Predicting and Arresting the Mechanisms of Autoimmunity

Tom O'Bryan, DC, CCN, DACBN

Oct 29, 2016

Austin, Texas

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- **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**

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

SHOCK, Vol. 00, No. 00, pp. 00–00, 2009

Shock. 2009 Oct;32(4):374-8

SYSTEMIC INFLAMMATION INCREASES INTESTINAL PERMEABILITY DURING EXPERIMENTAL HUMAN ENDOTOXEMIA

Falco Hietbrink,* Marc G.H. Besselink,* Willem Renooij,* Martin B.M. de Smet,* Annelies Draisma,† Hans van der Hoeven,† and Peter Pickkers†

*Department of Surgery, University Medical Center Utrecht, Utrecht; and †Department of Intensive Care Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

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ABSTRACT—Although the gut is often considered the motor of sepsis, the relation between systemic inflammation and intestinal permeability in humans is not clear. We analyzed intestinal permeability during experimental endotoxemia in humans. Before and during experimental endotoxemia (*Escherichia coli* LPS, 2 ng/kg), using polyethylene glycol (PEG) as a permeability marker, intestinal permeability was analyzed in 14 healthy subjects. Enterocyte damage was determined by intestinal fatty acid binding protein. Endotoxemia induced an inflammatory response. Urinary PEGs 1,500 and 4,000 recovery increased from 38.8 ± 6.3 to 63.1 ± 12.5 and from 0.58 ± 0.31 to 3.11 ± 0.93 mg, respectively ($P < 0.05$). Intestinal fatty acid binding protein excretion was not affected by endotoxemia. The peak serum IL-10 concentrations correlated with the increase in PEG 1,500 recovery ($r = 0.48$, $P = 0.027$). Systemic inflammation results in an increased intestinal

We demonstrated a correlation between the degree of systemic inflammation and an increase in intestinal permeability.

ability in critically ill patients. In these tests, two sugar probes are orally administered and passively absorbed. It is assumed that absorption of the smaller molecule is relatively constant, whereas absorption of the larger molecule is influenced by alterations in intestinal permeability. However, it was recently shown that several confounders occurring in clinical practice may have contributed to the inconclusive results of permeability studies (3, 4). This seems to represent the main reason why many clinical studies have yielded conflicting results concerning the relation between severity of disease or incidence of infectious complications and intestinal permeability (5).

In animal sepsis models, both gastrointestinal mucosal perfusion deficits and systemic inflammation were found to be associated with a decrease in gut barrier function. In rodent studies, increased intestinal permeability was shown to enhance and sustain systemic inflammation by facilitating bacterial translocation (2). In addition, inflammation was found to induce or sustain increased intestinal permeability (6, 7). The relation between systemic inflammation and intestinal permeability has not been tested in humans.

size of bacterial products such as LPS (10). Thus, PEGs allow a broader range of molecular weight, thereby possibly providing more information regarding the changes in intestinal permeability. Polyethylene glycols are not therapeutically applied or endogenously produced in contrast to several components of differential sugar absorption tests, so that recovery is not influenced by administration of packed red blood cells or mannitol (3, 4).

It has been demonstrated previously that acute systemic inflammation can be induced by a low-dose infusion of *Escherichia coli* LPS in healthy volunteers (11), as a model of the pathophysiological changes observed in septic patients, resulting in, for example, cardiac dysfunction (12), vascular and endothelial dysfunction (13, 14), coagulation abnormalities (15), and other subclinical end-organ dysfunction (16).

The present study addresses three questions: 1) Does experimental endotoxemia resulting in systemic inflammation induce an increase in intestinal permeability in humans? 2) Are the kinetics of urinary recovery of PEGs altered during experimental endotoxemia? 3) Is increased intestinal permeability the result of inflammation or damage (ischemic injury) of enterocytes?

MATERIALS AND METHODS

Subjects

The local ethics committee of the Radboud University Nijmegen Medical Centre approved the study protocol, and written informed consent was obtained from all 14 subjects who participated in the experiments that were part of a larger endotoxin trial (NCT 00184990). Volunteers participated in a study concerning the development of LPS tolerance. During the first day,

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The production of the PEG test was funded by a "Gastrostart" fund of the Dutch Gastroenterology Association 2004.
DOI: 10.1097/SHK.0b013e3181a2bcd6

Thus the more the inflammation a person has, the greater the degree of pathogenic intestinal permeability

Detective Adrian Monk

Dietary Influences on Chronic and Autoimmune Thyroid Disease

Tom O' Bryan, DC, CCN, DACBN

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Premise #1

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

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Premise #2

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

Detective Adrian Monk

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

Detective Adrian Monk

Premise #4

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

Detective Adrian Monk

Premise #5

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

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

Detective Adrian Monk

Premise #6

A GFD may contribute to dysbiosis

Detective Adrian Monk

Premise #7

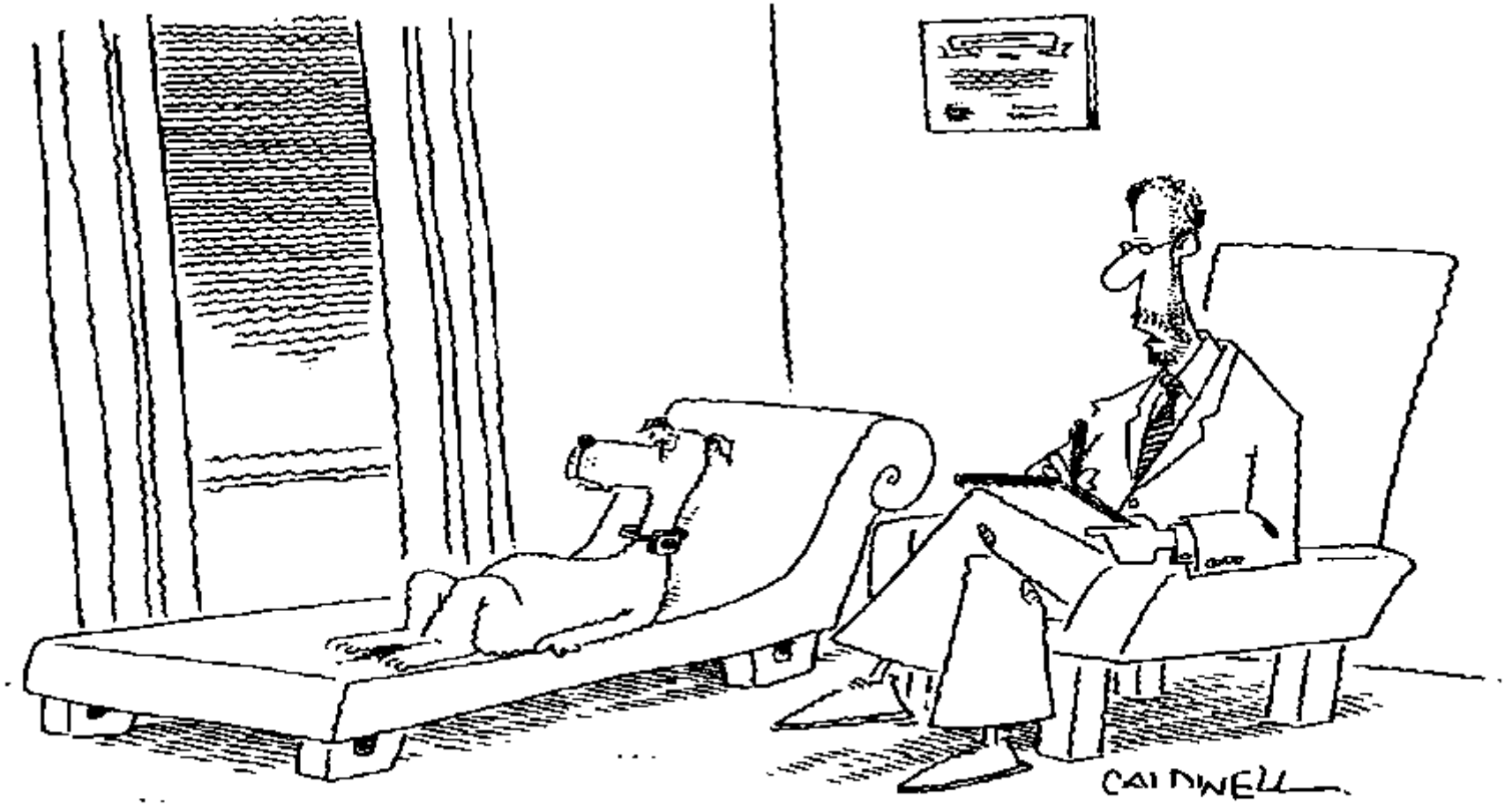
Every Office benefits from offering SUCCESSFUL, Comprehensive, Thorough Guidance for Patients to Transition into a Microbiome-balancing dietary lifestyle via a Well-Trained Nutritionist, Registered Dietician, or Staff Specialist

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?

Detective Adrian Monk



“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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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).**

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

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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>.

Scandinavian Journal of Gastroenterology, 2006; 41: 408–419

Taylor & Francis

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

SANDRO DRAGO[1,2], RAMZI EL ASMAR[1], MARIAROSARIA DI PIERRO[1,2], MARIA GRAZIA CLEMENTE[1], AMIT TRIPATHI[1], ANNA SAPONE[1], MANJUSHA THAKAR[1], GIUSEPPE IACONO[3], ANTONIO CARROCCIO[3], CINZIA D'AGATE[4], TARCISIO NOT[5], LUCIA ZAMPINI[6], CARLO CATASSI[1,6] & ALESSIO FASANO[1]

[1]*Mucosal Biology Research Center, Center for Celiac Research and Division of Pediatric Gastroenterology and Nutrition, University of Maryland, School of Medicine, Baltimore, USA,* [2]*Bionat Italia S.r.l., Palermo, Italy,* [3]*Clinica Medica,*

Gliadin activates the zonulin signaling, resulting in <u>immediate</u> reduction of intestinal barrier function and passage of gliadin into the subepithelial compartment.

released zonulin in the cell medium with subsequent zonulin binding to the cell surface, rearrangement of the cell cytoskeleton, loss of occludin-ZO1 protein–protein interaction, and increased monolayer permeability. Pretreatment with the zonulin antagonist FZI/0 blocked these changes without affecting zonulin release. When exposed to luminal gliadin, intestinal biopsies from celiac patients in remission expressed a sustained luminal zonulin release and increase in intestinal permeability that was blocked by FZI/0 pretreatment. Conversely, biopsies from non-celiac patients demonstrated a limited, transient zonulin release which was paralleled by an increase in intestinal permeability that never reached the level of permeability seen in celiac disease (CD) tissues. Chronic gliadin exposure caused down-regulation of both ZO-1 and occludin gene expression. ***Conclusions.*** Based on our results, we concluded that gliadin activates zonulin signaling irrespective of the genetic expression of autoimmunity, leading to increased intestinal permeability to macromolecules.

Key Words: *Celiac disease, gliadin, gut permeability, tight junctions, zonulin*

Introduction

Gliadin, the main fraction of wheat gluten responsible for the intestinal damage typical of celiac disease (CD), is the environmental factor that triggers this disorder [1]. It is known that CD is the result of an inappropriate T-cell-mediated immune response against ingested gliadin [2]. CD is associated with the HLA alleles DQA1*0501/DQB1*0201, and in the continued presence of gliadin the disease is self-perpetuating [3]. One of the autoimmune targets of CD is tissue transglutaminase (TTG) [4]. The deamidating activity of this enzyme generates gliadin peptide fragments that bind to DQ2 and to DQ8 so as to be recognized by disease-specific intestinal T cells [5]. This process activates a cascade of events in which cytokines and matrix metalloproteinases are

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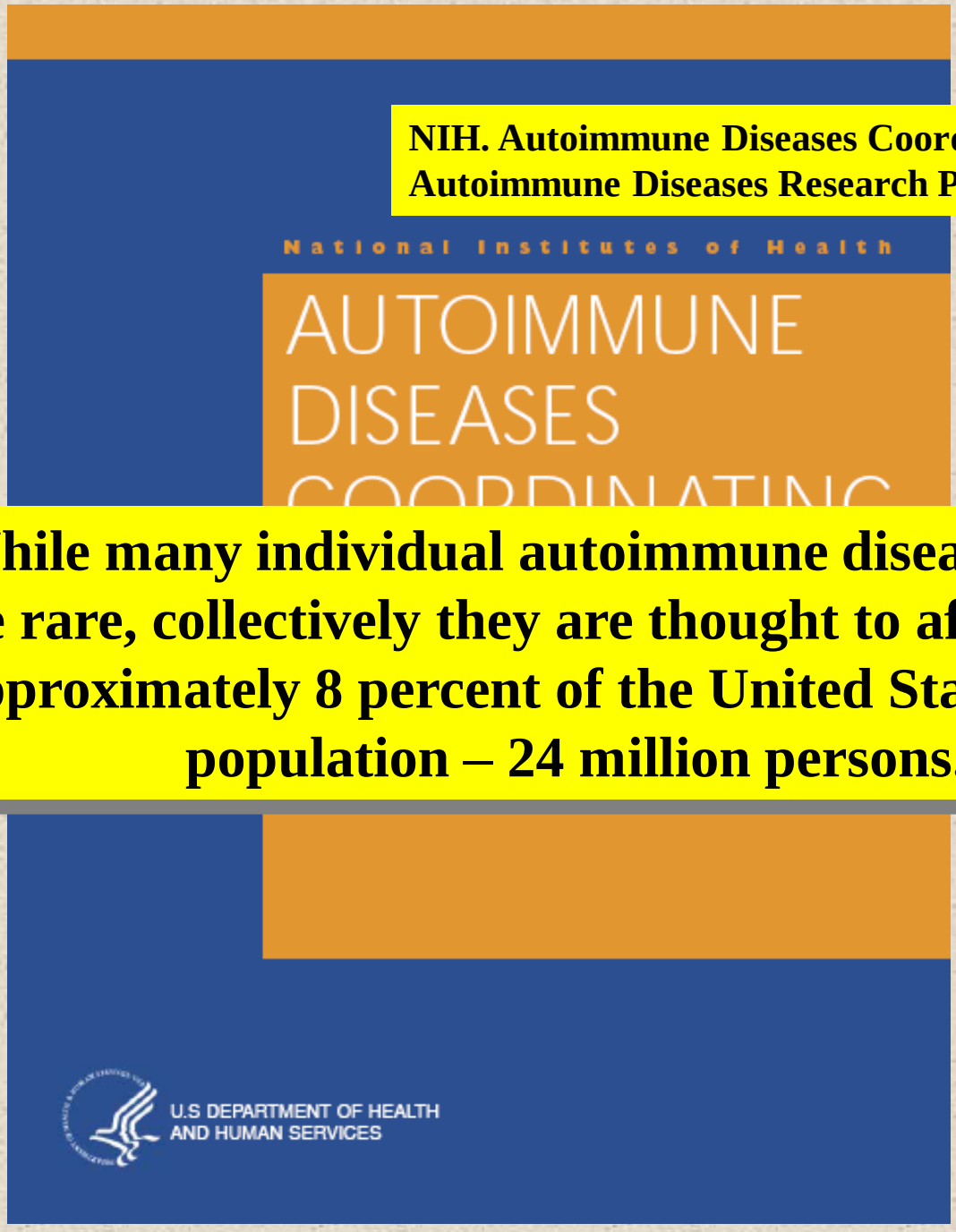
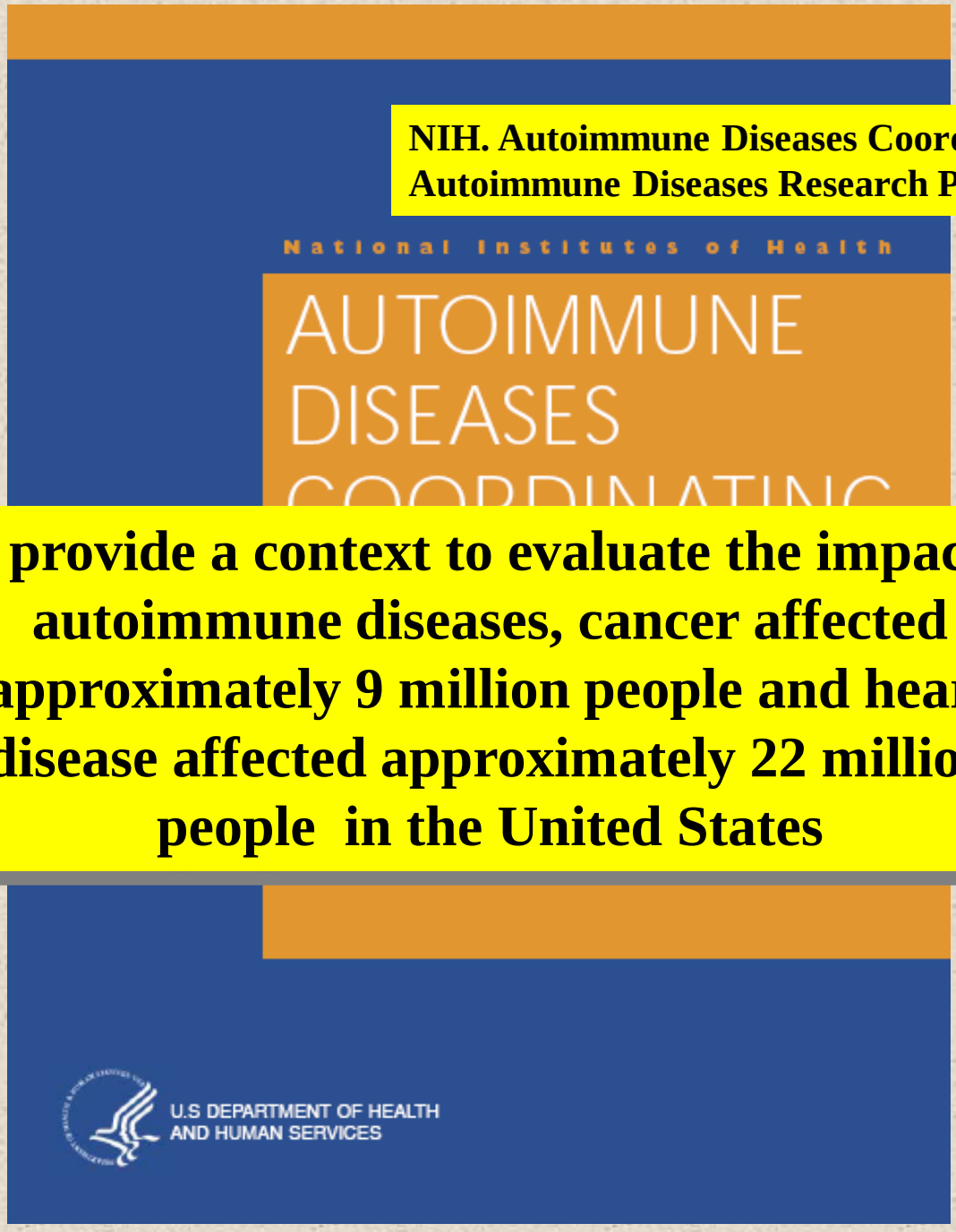
8 Premises to Look at Today


AUTOIMMUNITY



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

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



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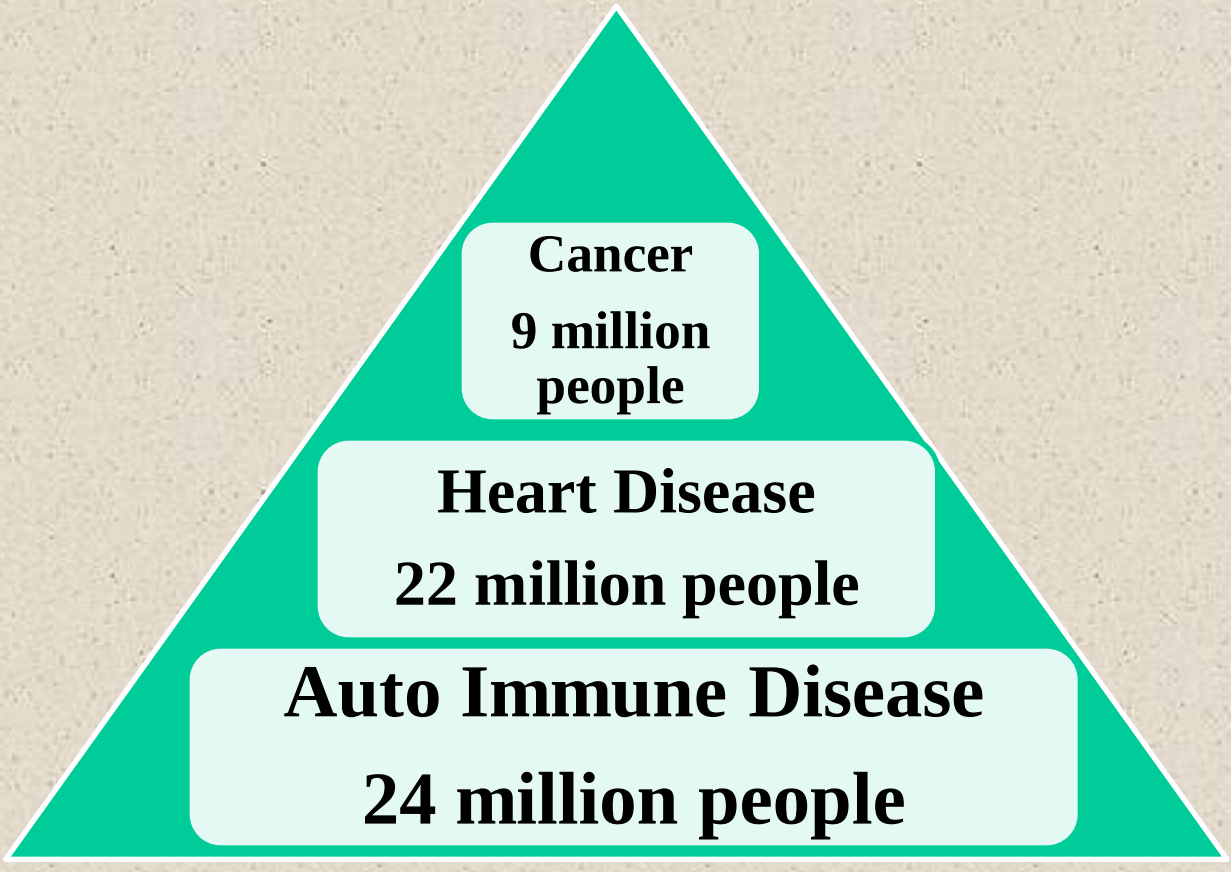
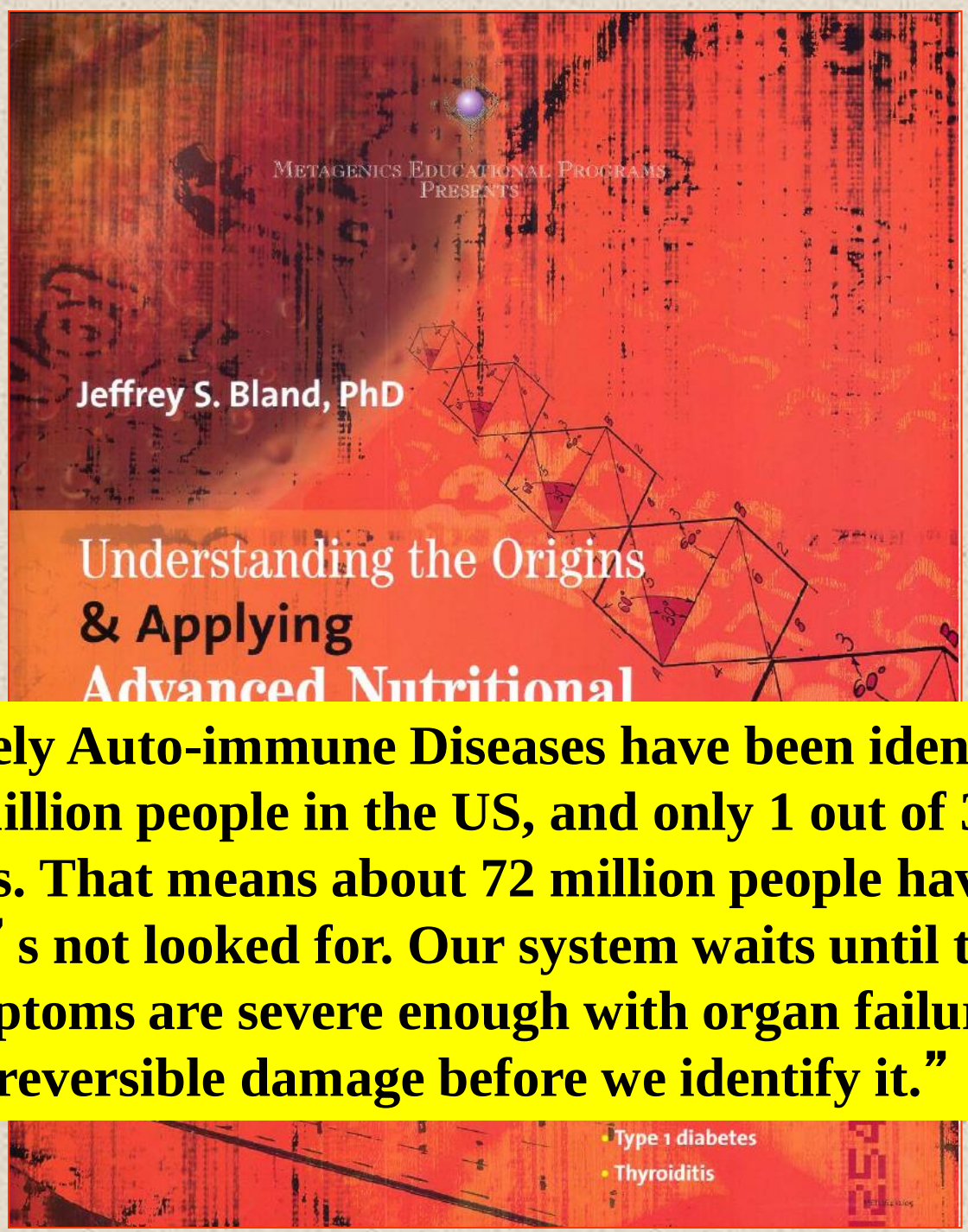
To provide a context to evaluate the impact of autoimmune diseases, cancer affected approximately 9 million people and heart disease affected approximately 22 million people in the United States





"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

Yoav Arnson, Howard Amital, Yehuda Shoenfeld

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

Ann Rheum Dis

Vitamin D is frequently prescribed by rheumatologists to prevent and treat osteoporosis. Several observations have shown that vitamin D inhibits proinflammatory processes by suppressing the enhanced activity of immune cells that take part in the autoimmune reaction. Moreover, recent evidence strongly suggests that vitamin D supplementation may be therapeutically beneficial, particularly for Th1-mediated autoimmune disorders. Some reports imply that vitamin D may even be

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

cancer and heart disease.[1] Despite this relatively high prevalence rate, the aetiology and pathogenesis of most autoimmune disorders remain obscure and a number of factors have been implicated in their pathogenesis. One of the most recent agents found to be associated with autoimmunity is vitamin D.

Vitamin D has multiple immunosuppressant properties. Supplementation of vitamin D was shown to be therapeutically effective in various animal models such as autoimmune encephalomyelitis,[2 3] collagen-induced arthritis,[4] type 1 diabetes mellitus,[5] inflammatory bowel disease,[6] autoimmune thyroiditis[7] and systemic lupus erythematosus (SLE),[8] and in some models of SLE it prevented disease development. A recent study showed that high circulating levels of vitamin D were associated with a lower risk of future multiple sclerosis.[9]

See end of article for authors' affiliations

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PHYSIOLOGY OF VITAMIN D

The classic prominent function of vitamin D is regulation of calcium homeostasis, which is primarily maintained via bone formation and resorption.[10–12] Homeostasis is maintained in addition through the interaction of vitamin D with the parathyroid, kidney and intestinal tissues.[13]

Vitamin D can be ingested orally or can be formed endogenously in cutaneous tissue following exposure to ultraviolent B light.[14] Vitamin D_3 from both sources is metabolised in the liver to 25-hydroxyvitamin D (25(OH)D) which is the major circulating form of vitamin D. This form of the vitamin is the one measured by clinicians to determine vitamin D levels in patients. However, 25(OH)D is biologically inert and requires additional hydroxylation within the kidney to form the biologically active derivative of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)$_2$D). 1,25(OH)$_2$D is a lipid-soluble hormone that interacts with its vitamin D receptors (VDRs) in the small intestine. Its action leads to enhanced expression of the

cells.[14 15] However, in contrast to the renal cells, in antigen presenting cells the enzyme is non-responsive to suppression by either parathyroid hormone or 1,25(OH)$_2$D. Instead, it is inducible in the cells by a number of factors such as interferon γ (IFNγ) and is downregulated as the dendritic cell matures.[16]

Vitamin D deficiency is typically found in countries where there is no (or hardly any) ultraviolet light during the winter months and people must rely on the diet as their main source of the vitamin.[17] The optimal level for 25(OH)D for bone health begins at 75 nmol/l (30 ng/ml), with the best concentrations at 90–100 nmol/l (36–40 ng/ml),[18–21] but the vitamin D level required to maintain optimal immune system homeostasis has not yet been established.

VITAMIN D AND THE IMMUNE SYSTEM

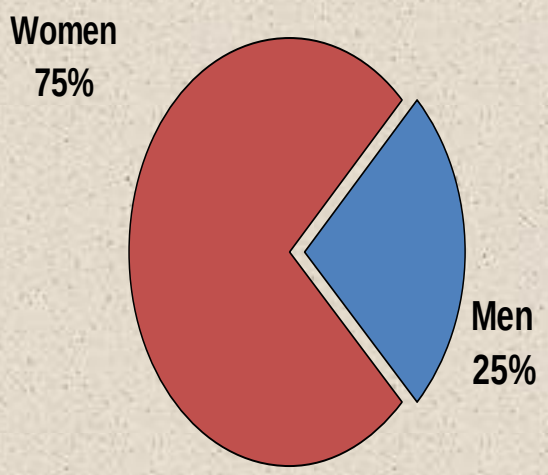
Vitamin D interacts with the immune system. It takes part in the regulation and differentiation of the cells of the immune system directly and indirectly. Early reports linking vitamin D metabolism to the prevalence of autoimmune diseases were largely anecdotal and circumstantial. For instance, associations were detected between the

Abbreviations: 1, 25(OH)$_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; GM-CSF, granulocyte-macrophage colony stimulating factor; IFNγ, interferon γ; IL, interleukin; NFκB, nuclear factor κB; SLE, systemic lupus erythematosus; VDR, vitamin D receptor

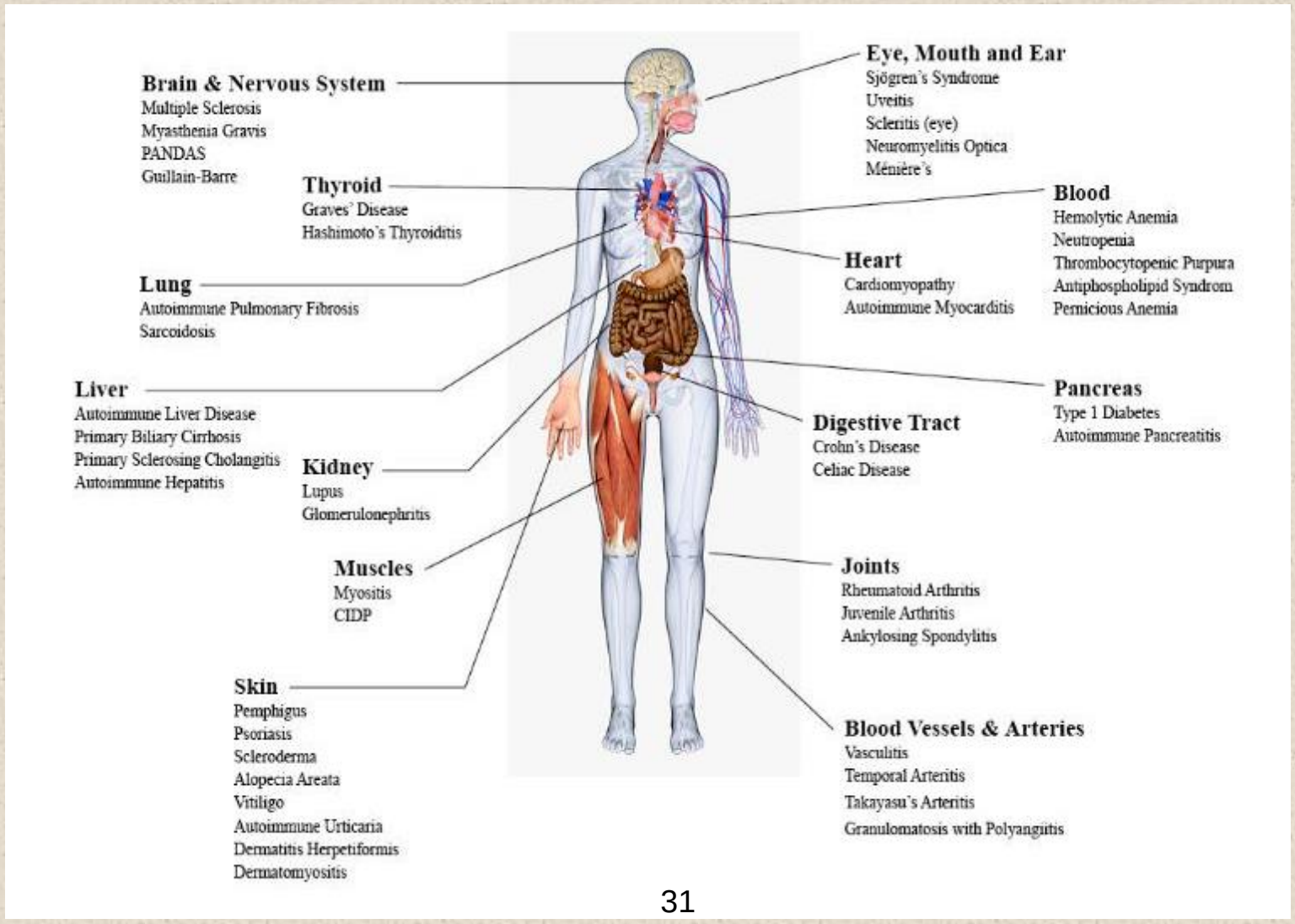
Autoimmunity at a Glance

American Autoimmune Related Disease Association

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



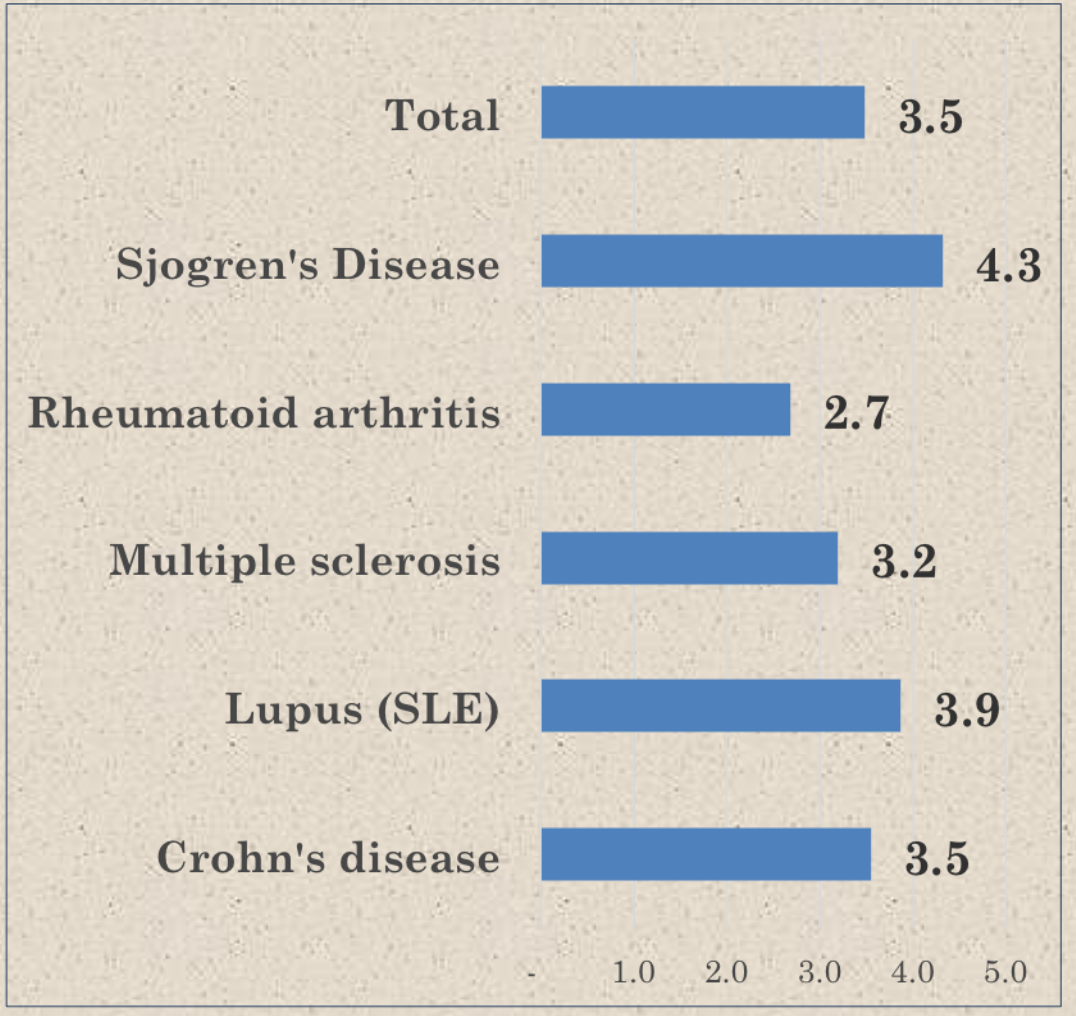
Autoimmune disease can affect any part of the body



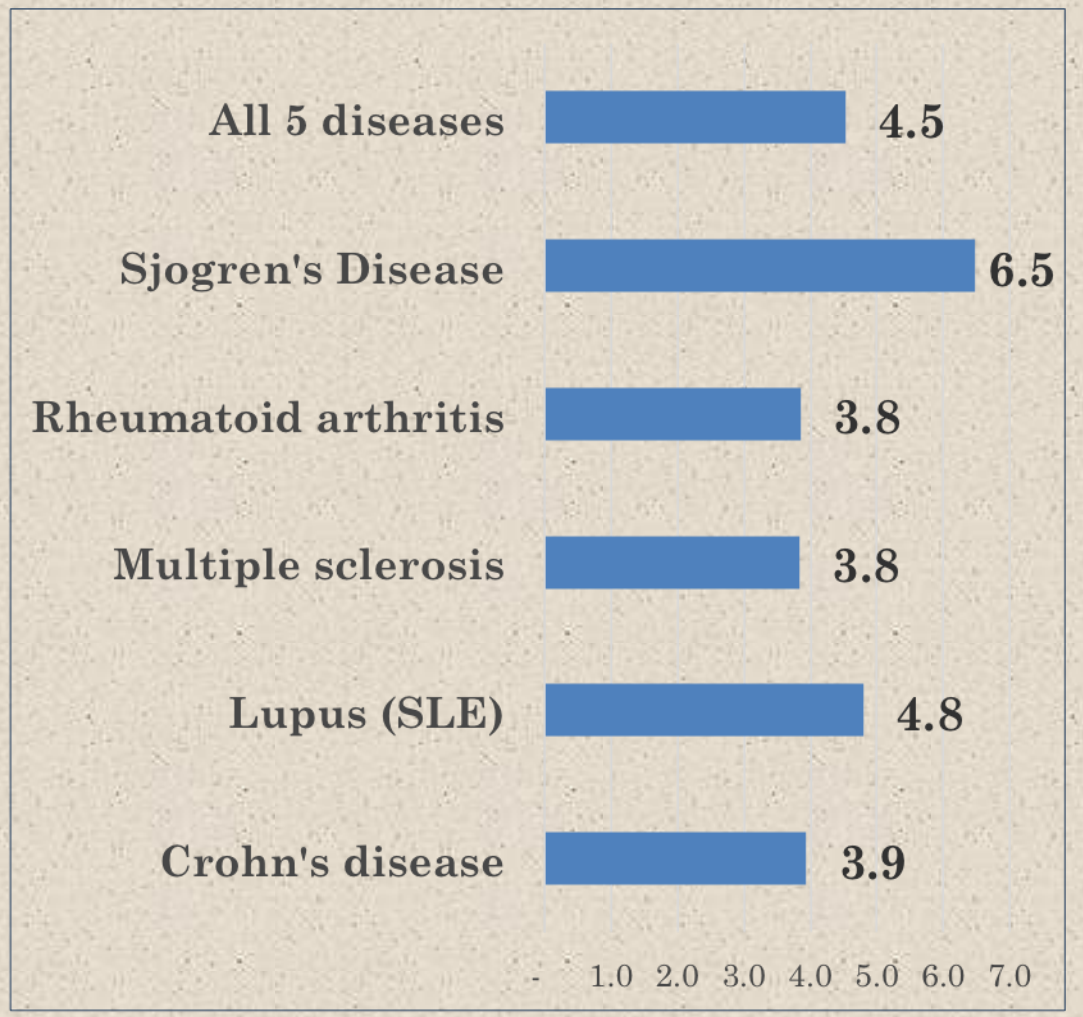
AD Diagnosis Takes an Inordinate Amount of Time and Perseverance by the Patient

