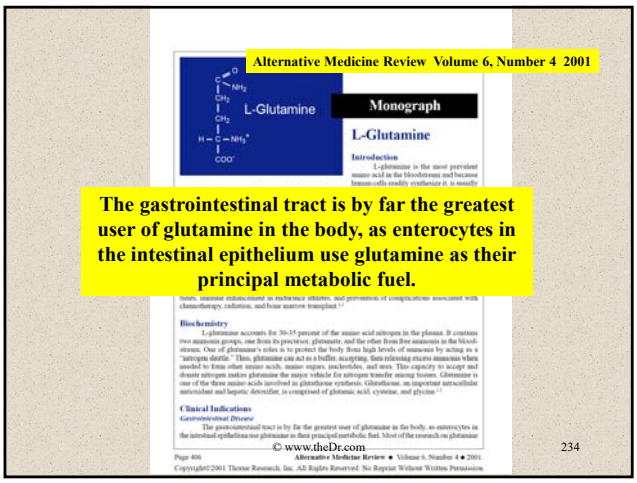
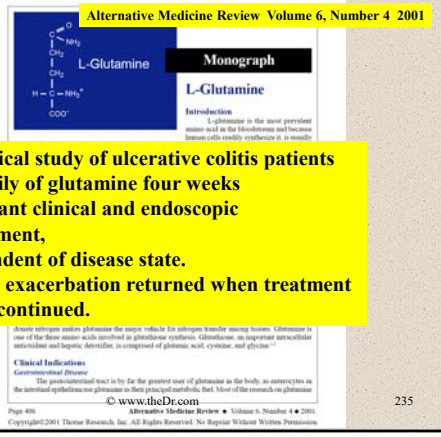


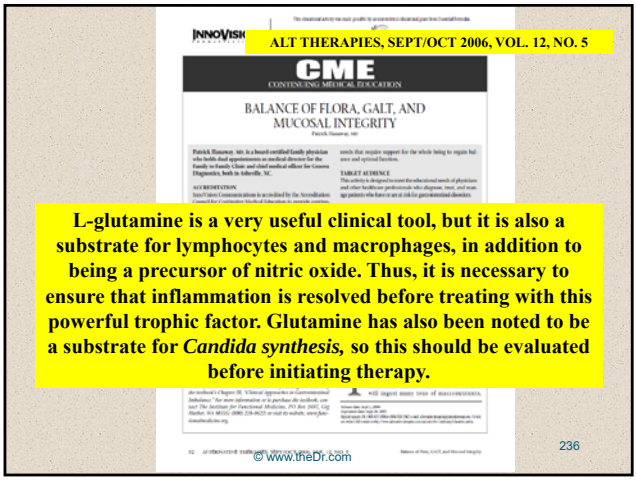
The gastrointestinal tract is by far the greatest user of glutamine in the body, as enterocytes in the intestinal epithelium use glutamine as their principal metabolic fuel.

 234



A clinical study of ulcerative colitis patients
- **30 g daily of glutamine four weeks**
- **significant clinical and endoscopic improvement, independent of disease state.**
- **Disease exacerbation returned when treatment was discontinued.**

 235



L-glutamine is a very useful clinical tool, but it is also a substrate for lymphocytes and macrophages, in addition to being a precursor of nitric oxide. Thus, it is necessary to ensure that inflammation is resolved before treating with this powerful trophic factor. Glutamine has also been noted to be a substrate for *Candida synthesis,* so this should be evaluated before initiating therapy.

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Treatment Protocols
(personal recommendations-Glutamine)

Therapeutic dosages:

Dosages vary greatly depending on the clinical situation

- **2-4 g/d in divided dosages for wound healing and general intestinal support**
- **10-40 g/d in divided dosages for critically ill and advanced disease**

 237


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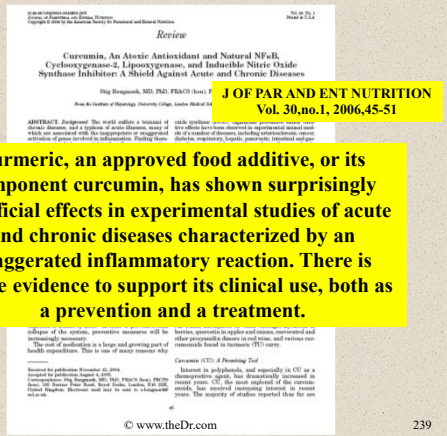