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%

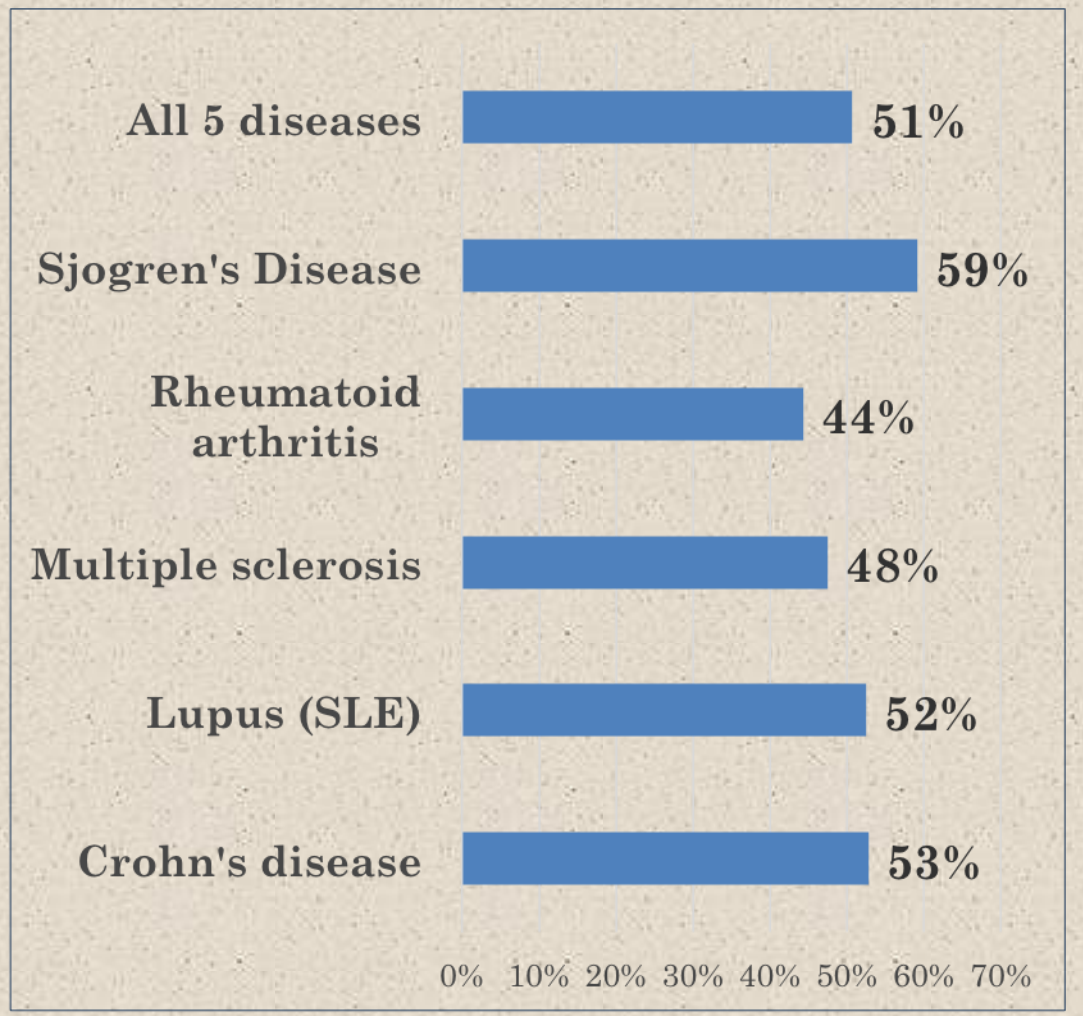
Years to Diagnosis



Number of Doctors Seen to get a Diagnosis



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



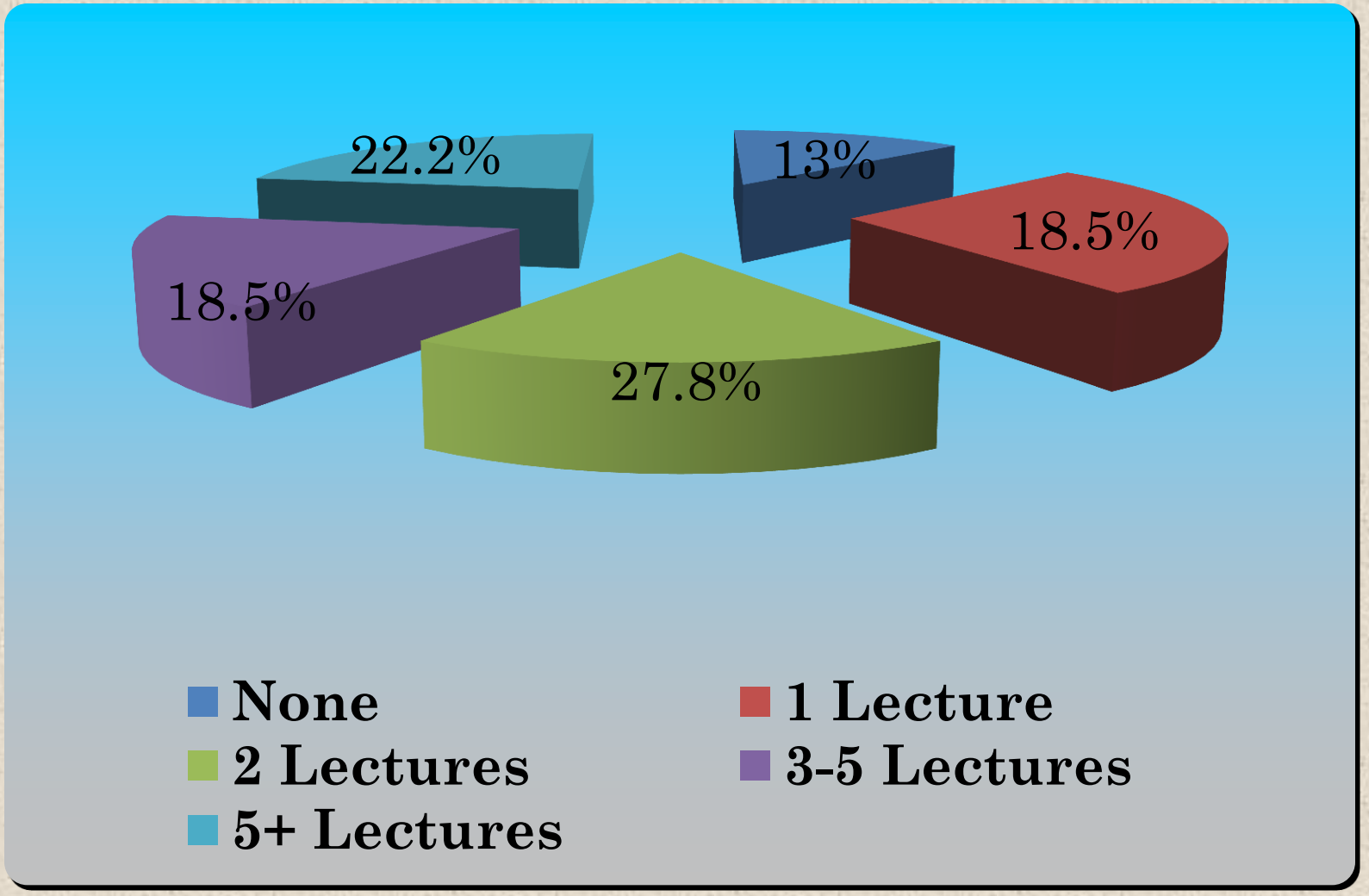
Why so Long and Difficult to Get a Correct Diagnosis?

Physician Education was identified as a contributing factor.

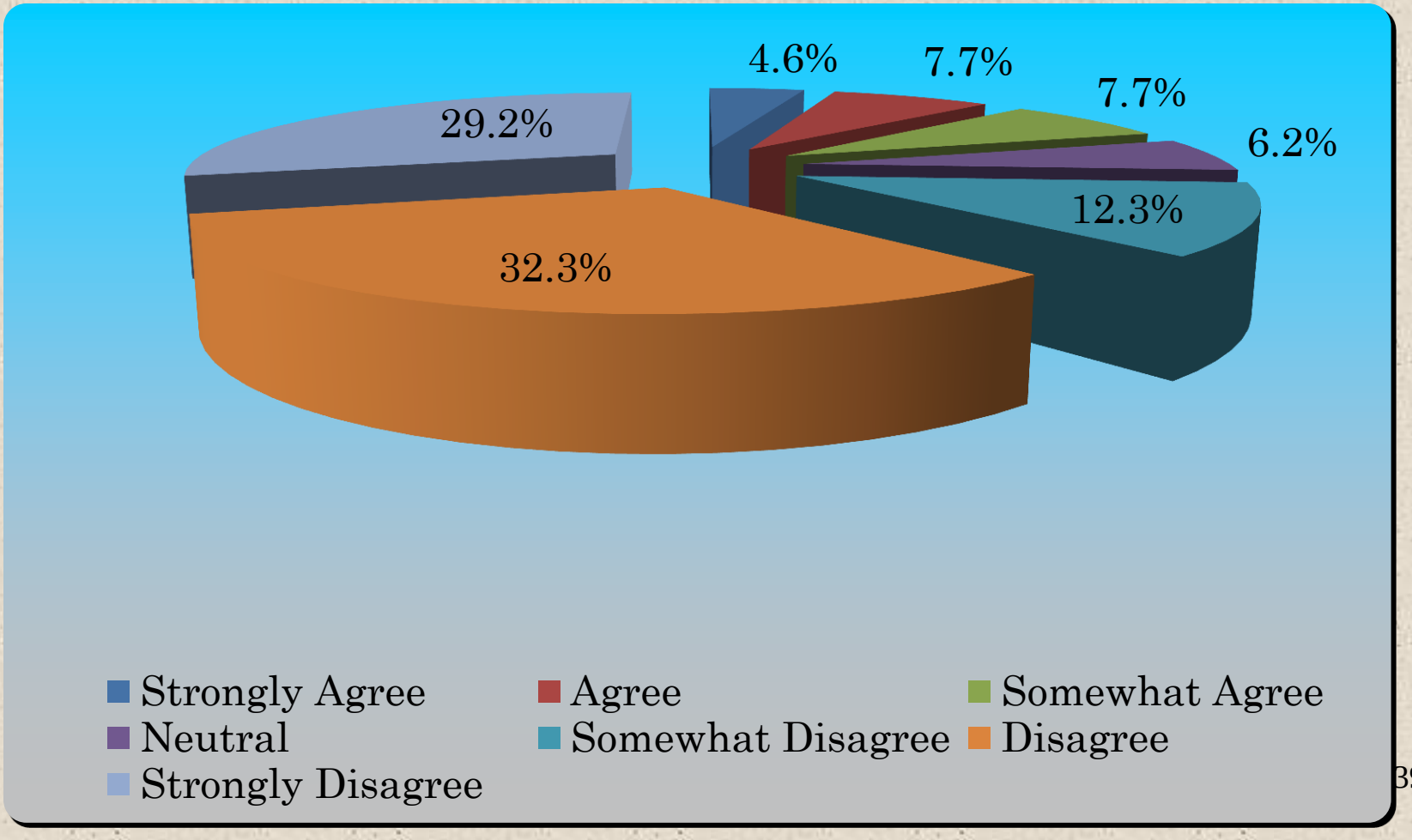
AARDA Conducted a Survey of Physicians

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

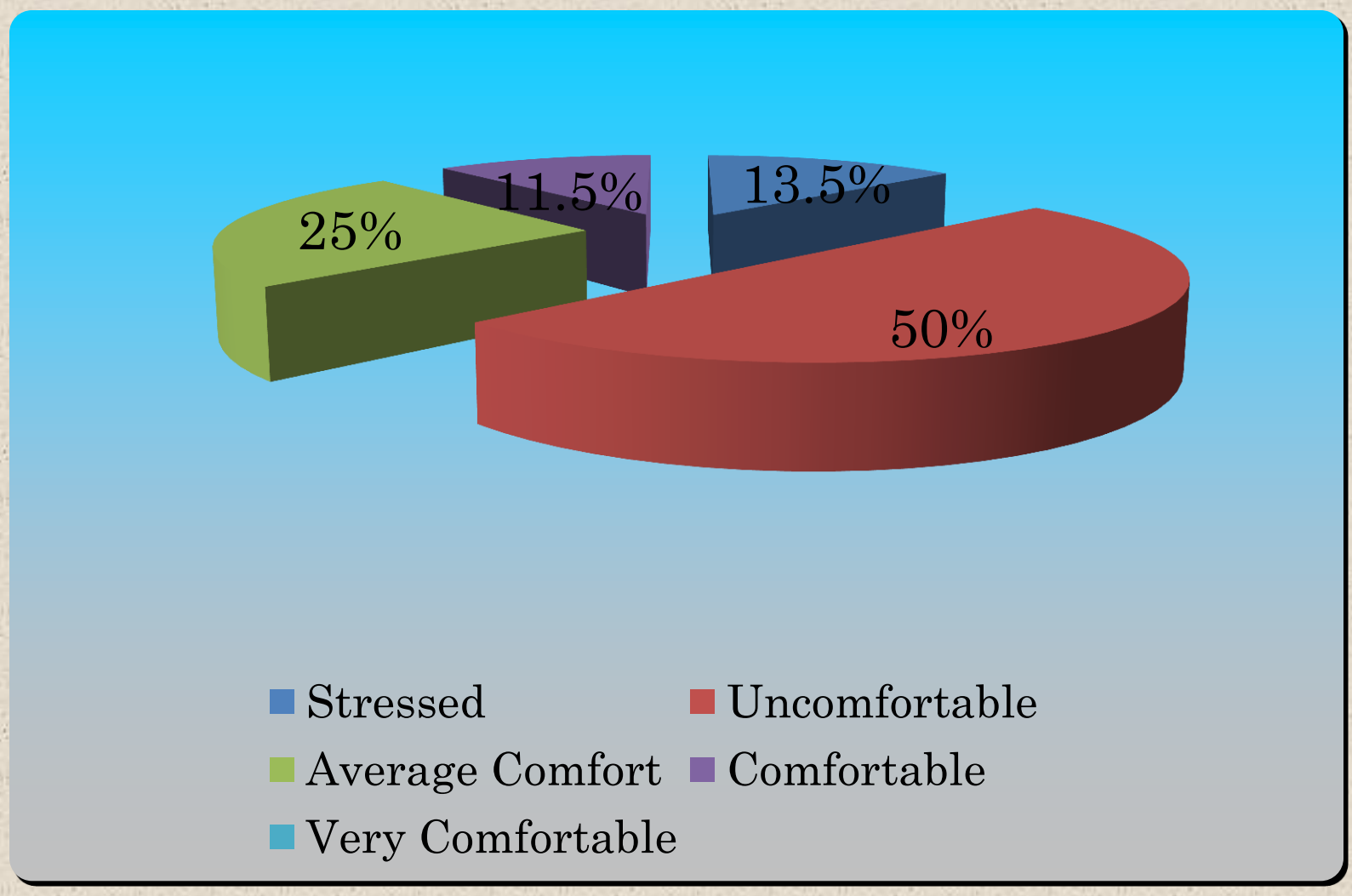
In medical school, how much training in autoimmune diseases did you receive?



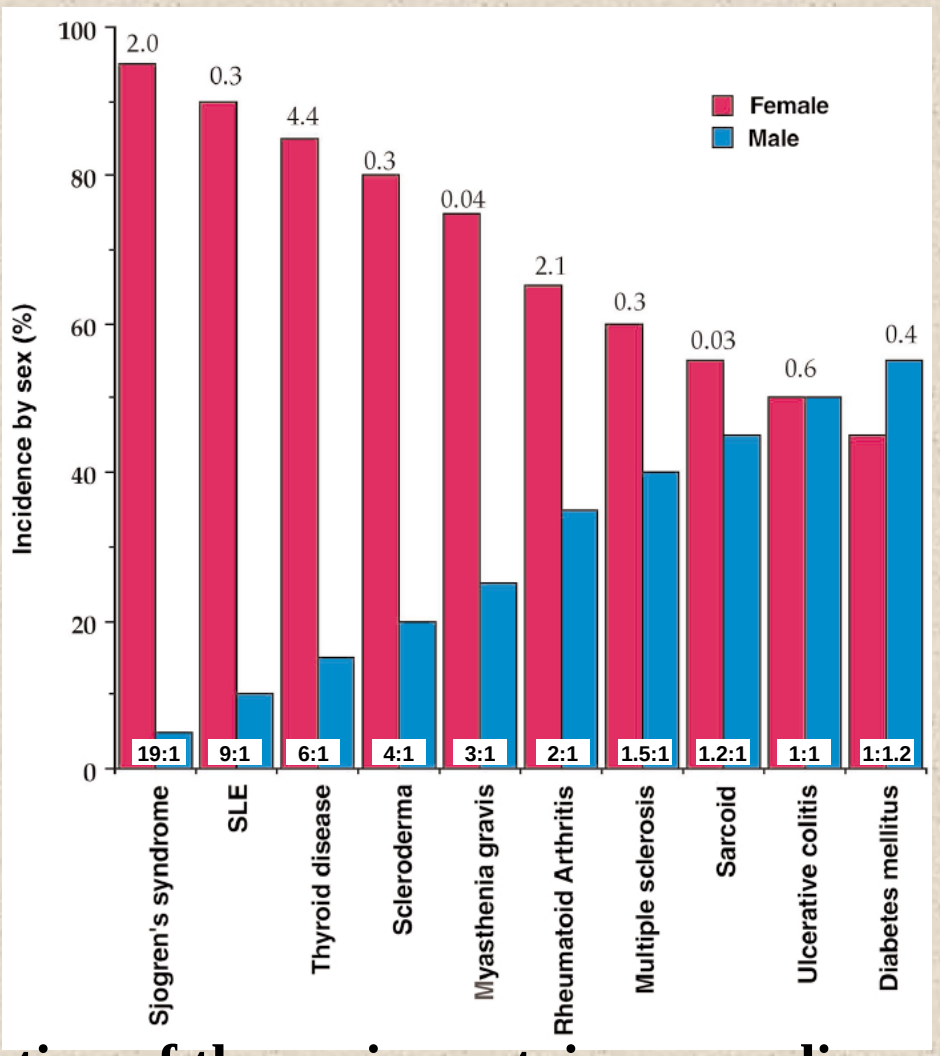
Would you agree that you received enough training to diagnose and treat autoimmune disease



What is your level of comfort in diagnosing autoimmune disease?



Women are generally more susceptible to autoimmune diseases than men.



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

Premise #1

Just How Prevalent is the Development of Autoimmune Disease?

Detective Adrian Monk

New Concept
True Prevalence of Autoimmunity

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

REVIEW

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AND

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

World Journal of Cardiology

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DOI: 10.4330/wjc.v6.i5.314

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REVIEW

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

Nicolas Vuilleumier, Fabrizio Montecucco, Oliver Hartley

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.

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Abstract

Immune-driven inflammation plays an important part in atherogenesis and is therefore believed to be key to the development of cardiovascular disease (CVD), which is currently the leading cause of death in the Western world. By fulfilling some of the Koch postulates, atherogenesis has even been proposed to be considered as an autoimmune disease, raising the hope that CVD could be prevented by immunomodulation. Nevertheless, the role of the immune system and autoimmune reactions in atherosclerosis appear to be a double edged-sword, with both pro-atherogenic and anti-atherogenic attributes. Hence, if immunomodulation is to become a therapeutic option for atherosclerosis and CVD, it will

Key words: Autoantibodies; Cardiovascular disease; Atherosclerosis; Apolipoprotein A-1; Autoimmunity; Biomarkers

Core tip: This review provides a comprehensive and critical analysis of the most recent basic research articles and clinical trials on the role of autoantibodies to apolipoprotein A-1 as biomarkers and potential mediators of cardiovascular diseases (CVD). Evidence from both *in vitro* and *in vivo* studies showed that anti-apolipoprotein A-1 IgG might have critical pro-atherosclerotic activities by activating immune cells to release pro-inflammatory mediators and proteases. In addition, these autoantibodies might increase heart rate and arrhythmias both in humans and animal models. These studies suggest a causal role of anti-apolipoprotein A-1 immunoglobulins of G class in CVD, indicating that those autoantibodies could potentially represent an emerging therapeutic target to better fight CVD.

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

Supported by Swiss National Science Foundation Grants to Dr. Vuilleumier N No. 310030_140736; and to Dr. Montecucco F No. 32003B_134963/1; a grant from the Foundation "Gustave and Simone Prévot" to Dr. Montecucco F
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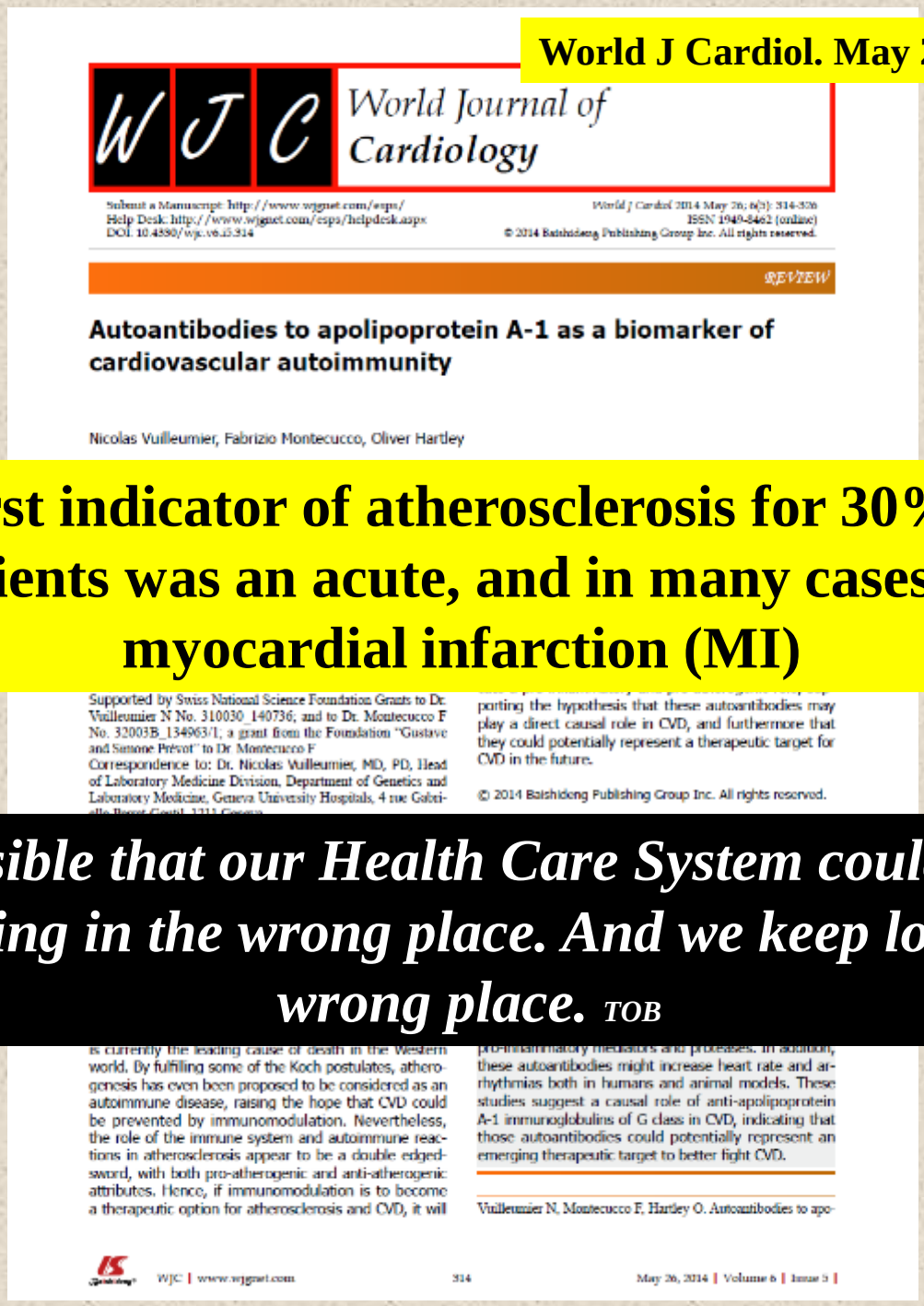

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The first indicator of atherosclerosis for 30%-50% of patients was an acute, and in many cases fatal, myocardial infarction (MI)

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porting the hypothesis that these autoantibodies may play a direct causal role in CVD, and furthermore that they could potentially represent a therapeutic target for CVD in the future.

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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. *ТОВ*

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Perhaps if We Open to More Current Information…..

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

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Author contributions: All the authors contributed to this manuscript.
Supported by Swiss National Science Foundation Grants to Dr. Vuilleumier N No. 310030_140736; and to Dr. Montecucco F No. 32003B_134963/1; a grant from the Foundation "Gustave and Simone Prévot" to Dr. Montecucco F.
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Current clinical studies indicate that high levels of anti-apoA-1 IgG are associated with a worse cardiovascular prognosis. In addition, *in vitro* and animal studies indicate a pro-inflammatory and pro-atherogenic role, supporting the hypothesis that these autoantibodies may play a direct causal role in CVD, and furthermore that they could potentially represent a therapeutic target for CVD in the future.

Key words: Autoantibodies; Cardiovascular disease; Atherosclerosis; Apolipoprotein A-1; Autoimmunity; Biomarkers

Core tip: This review provides a comprehensive and critical analysis of the most recent basic research articles and clinical trials on the role of autoantibodies to apolipoprotein A-1 as biomarkers and potential mediators of cardiovascular diseases (CVD). Evidence from both *in vitro* and *in vivo* studies showed that anti-apolipoprotein A-1 IgG might have critical pro-atherosclerotic activities by activating immune cells to release pro-inflammatory mediators and proteases. In addition, these autoantibodies might increase heart rate and arrhythmias both in humans and animal models. These studies suggest a causal role of anti-apolipoprotein A-1 immunoglobulins of G class in CVD, indicating that those autoantibodies could potentially represent an emerging therapeutic target to better fight CVD.

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Contemporary Reviews in Cardiovascular Medicine

Accelerated Atherosclerosis in Autoimmune Rheumatic Diseases

Yehuda Shoenfeld, MD, FRCP (Hon); Roberto Gerli, MD; Andrea Doria, MD; E
Marco Matucci Cerinic, MD; Nicoletta Ronda, MD; Luis J. Jara, MD; Mahmud
Pier Luigi Meroni, MD; Yaniv Sherer, MD

Circulation. 2005;112:3337-3347

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

Atherosclerosis is a multifactorial process that commences in childhood but manifests clinically later in life. Atherosclerosis is increasingly considered an immune system–mediated process of the vascular system. The pres-

immunodeficient mice, they increased lesion area in the latter by 164%.[4] It is therefore not surprising that as in autoimmune diseases, the cellular components within atherosclerotic plaques secrete various cytokines, including many interleu-

inflammatory mechanisms that are aggravated in AIRDs. Several AIRDs exhibit increased overt cardiovascular disease (CVD) prevalence as well as findings of advanced subclinical atherosclerosis, which may precede the appearance of a clinical disease and thus be a target of early identification and preventive therapy.

Cells of the immune system can be found within atherosclerotic plaques, which suggests that they have a role in the atherogenic process. Their migration and activation within the plaques can be secondary to various stimuli, including infectious agents.[4] These cells probably aggravate atherosclerosis, because CD4+ and CD8+ T-cell depletion reduced fatty streak formation in C57BL/6 mice. In addition, after crossing of apolipoprotein E (ApoE)-knockout mice with immunodeficient scid/scid mice, the offspring had a 73% reduction in aortic fatty streak lesions compared with the immunocompetent apoE mice. Moreover, when CD4+ T cells were transferred from the immunocompetent to the

ited larger fatty streaks compared with mice that received lymphocytes from control mice. However, T-cell depletion of lymphocytes failed to induce this effect.[6] Therefore, T cells specific for β2GPI are capable of increasing atherosclerosis, suggesting that β2GPI is a target autoantigen in atherosclerosis. There are probably many more such specific cell lines reacting with specific antigens that can modulate atherosclerosis by either aggravating or decreasing its extent (proatherogenic or antiatherogenic).

Several autoantibodies are associated with atherosclerosis and its manifestations in humans. Animals provide good models for studying the effect of these autoantibodies on atherosclerosis. Active immunization of LDL-receptor–deficient mice with anti-cardiolipin (aCL) antibodies resulted in development of high titers of mouse aCL and increased atherosclerosis compared with control subjects.[7] Immunization of mice with β2GPI resulted in pronounced cellular and humoral responses to β2GPI, with high titers of anti β2GPI

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(*Circulation.* 2005;112:3337-3347.)

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

Dyslipidaemia in Rheumatological Autoimmune Diseases

Tracey E. Toms[1], Vasileios F. Panoulas[1] and George D. Kitas[1,2,*]

[1]Department of Rheumatology, Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Dudley, West Midlands, UK

[2]arc Epidemiology Unit, Manchester University, Manchester, UK

Abstract: Autoimmunity forms the basis of many rheumatological diseases, and may contribute not only to the classical clinical manifestations but also to the complications. Many of the autoimmune rheumatological diseases, including rheu-

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

Keywords: Autoimmune disease, dyslipidaemia, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary sjogrens syndrome, anti-phospholipid syndrome.

INTRODUCTION

The complexity and diversity of many rheumatological conditions is often attributed to their underlying autoimmune nature. Autoimmunity contributes to the clinical manifestations, as well as complications of disease and response to treatment. Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have been found to associate with an increased risk for cardiovascular disease (CVD) [1-3], resulting in a significantly shortened lifespan. As a consequence, much speculation and research has focused on the role of both traditional and novel, disease specific, risk factors. In the general population, dyslipidaemia has been shown to be one of the strongest predictors of CVD, with elevated levels of low-density lipoproteins (LDL) forming the primary treatment target according to national guidelines [4]. In this review we discuss the association between several of the autoimmune rheumatological conditions (RA, SLE, primary antiphospholipid sysndrome (primary APS), systemic sclerosis (SSc), and primary Sjogrens syndrome (PSS)) and dyslipidaemia, and the potential impact this has on cardiovascular risk, in particular atherosclerotic plaque formation.

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Coronary artery disease develops due to the formation and rupture of atherosclerotic plaques. The term atherosclerosis covers a spectrum of disease ranging from endothelial dysfunction and fatty streak development, through to the formation and rupture of a mature plaque. The development of atherosclerotic plaques is complex. Inflammation is fundamental to all stages of atherosclerotic plaque [5], with an intense bi-directional interaction occurring between lipids and inflammation. Rheumatological autoimmune diseases are associated with a heightened inflammatory state in varying degrees, thus these processes may be accelerated.

Endothelial dysfunction is the initiating step in plaque development [6]. Healthy endothelium exerts a number of vasoprotective effects such as vasodilation, suppression of smooth muscle cell growth and inhibition of inflammatory responses, thereby helping to protect against atherosclerosis. Nitric oxide mediates many of these effects by inhibiting platelet aggregation and LDL oxidation, as well as opposing the effects of endothelium-derived vasoconstrictors [7]. Endothelial damage occurs when the fine balance between vasoconstrictive and vasodilatory pathways is disrupted. Although endothelial dysfunction is likely to be a multifactorial process, the major cardiovascular risk factors such as hypercholesterolaemia, hypertension, diabetes and smoking have been implicated *via* their ability to increase the production of reactive oxygen species [8]. It is postulated that the increase in reactive oxygen species may in turn reduce endothelial nitric oxide (NO) availability [9, 10]. Multiple lipid abnormalities have been associated with endothelial dysfunction. Hypercholesterolaemia has been shown to cause focal activation of the endothelium in medium and large arteries and has been associated with an increased number of monocytes entering the intima [11]. High levels of oxidised LDL (oxLDL) may down regulate endothelial NO synthase (eNOS), thus reducing available NO and restricting coronary vasodilation [12]. High levels of circulat-

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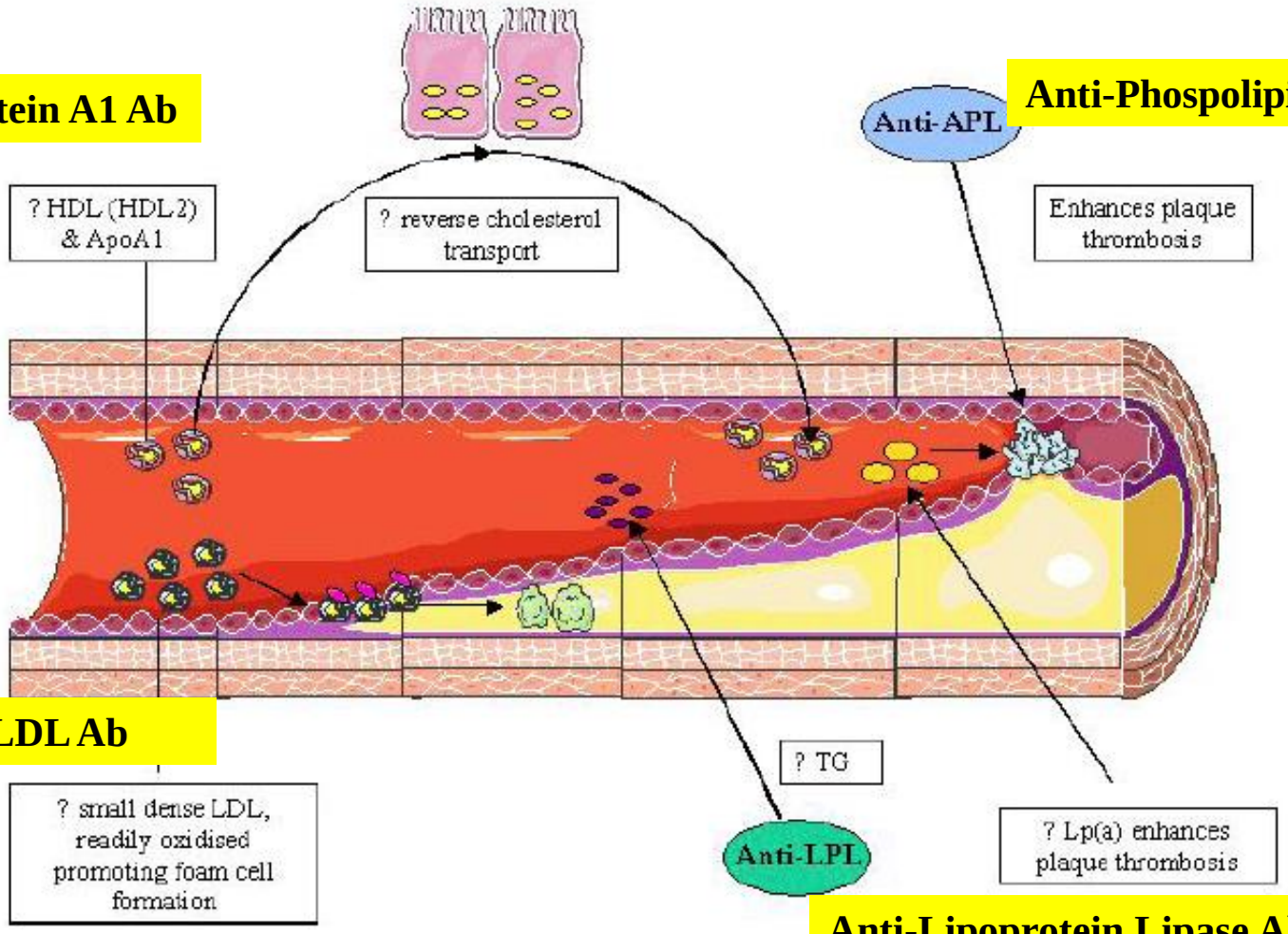
Anti-Lipoprotein A1 Ab

Anti-Phospolipid Ab



Anti-Oxidative LDL Ab

Anti-Lipoprotein Lipase Ab

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

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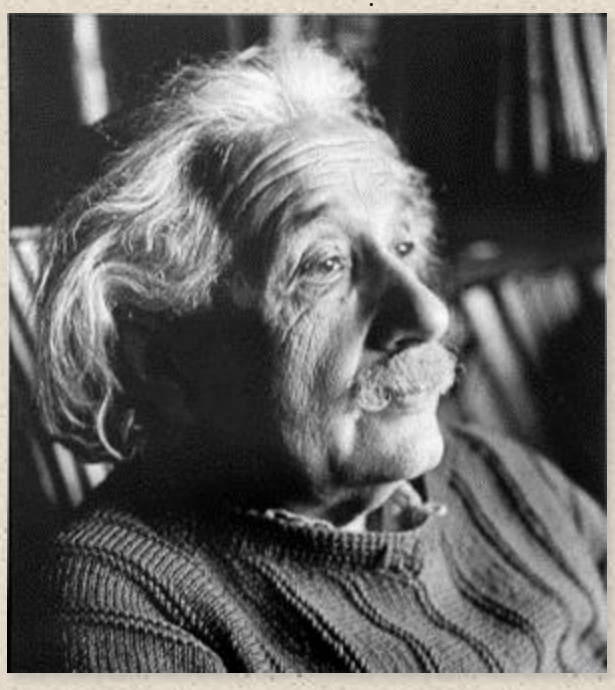
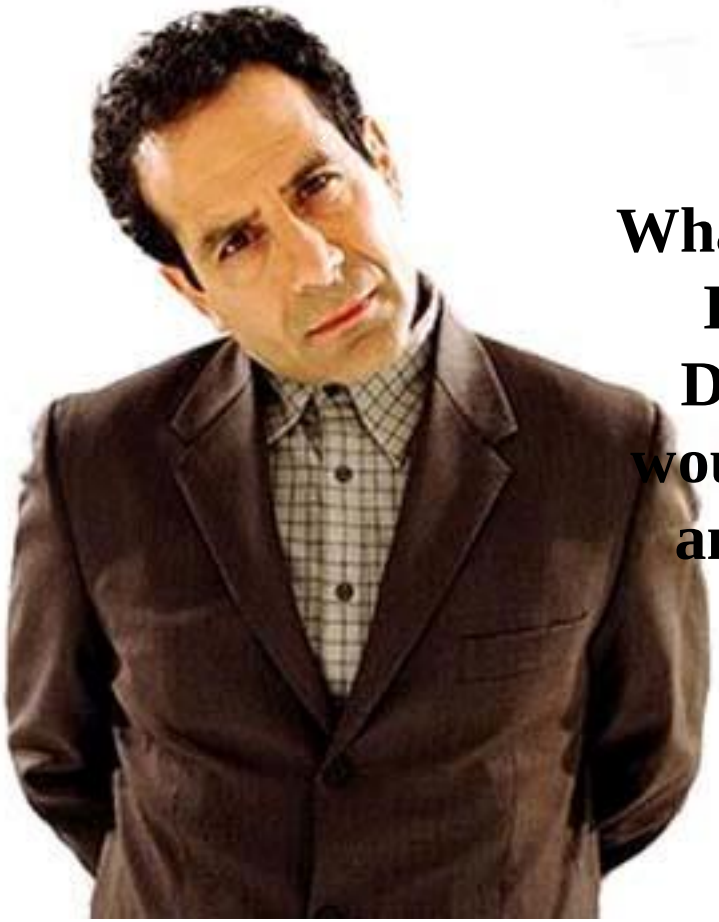
Thus, If CVD has an Initiating Autoimmune Component, Arguably, What Becomes the #1 Mechanism in the Progression of Morbidity and Mortality in the Industrialized World?





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.

Detective Adrian Monk

Premise #2

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

Detective Adrian Monk

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

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are associated with a heightened inflammatory state in varying degrees, thus these processes may be accelerated.

Endothelial dysfunction is the initiating step in plaque development [6]. Healthy endothelium exerts a number of vasoprotective effects such as vasodilation, suppression of smooth muscle cell growth and inhibition of inflammatory responses, thereby helping to protect against atherosclerosis. Nitric oxide mediates many of these effects by inhibiting platelet aggregation and LDL oxidation, as well as opposing the effects of endothelium-derived vasoconstrictors [7]. Endothelial damage occurs when the fine balance between vasoconstrictive and vasodilatory pathways is disrupted. Although endothelial dysfunction is likely to be a multifactorial process, the major cardiovascular risk factors such as hypercholesterolaemia, hypertension, diabetes and smoking have been implicated *via* their ability to increase the production of reactive oxygen species [8]. It is postulated that the increase in reactive oxygen species may in turn reduce endothelial nitric oxide (NO) availability [9, 10]. Multiple lipid abnormalities have been associated with endothelial dysfunction. Hypercholesterolaemia has been shown to cause focal activation of the endothelium in medium and large arteries and has been associated with an increased number of monocytes entering the intima [11]. High levels of oxidised LDL (oxLDL) may down regulate endothelial NO synthase (eNOS), thus reducing available NO and restricting coronary vasodilation [12]. High levels of circulat-

Understanding auto-antibodies

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

Taylor&Francis
healthsciences

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

Principles of Autoantibodies as Disease-specific Markers

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

INTRODUCTION

The immune system is designed by nature to protect us from our environment.[1] But activation of the immune response not only protects us from disease, as in infectious

be predicted to a degree by the number of autoantibodies, the type of autoantibody and the titer of the autoantibody.[6–8] In addition, associated features including genetic risk and evidence of target organ failure can enhance the predictive value of autoantibodies.[9,10] These

detected.[2] Realising the clinical potential of autoantibodies could be extremely valuable, and in this article we set out the principles for measuring autoantibodies both as diagnostic markers of disease activity and disease classification or as predictive markers of progression to clinical disease. Observations supporting this position are presented and whilst they are broadly based on the study of autoimmune diseases, it remains possible that the general principles they encompass can be applied to other disease processes, including cancer.

Studies using autoantibodies in autoimmune diseases suggest several principles. First, autoantibodies can reflect the disease process and, when detected during a prolonged disease prodrome, autoantibodies can predict clinical disease.[3] Second, when there is aetiological heterogeneity in clinical disease, autoantibodies can help classify the disease process.[4] Both these points are particularly relevant when autoantibodies themselves have the capacity to damage tissue. Third, a number of distinct autoantibodies are associated with any one disease, and some are more predictive of progression to clinical symptoms than others.[5] Fourth, the risk of progression to disease, the rate of progression, and the severity of the clinical disease can

bodies.[11] This assay format is valuable in identifying autoimmunity but of little help in determining the precise autoantigen identified by the autoantibody. The subsequent introduction of certain molecular techniques enable the identification of disease-specific autoantigens and then the use of recombinant technology to establish assays to detect serum autoantibodies with a high degree of precision. The high-throughput of these recombinant assays has made population screening a feasible proposition.

One important feature of an autoantibody, or any laboratory determined marker, is the precision of detecting that marker. If that precision is so sensitive that individuals are detected as positive when they do not have the disease process (a false positive) then that individual will either be inappropriately classified as having a disease or be exposed to unnecessary therapy. Performance characteristics of autoantibody assays must be of the highest standards to minimise this risk. To that end assays must be standardised and validated with rigorous quality control schemes.[12] Moreover, a single autoantibody test to a single autoantigen on a single occasion should not be the basis for important clinical decisions. Maximal predictive sensitivity and specificity may require testing of different sets of

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Expert Opinion

1. Introduction
2. Present diagnostic tools in autoimmune diseases based on tissue-specific antibodies and etiologic factors associated with them
3. Biomarkers for neuroautoimmune disorders
4. Search for antibodies as

Antibodies as predictors of autoimmune diseases and cancer

Aristo Vojdani
Immunosciences Lab., I

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

Background: Autoantibodies targeted against a variety of self-antigens are detected in autoimmune diseases and cancer. Emerging evidence has suggested the involvement of environmental factors such as infections and xenobiotics, and some dietary proteins and their antibodies in the pathogenesis of many autoimmune diseases. These antibodies appear in the blood years before presentation of symptoms in various disorders. Therefore, these antibodies may be used as biomarkers for early detection of various diseases. *Objective*: To provide an overview of antibody arrays

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.

predictive antibodies

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1. Introduction

Antibodies are molecules produced by plasma cells and B cells against bacteria, viruses, parasites, antigens, dietary proteins and peptides, and even haptenic chemicals such as medications [1-6]. In response to bacterial, viral and parasitic infection, the immune system jumps into action, deploying cells as well as antibodies in order to recognize and destroy the invaders. However, owing to molecular mimicry or antigenic similarity between these infectious agents and human tissue structure, in a genetically susceptible individual, components of the body's immune system target one or more types of the person's own tissue, which may result in autoimmunity [7-9]. In relation to dietary proteins and peptides, the mucosal immune system regulates responses to these substances in order to avoid harmful reactions to common mucosal antigens. This homeostasis between the host and antigenic stimulus is maintained by the mucosal immune system's induction of immunologic ignorance or oral tolerance against dietary proteins and commensal bacteria [10]. In the absence of oral tolerance, specific antibody-dependent protection is induced by secretory IgA and IgM, the predominant isotypes in human external secretions, including saliva. This breach of the intestinal barrier by dietary proteins through loss of tolerance can lead not only to antibody production in blood, but

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ORIGINAL ARTICLE

Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus

Melissa R. Arbuckle, M.D., Ph.D., Micah T. McClain, Ph.D., Mark V. Rubertone, M.D., R. Hal Scofield, M.D., Gregory J. Dennis, M.D., Judith A. James, M.D., Ph.D., and John B. Harley, M.D., Ph.D.

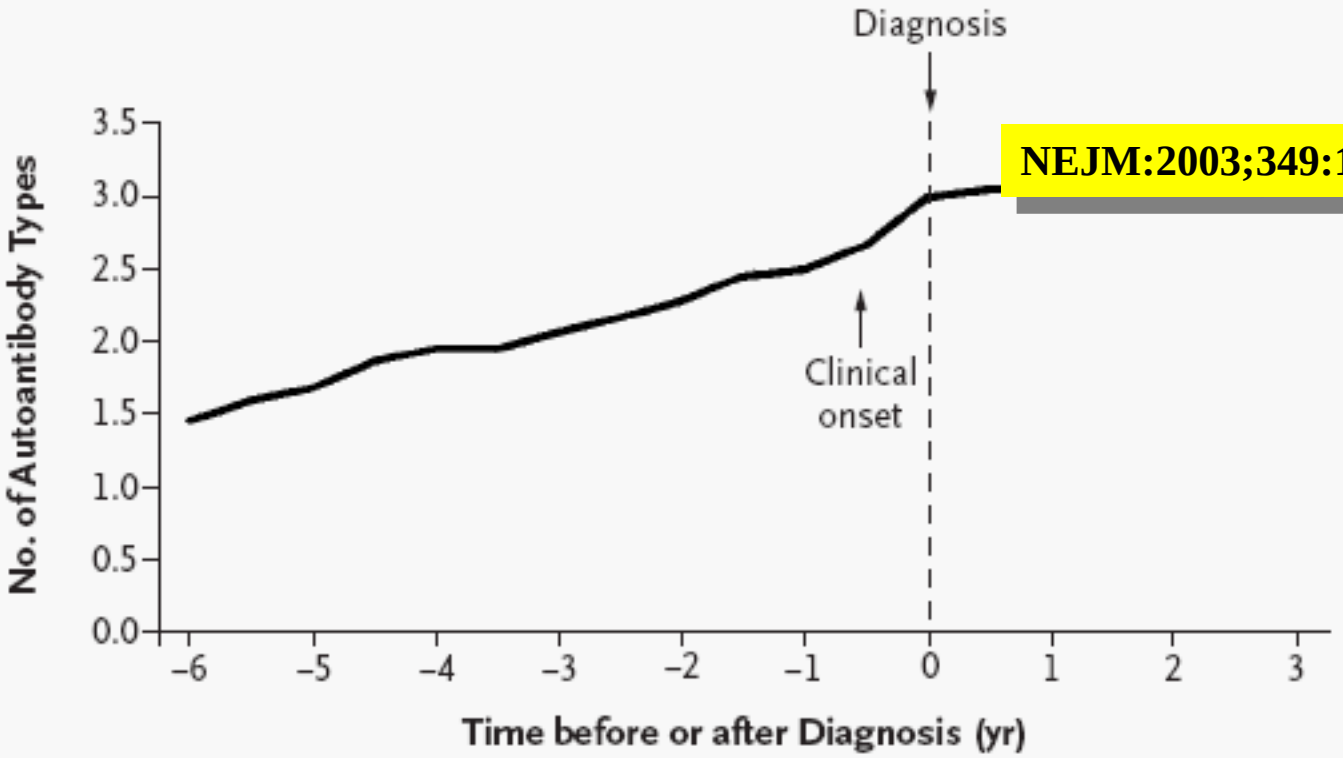
ABSTRACT

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.

many patients, the earliest available serum sample was positive; therefore, these measures of the average time from the first positive antibody test to the diagnosis are underestimates of the time from the development of antibodies to the diagnosis. Of the 130 initial matched controls, 3.8 percent were positive for one or more autoantibodies.

CONCLUSIONS

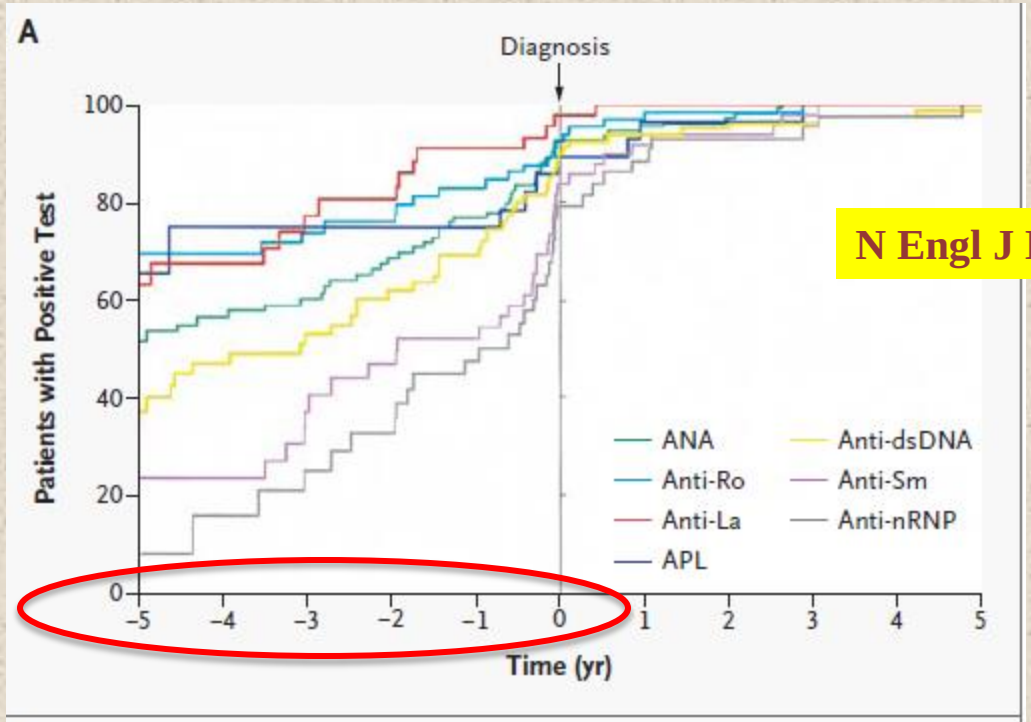
Autoantibodies are typically present many years before the diagnosis of SLE. Furthermore, the appearance of autoantibodies in patients with SLE tends to follow a predictable course, with a progressive accumulation of specific autoantibodies before the onset of SLE, while patients are still asymptomatic.



NEJM:2003;349:1526-1533

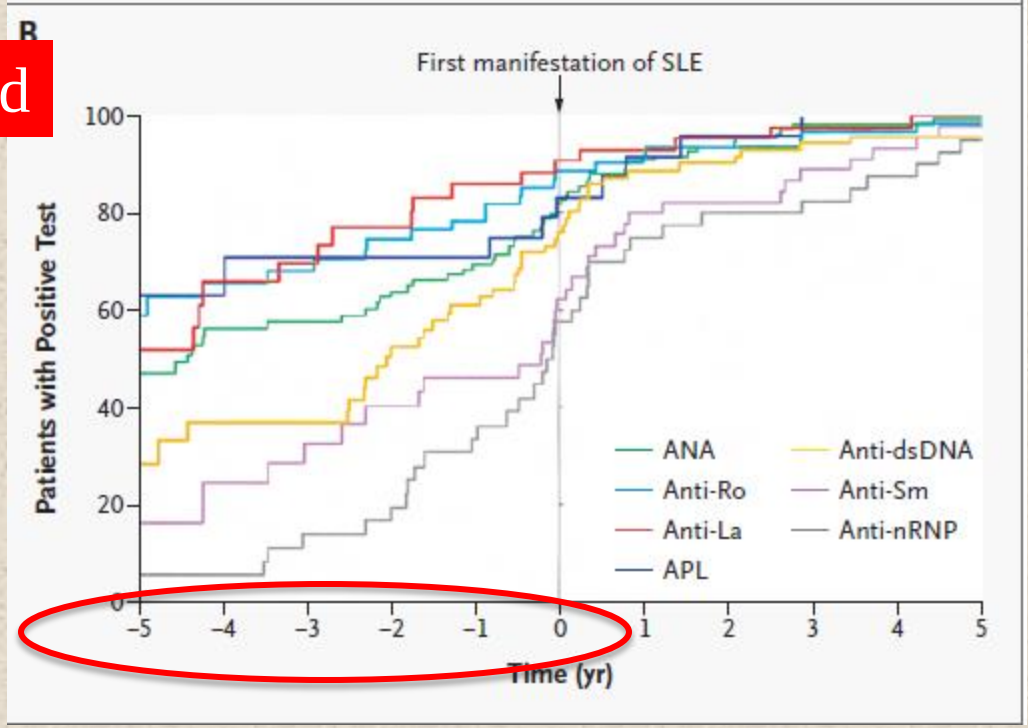
Figure 2. Accumulation of Systemic Lupus Erythematosus Autoantibodies.

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.



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

Prodromal period



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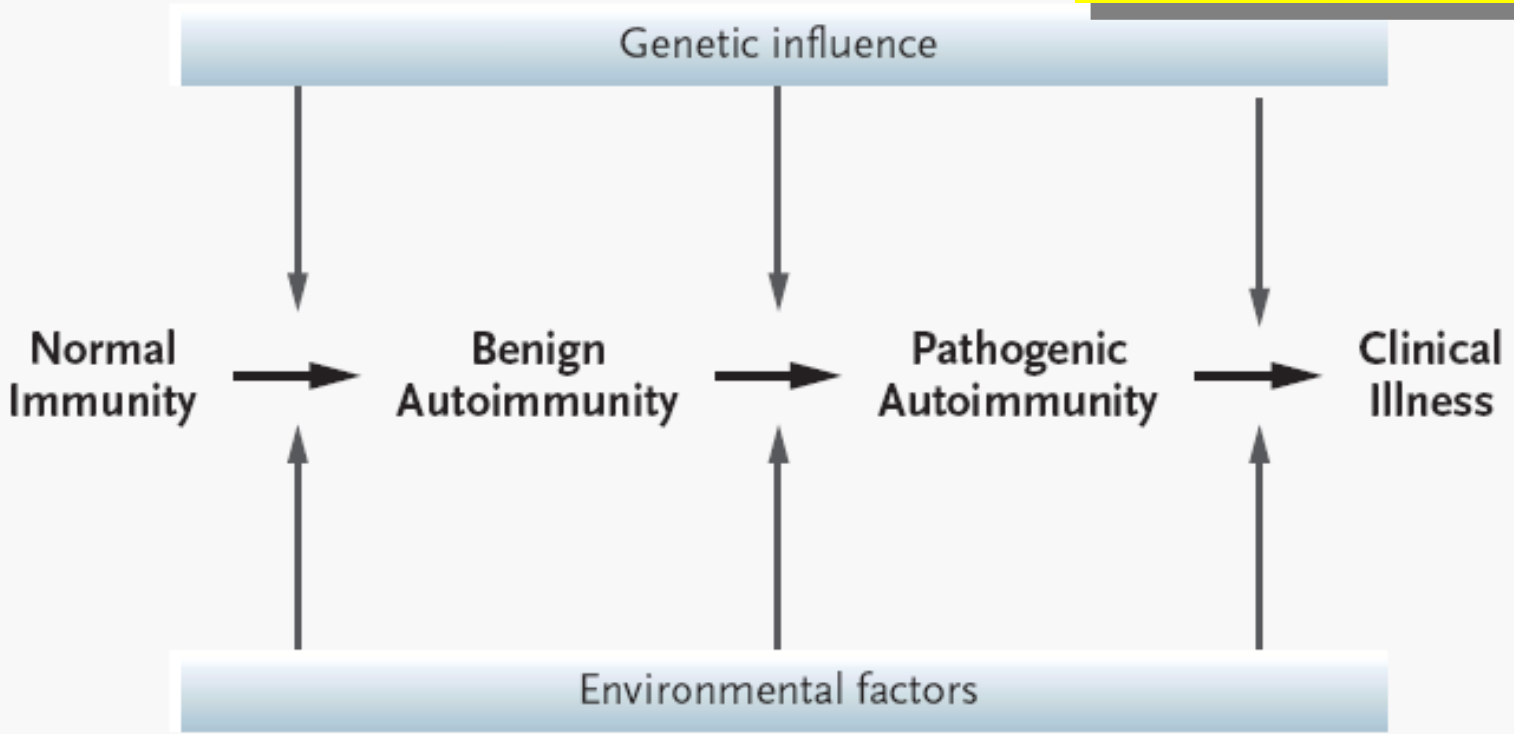

Figure 3. Phases in the Development of Pathogenic Autoimmunity.

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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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.

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?

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.

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."

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.

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

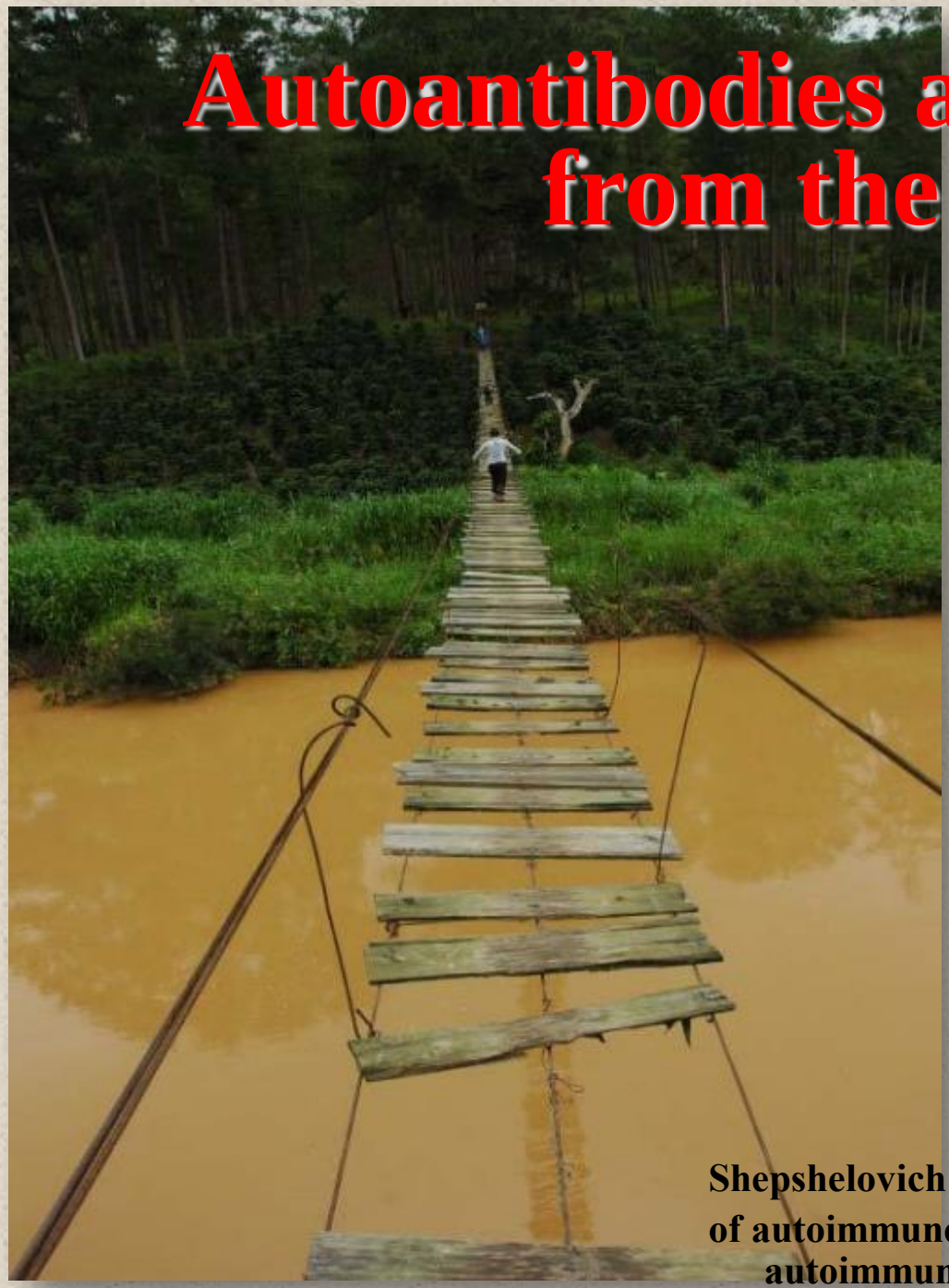
Dr. Shoenfeld: In some ways we do have some measurements. But I would like to refer to one of them, which is very simple, it's cheap, and it has no side effects whatsoever. And this is vitamin D.

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.

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

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

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Premise #3
How does Autoimmunity Develop?

Detective Adrian Monk

REVIEW

www.nature.com/clinicalpractice/gasthep

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

Alessio Fasano* and Terez Shea-Donohue

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

SUMMARY

The primary function
perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis. A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that another extremely important function of this organ is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity

the use of probiotics.

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

REVIEW CRITERIA

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

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means that they are the third most common category of diseases in the US after cancer and heart disease. They can affect virtually every site in the body, including the gastrointestinal tract. At least 15 diseases are known to be the direct result of an autoimmune response, and circumstantial evidence links more than 80 conditions to autoimmunity.[1]

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

self-antigens.[2] The induction of an immune response to the microbial antigens results in a cross-reaction with the self-antigens and the induction of autoimmunity. According to this theory, once the autoimmune process is activated it becomes independent of continuous exposure to the environmental trigger, and is therefore self-perpetuating and irreversible. Epitope-specific cross-reactivity between microbial antigens and self-antigens has been shown in some animal models to initiate autoimmunity.[3] Conversely, in most human autoimmune diseases, molecular mimicry seems to be a factor in the progression of a pre-existing subclinical autoimmune response, rather than in the initiation of autoimmunity.[3]

Another theory suggests that microorganisms expose self-antigens to the immune system by directly damaging tissues during active infection, and that this leads to the development of autoimmunity. This mechanism has been referred to as the 'bystander effect', and it occurs only when the new antigen is presented with the

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When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur.

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

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many fields and is currently receiving a great deal of attention. This review is timely given the increased interest in the role of a 'leaky gut' in the pathogenesis of gastrointestinal diseases and the advent of novel treatment strategies, such as the use of probiotics.

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

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The autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented…

infection and autoimmune disease is often explained by a mechanism known as 'molecular mimicry', whereby microbial antigens (or, more specifically, EPITOPES) are postulated to resemble self-antigens.[2] The induction of an immune response to the microbial antigens results in a cross-reaction with the self-antigens and the induction of autoimmunity. According to this theory, once the autoimmune process is activated it becomes independent of continuous exposure to the environmental trigger, and is therefore self-perpetuating and irreversible. Epitope-specific cross-reactivity between microbial antigens and self-antigens has been shown in some animal models to initiate autoimmunity.[3] Conversely, in most human autoimmune diseases, molecular mimicry seems to be a factor in the progression of a pre-existing subclinical autoimmune response, rather than in the initiation of autoimmunity.[3]

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Premise #4
Can Foods Trigger Pathogenic Intestinal Permeability

Detective Adrian Monk

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ASIP Journal CME Program

Amer Jour of Path, Vol. 169, No. 6, Dec 2006

Amgen Award Lecture

Molecular Basis of Epithelial Barrier Regulation

From Basic Mechanisms to Clinical Application

Jerrold R. Turner

From the Department of Pathology, The University of Chicago, Chicago, Illinois

One critical function of epithelial-lined surfaces is to define the interface between separate body compartments.

mechanisms is central to barrier dysfunction in both *in vitro* and *in vivo* models of disease. Although the contribution of barrier dysfunction to pathogenesis of chronic disease remains incompletely understood, it is now clear that cytoskeletal regulation of barrier function is both an important pathogenic process and that targeted inhibition of myosin light chain kinase, which affects this cytoskeleton-dependent tight junction dysfunction, is an attractive candidate for therapeutic intervention. *(Am J Pathol 2006, 169:1901–1909; DOI: 10.2353/ajpath.2006.060681)*

The economic and social costs associated with gastrointestinal disease continue to expand. It is estimated that in 2000, the most recent year for which data are available, ulcerative colitis, Crohn's disease, chronic diarrheal disease, and other infectious and inflammatory intestinal diseases in the United States had total costs in excess of $4.7 billion.[1] These diseases are complex and likely involve multiple mechanisms of injury, including immune dysregulation, epithelial apoptosis, and signal transduction events. Many diseases, particularly inflammatory bowel disease, celiac disease, ischemic disease, and graft-versus-host disease, are also associated with loss of intestinal barrier function.[2–15] Although incompletely explored, significant data suggest that tumor necrosis factor (TNF)-induced dysregulation of the intestinal barrier may be a critical pathogenic component of these diseases. The goals of this article are to review current understanding of mechanisms of barrier regulation, con-

the sterile tubular lumen to allow active and passive transport to regulate urine composition.[17] 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.

The intestinal barrier is primarily formed by the epithelium. The individual epithelial cell membranes form the majority of this barrier; they are impermeable to hydrophilic solutes except where specific transporters exist.

Supported by the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases) and the Crohn's & Colitis Foundation of America.

Accepted for publication September 6, 2006.

The ASIP-Amgen Outstanding Investigator Award is given by the American Society for Investigative Pathology to recognize excellence in experimental pathology research. Jerrold R. Turner, a recipient of the 2006 Amgen Outstanding Investigator Award, delivered a lecture entitled "Molecular Basis of Epithelial Barrier Regulation: From Basic Science to Clinical Application" on April 2, 2006 at the annual meeting of the American Society for Investigative Pathology in San Francisco, CA.

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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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REVIEW

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

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CLASSICAL THEORIES ON THE

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CLASSICAL THEORIES ON THE PATHOGENESIS OF AUTOIMMUNE DISEASE

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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**

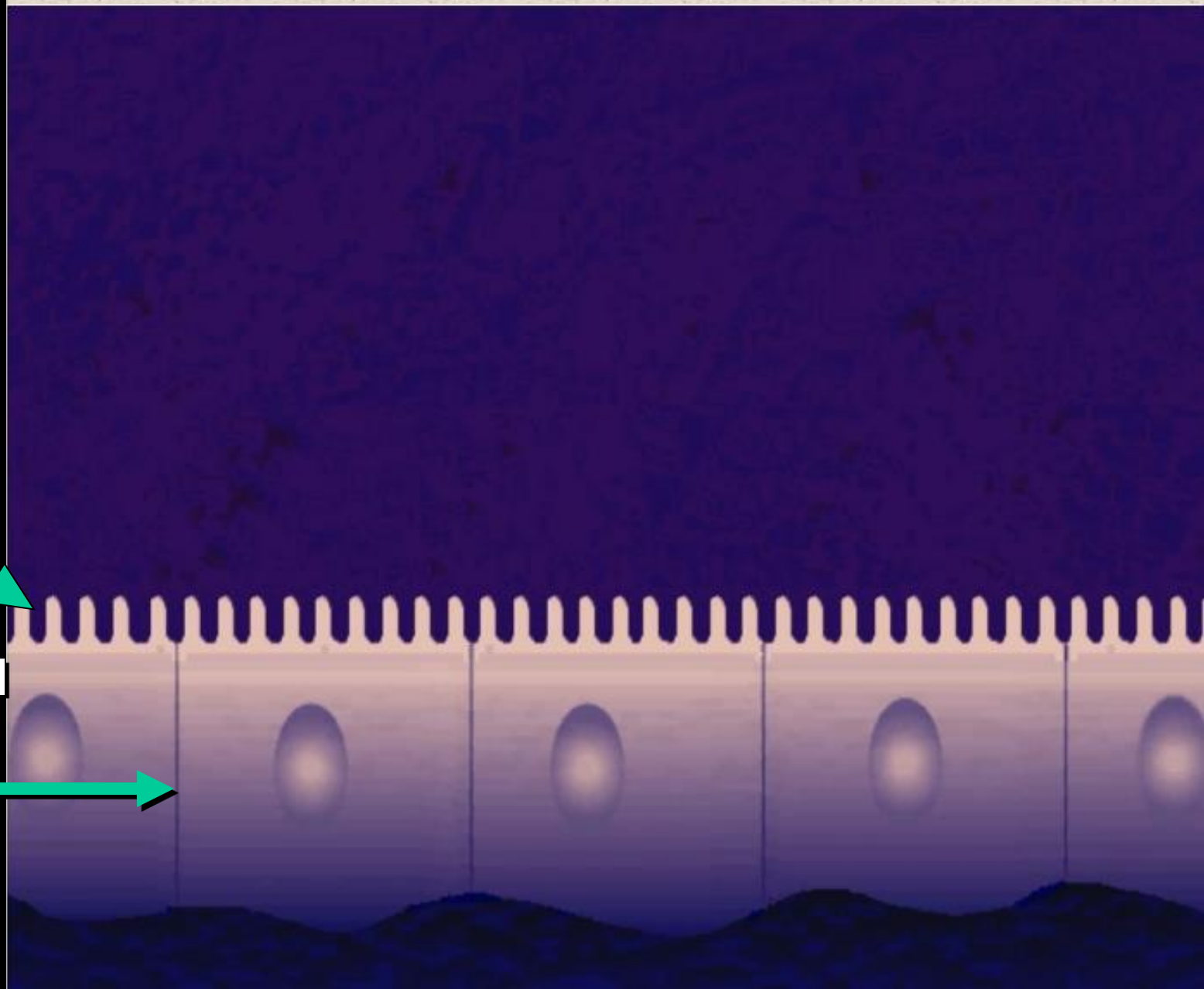
→ **Antigen translocation(foods, LPS, chemical toxins…)**

→ **Immune Response = Antibody Production**

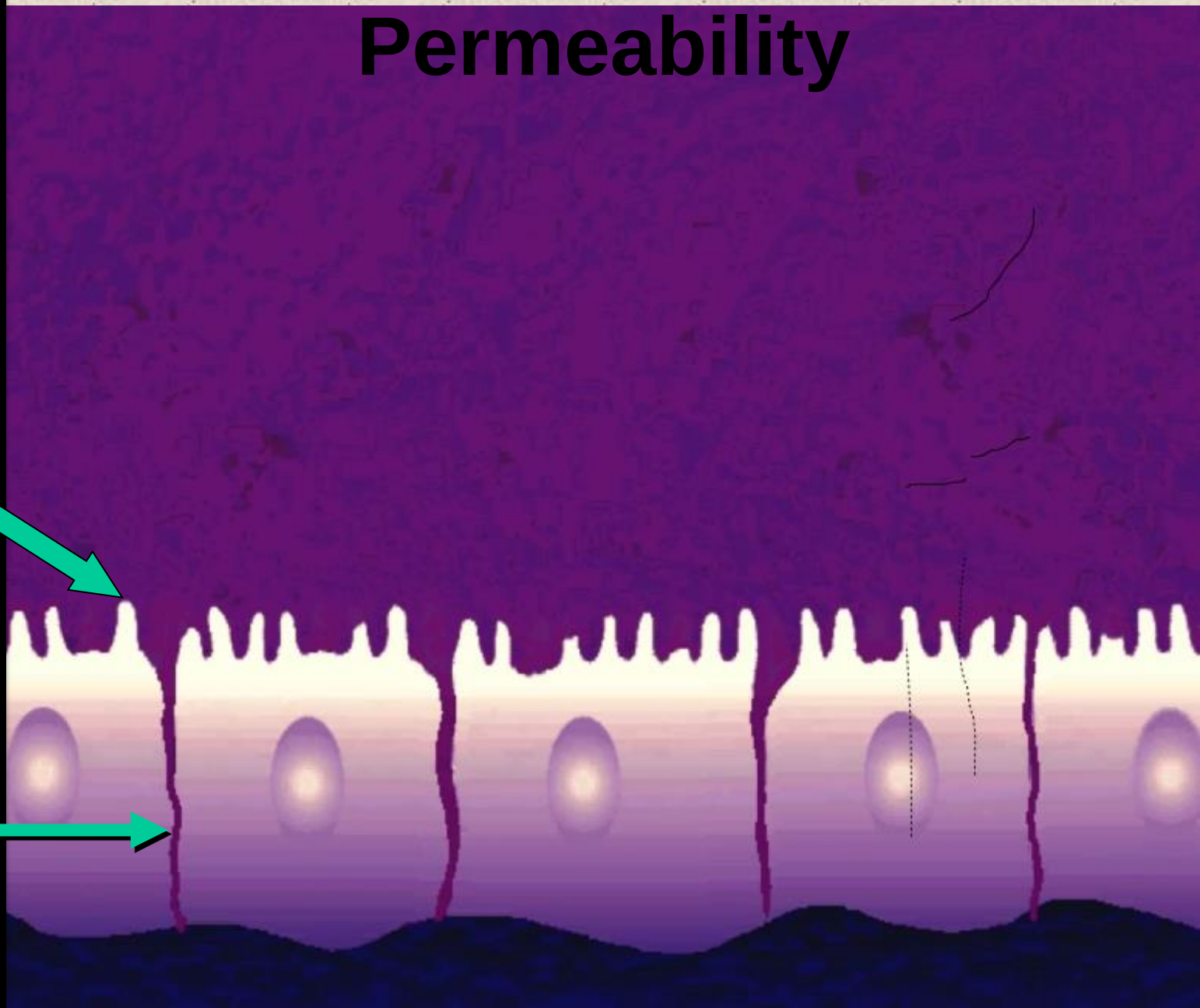
→ **Molecular Mimicry**

→ **Autoimmune Mechanism initiated**

Healthy Gut



Pathogenic Intestinal Permeability



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CLINICA

ADVANCES IN TRANSLATIONAL SCIENCE

Joseph H. Sellin, Section Editor

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

ALESSIO FASANO

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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.

Technological Primer

Recent studies indicate that besides water and salt homeostasis and digestion and absorption of nutrients, another key function of the intestine is to regulate the trafficking of environmental antigens across the host mucosal barrier.[1] Intestinal tight junctions (TJ) are responsible for the paracellular trafficking of macromolecules; therefore, they contribute to the balance between tolerance and immune response to non-self antigens.[1] Although considerable knowledge exists about TJ ultrastructure, relatively little is known about their pathophysiological regulation leading to local and/or systemic inflammation. Technologies that are capable to restore intestinal barrier function and, therefore, proper antigen trafficking may represent an innovative approach to prevent and/or treat immune-mediated diseases in which increased intestinal permeability seems to be an integral part of their pathogenesis.

What Are the Findings

Regulation of Intestinal Permeability: The Zonulin Pathway

In the past decade we have focused our research effort on the discovery of physiological modulators of intestinal TJ. Our studies led to the discovery and characterization of zonulin as the only human protein discovered to date that is known to reversibly

intestines exposed to enteric bacteria secreted zonulin.[2] This secretion was independent of the virulence of the microorganisms tested, occurred only on the luminal aspect of the bacteria-exposed small intestinal mucosa, and was followed by an increase in intestinal permeability coincident with the disengagement of the protein zonula occludens 1 from the tight junctional complex.[2] This zonulin-driven opening of the paracellular pathway may represent a defensive mechanism, which flushes out microorganisms so contributing to the innate immune response of the host against bacterial colonization of the small intestine.

Besides bacterial exposure, we have shown that gliadin, the main staple protein in wheat, also affects the intestinal barrier function by releasing zonulin by engaging the chemokine receptor CXCR3.[3] Our data demonstrate that in the intestinal epithelium, CXCR3 is expressed at the luminal level, is overexpressed in celiac disease (CD) patients, colocalizes with specific gliadin peptides, and that this interaction coincides with recruitment of the adapter protein, MyD88, to the receptor.[3]

Abbreviations used in this paper: BBDP, BioBreeding diabetic prone; CD, celiac disease; HP, haptoglobin; TJ, tight junctions; T1D, type 1 diabetes; Zot, zonula occludens toxin.

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doi:10.1016/j.cgh.2012.08.012

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]

[1]Unit of Experimental Endoscopy, Department of Internal Medicine I, [5]Department of Pathology, [6]Department of Dermatology

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]

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

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

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

Keywords: Imaging; FODMAP; Food Allergy; Gluten.

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]

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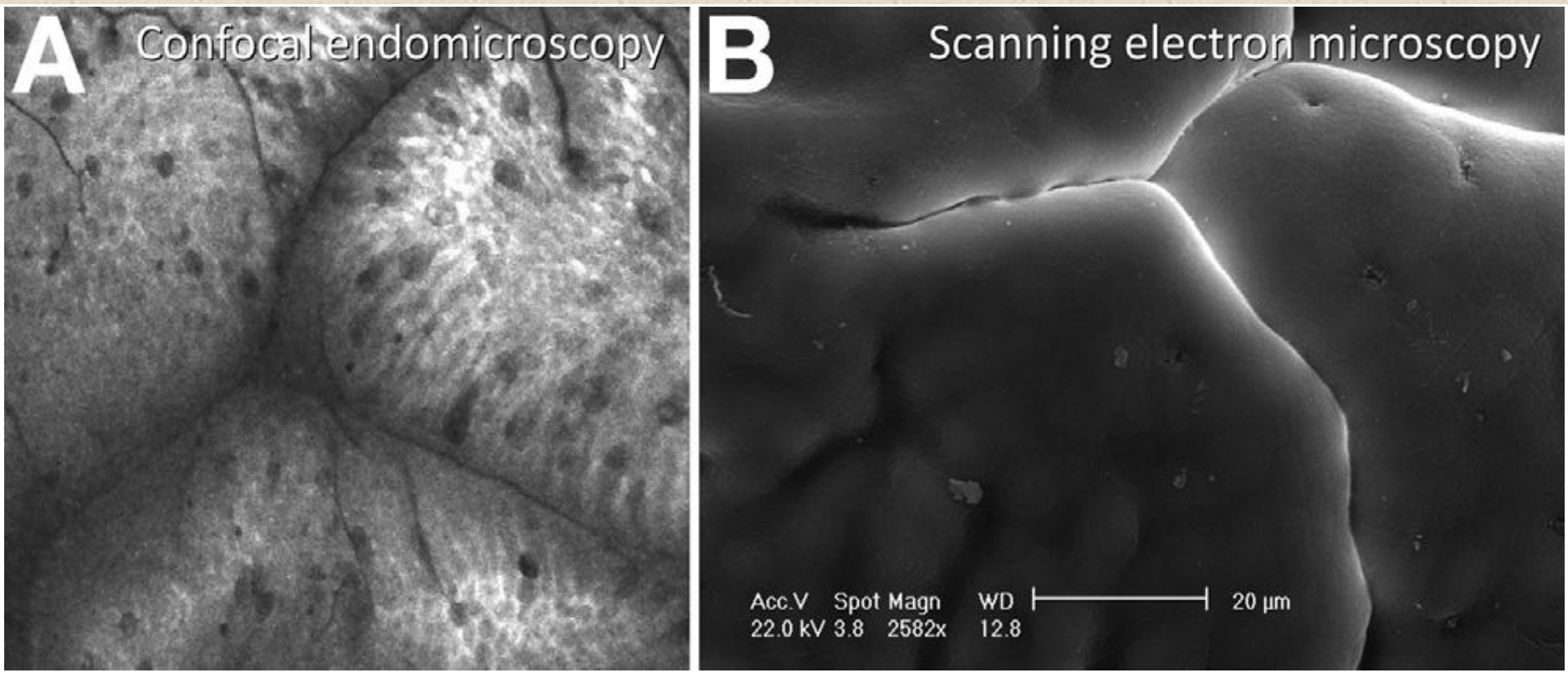

Figure 5. Intervillous space at baseline as visualized with endomicroscopy and scanning electron microscopy.