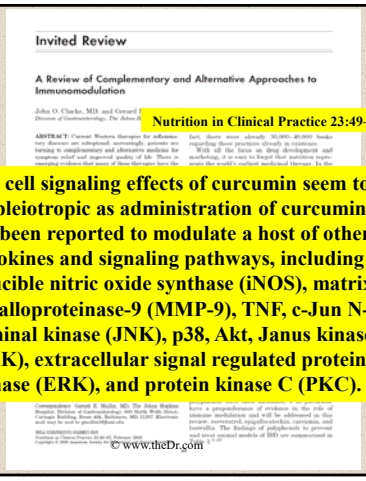
Review

Curcumin, An Atoxic Antioxidant and Natural NFκB, Cyclooxygenase-2, Lipooxygenase, and Inducible Nitric Oxide Synthase Inhibitor: A Shield Against Acute and Chronic Diseases

J OF PAR AND ENT NUTRITION Vol. 30,no.1, 2006,45-51

Turmeric, an approved food additive, or its component curcumin, has shown surprisingly beneficial effects in experimental studies of acute and chronic diseases characterized by an exaggerated inflammatory reaction. There is ample evidence to support its clinical use, both as a prevention and a treatment.

 239



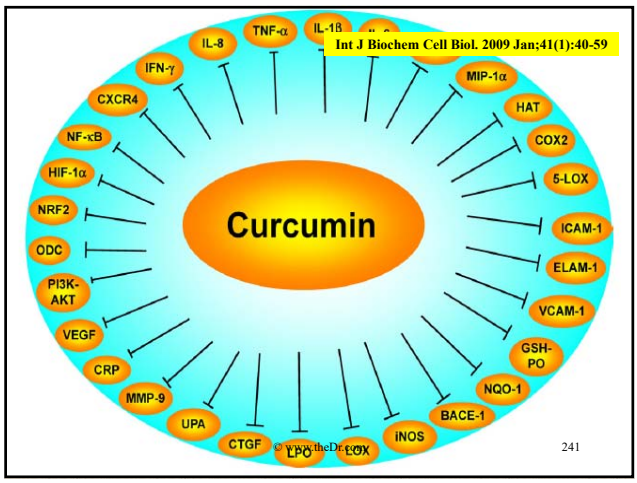
Invited Review

A Review of Complementary and Alternative Approaches to Immunomodulation

Nutrition in Clinical Practice 23:49–62, Feb 2008

The cell signaling effects of curcumin seem to be pleiotropic as administration of curcumin has been reported to modulate a host of other cytokines and signaling pathways, including inducible nitric oxide synthase (iNOS), matrix metalloproteinase-9 (MMP-9), TNF, c-Jun N-terminal kinase (JNK), p38, Akt, Janus kinase (JAK), extracellular signal regulated protein kinase (ERK), and protein kinase C (PKC).

 240



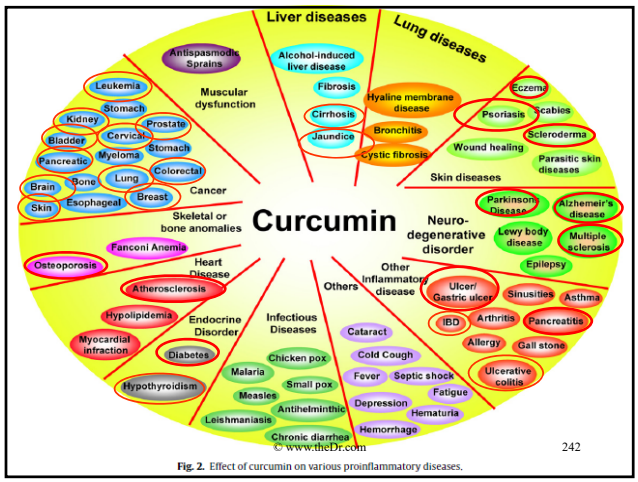


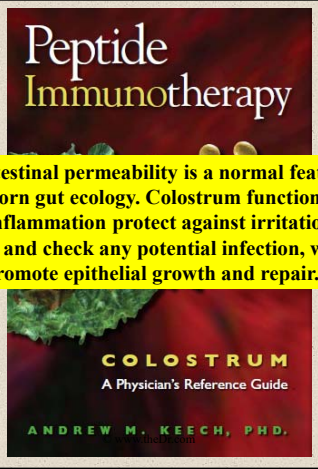
Fig. 2. Effect of curcumin on various proinflammatory diseases.