Gastroenterology 2014;147:1012–1020

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[1]Unit of Experimental Endoscopy, Department of Internal Medicine I, [5]Department of Pathology, [6]Department of Dermatology,

CLINICAL AT

Four commonly encountered major antigen mixtures and suspensions were applied;

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

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

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

proven by conventional tests. Thus, numerous patients remain symptomatic despite having undergone a variety of tests and diets.[4]

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[1]Unit of Experimental Endoscopy, Department of Internal Medicine I, [5]Department of Pathology, [6]Department of Dermatology, University
[3]Research
Medical Ce
Kiel, Germ

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

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see edi

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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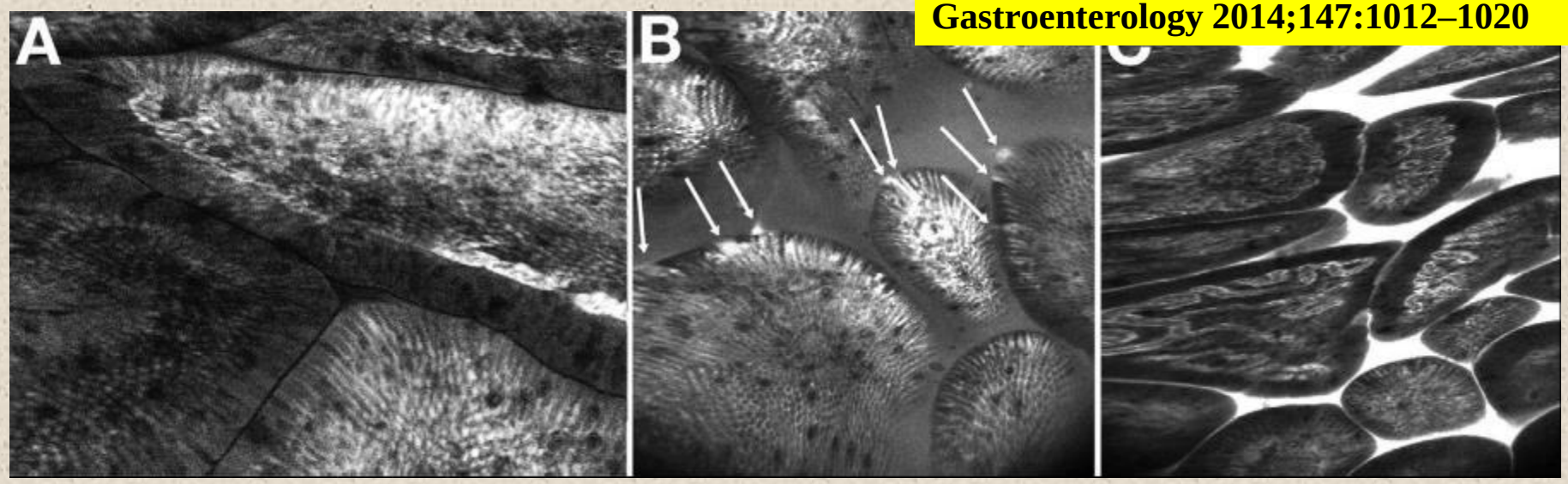
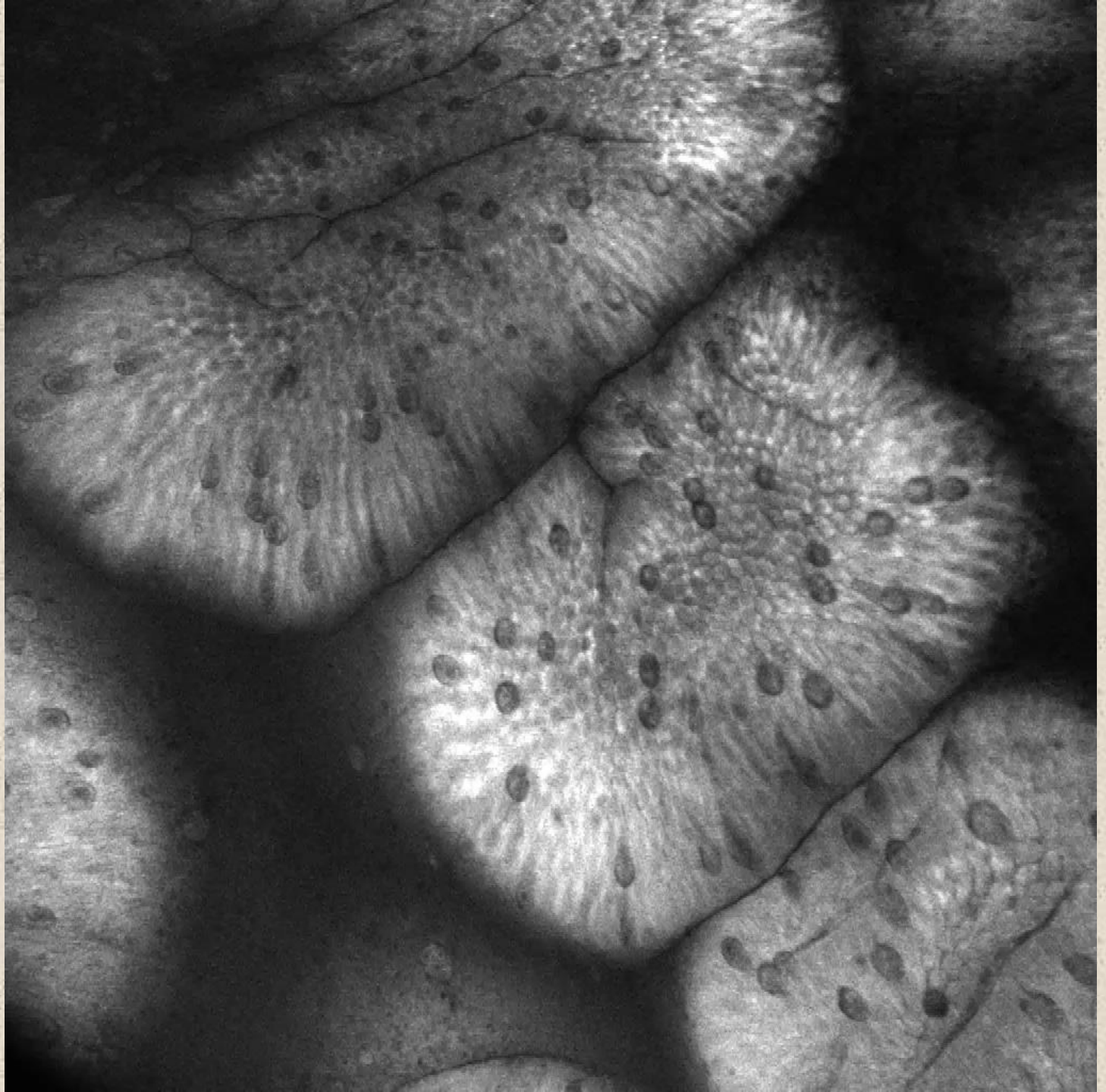


CLE images of (A) baseline and (B and C) after food challenge

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

See REVIEW page 213
See COMMENTARY page

Mucosal Immunology | VOLUME 3 NUMBER 3 | MAY 2010

Multiple facets of intestinal permeability and epithelial handling of dietary antigens

S Ménard[1], N Cerf-Bensussan[1] and M Heyman[1]

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.

organisms participates in the induction of a homeostatic immune response dominated by immune tolerance to dietary antigens[1,2] and the local production of secretory immunoglobulin A (SIgA),[3] preventing pathogenic and commensal microbes from entering internal compartments. Conversely, primary or secondary defects of the intestinal barrier can lead to excessive entrance of dietary or microbe-derived macromolecules, which are putative contributors to the pathogenesis of a spectrum of human diseases, including food allergy and inflammatory bowel diseases (IBDs), and could even be related to autoimmune diseases and metabolic syndrome.[4] Reinforcing the intestinal barrier and more particularly the paracellular pathway has recently been suggested as a therapeutic strategy to treat or prevent diseases driven by luminal antigens. Delineating how antigens are transported across the epithelium in healthy and diseased states should help in the design of appropriate therapeutic tools.

by digestive enzymes and are absorbed in the form of nutrients (amino acids or dipeptides/tripeptides), some however can resist both the low pH of the gastric fluid and proteolytic enzyme hydrolysis,[5] meaning that large immunogenic peptides or intact proteins are capable of reaching the small intestinal lumen.[6] For example, β-lactoglobulin, a major cow's milk allergen, is stable under acidic conditions and resists digestion by pepsin, whereas the resistance of gluten/gliadins to digestive enzymes is a major factor underlying celiac disease (CD). The high proline content (20%) of gliadins prevents their efficient intraluminal digestion and leads to the release of large irreducible 33- and 26-mer immunogenic peptides[7,8] able to activate the lamina propria $CD4^+$ T cells in celiac patients. The deleterious role of impaired protein digestion is highlighted by the increased risk of food allergy reported in patients taking antiulcer medication, which likely impairs gastric protein digestion.[9] Despite this

[1]INSERM, U989, Interactions of the intestinal epithelium with the immune system, Université Paris Descartes, Paris, Cedex 15, France. Correspondence: M Heyman (martine.heyman@inserm.fr)

Received 15 December 2009; accepted 28 January 2010;

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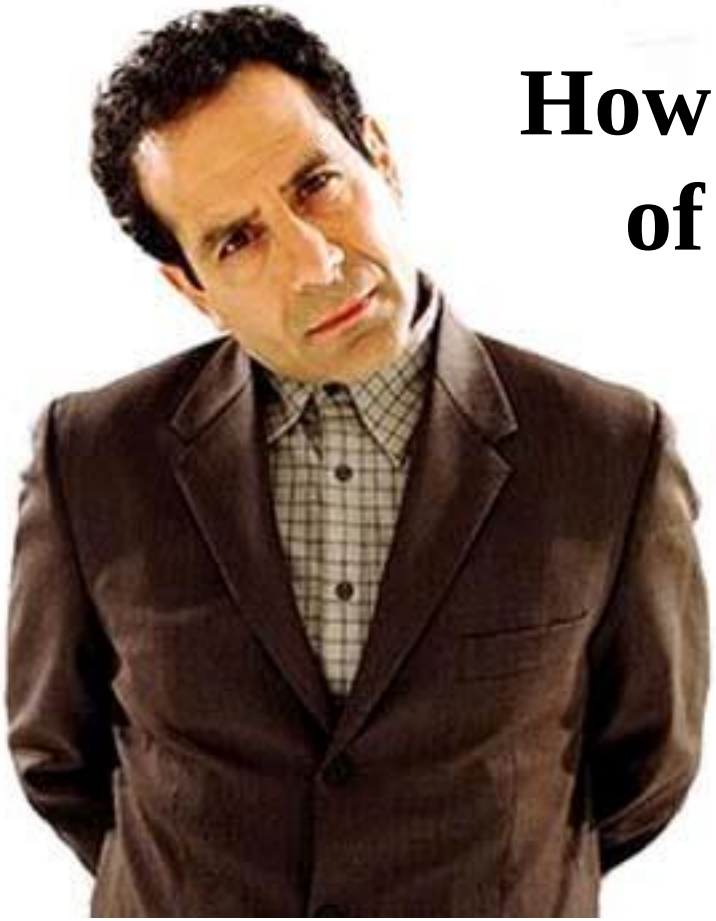

How Frequent is the Production of Antibodies To Dairy and Wheat?

Detective Adrian Monk

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

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

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Article

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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

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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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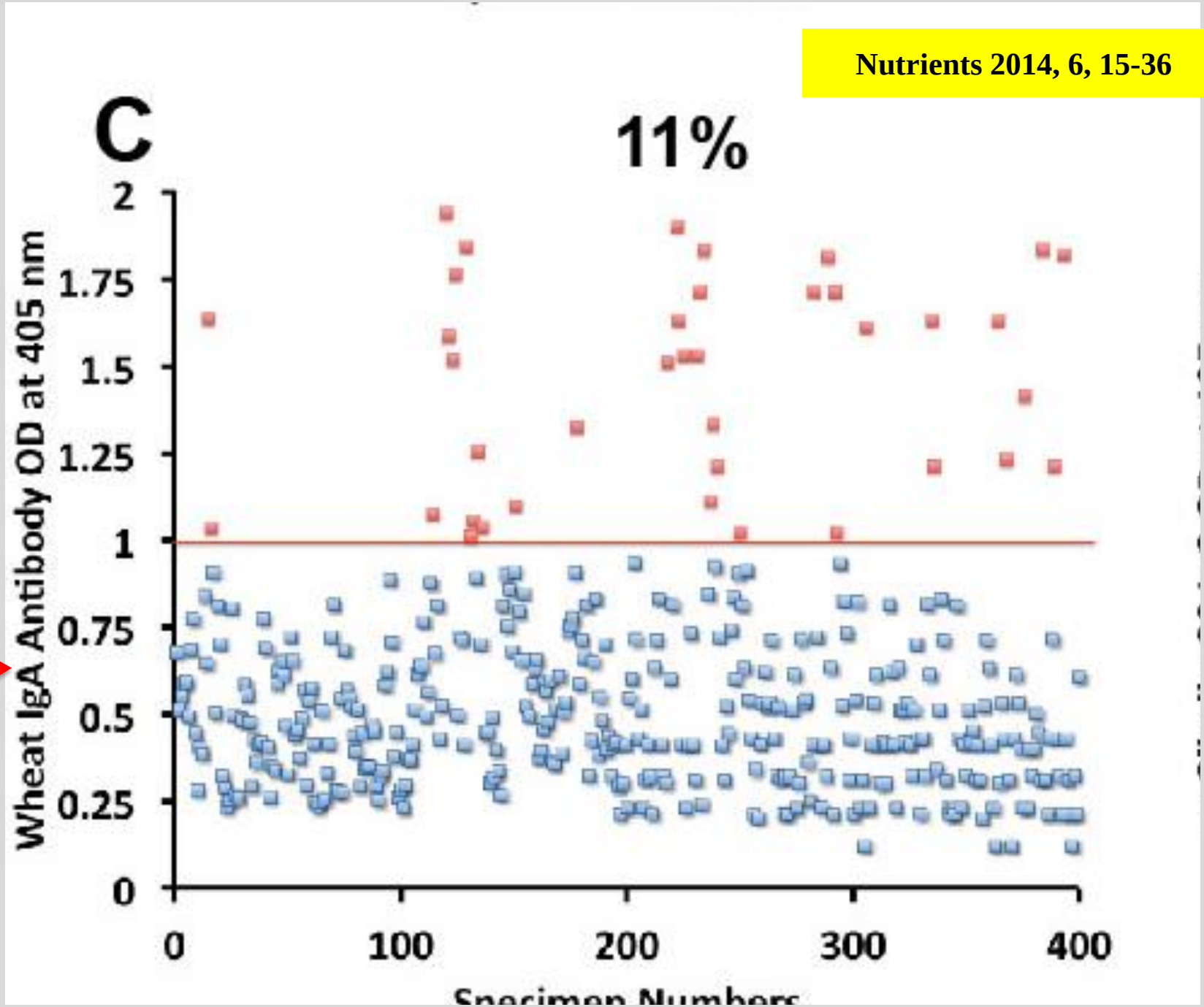

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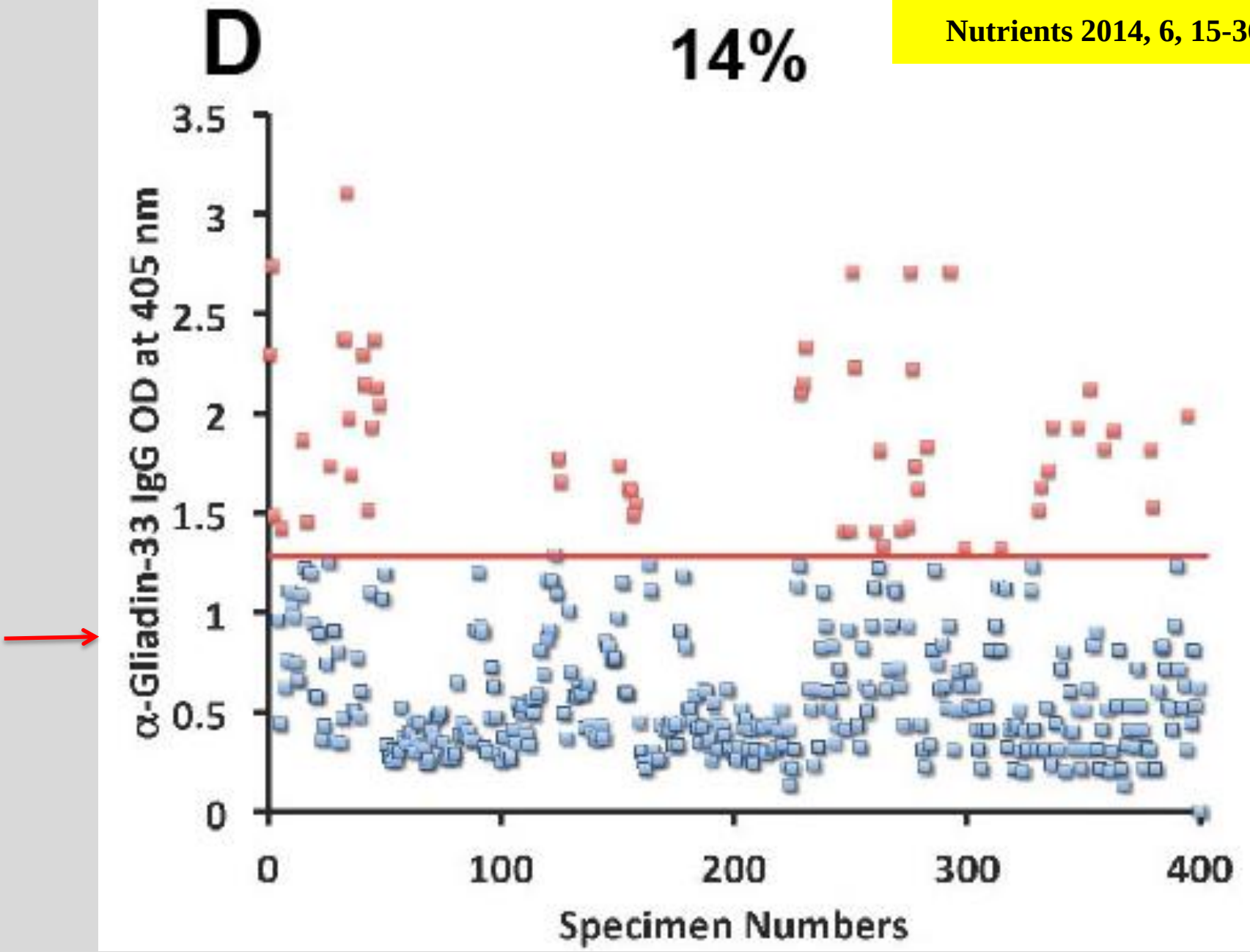

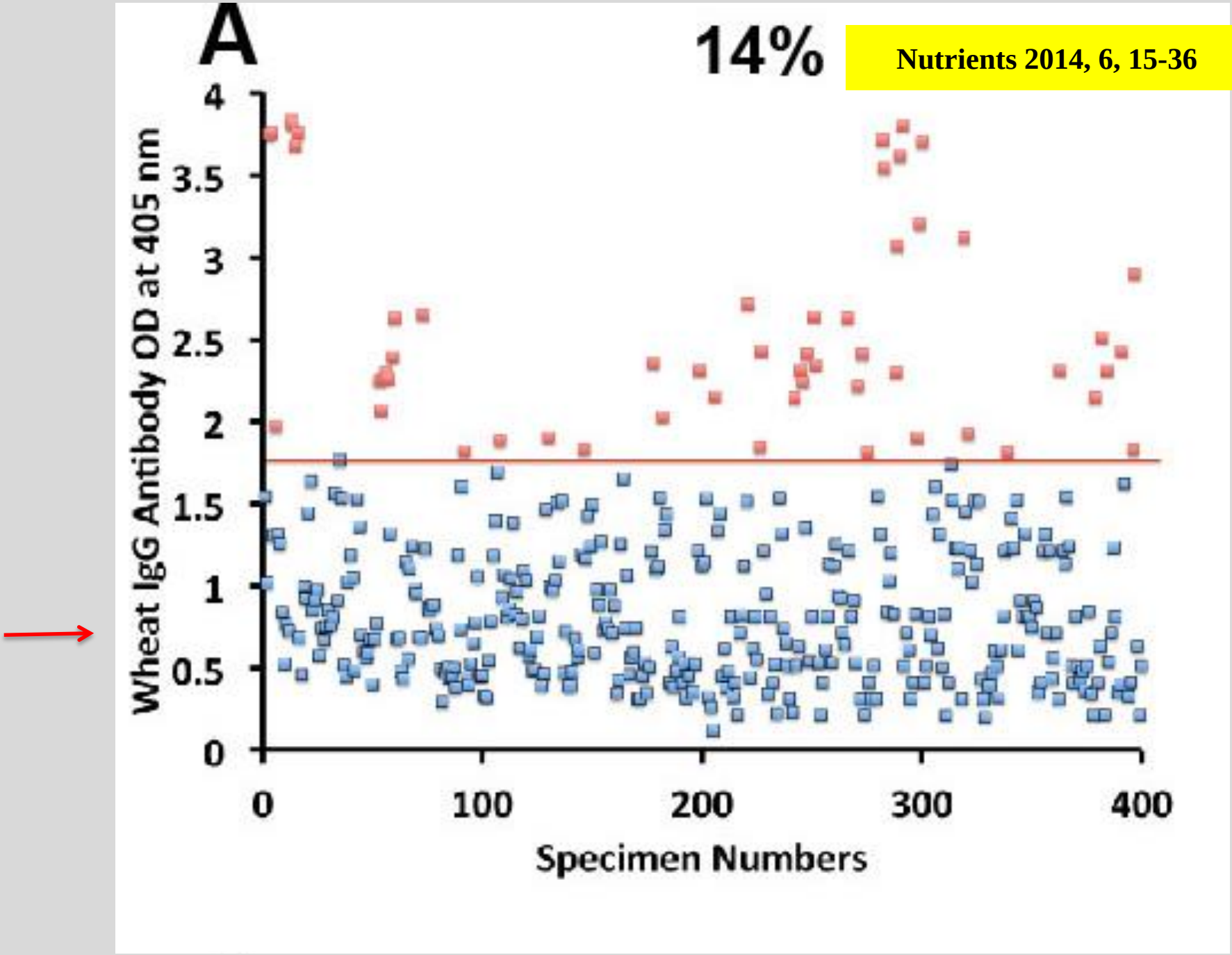
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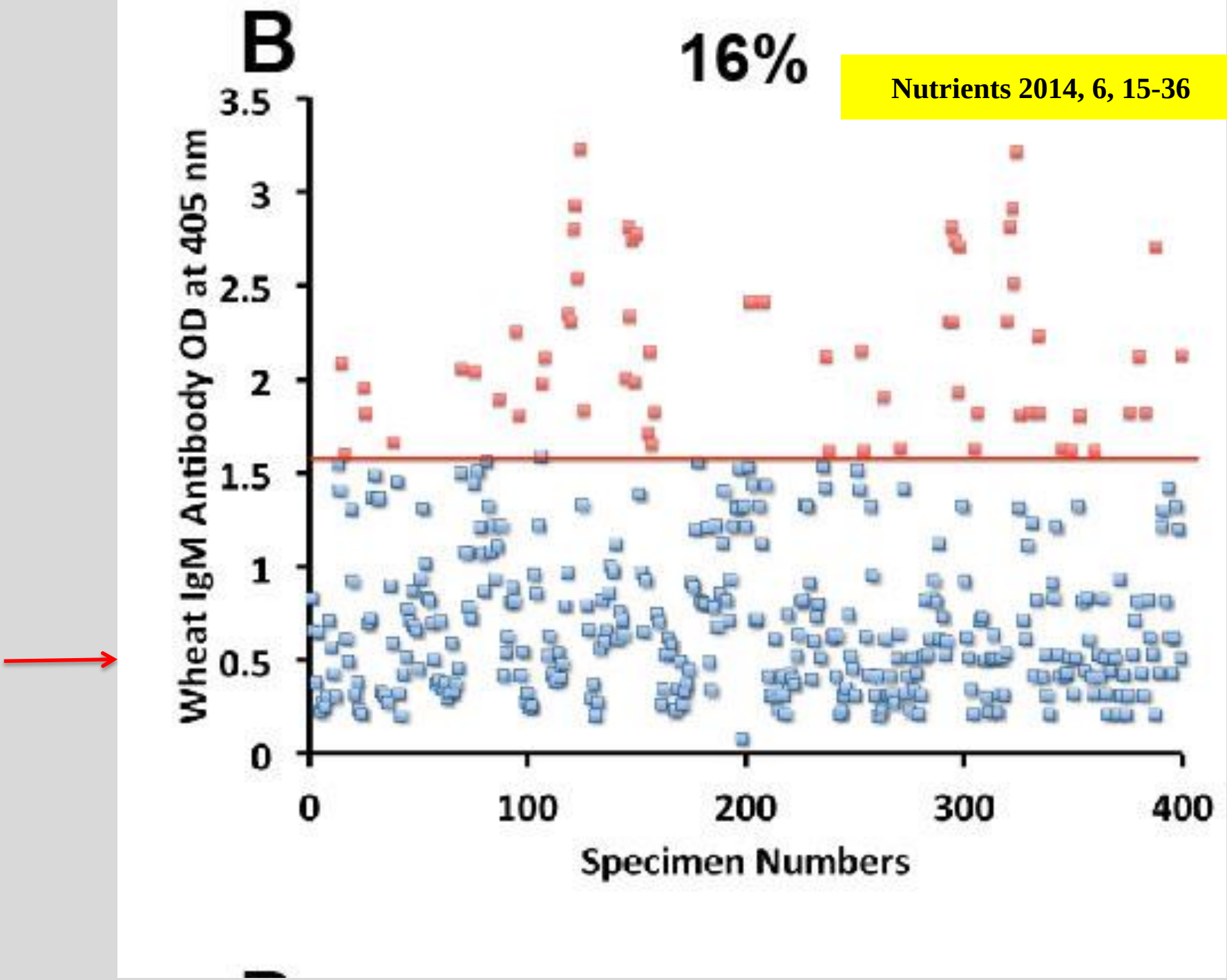
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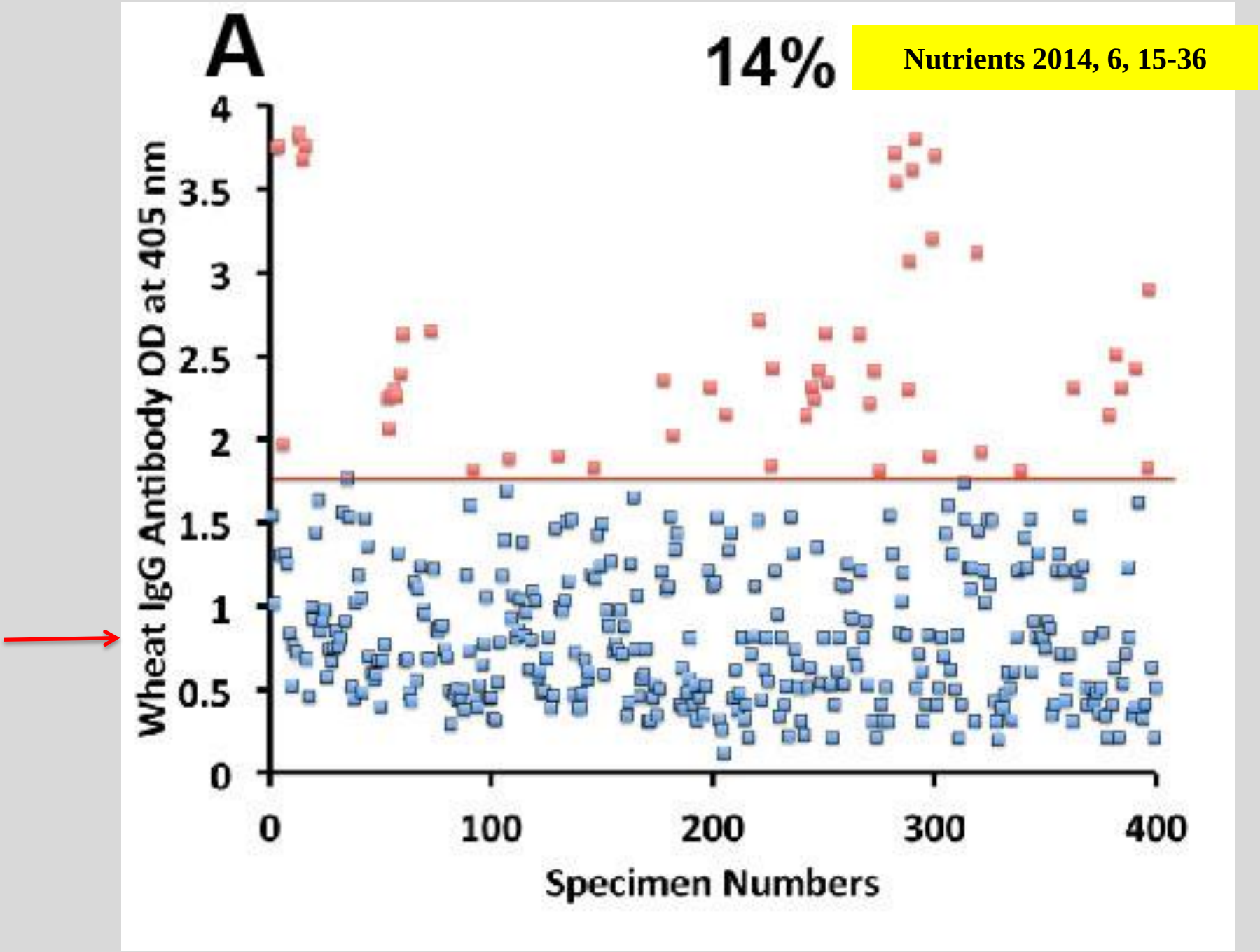
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Wheat IgG Antibody OD at 405 nm
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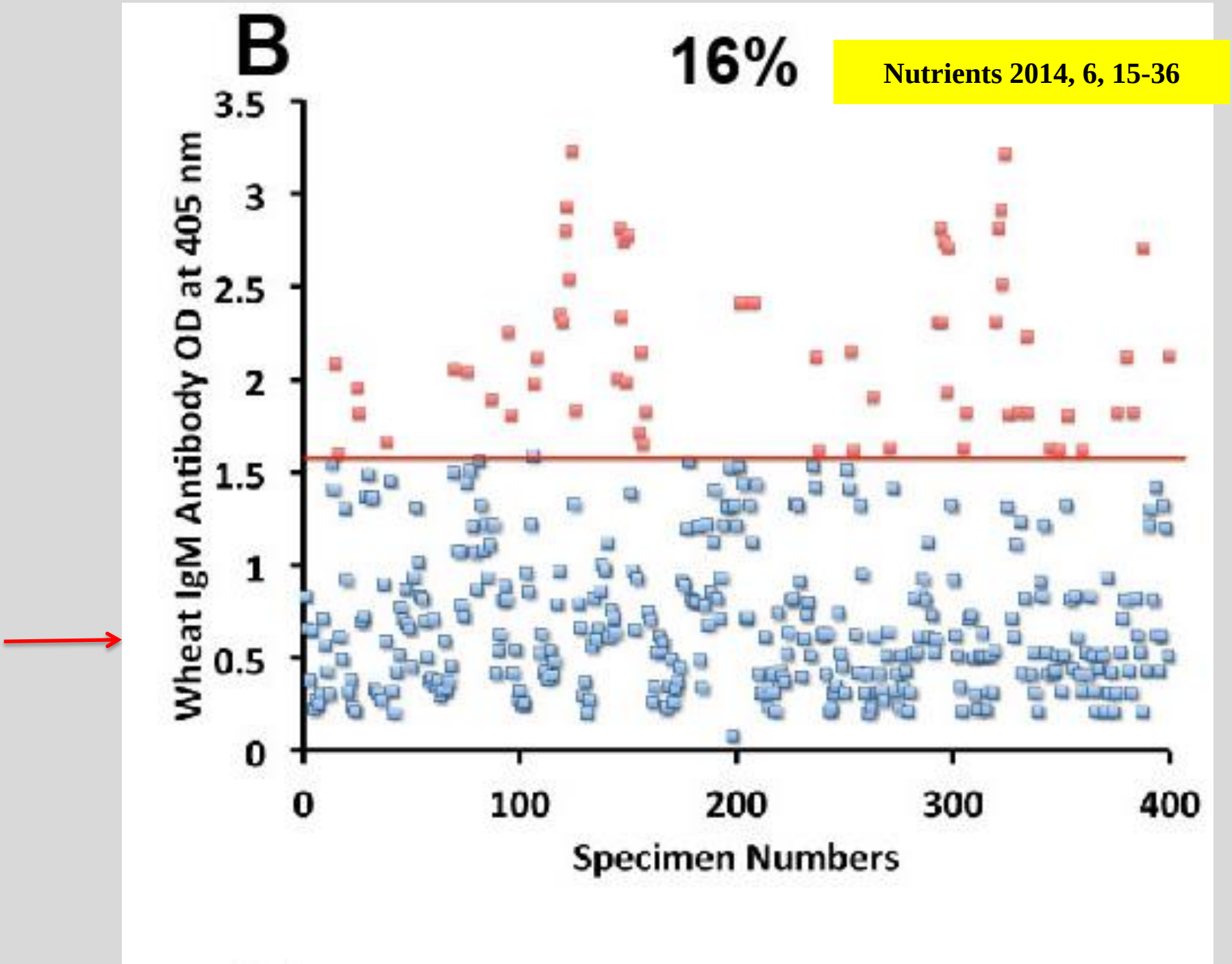
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Wheat IgM Antibody OD at 405 nm
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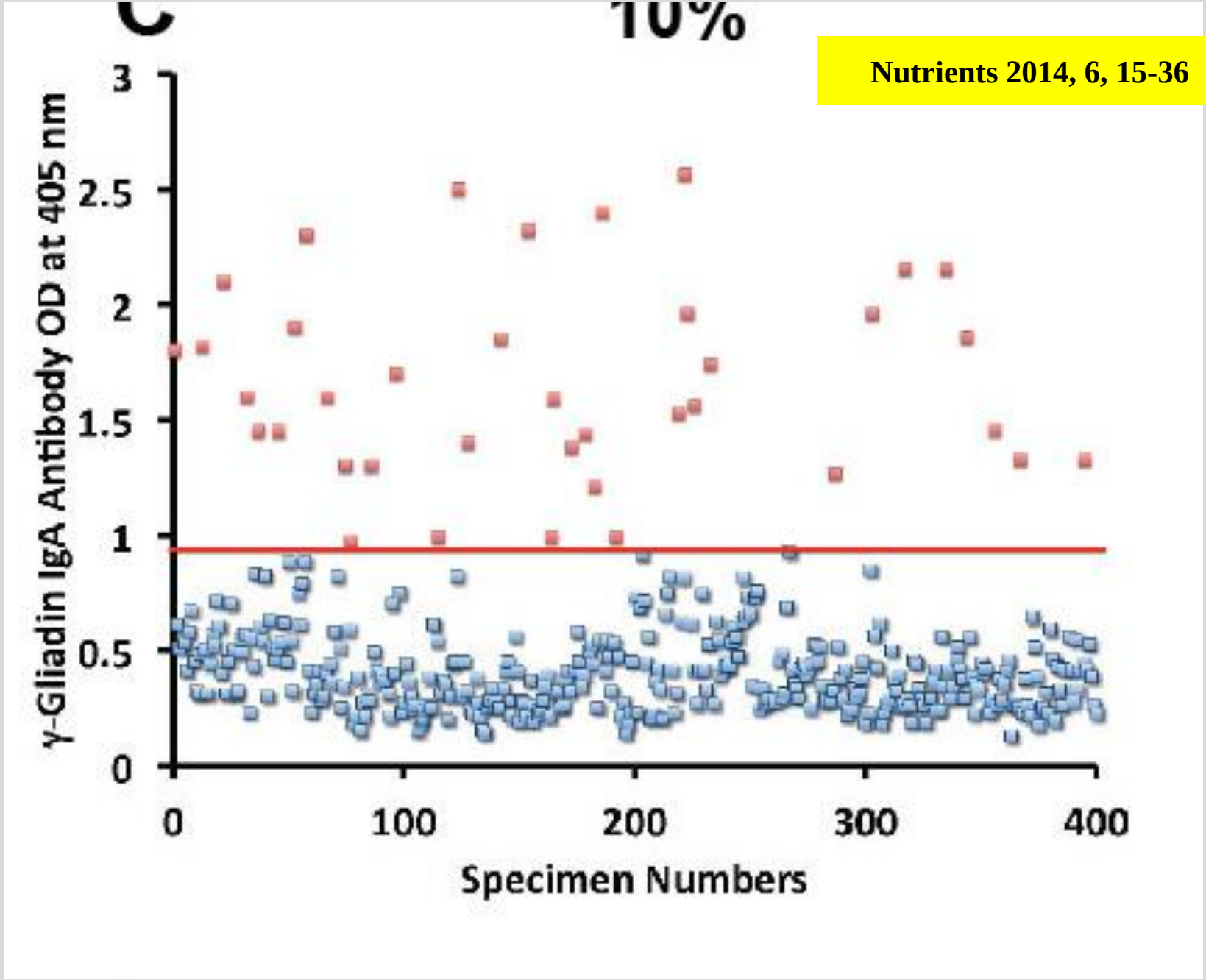

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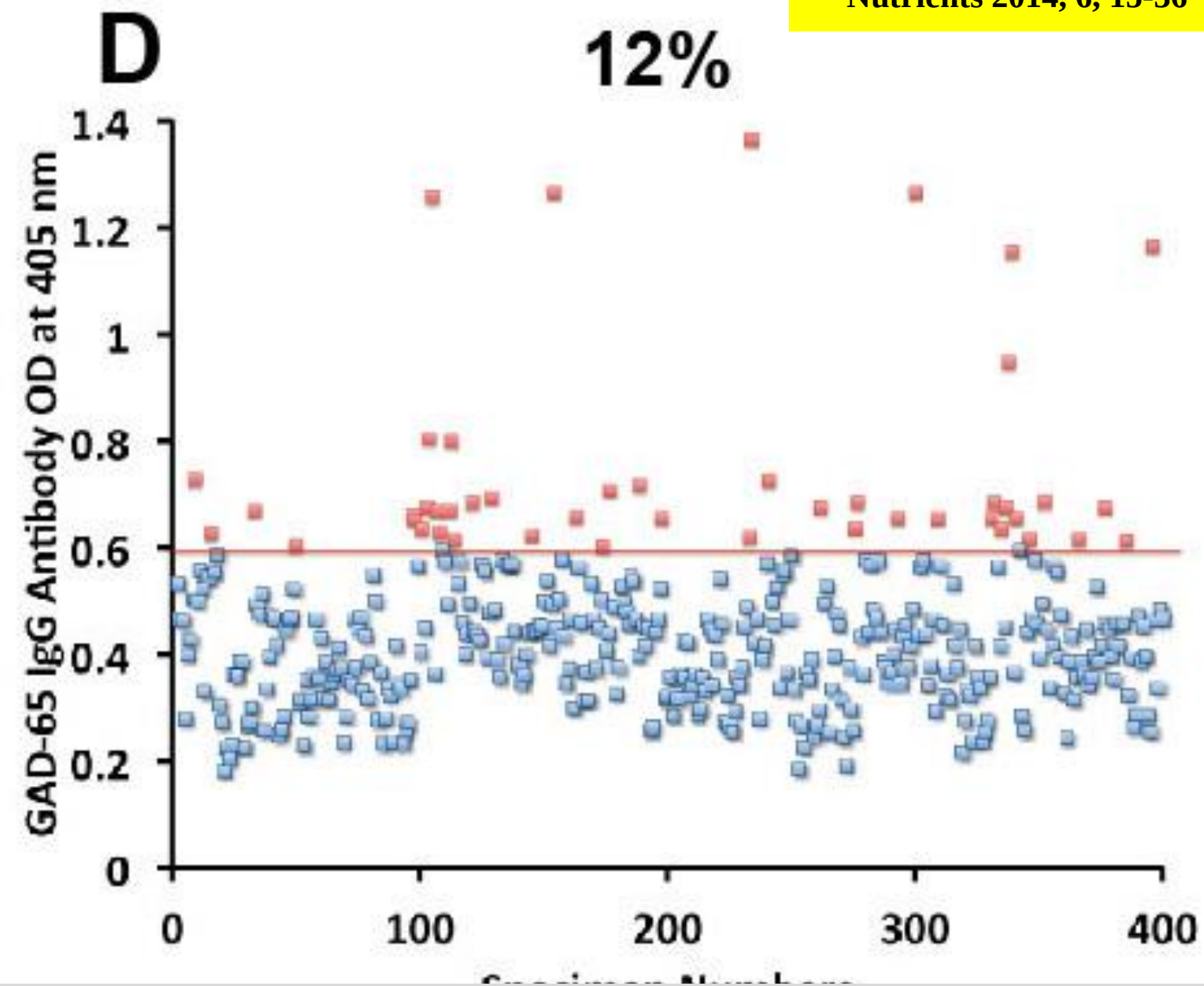

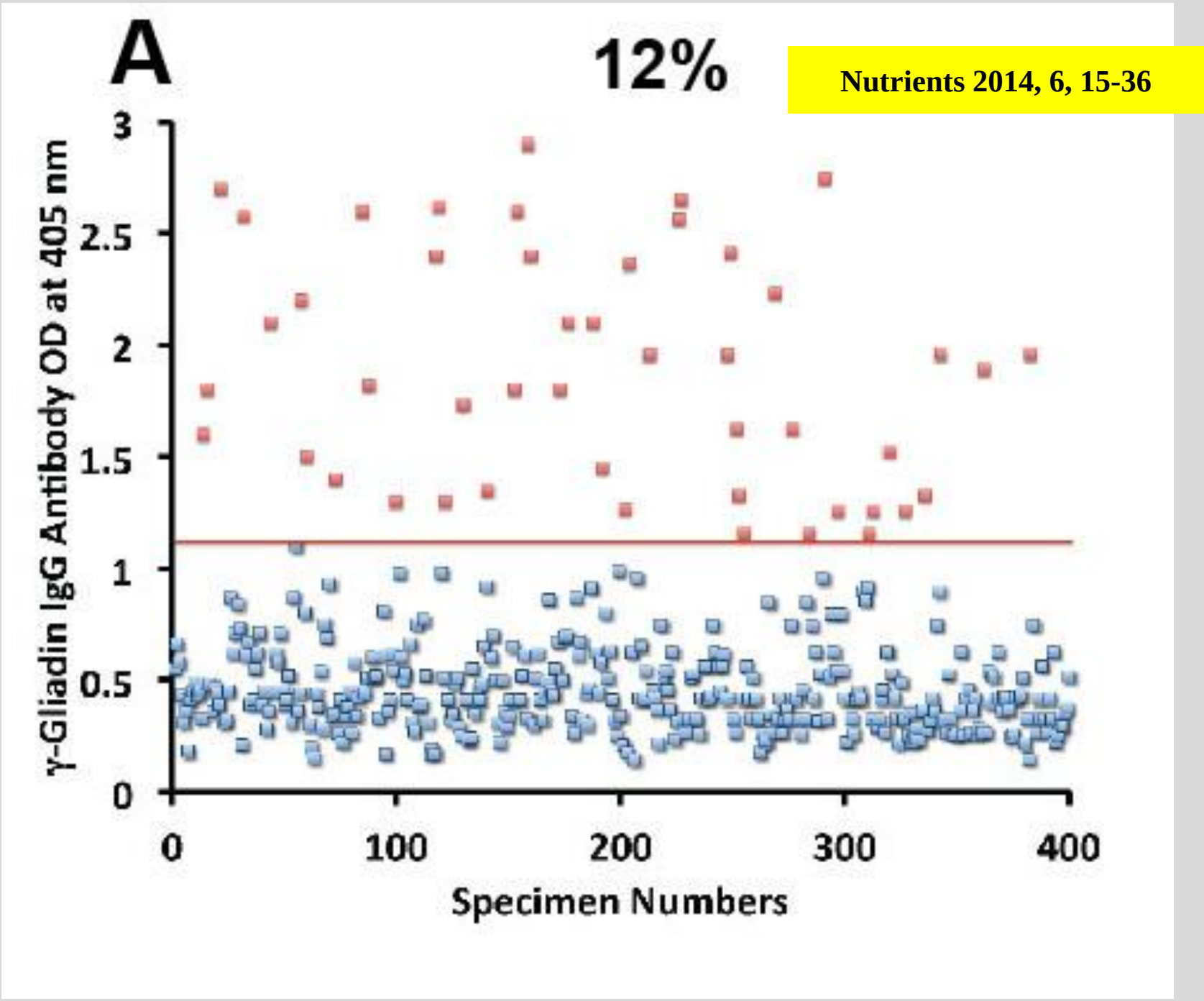

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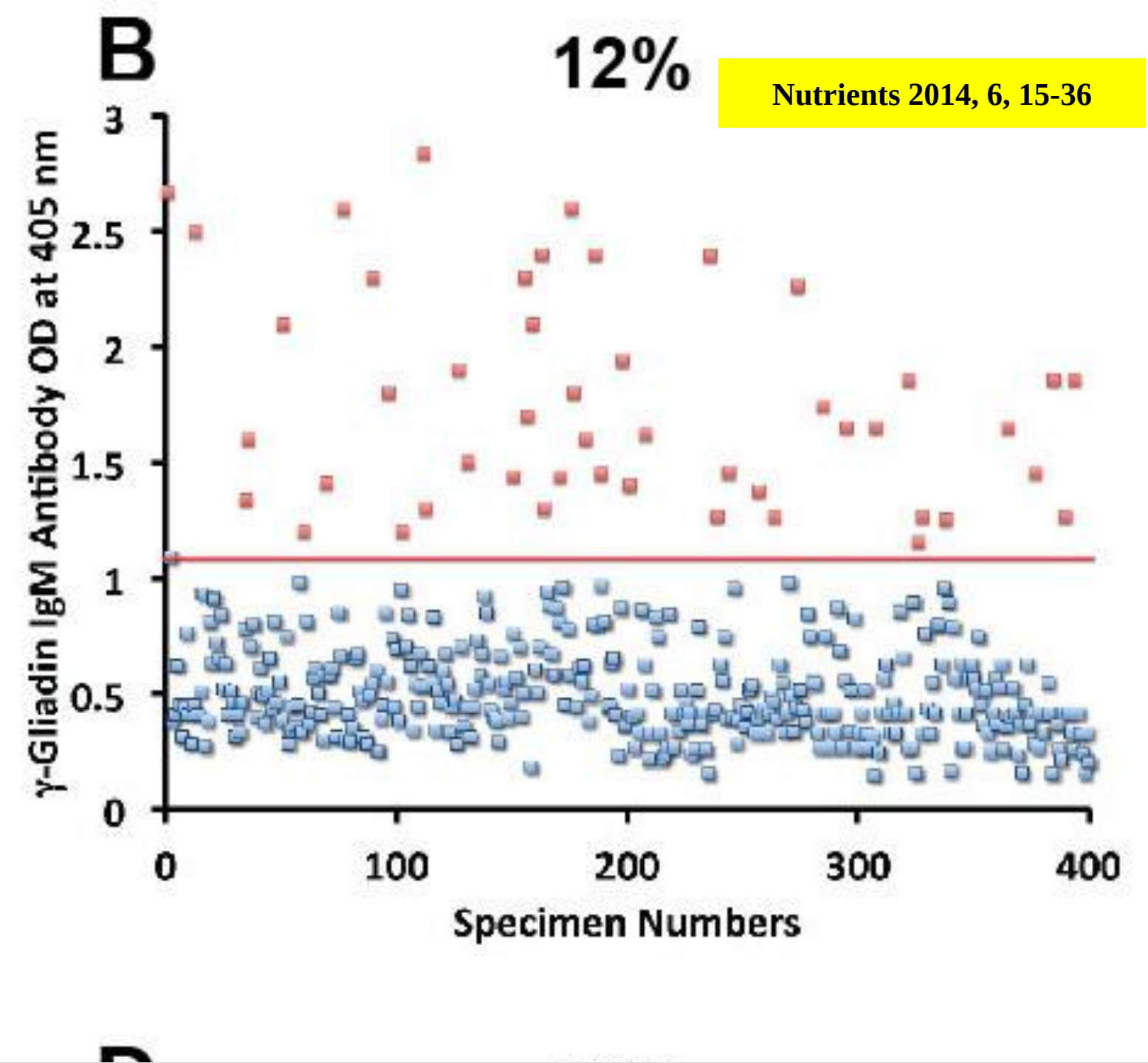

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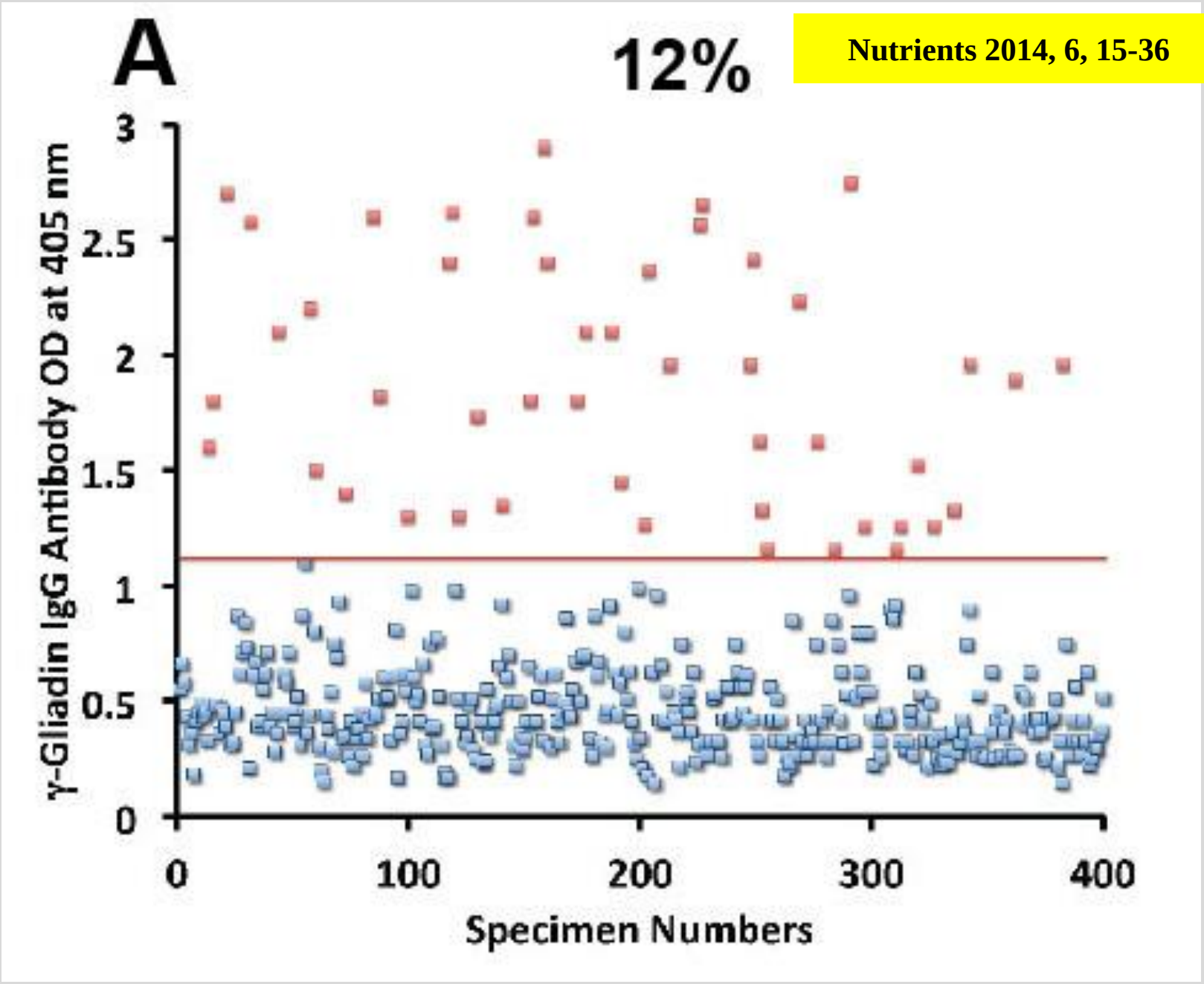

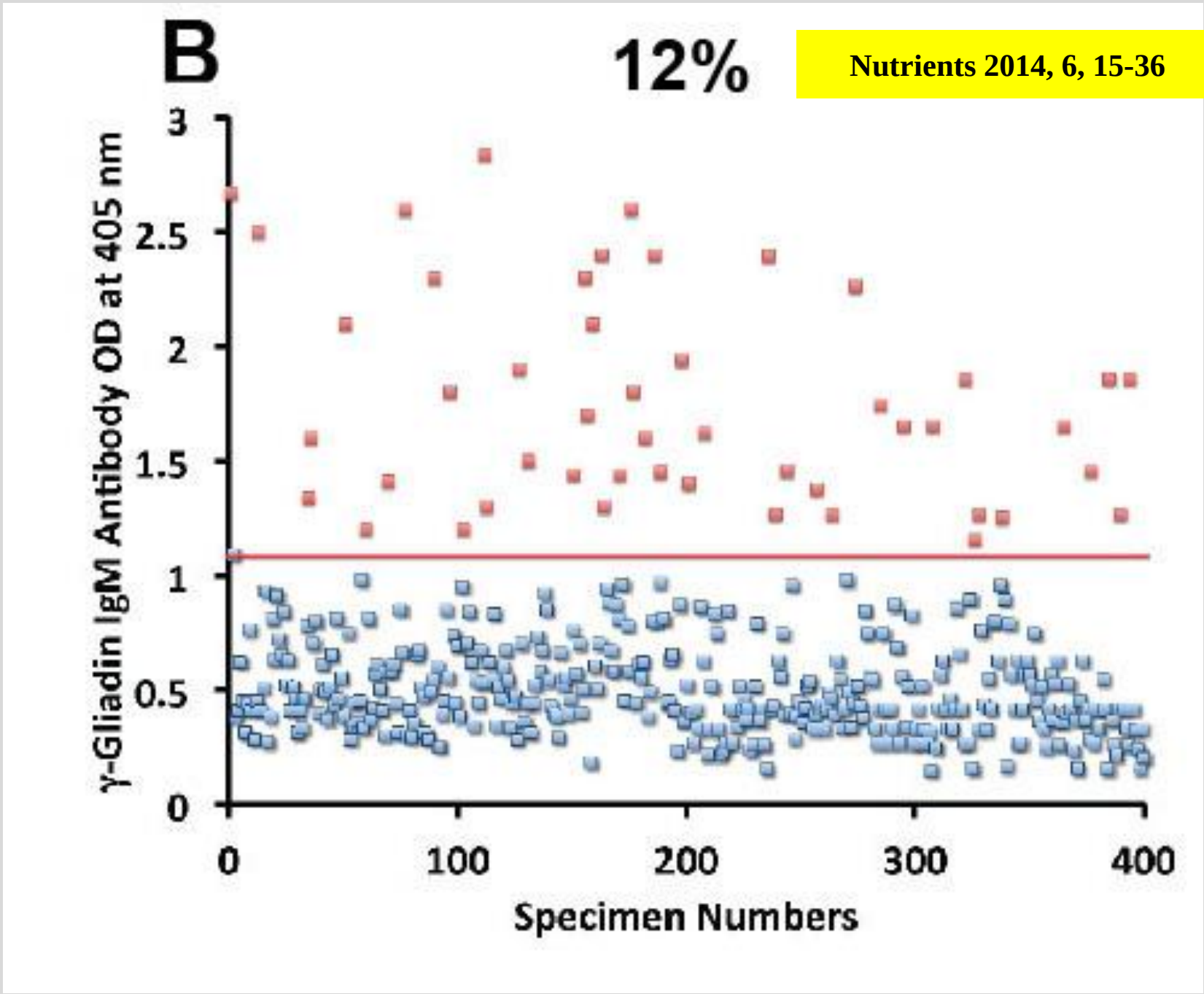
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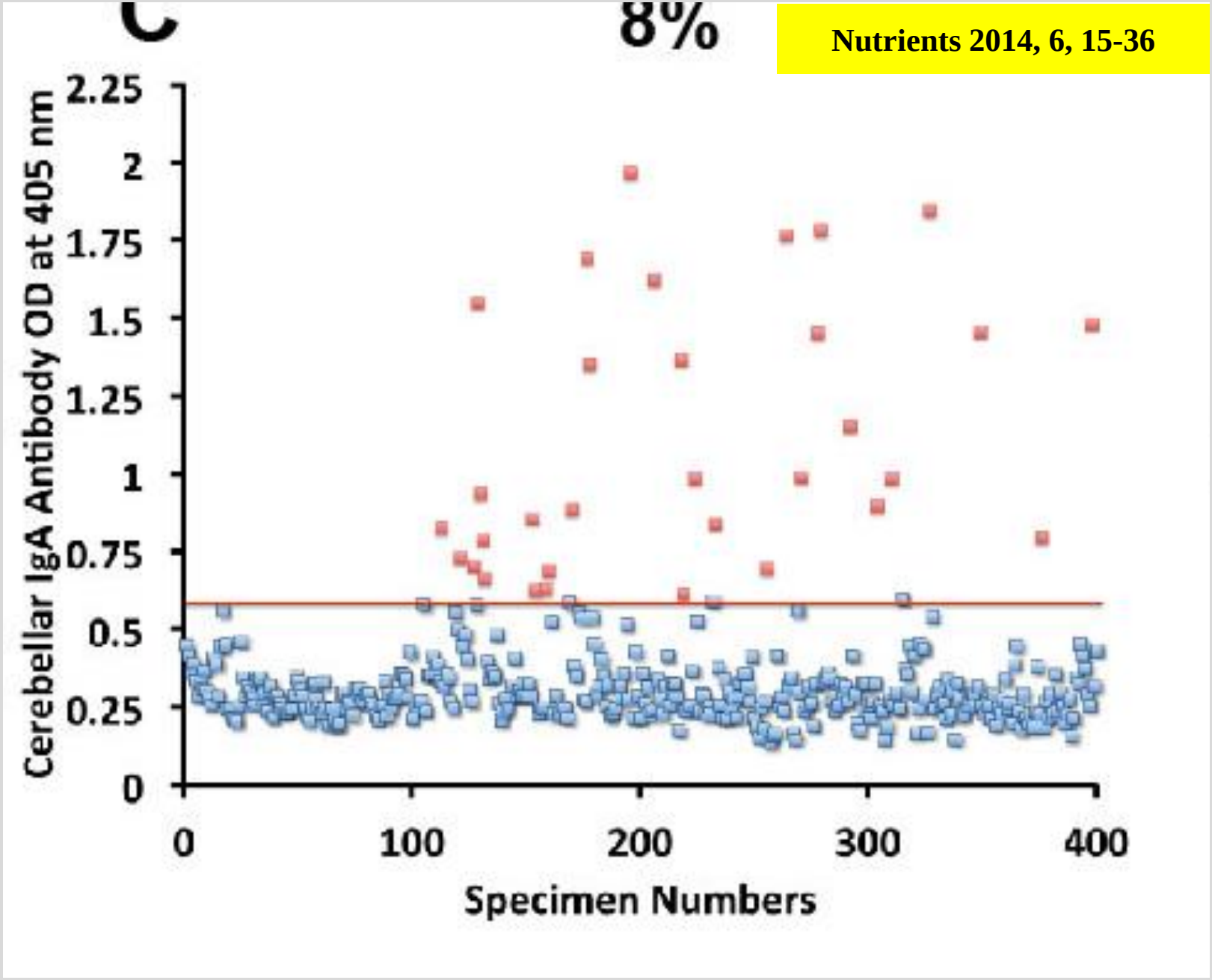
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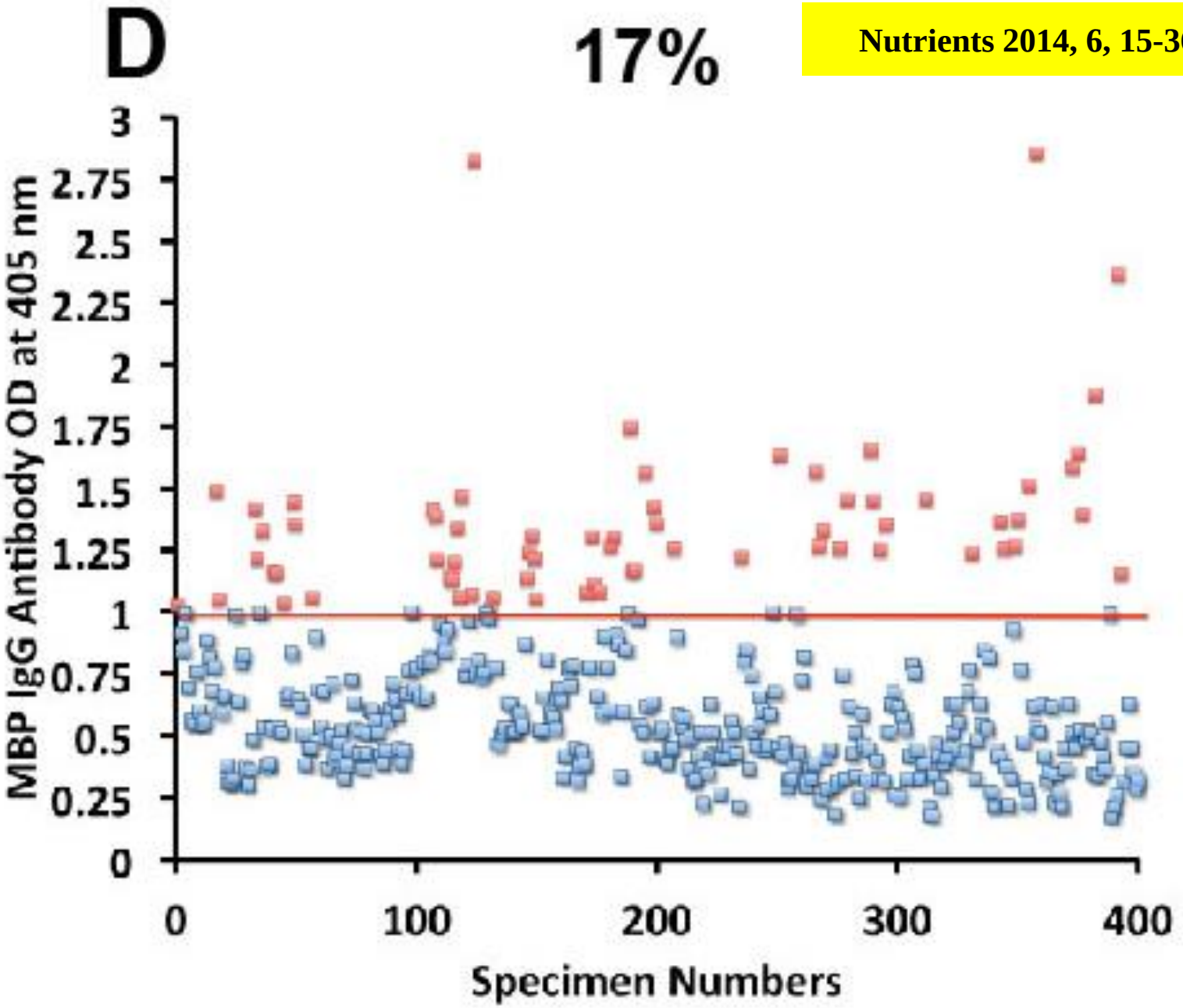

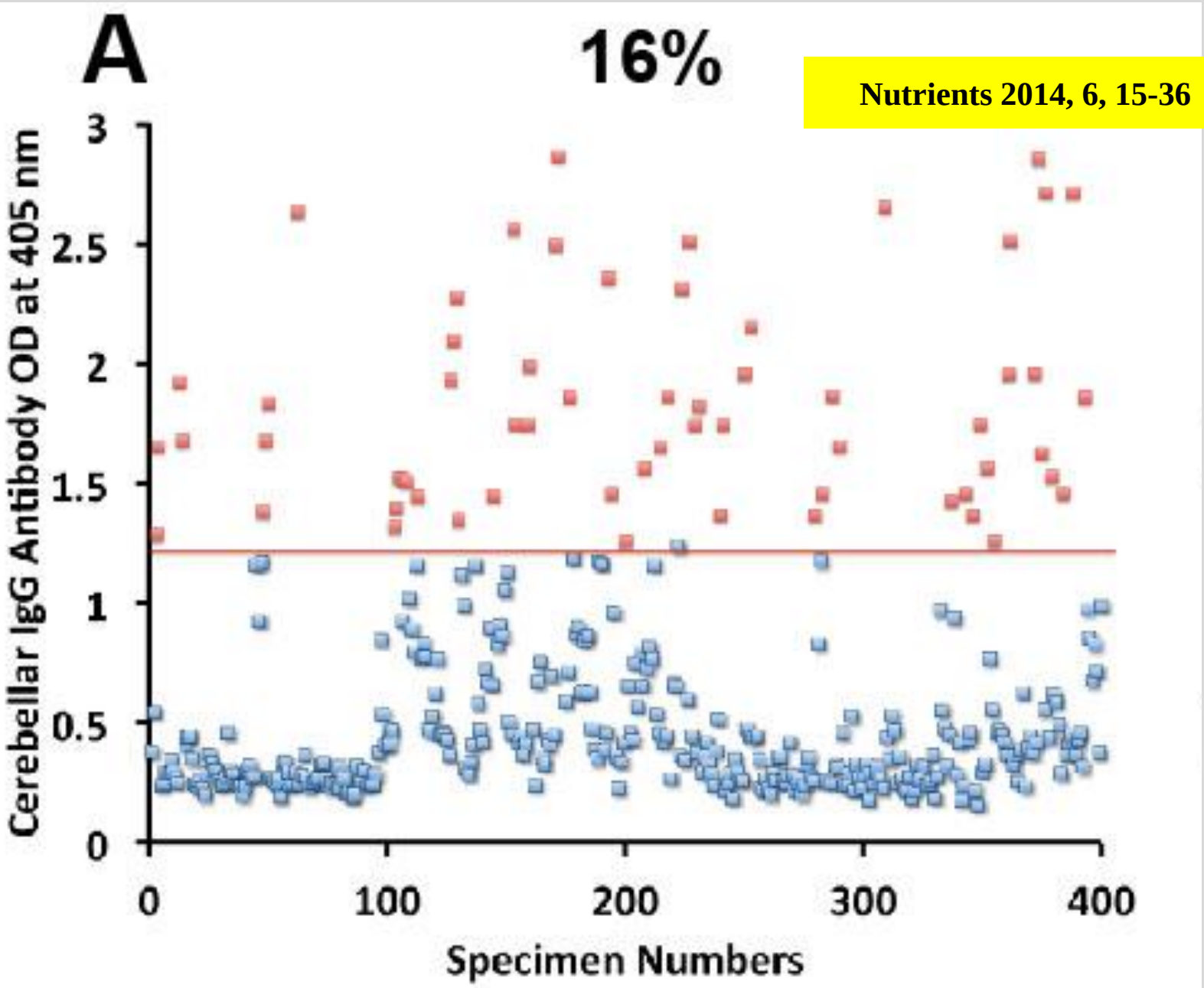

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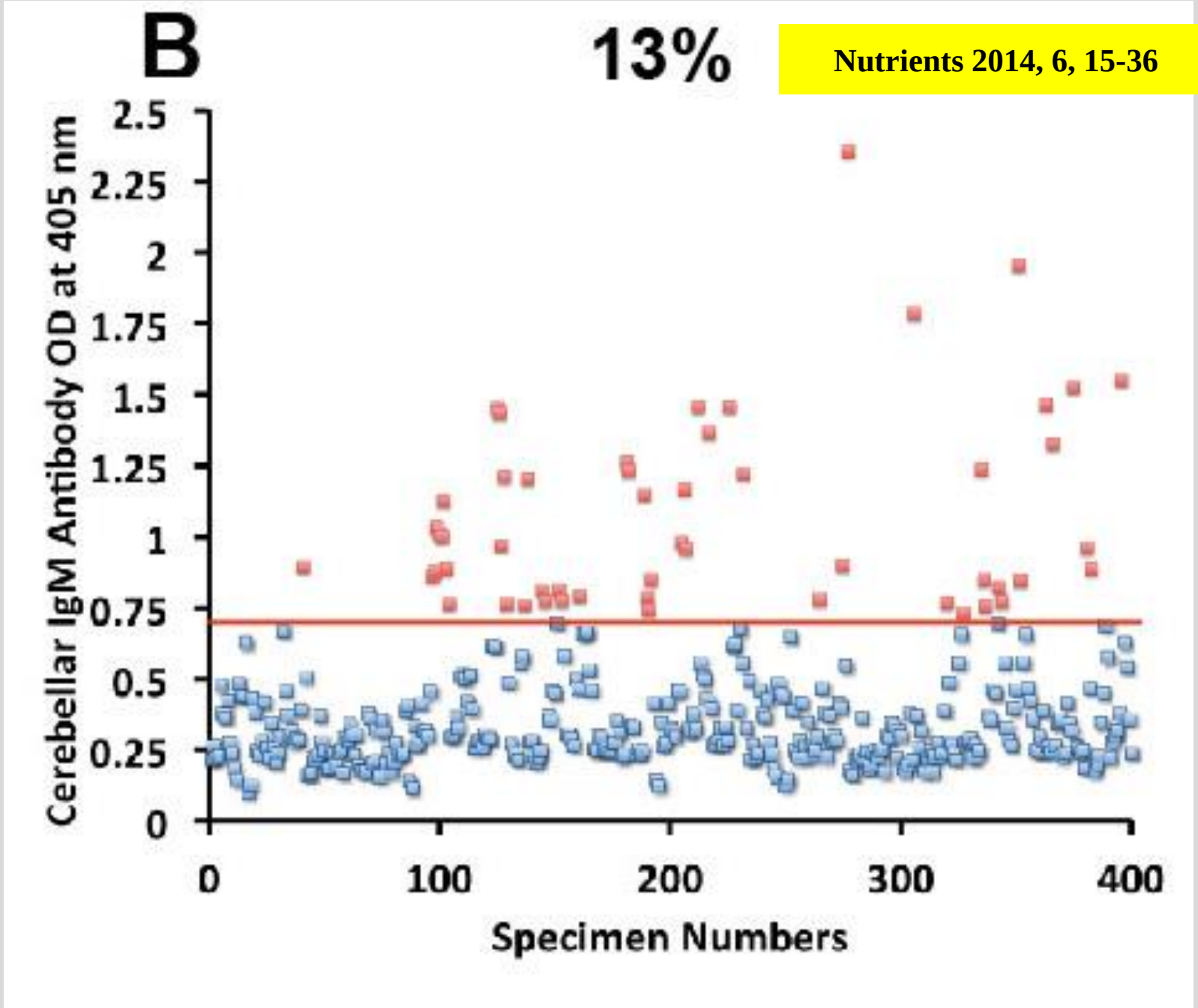
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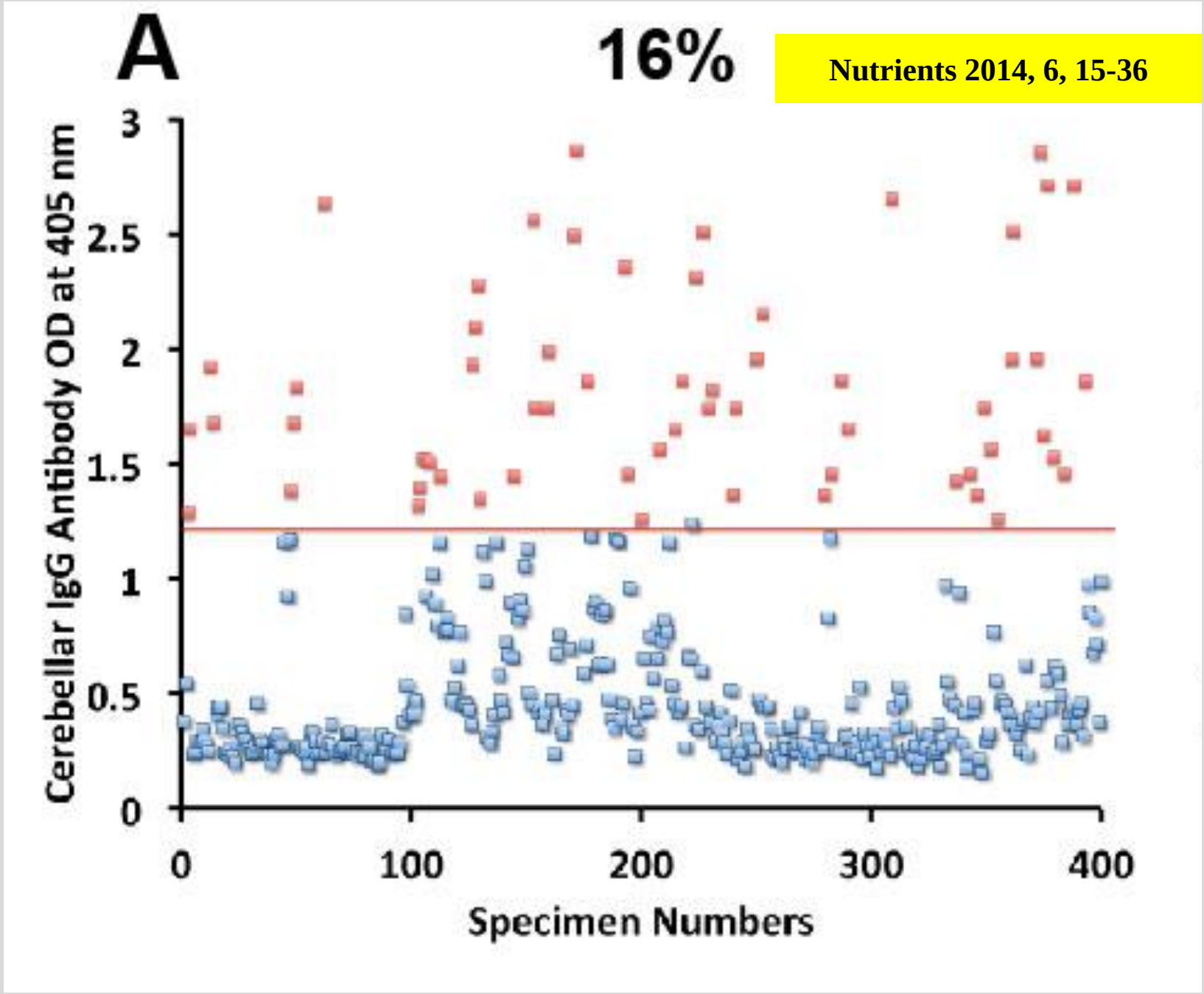
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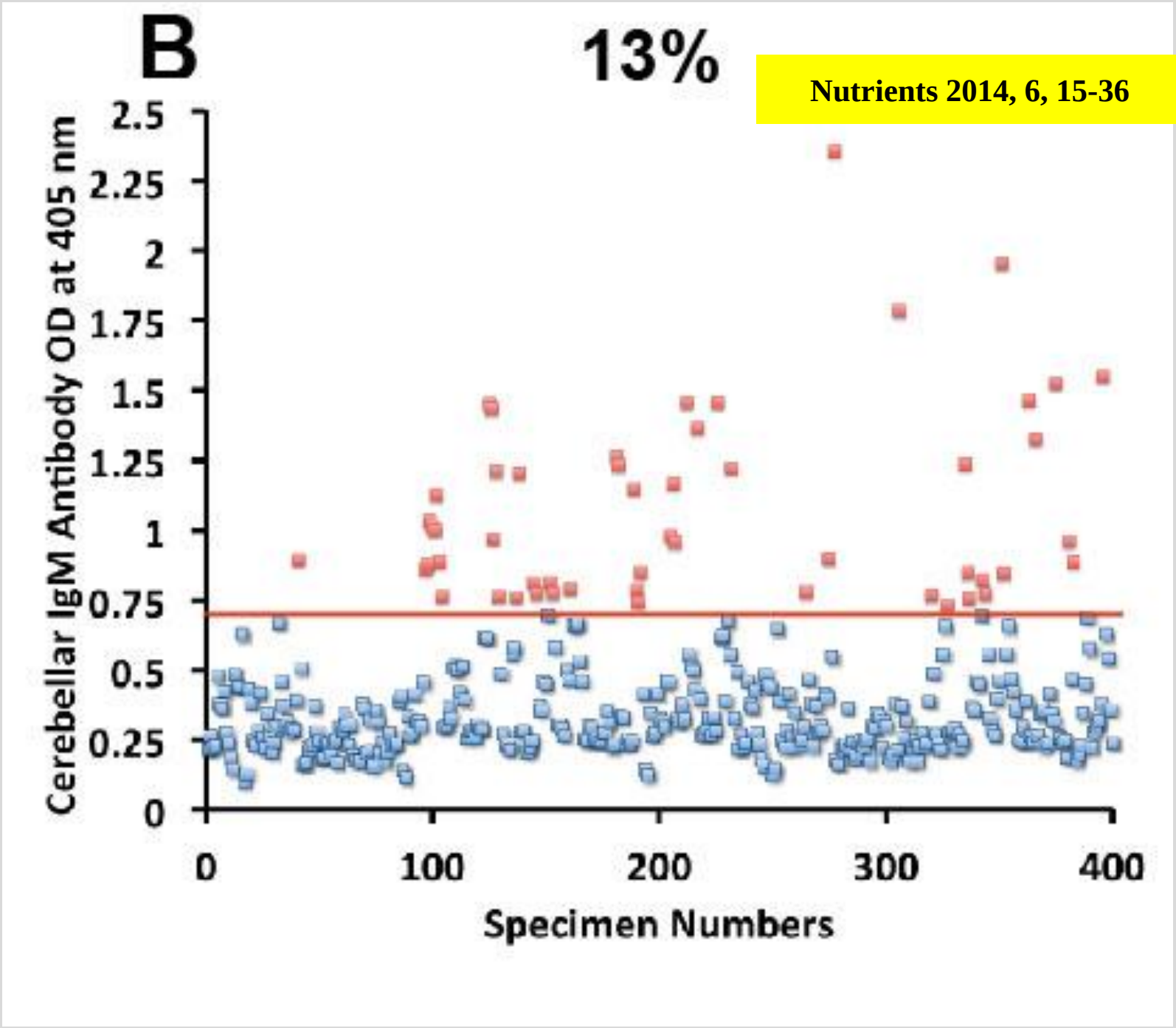
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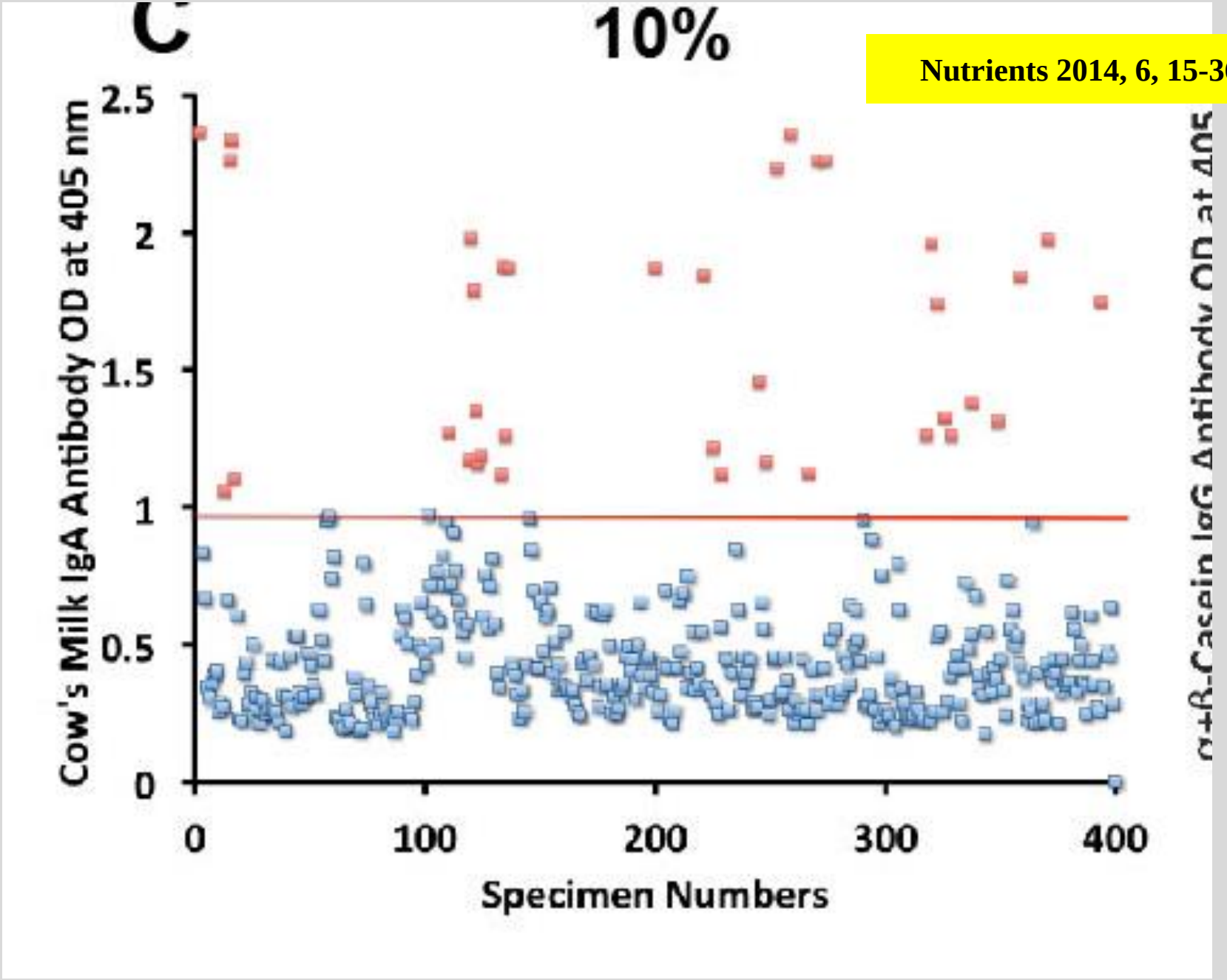