Treatment Protocols
(personal recommendations-Curcumin)

Therapeutic dosages:

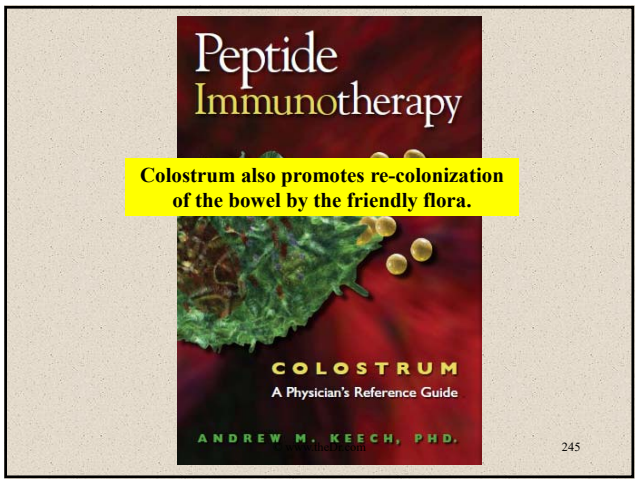
<u>Turmeric</u> (*Curcuma longa*) standardized to curcuminoids 200-1000 mg TID

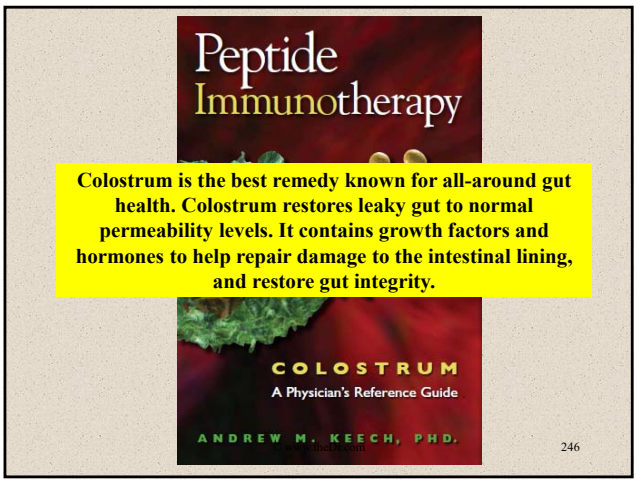
243

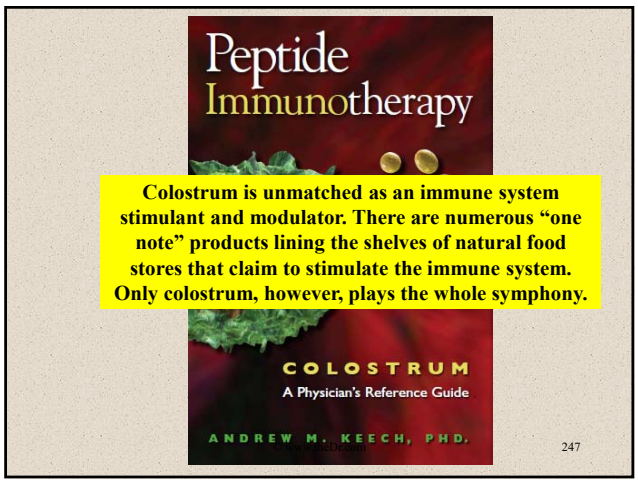


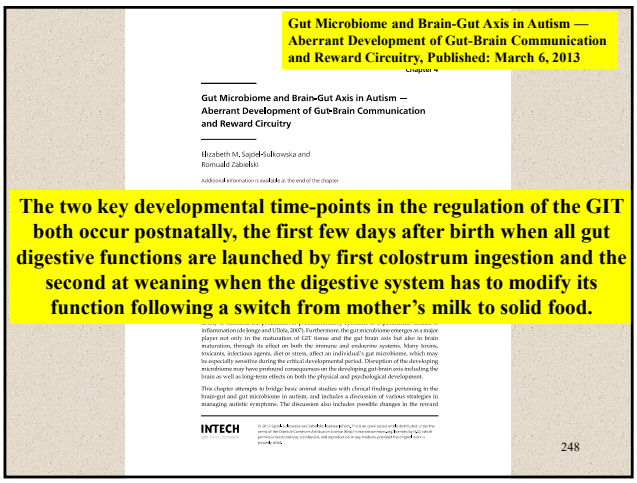
High intestinal permeability is a normal feature of newborn gut ecology. Colostrum functions to reduce inflammation protect against irritation from toxins and check any potential infection, while promote epithelial growth and repair.