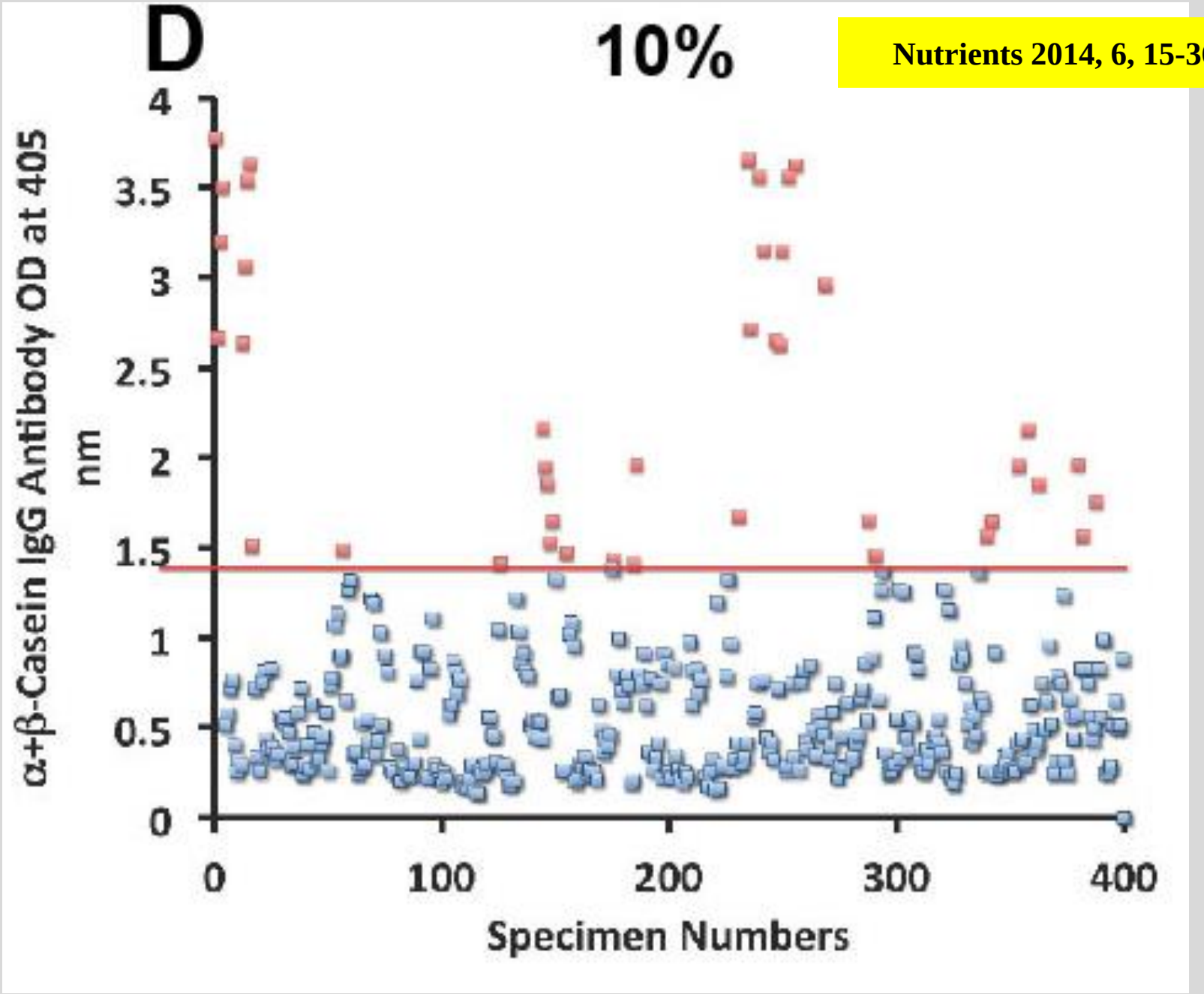

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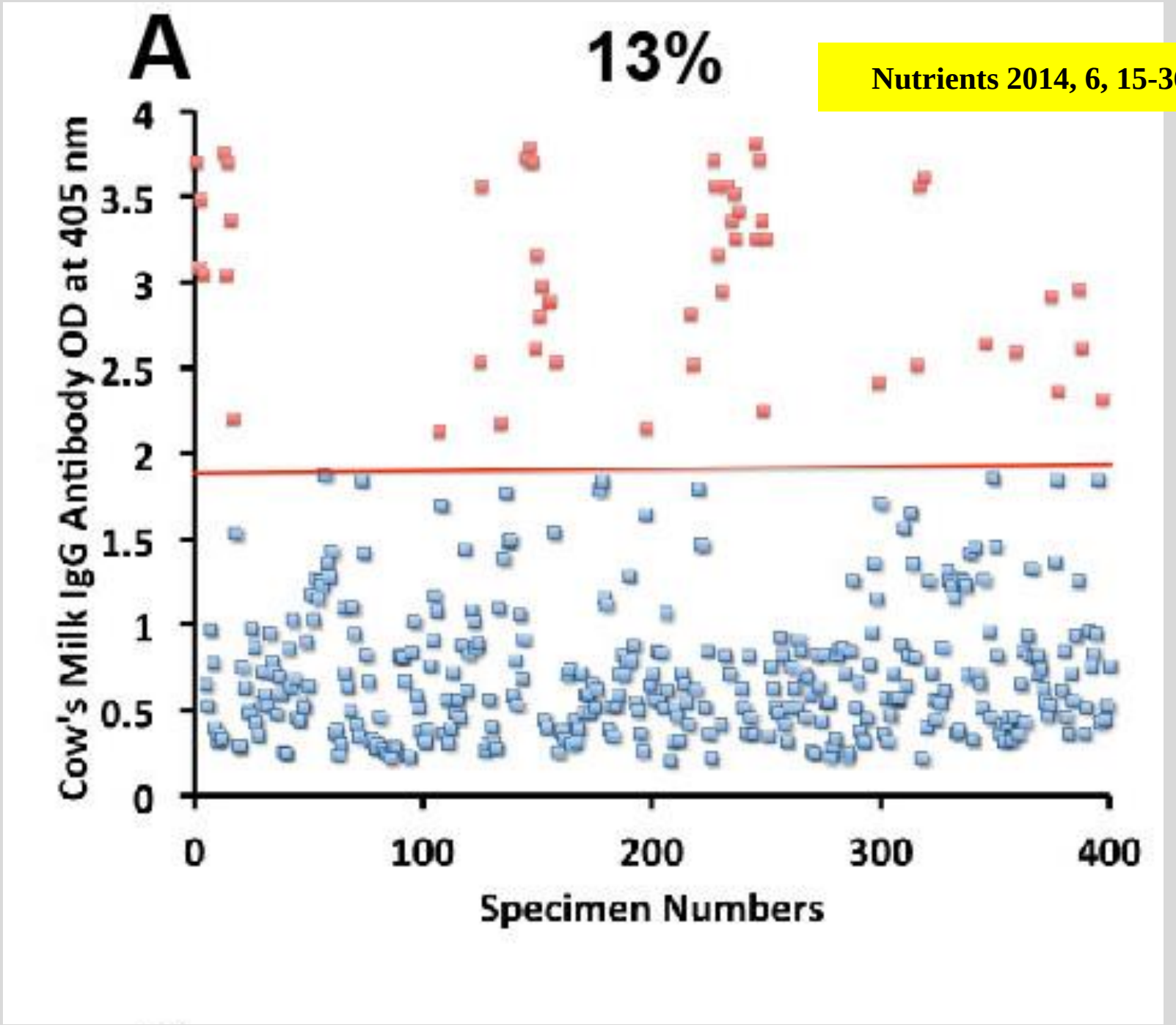

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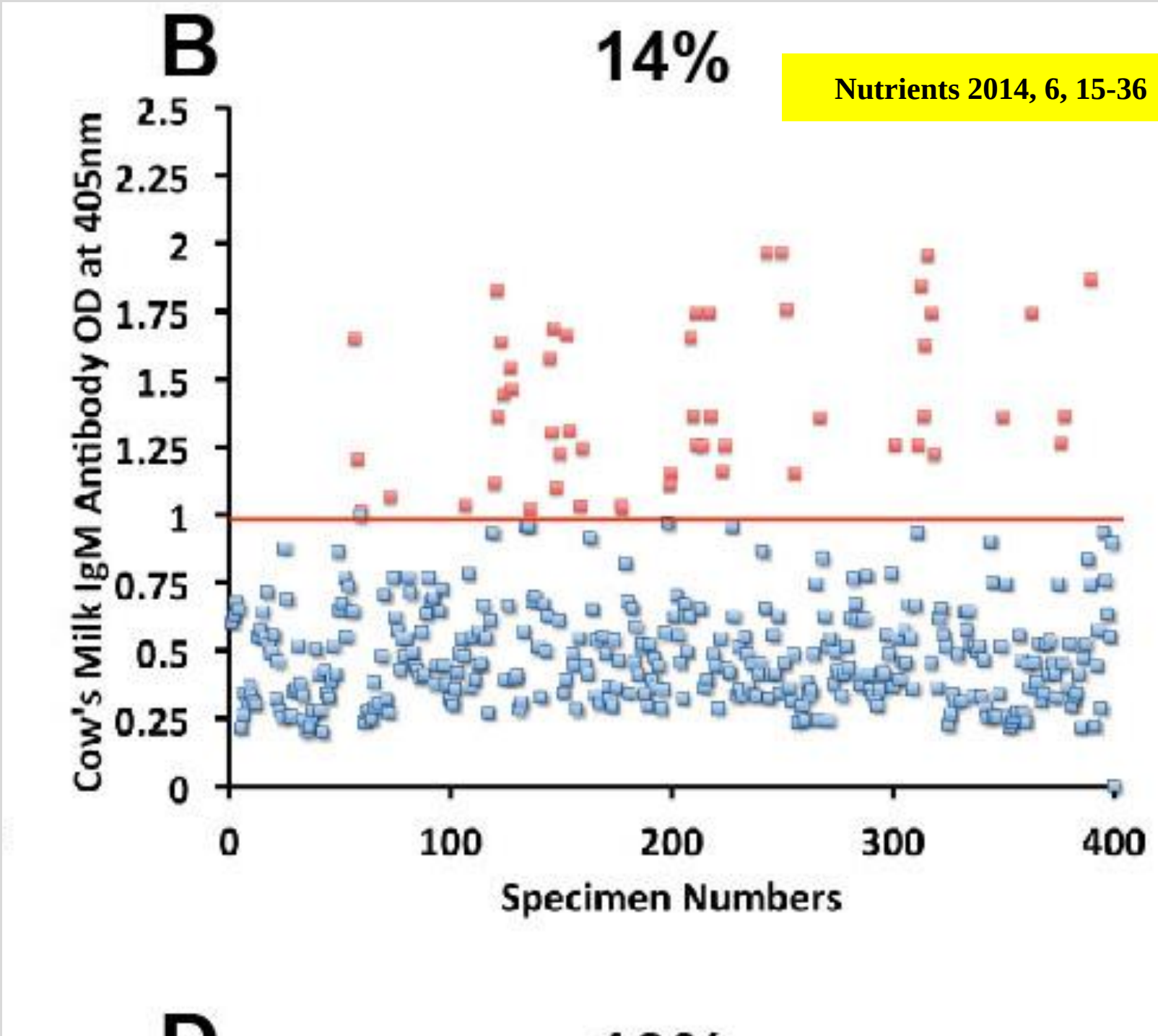

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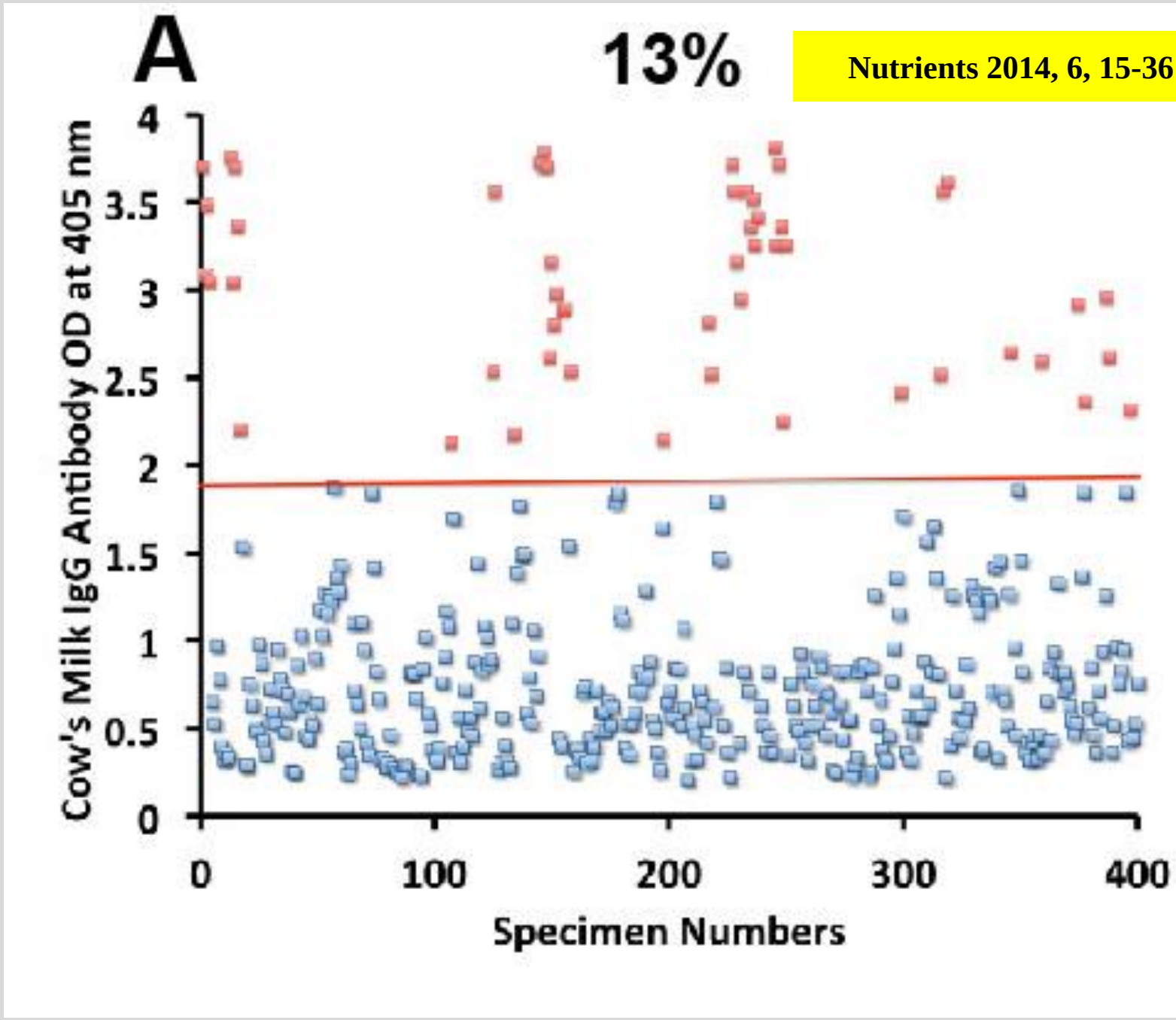
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13%
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Cow's Milk IgG Antibody OD at 405 nm
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2.5
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0.5
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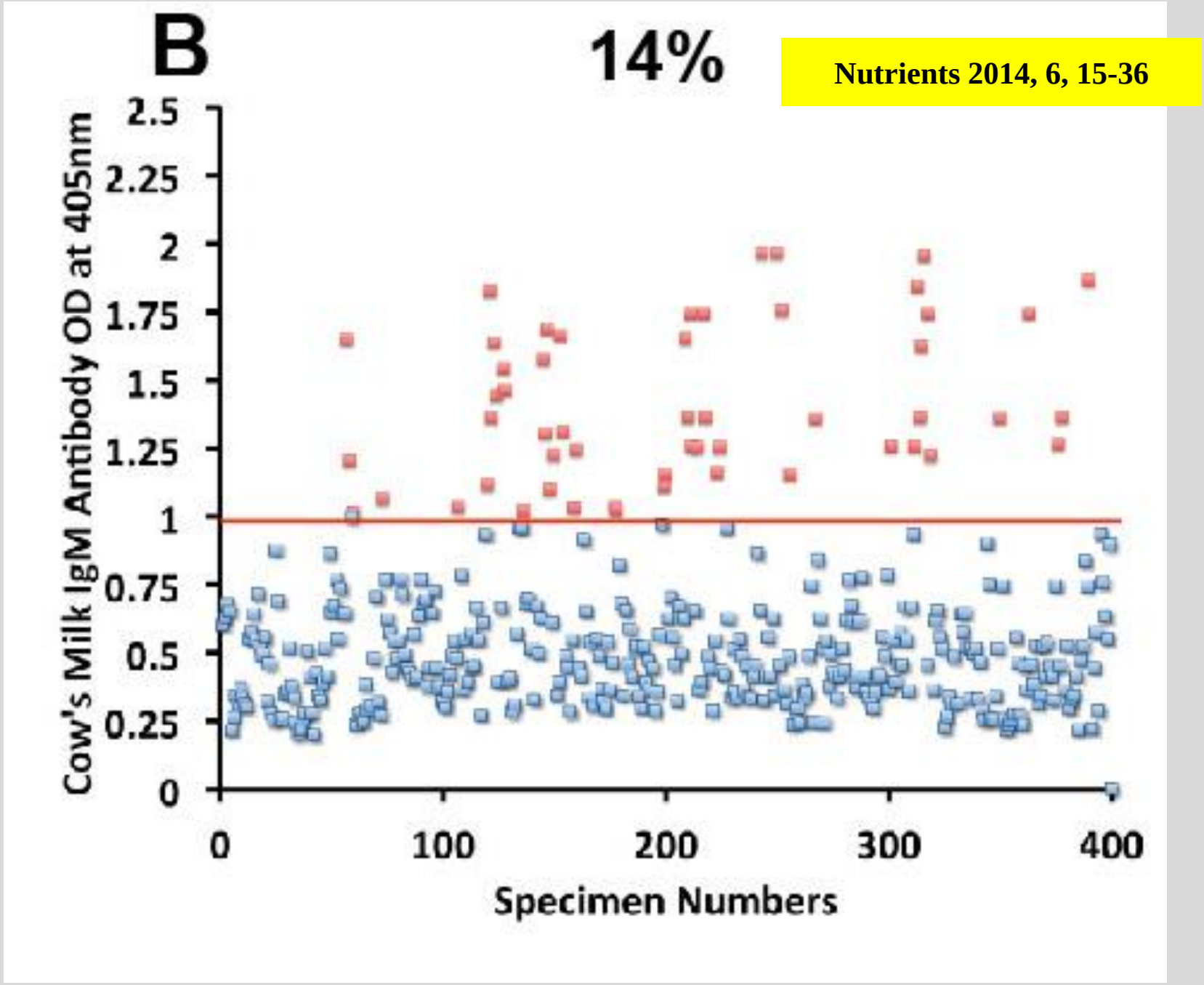
0
100
200
300
400
Specimen Numbers


B
14%
Nutrients 2014, 6, 15-36
Cow's Milk IgM Antibody OD at 405nm
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
0
100
200
300
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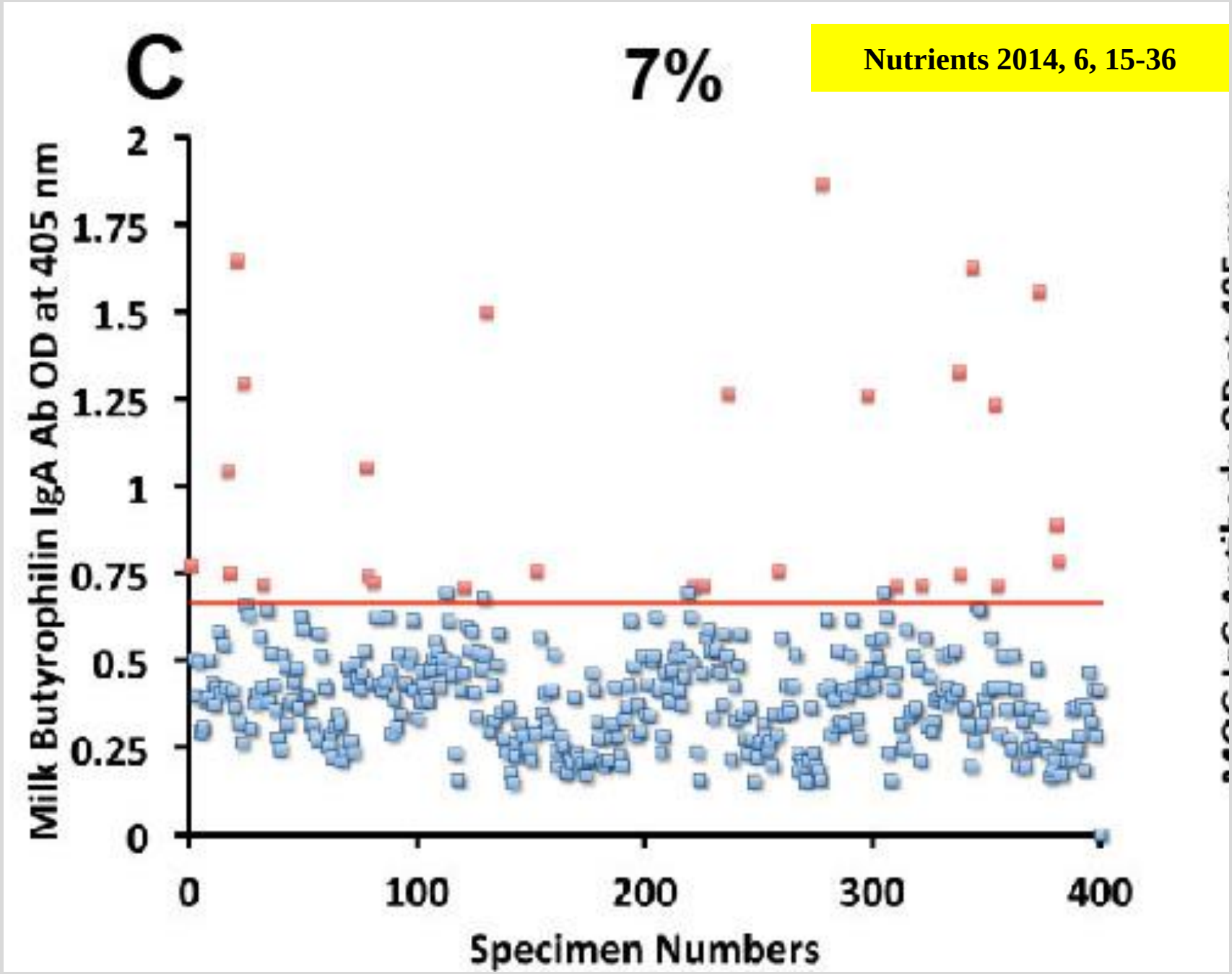
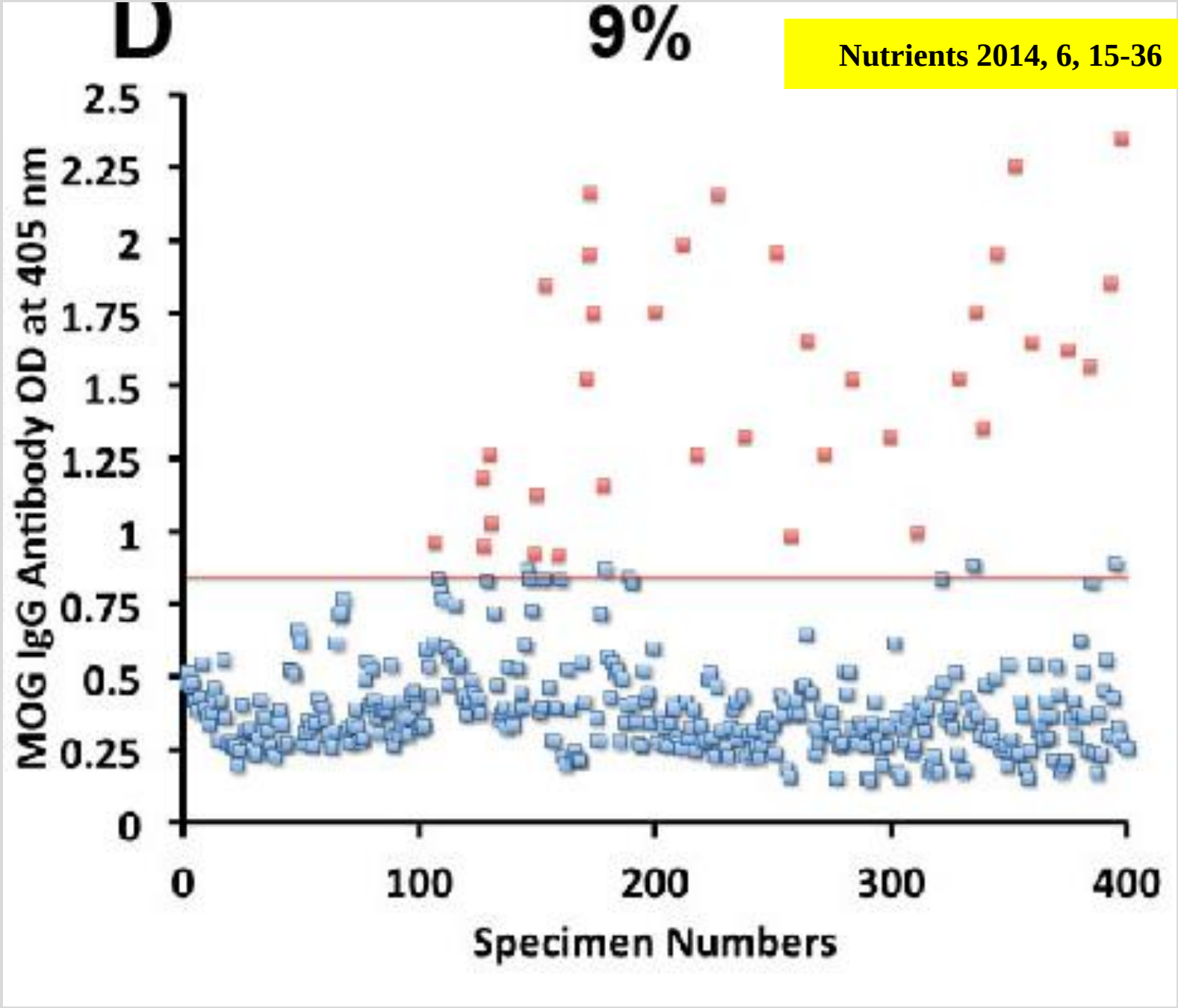
Specimen Numbers


C
7%
Nutrients 2014, 6, 15-36
Milk Butyrophilin IgA Ab OD at 405 nm
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
0
100
200
300
400
Specimen Numbers


D
9%
Nutrients 2014, 6, 15-36
MOG IgG Antibody OD at 405 nm
2.5
2.25
2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
0
100
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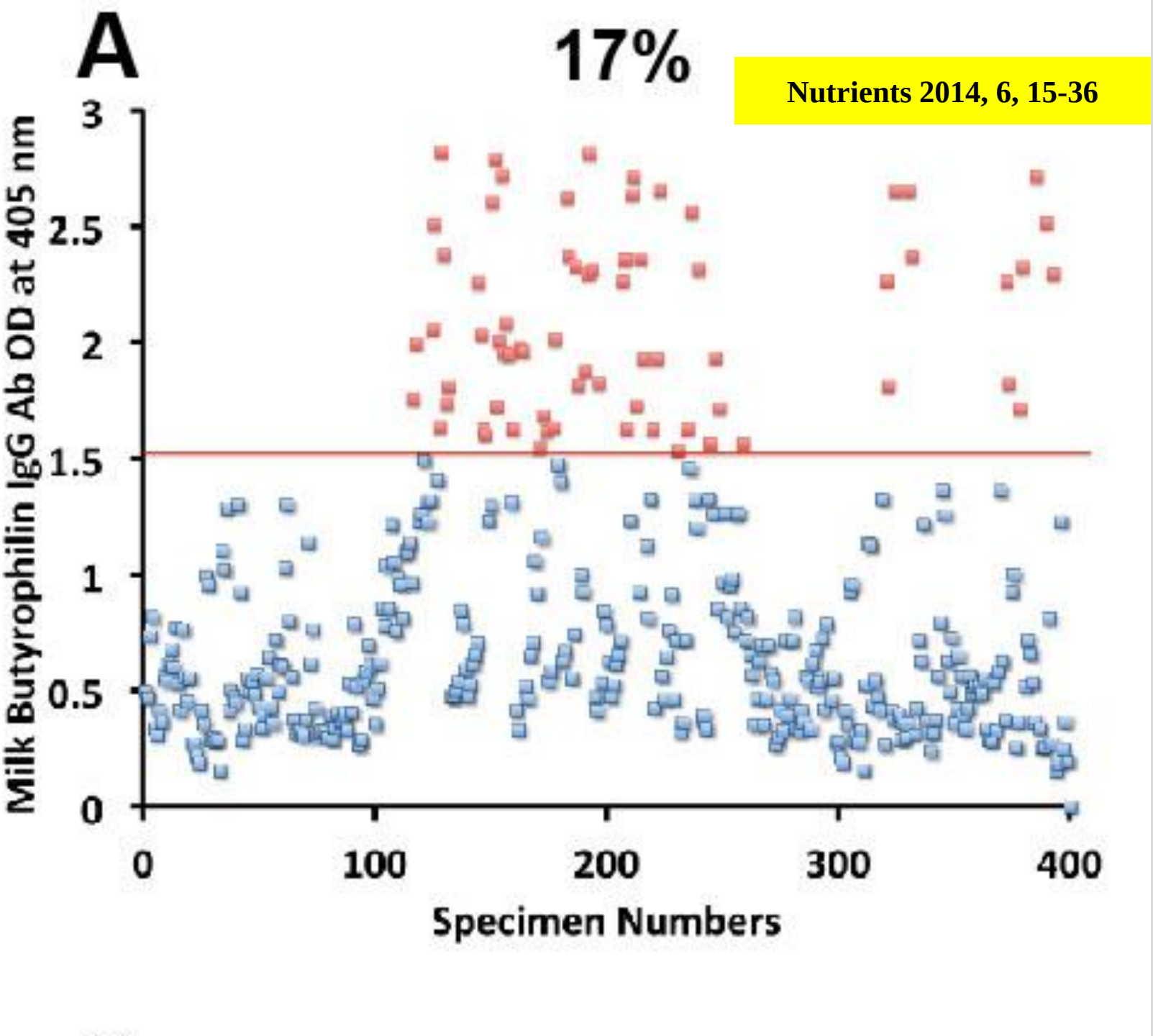
300
400
Specimen Numbers


A
17%
Nutrients 2014, 6, 15-36
Milk Butyrophilin IgG Ab OD at 405 nm
3
2.5
2
1.5
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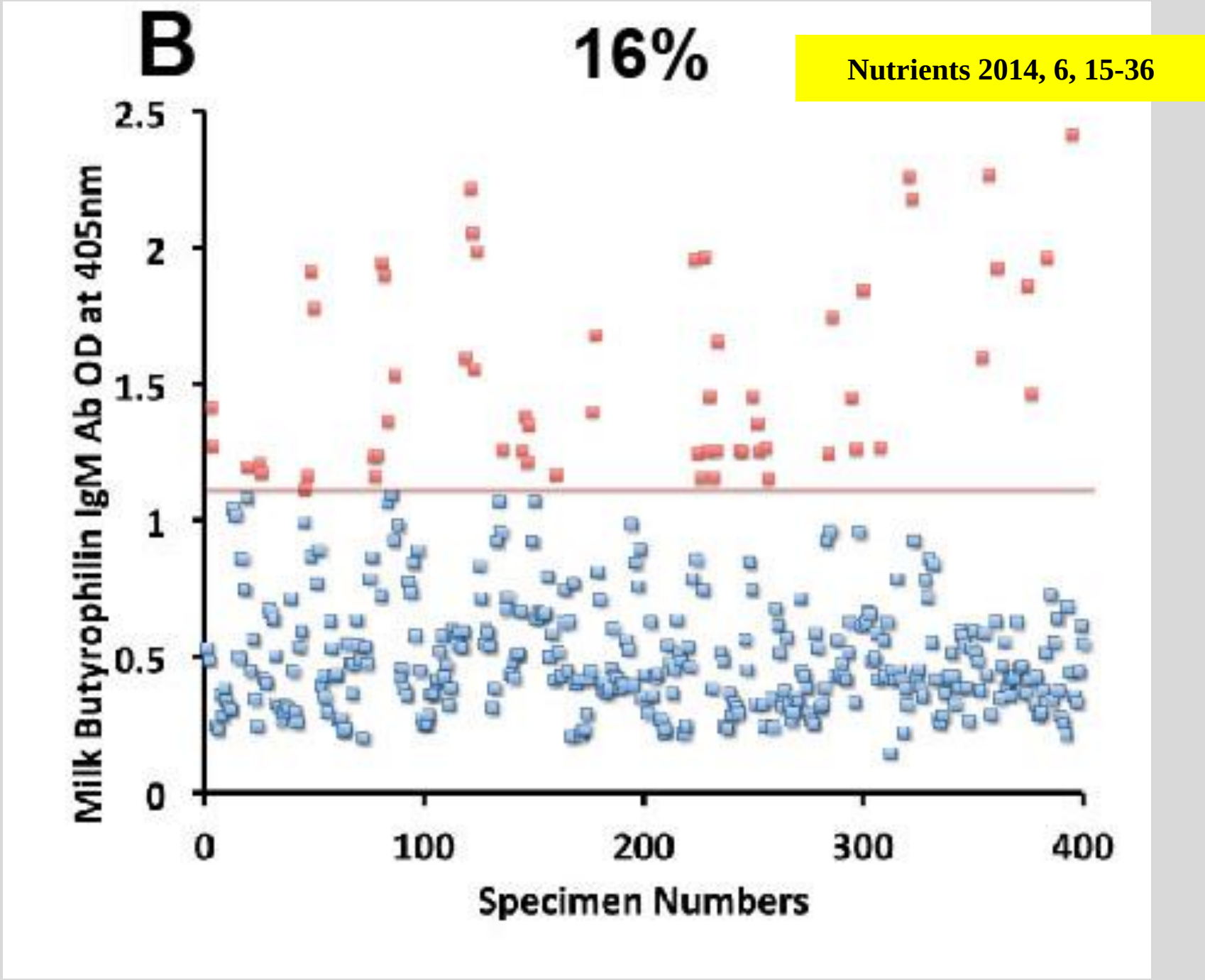
100
200
300
400
Specimen Numbers


B
16%
Nutrients 2014, 6, 15-36
Milk Butyrophilin IgM Ab OD at 405nm
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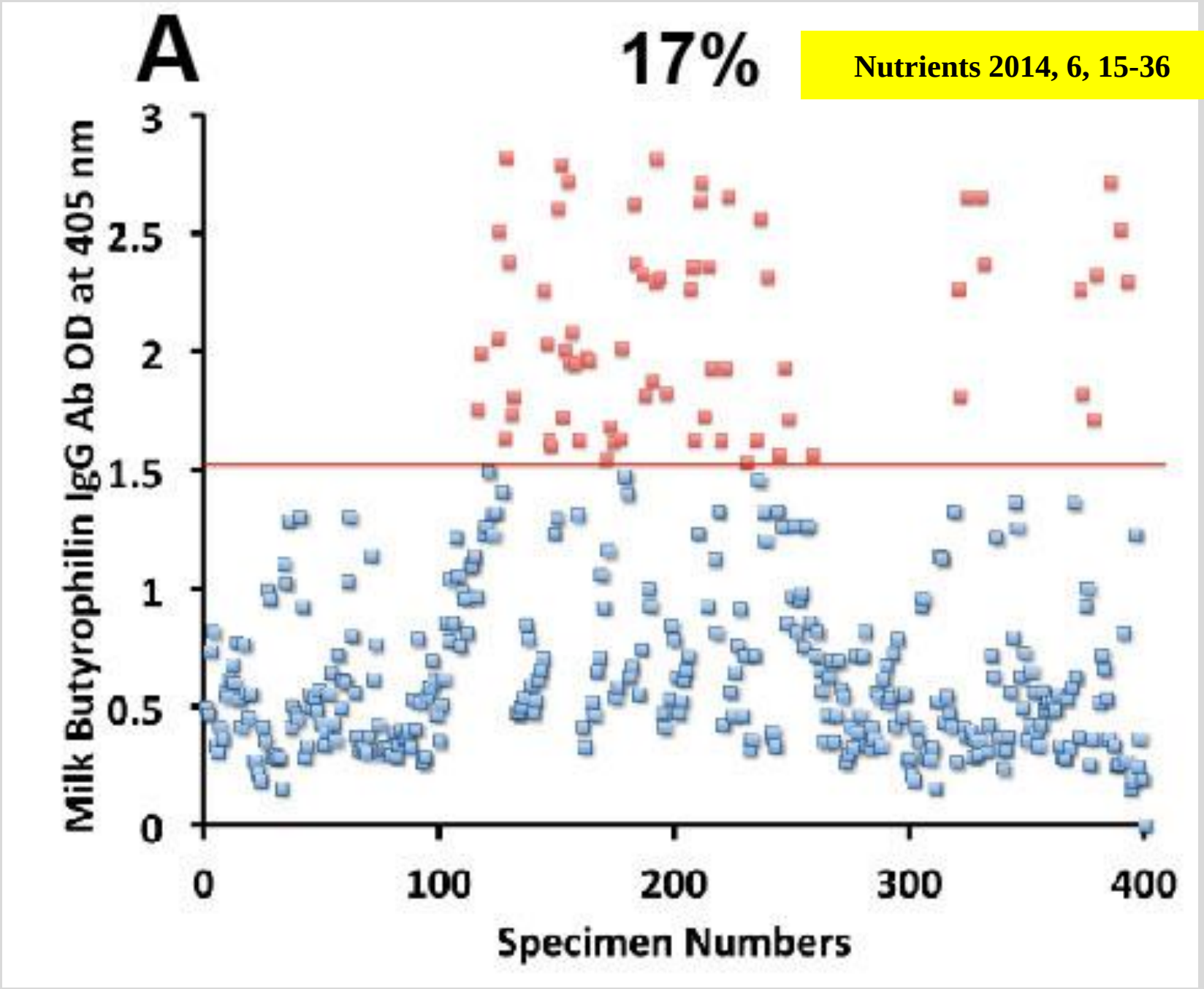
Specimen Numbers


A
17%
Nutrients 2014, 6, 15-36
Milk Butyrophilin IgG Ab OD at 405 nm
3
2.5
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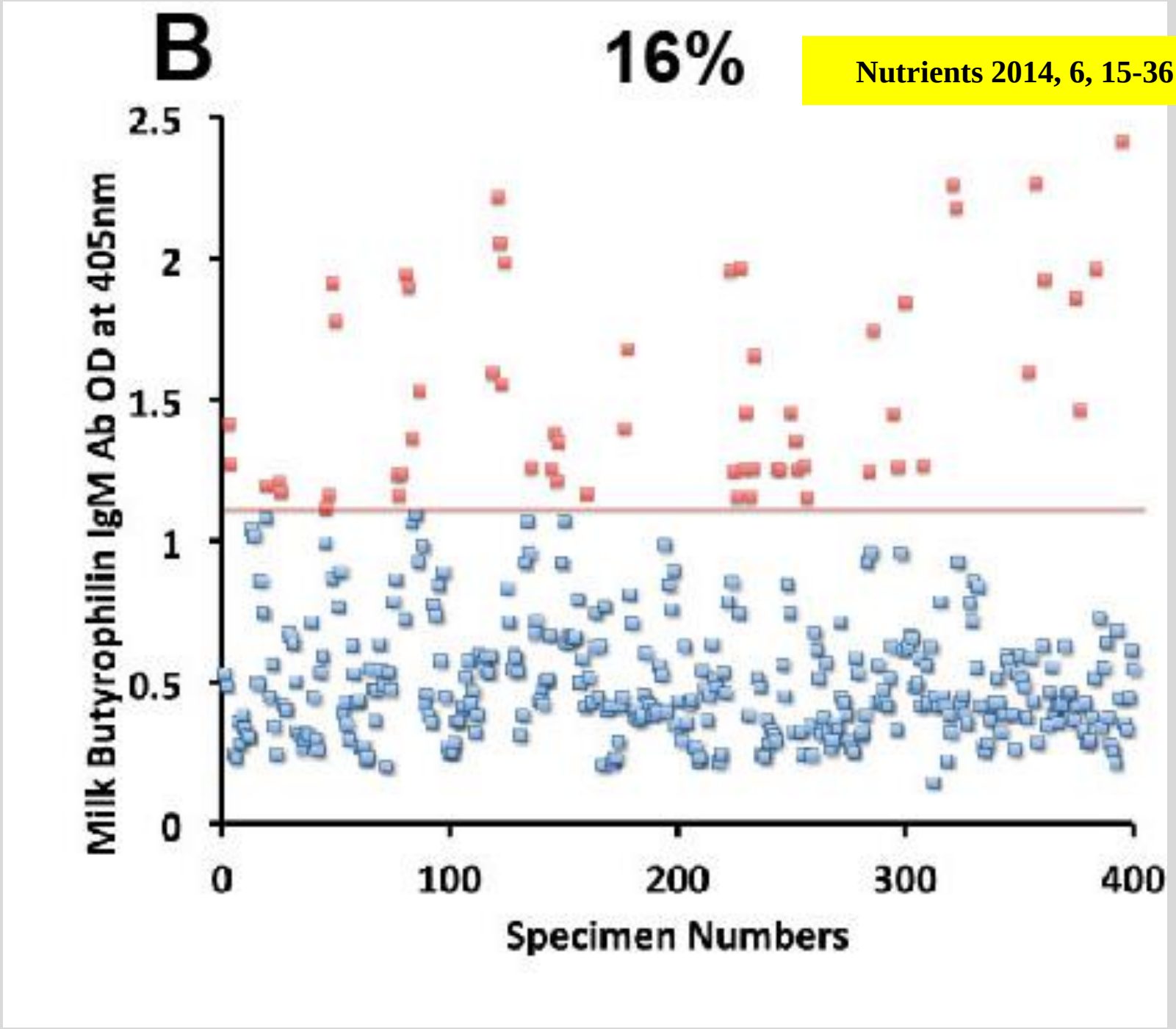
400
Specimen Numbers


B
16%
Nutrients 2014, 6, 15-36
Milk Butyrophilin IgM Ab OD at 405nm
2.5
2
1.5
1
0.5
0
0
100
200
300
400
Specimen Numbers

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 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

Nutrients 2014, 6, 15-36

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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.

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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.

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Article

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

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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.

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Premise #6

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

Detective Adrian Monk

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**

ARTICLE IN PRESS

Journal of Autoimmunity xxx (2011) 1–6

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

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

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

Antigenic challenge in the etiology of autoimmune disease in women

Mary A.M. Rogers [a,*], Deborah A. Levine [a], Neil Blumberg [b], Gwenith G. Fisher [c], Mohammed Kabeto [a], Kenneth M. Langa [a,c,d,e]

[a] Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
[b] Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA
[c] Institute for Social Research, University of Michigan, Ann Arbor, MI, USA
[d] HSR&D Center for Clinical Management Research, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, MI, USA
[e] Institute of Gerontology, University of Michigan, Ann Arbor, MI, USA

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.

1. Introduction

Female predominance in many autoimmune diseases is remarkable [1,2]. Jacobson and colleagues reported that 95% of patients with thyroiditis, 92% of adults with systemic sclerosis, 88% of patients with systemic lupus erythematosus, and 88% of patients with Graves' disease are women [3]. While gender is a known predictor of many autoimmune diseases, the reasons why women are at greater risk of autoimmune diseases remain speculative [4].

Infectious agents have been hypothesized as triggers of autoimmune disease through molecular mimicry, alterations in self-antigens, immune cell activation or infection-mediated inflammation [4–6]. Conversely, some investigators have argued for the "hygiene hypothesis" which suggests that increases in autoimmune diseases over time are correlated with decreases in the incidence of infection, particularly during childhood [7–9]. Unfortunately, there have been few population-based studies to substantiate or refute these hypotheses.

Other antigenic challenges include exposure to allogeneic tissue – that is, from genetically dissimilar individuals – either through a blood transfusion or tissue/organ transplantation. Such exposures have been shown to induce an inflammatory response, often with the production of proinflammatory cytokines and changes in chemokine expression [10–12]. Interrupters of selected chemokine pathways have been shown to suppress inflammation in mouse models of rheumatoid arthritis and systemic lupus [13,14].

Pregnancy is another instance in which genetically dissimilar cells may be transferred, in this case, between mother and fetus [15,16]. Microchimerism, the presence of genetically dissimilar cells within an individual, has been shown to persist in women for up to 38 years after delivery [17]. Preliminary studies have suggested a possible relationship between fetal microchimerism (fetal cells in parous women) and systemic sclerosis, Sjögren syndrome, Hashimoto's thyroiditis and Graves' disease [18–20]. Moreover, iatrogenic microchimerism has been shown to occur in patients after

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E-mail address: maryroge@umich.edu (M.A.M. Rogers).

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doi:10.1016/j.jaut.2011.08.001

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**

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**

- **Molecular Mimicry to Food Antigens**

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.

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* 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.

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- **Antibodies to Neoepitopes**

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

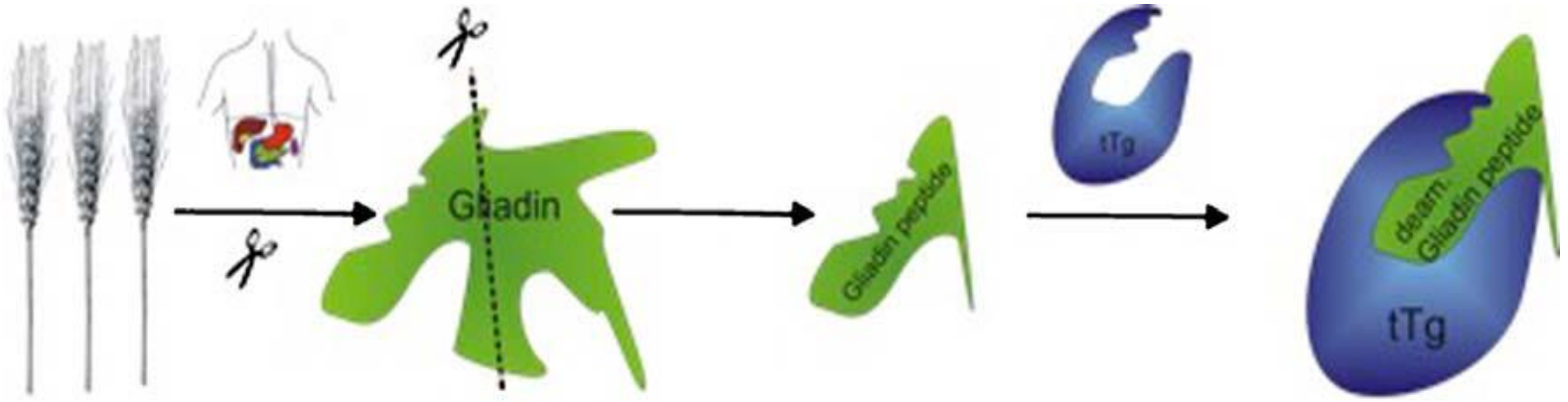


Fig. 1 The gliadin processing pathway. Cereal products are digested in the intestine and in this process gliadin is cleaved into peptides which react in the subsequent steps with tissue transglutaminase to form covalently cross-linked complexes

Journal of Im **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 Jeremias [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

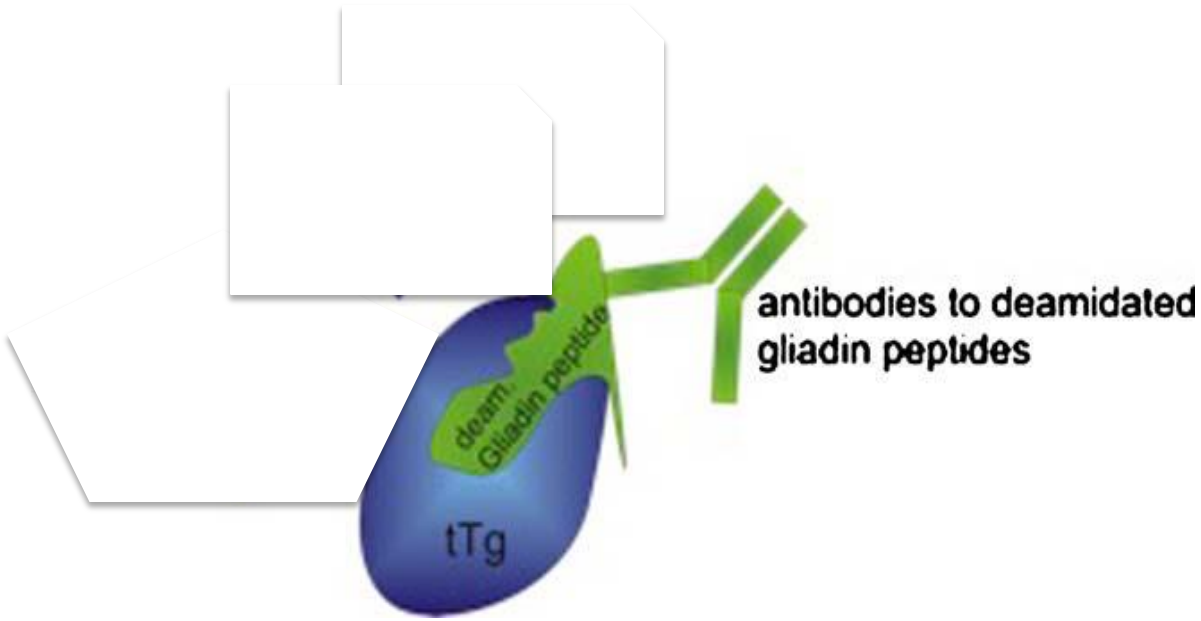


Fig. 3 The complex of deamidated gliadin peptides cross-linked with tissue transglutaminase (tTG) can detect three different antibodies entities: antibodies to tTg, to deamidated gliadin peptides and to the neo-epitope

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

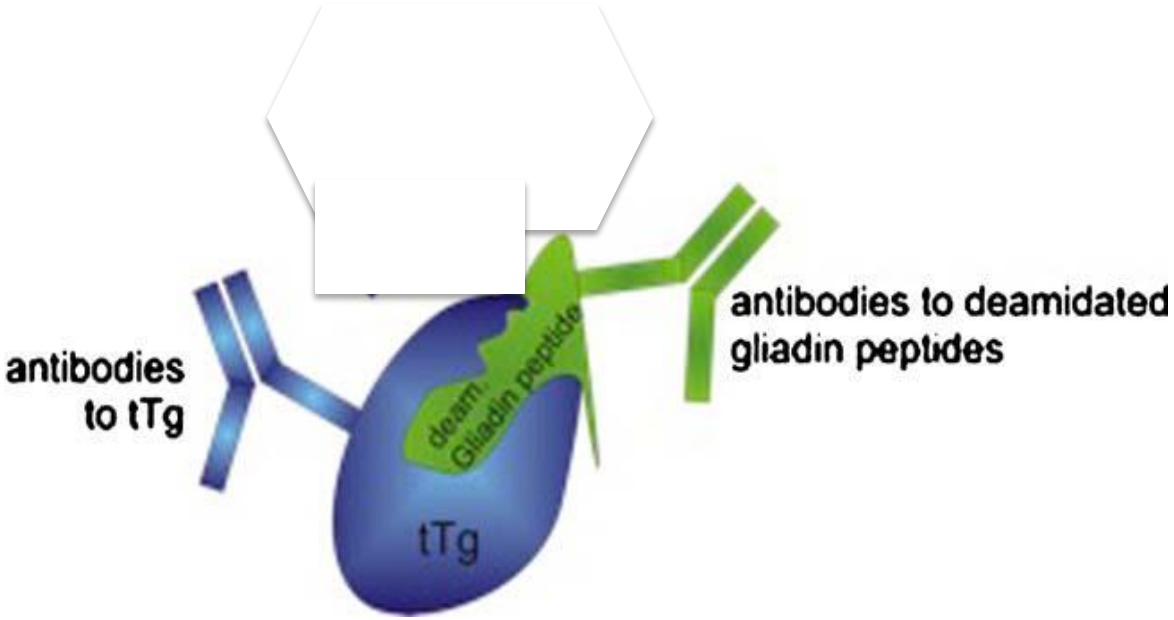
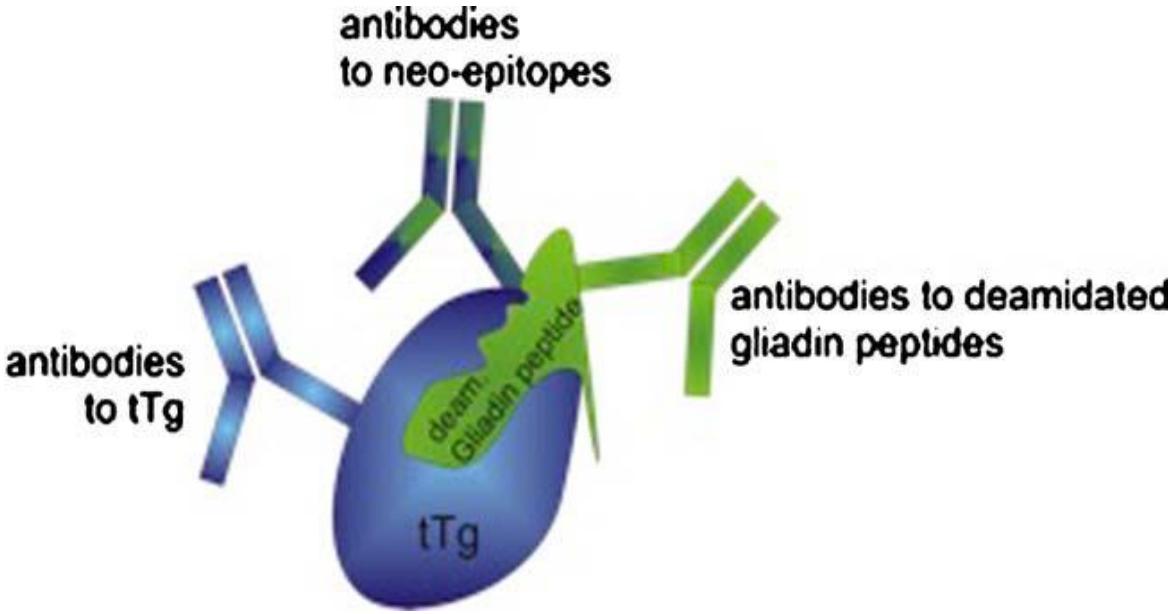


Fig. 3 The complex of deamidated gliadin peptides cross-linked with tissue transglutaminase (tTG) can detect three different antibodies entities: antibodies to tTg, to deamidated gliadin peptides and to the neo-epitope

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



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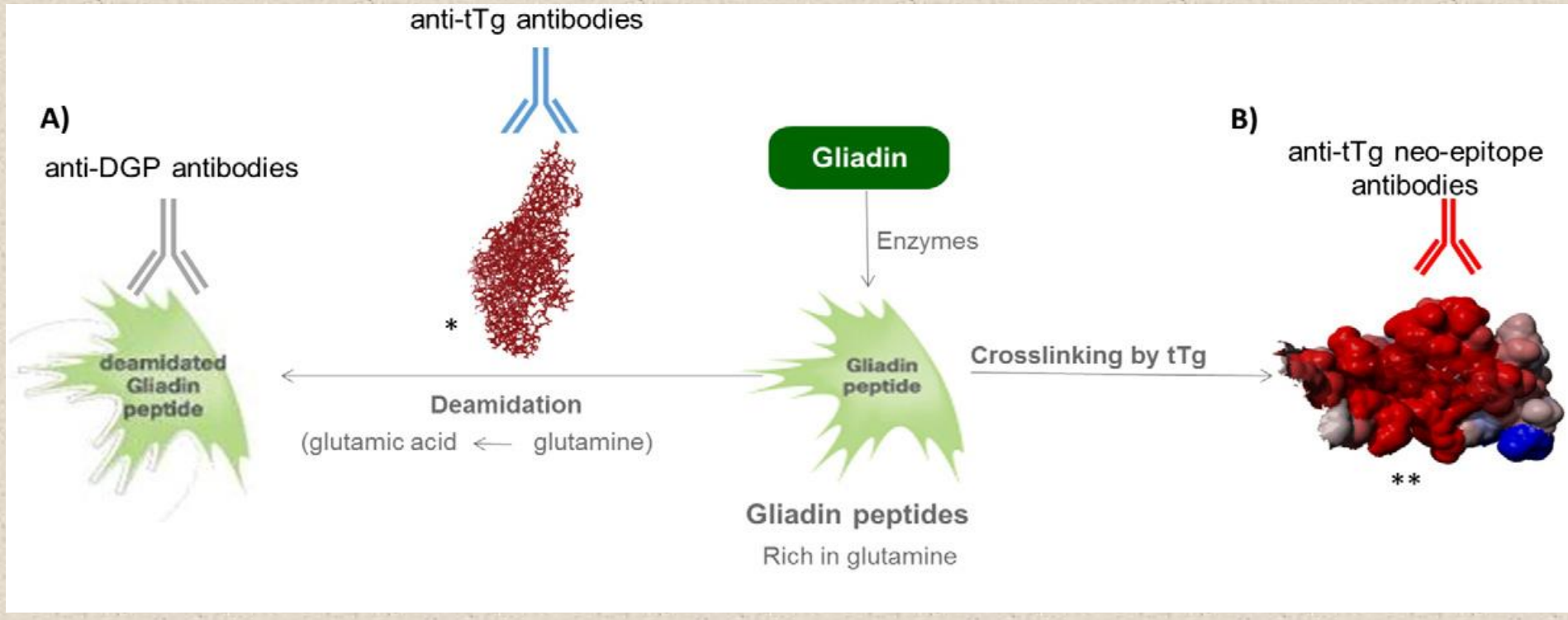
Journal of Immunological Methods 429 (2016) 15–20



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

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

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

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

When checked, it seems that the neo-tTg antibodies precede the appearance of tTg antibodies and thus have also a potential predictive value

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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.

CASE STUDY #1

Reversal of Type 1 Diabetes by eliminating an environmental trigger

BMJ Case Reports

BMJ Case Rep. 2012 Jun 21;2012.

Novel treatment (new drug/intervention; established drug/procedure in

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

Stine Møller Sildorf,[1] Siri Fredheim,[1] Jannet Svensson,[1] Karsten Buschard[2]

[1]Paediatric Unit, Copenhagen University Hospital, Herlev, Denmark;
[2]Bigshospitalet Section 3733, The Panum Institute, Copenhagen N, Denmark

Correspondence to Dr Stine Møller Sildorf, stinesildorf@dadlnet.dk

Summary

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%

remission and preserve or regenerate β cells is improvement of the quality of life for many patients and lowering the risk of acute and late complications to T1DM.

CASE PRESENTATION

Introduction

Up to 10% of patients with T1DM also have celiac disorder and, interestingly, the two diseases are by far the most common observed combined, if diabetes is the first to appear, and seldom if celiac disease develops first and gluten-free diet is implemented.[1]

Several attempts have been aimed to delay the loss of β cells, but most studies have shown none[2] or only temporary effects or have serious side effects. Gluten-free diet may be a promising alternative. 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%.[3] The result has been confirmed by several groups and by corresponding studies in BB rats.[4]

Patient

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. Glutamic acid decarboxylase (GAD) antibody was positive, islet cell antibody (ICA) and insulinoma associated antigen-2A (IA-2) were negative. Gliadin, human transglutaminase and endomysium antibodies were also negative. There has been no human leucocyte antigen-typing. He was diagnosed with classical T1DM without celiac disease.

meal stimulated tests as planned for the coming project on gluten-free diet for newly diagnosed patients with T1DM.

Our patient was treated with insulin for a total of 5 weeks with the mean insulin requirement of 0.69 IE/kg/24 h. At the end of the 5 weeks the insulin requirement declined, and the patient entered the remission phase without any insulin requirement for the following 3 weeks, with blood glucose values in the range 4–6 mmol/l. Gluten-free diet was initiated 8 weeks postdiagnosis. HbA1c was at this time 7.8% and 12 weeks postdiagnosis 6.7% (ref. range 4.8%–5.8%). His diet before the gluten-free diet was normal with preference for pasta, burger and pizza like most children at his age.

Following nutritional advice, the patient was started on a gluten-free diet with a low glycemic index. The average calorie intake was 7085 KJ/day split into six to seven courses, with 24% energy from carbohydrates, 26% from protein and 49% from fat. 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.

Stimulated C-peptide and proinsulin were tested after an individualised mixed meal (including 35–39 g carbohydrates, 5–7 g protein and 3–3.5 g fat) 8 and 12 months after diagnosis. At 8 months postdiagnosis, stimulated C-peptide was 580 pmol/l, stimulated proinsulin was 26 pmol/l. At 12 months postdiagnosis, fasting and stimulated C-peptide levels were 2 and 147 pmol/l (figure 1A, patient highlighted in red) respectively, and proinsulin 15 pmol/l. C-peptide test was performed with Immulite2500 C-peptide. Auto-antibody titres (GAD, ICA and IA-2) were unaltered. At 16 months postdiagnosis, the fasting serum

BMJ Case Reports

BMJ Case Rep. 2012 Jun 21;2012.

Novel treatment (new drug/intervention; established drug/procedure in

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

Stine Møller Sildorf,[1] Siri Fredheim,[1] Jannet Svensson,[1] Karsten Buschard[2]

[1]Paediatric Unit, Copenhagen University Hospital, Herlev, Denmark;
[2]Rigshospitalet Section 3733, The Panum Institute, Copenhagen N, Denmark

Correspondence to Dr Stine Møller Sildorf, stinesildorf@dadlnet.dk

Summary

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.

most common observed combined, if diabetes is the first to appear, and seldom if celiac disease develops first and gluten-free diet is implemented.[1]

Several attempts have been aimed to delay the loss of β cells, but most studies have shown none[2] or only temporary effects or have serious side effects. Gluten free diet may be a promising alternative. 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%.[3] The result has been confirmed by several groups and by corresponding studies in BB rats.[4]

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Correspondence to Dr Stine Møller Sildorf, stinesildorf@dadlnet.dk

Summary

The result has been confirmed by several groups.

BACKGROUND

We think that this case report is of great importance because it represents the first human trial of efficiently treating a patient with type 1 diabetes mellitus (T1DM) with gluten-free diet. The potential of an efficient treatment to prolong remission and preserve or regenerate β cells is improvement of the quality of life for many patients and lowering the risk of acute and late complications to T1DM.

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The parents requested a β-preserving treatment and were offered gluten free diet, because our clinic was preparing a study with such an intervention. The parents were offered guidance and advice on gluten-free diet and wished to start the therapy on their own, but with the control visits and meal stimulated tests as planned for the coming project on gluten-free diet for newly diagnosed patients with T1DM.

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Stimulated C-peptide and proinsulin were tested after an individualised mixed meal (including 35–39 g carbohydrates, 5–7 g protein and 3–3.5 g fat) 6 and 12 months after diagnosis. At 6 months postdiagnosis, stimulated C-peptide was 580 pmol/l, stimulated proinsulin was 26 pmol/l. At 12 months postdiagnosis, fasting and stimulated C-peptide levels were 2 and 147 pmol/l (figure 1A, patient highlighted in red) respectively, and proinsulin 15 pmol/l. C-peptide test was performed with Immulite2500 C-peptide. Auto-antibody titres (GAD, ICA and IA-2) were unaltered. At 16 months postdiagnosis, the fasting serum

BMJ Case Reports

Novel treatment (new drug/intervention; established drug/procedure in

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

Stine Møller Sildorf,[1] Siri Fredheim,[1] Jannet Svensson,[1] Karsten Buschard[2]

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Summary

A 5-year and 10-month old boy was diagnosed with classical type 1 diabetes mellitus (T1DM) without celiac disease. He started on a

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.

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. Glutamic acid decarboxylase (GAD) antibody was positive, islet cell antibody (ICA) and insulinoma associated antigen-2A (IA-2) were negative. Gliadin, human transglutaminase and endomysium antibodies were also negative. There has been no human leucocyte antigen-typing. He was diagnosed with classical T1DM without celiac disease.

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DOI 10.1186/s40064-016-2641-3

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RESEARCH Open Access

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

Jannet Svensson[1*], Stine Møller Sildorf[1], Christian B. Pipper[2], Julie N. Kyvsgaard[1], Julie Bøjstrup[1], Flemming M. Pociot[1], Henrik B. Mortensen[1] and Karsten Buschard[3]

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).

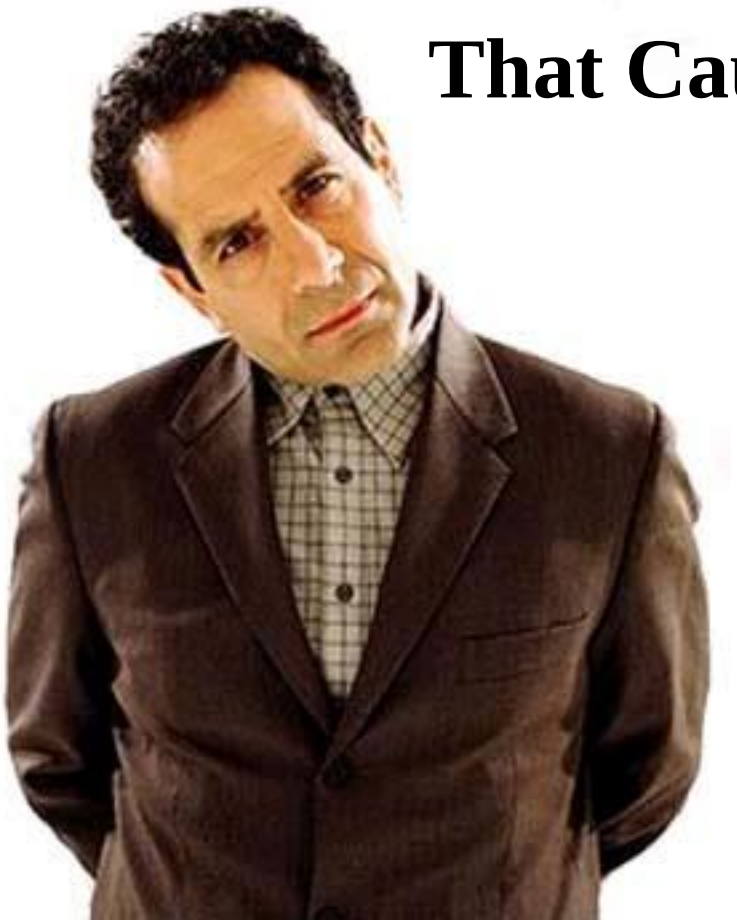
as many children were still in PR based on IDAA1c ($p < 0.05$). Twelve months after onset HbA1c were 21 % lower and IDAA1c >1 unit lower in the cohort on a gluten-free diet compared to the two previous cohorts ($p < 0.001$).

Conclusion: Gluten-free diet is feasible in highly motivated families and is associated with a significantly better out-come as assessed by HbA1c and IDAA1c. This finding needs confirmation in a randomized trial including screening for quality of life. (Clinicaltrials.gov number NCT02284815).

Keywords: Type 1 diabetes, Remission phase, Gluten, Insulin dose-adjusted HbA1c

Premise #7

How Does the Inflammatory Cascade Begin That Causes Intestinal Permeability?



Detective Adrian Monk

0031-3998/01/5003-0315
PEDIATRIC RESEARCH

Vol. 50, No. 3, 2001
Printed in U.S.A.

Pediatr Res. 2001 Sep;50(3):315-21

Toll-like Receptors as Sensors of Pathogens

MIKKO HALLMAN, MIKA RÄMET, AND R. ALAN EZEKOWITZ

Department of Pediatrics [M.H., M.R.] and Biocenter Oulu [M.H., M.R.], University of Oulu, 90220 Oulu, Finland, and Laboratory of Developmental Immunology, Mass General Hospital for Children and Harvard Medical School, Jackson 14; GRJ 1402, 55 Fruit Street, Boston, MA 02114, USA [M.R., A.E.]

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.

allows the body to respond immediately to the microbial invasion before the development of active immunity. The signal-transducing receptors that trigger the acute inflammatory cascade have been elusive until very recently. On the basis of their genetic similarity to the Toll signaling pathway in *Drosophila*, mammalian Toll-like receptors (TLRs) have been identified. By now, nine transmembrane proteins in the TLR family have been described. Mammalian TLR4 is the signal-transducing receptor activated by the bacterial lipopolysaccharide. The activation of TLR4 leads to DNA binding of the transcription factor NF-κB, resulting in activation of the inflammatory cascade. Activation of other TLRs is likely to have similar consequences. TLR2 mediates the host response to Gram-positive bacteria and yeast. TLR1 and TLR6 may participate in the activation of macrophages by Gram-positive bacteria, whereas TLR9 appears to respond to a specific sequence of bacterial DNA. The TLRs that control the onset of an acute inflammatory response are critical antecedents for the development of adaptive acquired immunity. Genetic and severe neonatal inflammatory diseases, allergies, and autoimmune diseases. (***Pediatr Res*** **50: 315–321, 2001)**

Abbreviations

CpG, cytosine phosphate-guanosine
IL-1RI, IL-1 type I receptor
IRAK, IL-1 receptor-associated kinase
LPS, lipopolysaccharide
LRR, leucine-rich repeat (segment of extracellular part of TLR)
MBL, mannose-binding lectin
NF, nuclear transcription factor
SP, surfactant protein
TIR domain, Toll-IL-1 receptor domain (cytoplasmic part of TLR, IL-1 and IL-18)
TLR, Toll-like receptor
TNF, tumor necrosis factor alpha

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The TLRs that control the onset of an acute inflammatory response are critical antecedents for the development of adaptive acquired immunity (autoimmunity).

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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

The molecular basis for the inflammatory activity of endotoxin involves Toll-like receptor 4 (TLR4) that induces innate and adaptive immune responses to LPS.

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

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

When pathogenic influx is excessive (via intestinal permeability), this induces immunopathology.

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

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1. INTRODUCTION

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Mak Adam Daulatzai*

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

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

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

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1. INTRODUCTION

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Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

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.

ATI
Barley
CNS
Dendritic cell
Extraintestinal
Gliadin
Intestine
Macrophage
Monocyte
Rye

to patients with prominent intestinal symptoms in the absence of general or intestinal signs of inflammation. There is consensus that the major wheat sensitivities, celiac disease and wheat allergy, have to be ruled out which may be difficult for wheat allergy. The non-inflammatory intolerances to carbohydrates, mainly lactose and FODMAPs (fermentable oligi-, di-, monosaccharides and polyols), which cause bloating or diarrhoea, can usually be excluded clinically or by simple tests. Recent studies and experimental data strongly indicate that NCWS exists in a substantial proportion of the population, that it is an innate immune reaction to wheat and that patients often present with extraintestinal symptoms, such as worsening of an underlying inflammatory disease in clear association with wheat consumption. Wheat amylase-trypsin inhibitors (ATIs) have been identified as the most likely triggers of NCWS. They are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa. Non-gluten containing cereals or staples display no or little TLR4 stimulating activity. Wheat ATIs are a family of up to 17 similar proteins of molecular weights around 15 kD and represent 2–4% of the wheat protein. With oral

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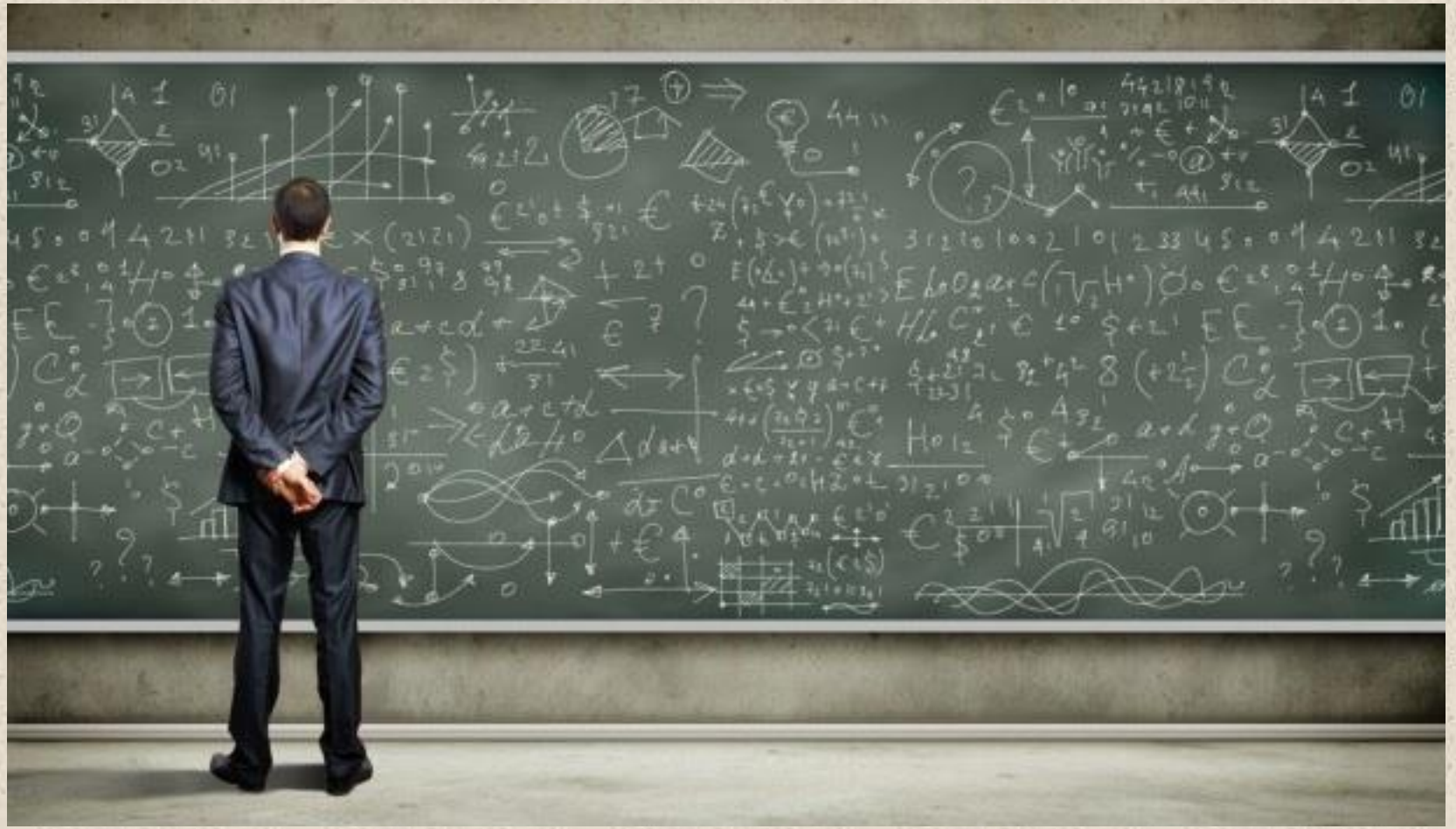
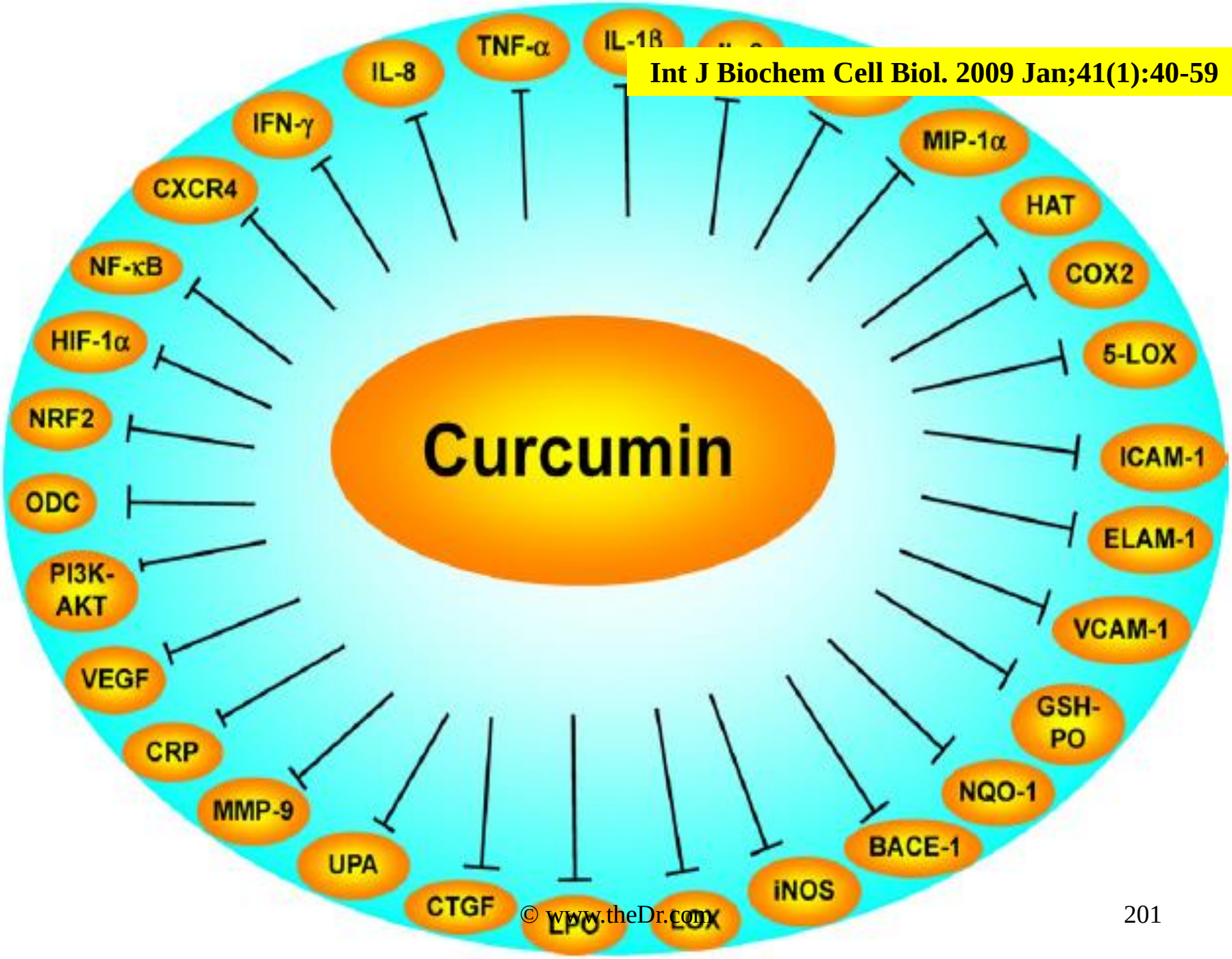


Premise #8
How do we Arrest Pathogenic Intestinal Permeability

Detective Adrian Monk

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.



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

PERSPECTIVES IN RENAL MEDICINE

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

ADEERA LEVIN and YAN CHUN LI

Division of Nephrology, University of British Colu
University of Chicago, Chicago, Illinois

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

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

Background. Patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease, and despite recent advances in hypertension control, anemia management, and dialysis adequacy, mortality remains high. Improved understanding of nontraditional risk factors, including those present at early phases in CKD, may lead to novel therapeutic strategies. CKD has been demonstrated to be an independent risk factor for cardiovascular disease in the general population, but data are

which underlies the pathogenesis of congestive heart failure; and vitamin D acts as a negative endocrine regulator for the renin-angiotensin system, which itself plays an important independent role in hypertension and cardiovascular health.