244


Peptide Immunotherapy
Colostrum also promotes re-colonization of the bowel by the friendly flora.
COLOSTRUM
A Physician's Reference Guide
ANDREW M. KEECH, PHD.
245


Peptide Immunotherapy
Colostrum is the best remedy known for all-around gut health. Colostrum restores leaky gut to normal permeability levels. It contains growth factors and hormones to help repair damage to the intestinal lining, and restore gut integrity.
COLOSTRUM
A Physician's Reference Guide
ANDREW M. KEECH, PHD.
246


Peptide Immunotherapy
Colostrum is unmatched as an immune system stimulant and modulator. There are numerous "one note" products lining the shelves of natural food stores that claim to stimulate the immune system. Only colostrum, however, plays the whole symphony.
COLOSTRUM
A Physician's Reference Guide
ANDREW M. KEECH, PHD.
247


Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry, Published: March 6, 2013
Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry
Elizabeth M. Sajdel-Sulkowska and Romuald Zabielski
The two key developmental time-points in the regulation of the GIT both occur postnatally, the first few days after birth when all gut digestive functions are launched by first colostrum ingestion and the second at weaning when the digestive system has to modify its function following a switch from mother's milk to solid food.
INTECH
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Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry, Published: March 6, 2013

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

Elizabeth M. Sajdel-Sulkowska and Romuald Zabielski

Additional information is available at the end of the chapter

The first time-point is particularly relevant for all mammalian species since it is associated with a complex of dynamic changes in the GIT structure and function leading to a temporary drop in the gut permeability barrier.

hormones involved in the regulation of food intake, such as cholecystokinin (CCK), ghrelin, leptin and insulin, and by the immunological signaling pathway involving cytokines. Recent studies indicate that the vagus nerve is involved in immunomodulation as suggested by its ability to attenuate the production of proinflammatory cytokines in experimental models of inflammation (de Jonge and Ulloa, 2007). Furthermore, the gut microbiome emerges as a major player not only in the maturation of GIT tissue and the gut brain axis but also in brain maturation, through its effect on both the immune and endocrine systems. Many toxins, toxicants, infectious agents, diet or stress, affect an individual's gut microbiome, which may be especially sensitive during the critical developmental period. Disruptions of the developing microbiome may have profound consequences on the developing gut-brain axis including the brain as well as long-term effects on both the physical and psychological development.

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

INTECH

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Gut on FIRE! Body on Fire

- •Elimination Diet
- • Probiotics
- •Vitamin D
- • Glutamine
- • EPA/DHA
- • Curcumin
- • Colostrum

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

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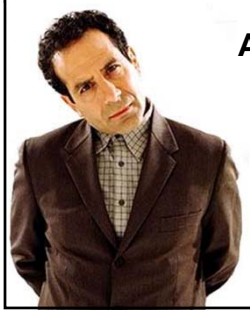
Premise #1

Just How Prevalent is the Development of Autoimmune Disease?



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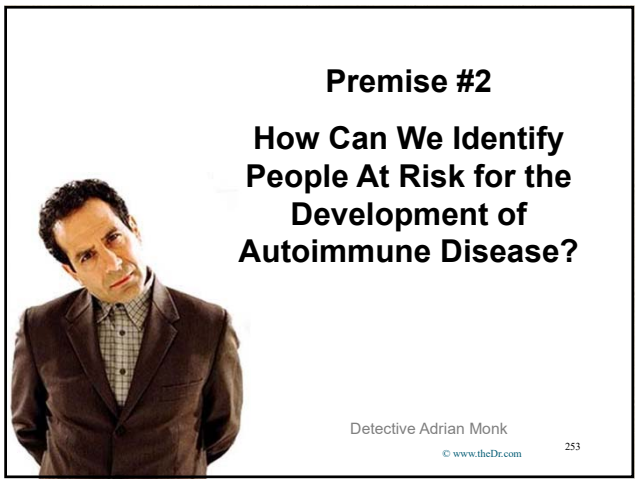
Premise #2
How Can We Identify People At Risk for the Development of Autoimmune Disease?
Detective Adrian Monk
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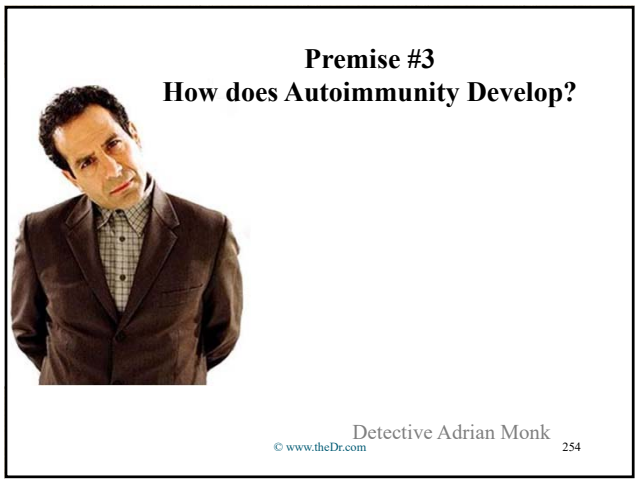
Premise #3
How does Autoimmunity Develop?
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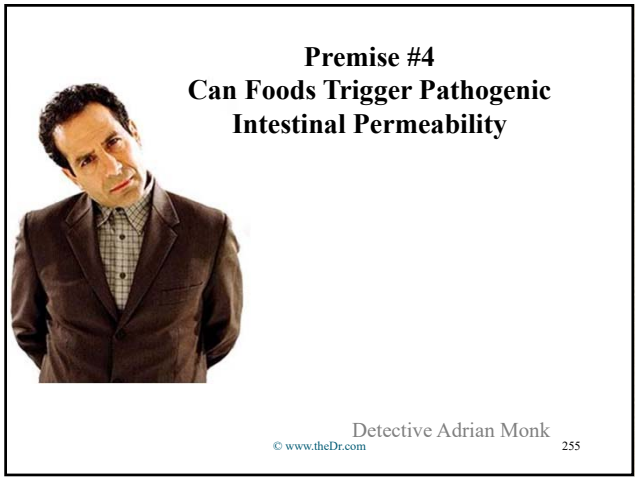
Premise #4
Can Foods Trigger Pathogenic Intestinal Permeability
Detective Adrian Monk
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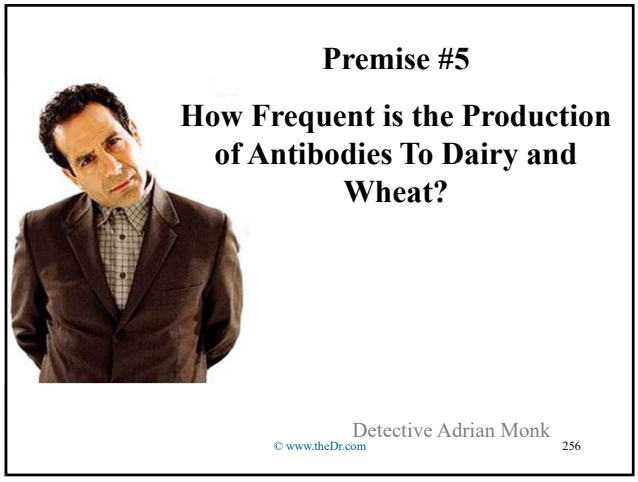
Premise #5
How Frequent is the Production of Antibodies To Dairy and Wheat?
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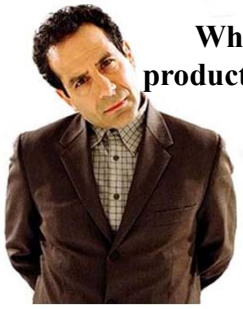
Premise #6



What is the Trigger in the production of Antibodies To Self?

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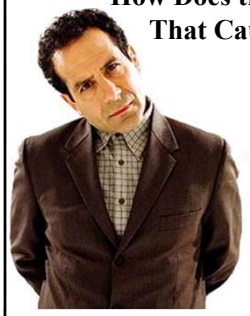
Premise #7

How Does the Inflammatory Cascade Begin That Causes Intestinal Permeability?



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Premise #8

How do we Arrest Pathogenic Intestinal Permeability

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What Triggers the Systemic Symptoms Initiating the Autoimmune Mechanism?

Genetic predisposition, environmental insult, hypochlorhydria, pancreatic insufficiency, medications, surgery, etc.

↓

Inadequately digested proteins in GI tract (associated with food sensitivities)

Irritation/inflammation/dysbiosis (activating immune inflammatory response)

↓

Eventually Developing into Pathogenic Intestinal Permeability

↓

Increased load on liver detoxification pathways (food antigens, toxins, endotoxin)

AND

Immune complexes in general circulation to macromolecules, neo-epitopes,…

↓

Molecular Mimicry and tissue specific symptoms determined by genetics and antecedents

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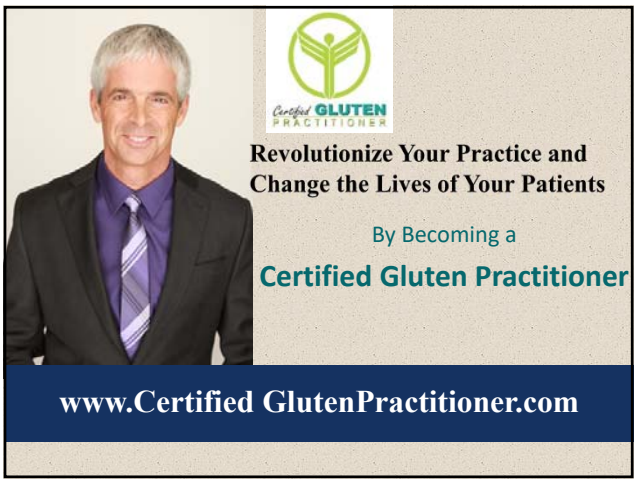
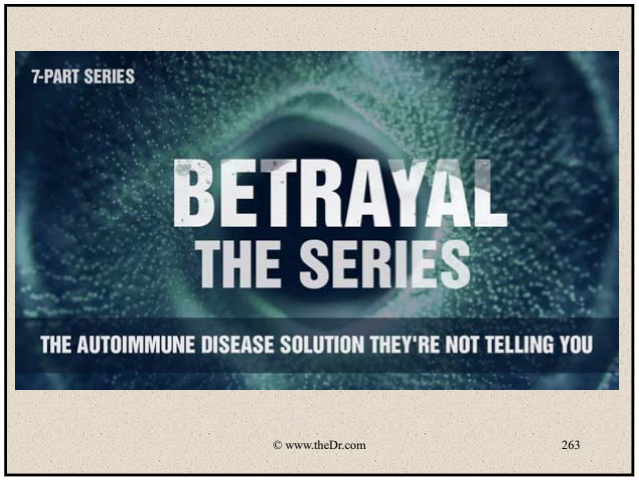
↓

Initiation of autoimmune mechanisms eventually developing into an AUTOIMMUNE DISEASE


Revolutionize Your Practice and Change the Lives of Your Patients
By Becoming a
Certified Gluten Practitioner
www.Certified GlutenPractitioner.com


7-PART SERIES
BETRAYAL
THE SERIES
THE AUTOIMMUNE DISEASE SOLUTION THEY'RE NOT TELLING YOU
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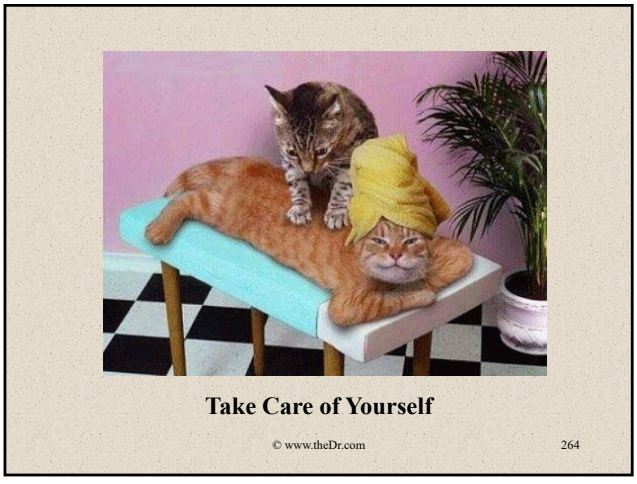
Take Care of Yourself
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Make Sure to Tell those Important to You How Much You Love them

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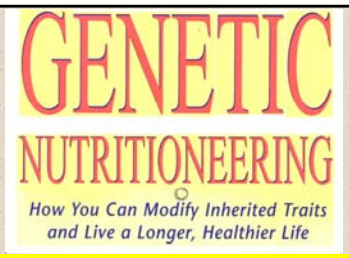

"Throughout your life the most profound influences on your health, vitality and function are not the Doctors you have visited or the drugs, surgery, or other therapies you have undertaken. The most profound influences are the cumulative effects of the decisions you make about your diet and lifestyle on the expression of your genes."

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

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