Conclusion. Vitamin D deficiency might be an underestimated nonclassical risk factor for cardiovascular disease in CKD. Based on a review of the evidence, from both basic science and clinical studies, this article supports the possible protective role of vitamin D beyond its effect on mineral metabolism, and suggests the need for ongoing evaluation of the role of vitamin

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

for the protective effects of vitamin D against cardiovascular disease mortality: vitamin D can inhibit various aspects of inflammation, which have been established as a key pathogenic mechanism in atherosclerosis; vitamin D exerts an antiproliferative effect on myocardial cell hypertrophy and proliferation,

cardiovascular protection that outside its effect on calcium and phosphate metabolism.

CARDIOVASCULAR DISEASE IS ASSOCIATED WITH CKD

Cardiovascular disease is more prevalent in patients with CKD than in the general population [5], and is the leading cause of death in patients with end-stage renal disease (ESRD) [6]. Because of the high prevalence of patients with CKD and their high risk for death, the National Kidney Foundation Task Force on Cardiovascular Disease has targeted two cardiovascular disease

Key words: vitamin D, vitamin D analogues, chronic kidney disease, cardiovascular disease, dialysis, inflammation, cardiac hypertrophy, renin-angiotensin system, mechanisms.

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and in revised form December 24, 2004 and January 25, 2005
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D-Hormone and the Immune System

MARGHERITA T. CANTORNA and BRETT D. MAHON

ABSTRACT. D-hormone [1,25(OH)$_2$ D$_3$] is an important immune system regulator that has been shown to inhibit development of autoimmune diseases including experimental inflammatory bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes. Paradoxi[cally] (experimental asthma) and immunity to infectious organisms were no[t affected by] treatment. The effectiveness of D-hormone treatment of autoimmun[e diseases is] development and function of Th1 cells and the induction of other Th cells including Th2 cells. We report results of microarray analysis of colons from D-hormone treated mice with experimental IBD. Two hundred thirty-nine genes were inhibited and 298 genes were upregulated in the colon by D-hormone treatment of mice with IBD. Of interest was the D-hormone mediated inhibition of 3 tumor necrosis factor-α (TNF-α, lipopolysaccharide-induced TNF-α factor, and TNF receptor) related genes in the colon. It is likely that the effectiveness of D-hormone treatment of experimental autoimmunity is due in part to the inhibition of the TNF family of genes. D-hormone is a selective regulator of the immune system, and the outcome of D-hormone treatment depends on the nature (infectious disease, asthma, autoimmune disease, etc.) of the immune response. (J Rheumatol 2005;32 Suppl 76:11-20)

Key Indexing Terms:
VITAMIN D RECEPTORS | IMMUNE SYSTEM | TUMOR NECROSIS FACTOR
CALCITRIOL | ANIMAL DISEASE MODELS

J Rheumatol 2005;32 Suppl 76:11-20

The discovery of the vitamin D receptor (VDR) in the cells of the immune system and the fact that activated dendritic cells produce the vitamin D hormone[1] suggested

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

myelopoiesis of the bone marrow, and no overt abnormalities in other immune system compartments[4]. Recently it has been shown that when activated, the VDR knockout mouse has overactive and inflammatory T cells; moreover, in animals susceptible to inflammatory bowel disease (IBD), this results in a fulminating form of IBD[5]. The function of VDR in the primary lymphoid tissues is not known, but arguably there is a role of the D-hormone in regulating the processes occurring there.

From the Department of Nutritional Sciences, Pennsylvania State University, University Park, Pennsylvania, USA.

Supported by Crohn's and Colitis Foundation of America, Senior Research Award, and NIH-NINDS 1R01 NS38888-01A4.

M.T. Cantorna, PhD, Assistant Professor of Nutrition Immunology; B.D. Mahon, PhD.

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VITAMIN D AND AUTOIMMUNITY

Autoimmune diseases are diseases where the immune system's ability to discriminate between self- and non-self

sis factor-α (TNF-α) have been shown to transfer autoimmune disease in mice. Treatments that can directly or indirectly block Th1 cell function are effective for suppressing autoimmunity. Type 2 helper cells (Th2) secrete interleukin 4 (IL-4), which inhibits the differentiation of Th1 cells. Other regulatory T cells produce transforming growth factor-β1 (TGF-β1) or IL-10, which also inhibit Th1 effector cell function.

Vitamin D status has been linked to autoimmune diseases in humans. Recently a large population study (Nurses Health Study I and II) showed that women in the highest quintile of vitamin D intake had a 40% reduced rate of developing MS[6]. Similarly, vitamin D intake was inversely associated with rheumatoid arthritis in the Women's Iowa Health Study, which contained data from 29,368 women[7]. Experimentally it has been shown that vitamin D deficiency exacerbates both IBD and MS in animals[8,9]. Further, D-hormone has been shown to suppress experimental MS and IBD in mice[8,9]. Interestingly, D-hormone has been shown to effectively inhibit autoimmunity even when animals were vitamin D sufficient.

MINIREVIEW

Exp Biol Med 229:1136–1142, 2004

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

MARGHERITA T. CANTORNA[1] AND BRETT D. MAHON
Department of Nutritional Sciences, Pennsylvania State University, University Park, Pennsylvania 16802

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

accumulating evidence pointing to a link between vitamin D and autoimmunity. Increased vitamin D intakes might decrease the incidence and severity of autoimmune diseases and the rate of bone fracture. Exp Biol Med 229:1136–1142, 2004

Key words: vitamin D; autoimmunity; multiple sclerosis; arthritis; inflammatory bowel disease; insulin-dependent diabetes mellitus

Introduction

Autoimmune diseases are characterized by the targeted destruction of self-tissue by the immune system. More than

The evidence linking vitamin D status as a potential environmental factor affecting autoimmune disease prevalence continues to accumulate. The data link vitamin D and insulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), inflammatory bowel diseases (IBD), and rheumatoid arthritis (RA) (2). Autoimmunity is driven by T helper cells (Th1), which attack various self-tissues in the body. It is clear that both genetic and environmental factors affect disease prevalence. The fact that vitamin D has been implicated as a factor in several different autoimmune diseases suggests that vitamin D might be an environmental factor that normally participates in the control of self-tolerance. In addition, there may be a higher vitamin D requirement for patients at risk for developing and those that already have an autoimmune disease. The optimal amount of vitamin D to support the immune response may be different from the amount required to prevent vitamin D deficiency or to maintain calcium homeostasis. The current recommended intake levels for vitamin D are too low to support bone mineralization, which is already a problem in patients with autoimmunity. New evidence from human, animal, and *in vitro* mechanistic experiments suggest that vitamin D may play a role in the etiology of autoimmunity.

This work was supported in part by Crohn's and Colitis Foundation of America, Senior Research Award to M.T.C., and the National Institutes of Health–National Institute of Neurological Disorders and Stroke Grant 1R01 NS38888.

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1535-3702/04/22911-1136$15.00

MINIREVIEW

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MARGHERITA T. CANTORNA[1] AND BRETT D. MAHON
Department of Nutritional Sciences, Pennsylvania State University, University Park, Pennsylvania 16802

Low vitamin D status has been implicated in the etiology of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, and inflammatory bowel disease. The optimal level of vitamin D intake required to support optimal immune function is not known but is likely to be at least that required for healthy bones. Experimentally, vitamin D deficiency results in the increased incidence of autoimmune disease. Mechanistically, the data point to a role for vitamin D in the development of self-tolerance. The vitamin D hormone (1,25-dihydroxy vitamin D_3) regulates T helper cell (Th1) and dendritic cell function while inducing regulatory T-cell function. The net

Vitamin D may play a role in the etiology of autoimmunity.

bone fracture. Exp Biol Med 229:1136–1142, 2004

Key words: vitamin D; autoimmunity; multiple sclerosis; arthritis; inflammatory bowel disease; insulin-dependent diabetes mellitus

Introduction

Autoimmune diseases are characterized by the targeted destruction of self-tissue by the immune system. More than 80 known autoimmune disorders exist; as a whole, they represent a leading cause of death of young to middle-aged women in the United States today (1). Despite their relatively high prevalence rate, the etiology and pathogenesis of most autoimmune disorders remain unknown, and cures remain elusive. To cure an autoimmune disorder, one would need to eradicate either the self-antigen or the immune cells responsible for the pathology. Eradication of the self-antigen is impossible; therefore, treatment options

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1535-3702/04/22911-1136$15.00

Endocrinology. 1997 Jun;138(6):2241-8

1,25-Dihydroxyvitamin D_3 Stimulates the Assembly of Adherens Junctions in Keratinocytes: Involvement of Protein Kinase C

ROBERT GNIADECKI, BARBARA GAJKOWSKA, AND MICHAEL HANSEN

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

We investigated whether 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] was able to stimulate the assembly of adherens junctions and/or desmosomes.

Endocrinology. 1997 Jun;138(6):2241-8

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

tional proteins (E-cadherin, P-cadherin, α-catenin, and vinculin) to the cell-cell borders. The presence of α-catenin and vinculin at cell-cell bor- and neoplastic diseases. (Endocrinology 1997 Jun;138(6):2241-8)

1,25-DIHYDROXYVITAMIN D 1,25-$(OH)_2D_3$ PLAYs an important role in regulation of growth of epithelial cells. The effects of 1,25-$(OH)_2D_3$ have been particularly well investigated in keratinocytes. 1,25-$(OH)_2D_3$ at concentrations 10^{-9}-10^{-6} M has been reproducibly shown to inhibit proliferation and induce differentiation of murine and human keratinocytes in culture (1–4). Inhibition of cell growth is also manifested *in vivo*, where 1,25-$(OH)_2D_3$ and its synthetic analogs inhibit excessive proliferation of keratinocytes in psoriasis (5). Recent evidence suggests that 1,25-$(OH)_2D_3$ may also be useful in the treatment of skin, breast, and colon cancer (6–9).

One of the aspects of epidermal cell differentiation is the formation of cell-cell junctions, which enable intercellular communication and are essential for regulation of epithelial morphogenesis, growth, and differentiation (10). In the epidermis, intercellular adhesion is mediated by two major types of junctional structures: the desmosomes and the adherens junctions (AJ) (11, 12). Ultrastructurally, desmosomes consist of two submembranous plaques separated by an electron-lucent 20- to 30-nm wide desmoglea with a distinct electron-dense midline(s) (13). The assembly of a desmosome is mediated by a homophylic interaction between the transmembrane proteins of the cadherin superfamily, desmoglein and desmocolin, the cytoplasmic tails of which bind to desmosome plaque proteins, placoglobin and desmoplakin. AJ are ultrastructurally similar to the desmosome, but are biochemically and functionally different from the latter. Rather than mainly strengthen the epidermis, AJ are dynamic structures capable of signal transduction and facilitate the so-called juxtacrine signaling (10, 14). AJ have been implicated in the regulation of morphogenesis, tissue remodeling, cell migration and stratification, cell spreading, epithelial compactness, and apoptosis (12, 15–18). AJ are stabilized due to the homophylic binding between N-terminal domains of the classic cadherins, E- and P-cadherin. The cytoplasmic tails of the cadherins interact with the proteins of the catenin family, α-, β-, and γ-catenin, and with a number of other accessory proteins, *e.g.* placoglobin or vinculin. α-Catenin is required for cadherin-mediated cell adhesion and has an actin-binding activity (19). Thus, AJ are associated with actin cytoskeleton, rather than with the keratin intermediate filaments such as the desmosomes.

Here we investigated whether induction of epidermal cell differentiation by 1,25-$(OH)_2D_3$ was associated with assembly of cell-cell junctions. It was found that keratinocytes cultured in the presence of 1,25-$(OH)_2D_3$ assemble AJ, but not desmosomes. Since in epithelial cells AJ formation seems to depend on the induction of protein kinase C (PKC) (20–22), we also studied whether PKC is involved in the mechanism of action of 1,25-$(OH)_2D_3$.

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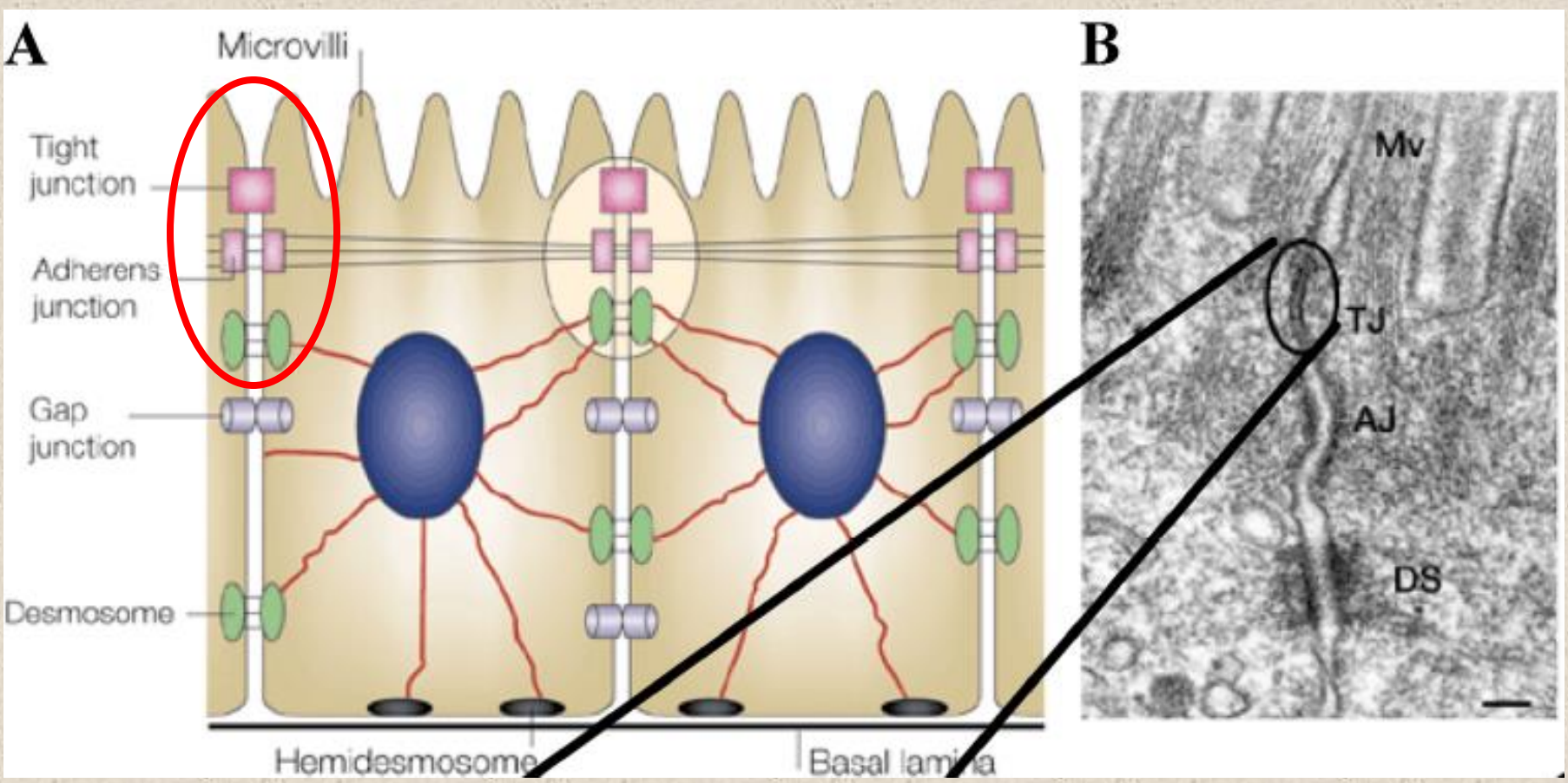
Materials and Methods

Chemicals

1,25-$(OH)_2D_3$ was obtained from the Chemical Research Department, Leo Pharmaceutical Products (Ballerup, Denmark), as a 4-mM solution

Ann. N.Y. Acad. Sci. 1165: 195–205 (2009)



Am J Physiol Gastrointest Liver Physiol 294: G000–G000, 2008.
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Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier

Juan Kong,[1] Zhongyi Zhang,[1] Mark W. Musch,[1] Gang Ning,[2] Jun Sun,[3] John Hart,[4] Marc Bissonnette,[1] and Yan Chun Li[1]

Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294(1):G208-16

Submitted 31 August 2007; accepted in final form 23 October 2007

Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M, Li YC. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol* 294: G000–G000, 2008. First published October 25, 2007; doi:10.1152/ajpgi.00398.2007.—Emerging evidence supports a pathological link between vitamin D deficiency and the risk of inflammatory bowel disease (IBD). To explore the mechanism we used the dextran sulfate sodium (DSS)-induced colitis model to investigate the role of the vitamin D receptor (VDR) in mucosal barrier homeostasis. While $VDR^{+/+}$ mice were mostly resistant to 2.5% DSS, $VDR^{-/-}$ mice developed severe diarrhea, rectal bleeding, and marked body weight loss, leading to death in 2 wk. Histological examination revealed extensive ulceration and impaired wound heal-

Vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.

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tight junction; inflammatory bowel disease; dextran sulfate sodium

THE INTESTINAL EPITHELIAL barrier consists of epithelial cells and the intercellular junctions. The barrier regulates macromolecule trafficking between the lumen and the internal milieu and protects the host by preventing harmful solutes, microorganisms, toxins, and luminal antigens from entering the body (40). Compromise or disruption of the intestinal barrier function causes deleterious effects and results in exposure of the host to luminal antigens and bacteria, leading to inflammation. Impaired barrier functions have been described in a number of common gastrointestinal disorders, including inflammatory bowel disease (IBD) (7).

The integrity of the intestinal mucosal barrier is preserved by the enormous regenerating capacity of the mucosal epithelium. The intestinal stem cells, located at the base of the crypt, are responsible for replenishing the epithelium through cell division and differentiation. After extensive destruction, rapid resealing of the surface epithelium is accomplished by epithelial cell restitution, proliferation, and differentiation (6). Another important component of the mucosal barrier is the apical and subapical intercellular junctions between the epithelial cells, namely tight junctions and adherens junctions (18). These junction structures seal the paracellular space and regulate the permeability of the mucosal barrier.

nism underlying the increased permeability seen in the intestinal epithelium of IBD patients.

Previous studies have suggested a link between vitamin D deficiency and IBD risk (23). The prevalence of IBD exhibits a north-south gradient (24), paralleling sunlight exposure, an important source of vitamin D. Populations near the equator are at relatively lower risk for developing IBD. Seasonal variations in the onset and exacerbation of IBD have also been reported (27, 36) with high incidence in the winter. Early studies have reported a high prevalence of vitamin D deficiency in patients with established Crohn's disease (12, 38). Decreased vitamin D levels have also been detected in patients with newly diagnosed IBD (17, 19, 35). In the IL-$10^{-/-}$ mouse model of intestinal inflammation, vitamin D deficiency or vitamin D receptor (VDR) deficiency exacerbates the symp-

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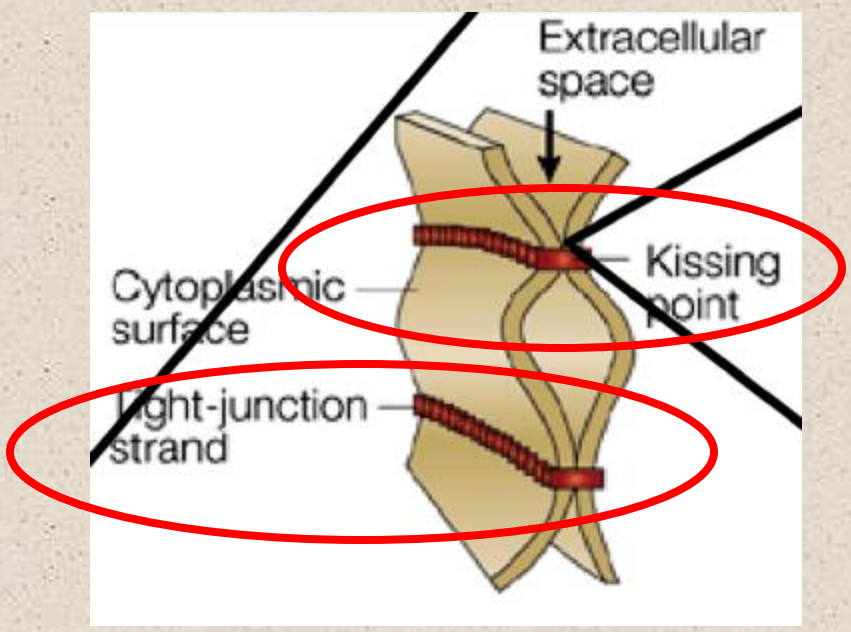

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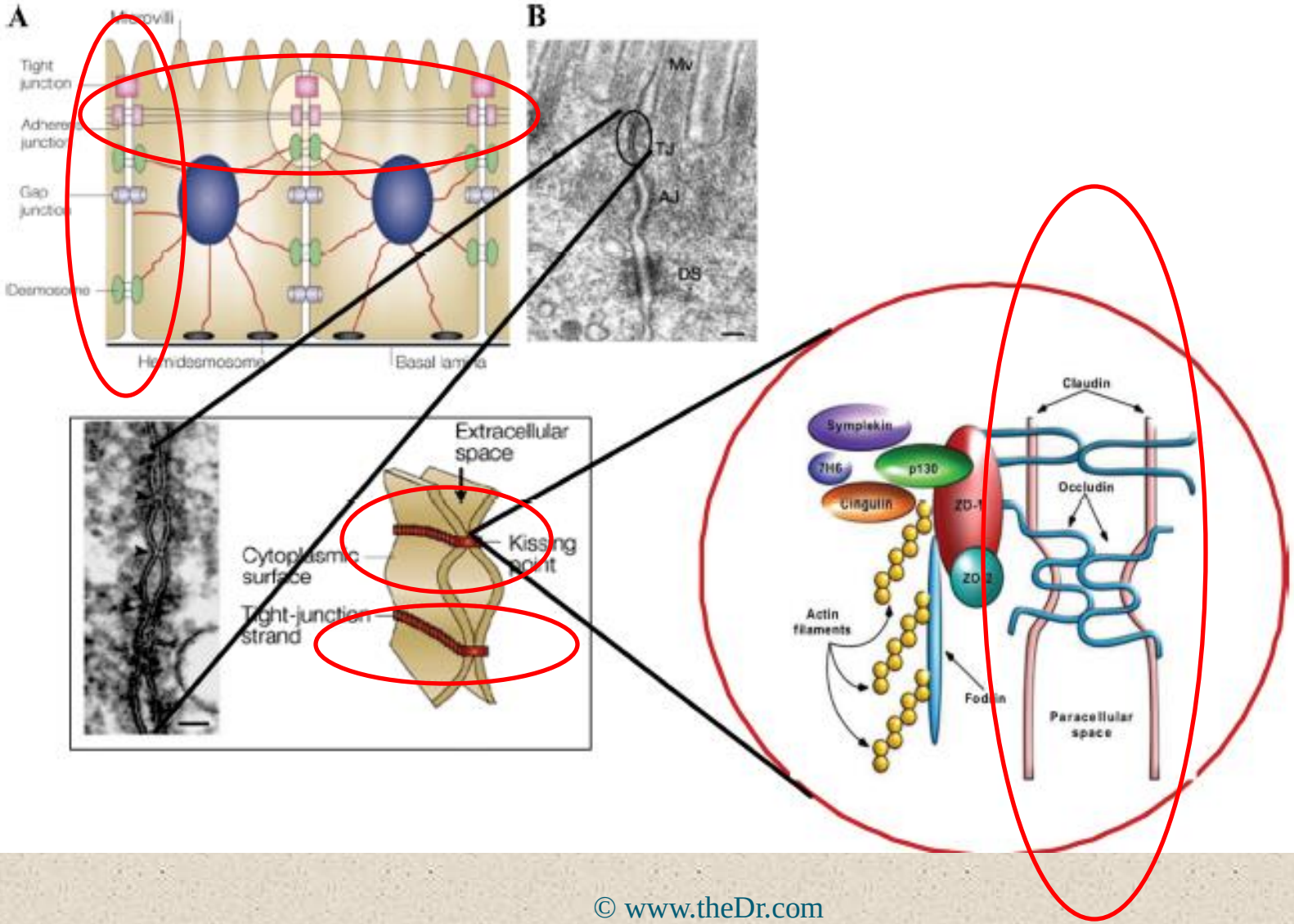

Baxter *et al. Genome Medicine* (2016) 8:37
DOI 10.1186/s13073-016-0290-3

Genome Medicine

RESEARCH Open Access

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.

fecal immunochemical test (FIT).

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.

Results: The microbiota-based random forest model detected 91.7 % of cancers and 45.5 % of adenomas while FIT alone detected 75.0 % and 15.7 %, respectively. Of the colonic lesions missed by FIT, the model detected 70.0 % of cancers and 37.7 % of adenomas. We confirmed known associations of *Porphyromonas assaccharolytica*, *Peptostreptococcus stomatis*, *Parvimonas micra*, and *Fusobacterium nucleatum* with CRC. Yet, we found that the loss of potentially beneficial organisms, such as members of the Lachnospiraceae, was more predictive for identifying patients with adenomas when used in combination with FIT.

Conclusions: These findings demonstrate the potential for microbiota analysis to complement existing screening methods to improve detection of colonic lesions.

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JOURNAL

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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

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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.

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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.

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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Recent evidence also suggests that the microbiome may also be seeded into the unborn fetus while still in the womb

While numerous changes in human lifestyle constitute modern life, our diet has been gaining attention as a 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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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

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This developmental dysbiosis leaves the offspring's immune system poorly trained to fight off infections and encourages autoimmune and allergic diseases

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Ian A Myles

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.

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.

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

Ian A. Myles

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.

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.

REVIEW ARTICLE

Effect of Intestinal Microbial Ecology on the Developing Brain

Martha Douglas-Escobar, MD; Elizabeth Elliott; Josef Neu, MD

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.

The mammalian gastrointestinal tract harbors a highly diverse microbial population that plays a major role in nutrition, metabolism, protection against pathogens, and development of the immune system. It is estimated that at least 1000 different bacterial species cohabit the human intestinal tract. Most recently, the Human Microbiome Proj-

boring approximately 150 times as many genes as the human genome. Various factors are involved in the development of this complex ecosystem. The infant's gestational age, mode of delivery, type of nutrition, and early use of antibiotics modify the composition of this microbiome and may have significant and long-lasting effects.[2-4]

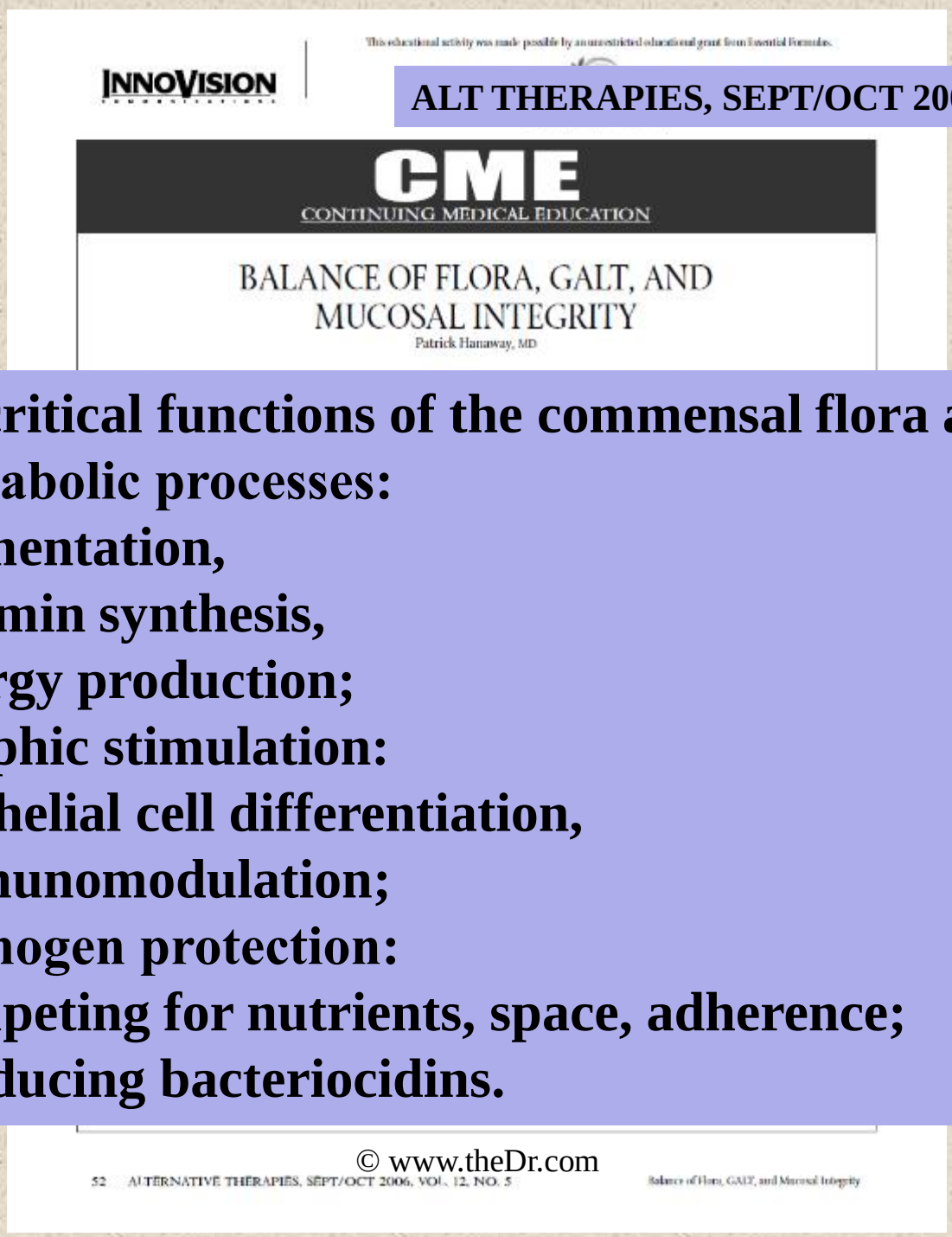
The use of newly developed nonculture-based technologies is providing new insights into the temporal colonization patterns in infants born at term[5,6] or preterm.[7,8] The combination of emerging microbial genomic technologies with metabolic and immunologic analyses is revealing impor-

Author Affiliations: Division of Neonatology, Department of Pediatrics, University of Florida, Gainesville.

ROLES OF THE MICROBIOTA

Metabolic Role

Although often thought of as pathogens, the vast majority of microbes harbored in our intestinal tracts are thought to have beneficial effects. These commensal and symbiotic microbiota have varied roles in the human host; they are directly involved in synthesizing vitamins and cofactors, breaking down complex lipids and polysaccharides, and detoxifying waste particles.[10] Microbes can alter metabolism by extracting 40% to 50% of the available energy from nutrients,[11] thus playing a role in obesity. Through fermentation, the microbiota produce short-chain fatty acids that play important roles


This educational activity was made possible by an unrestricted educational grant from Essential Formulas.

INNOVISION

ALT THERAPIES, SEPT/OCT 2006, VOL. 12, NO. 5

CME
CONTINUING MEDICAL EDUCATION

BALANCE OF FLORA, GALT, AND MUCOSAL INTEGRITY

Patrick Hanaway, MD

52 ALTERNATIVE THERAPIES, SEPT/OCT 2006, VOL. 12, NO. 5

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.**

APMIS ACTA PATHOLOGICA, MICROBIOLOGICA ET IMMUNOLOGICA SCANDINAVICA

APMIS 121: 403–421

APMIS. 2013 May;121(5):403-2

REVIEW ARTICLE

Two faces of microbiota in inflammatory and autoimmune diseases: triggers and drugs

MILOSLAV KVERKA and HELENA TLASKALOVA-HOGENOVA

Department of Immunology and Gnotobiology, Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic

Kverka M, Tlaskalova-Hogenova H. Two faces of microbiota in inflammatory and autoimmune diseases: triggers and drugs. APMIS 2013; 121: 403–21.

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**

increase. The role of genetics is probably over-

Received 25 July 2012. Accepted 13 September 2012

with potential pathogens and immunoregulation (2, 3). This knowledge led to intensive search for both the microbial triggers and

Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression

Alex Vasquez, D.C., N.D.

Abstract: Doctors and patients can achieve significant success in the treatment of pain and inflammation by using dietary modification along with nutritional, botanical, and fatty acid supplementation. The first article in this series reviewed recent diet research and the basic biochemistry of fatty acid metabolism, and this second article will provide doctors with a profound understanding of the importance of optimal fatty acid supplementation and will review the clinical benefits of this essential therapy. This review contains the most co
metabolism that has ever been published in a single

Nutritional Perspectives, Vol. 28, no. 1, 1-16

INTRODUCTION

Chiropractic and naturopathic physicians are the only doctorate-level healthcare providers with graduate-level training in therapeutic nutrition and are emerging as the leaders in the treatment and prevention of long-term health disorders, including nearly all of the chronic diseases seen in clinical practice such as obesity, hypertension, adult-onset diabetes, hypercholesterolemia, allergies, asthma, arthritis, depression and a long list of other musculoskeletal and non-musculoskeletal conditions.[1,2] With the increasing substantiation of the effectiveness and cost-effectiveness of the nutritional management of these problems, and the doc-

ing errors", hospital injuries, and what is described as "substandard care."[4] A recent article in the *New England Journal of Medicine*[5] concluded that deficits in allopathic medical care pose "serious threats to the health of the American public." A 1997 review published by the American Academy of Family Physicians[6] stated, "Recent estimates suggest that each year more than 1 million patients are injured while in the hospital and approximately 180,000 die because of these injuries. Furthermore, drug-related morbidity and mortality are common and are estimated to cost more than $136 billion a year." New research also shows that several popular "antidepressant" drugs actually increase the risk for suicide in children[7] and adults[8,9], and, similarly, "antipsychotic" drugs may worsen clinical outcomes in a large percentage of patients with mental illness.[10] Chiropractic diet therapy—not drugs—is the most effective treatment for chronic hypertension.[11, 12] Many anti-inflammatory drugs for the treatment of joint

newer selective cyclooxygenase inhibitors carry an unjustifiable cost[16, 17] and fail to deliver improved efficacy[18] despite significantly increasing the risk for kidney damage, hypertension, myocardial infarction, stroke, and sudden death.[19, 20, 21] On the other hand, natural treatments such as dietary improvements and fatty acid supplementation have been shown to safely reduce the need for medical treatments, to improve health, to alleviate many common diseases, and to prolong life at lower cost, negligible risk, and with improved overall outcomes.[22, 23] **In order to reduce costs, promote health, and reduce iatrogenic dis-**

the first article in this series[24] and in greater detail elsewhere[25] is the single most powerful approach for the effective treatment of a wide range of conditions. Following closely behind general dietary modification, fatty acid supplementation offers clinicians the opportunity to improve the health of their patients in ways that no other single treatment can.

FATTY ACID SUPPLEMENTATION: UNDERSTANDING IS THE KEY TO MASTERY

An accurate and detailed understanding of fatty acid metabolism is important for the complete and effective management of many clinical conditions including mental depression, coronary artery disease, hypertension, diabetes, other inflammatory/autoimmune disorders, and many of the musculoskeletal conditions encountered in clinical practice. The practical application of this information is

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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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

John O. Clarke, MD; and Gerard E
Division of Gastroenterology, The Johns H

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

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

ated, and explore the data to date for the prevention or treatment of IBD.

A dose of up to 3 g per day of EPA plus DHA has been determined to be safe for general consumption.

The majority of reimbursed care in the United States today is *via* Western medicine, a tradition that harkens back, in a primitive form, only to the Renaissance. Complementary and alternative medicine (CAM) refers to medical practices that are not currently considered to be part of conventional medicine. However, these "alternative" and "natural" approaches have significant time-proven history, just not in Western literature. Traditional Chinese medicine stretches back 5000 years, and traditional Indian (Ayurvedic) medicine can trace its history for over 2000 years. At the start of the 20th century, in fact, there were already 30,000–40,000 books regarding these practices already in existence.

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

gallocatechin, curcumin, and boswellia), ω-3 essential fatty acids (EFA; fish oil), vitamin D, and probiotics. Although many diseases can be examined as a model for inflammation (including inflammatory bowel disease [IBD], rheumatoid arthritis, and multiple sclerosis, to name a few), we have elected to focus on IBD exclusively because: (a) we are gastroenterologists and this is our bias, and (b) to dwell on every inflammatory condition would make this paper too unwieldy to be readable without coercion.

In the words of Hippocrates: "Let food be thy medicine."

Polyphenols

Polyphenols are phytochemicals that are found in food substances produced from plants. Polyphenols are separated from essential micronutrients in that a deficiency state has not been identified; nevertheless, these chemicals are believed to play a biologically active role and have been shown to be potentially immunomodulating.[2] Although numerous polyphenols have been identified, 4 in particular have a preponderance of evidence in the role of immune modulation and will be addressed in this review: resveratrol, epigallocatechin, curcumin, and boswellia. The findings of polyphenols to prevent and treat animal models of IBD are summarized in Table 1.[3–22]

Correspondence: Gerard E. Mullin, MD, The Johns Hopkins Hospital, Division of Gastroenterology, 600 North Wolfe Street, Carnegie Building, Room 464, Baltimore, MD 21287. Electronic mail may be sent to gmullin1@jhmi.edu.

0884-5336/08/2301-0049$03.00/0
Nutrition in Clinical Practice 23:49–62, February 2008

Treatment Protocols
(personal recommendations-EPA/DHA)

Therapeutic dosages:

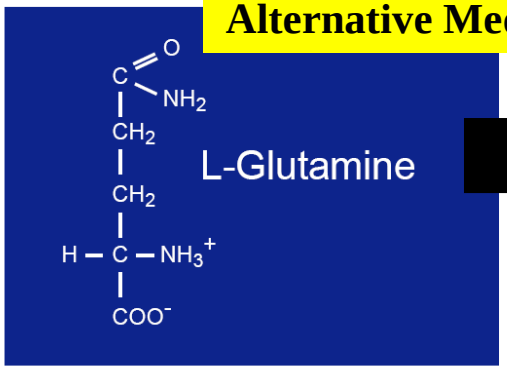
30-75 lbs = at least 1 g/d (Total Omega 3's)

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

Alternative Medicine Review Volume 6, Number 4 2001



Monograph

L-Glutamine

Introduction

L-glutamine is the most prevalent amino acid in the bloodstream and because human cells readily synthesize it, is usually

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.

tients, immune enhancement in endurance athletes, and prevention of complications associated with chemotherapy, radiation, and bone marrow transplant.[1,2]

Biochemistry

L-glutamine accounts for 30-35 percent of the amino acid nitrogen in the plasma. It contains two ammonia groups, one from its precursor, glutamate, and the other from free ammonia in the bloodstream. One of glutamine's roles is to protect the body from high levels of ammonia by acting as a "nitrogen shuttle." Thus, glutamine can act as a buffer, accepting, then releasing excess ammonia when needed to form other amino acids, amino sugars, nucleotides, and urea. This capacity to accept and donate nitrogen makes glutamine the major vehicle for nitrogen transfer among tissues. Glutamine is one of the three amino acids involved in glutathione synthesis. Glutathione, an important intracellular antioxidant and hepatic detoxifier, is comprised of glutamic acid, cysteine, and glycine.[1,2]

Clinical Indications

Gastrointestinal Disease

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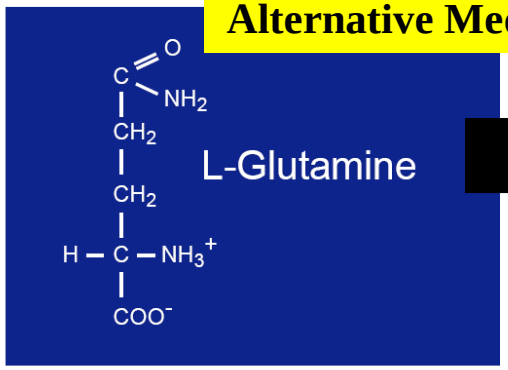

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A clinical study of ulcerative colitis patients

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

donate nitrogen makes glutamine the major vehicle for nitrogen transfer among tissues. Glutamine is one of the three amino acids involved in glutathione synthesis. Glutathione, an important intracellular antioxidant and hepatic detoxifier, is comprised of glutamic acid, cysteine, and glycine.[1,2]

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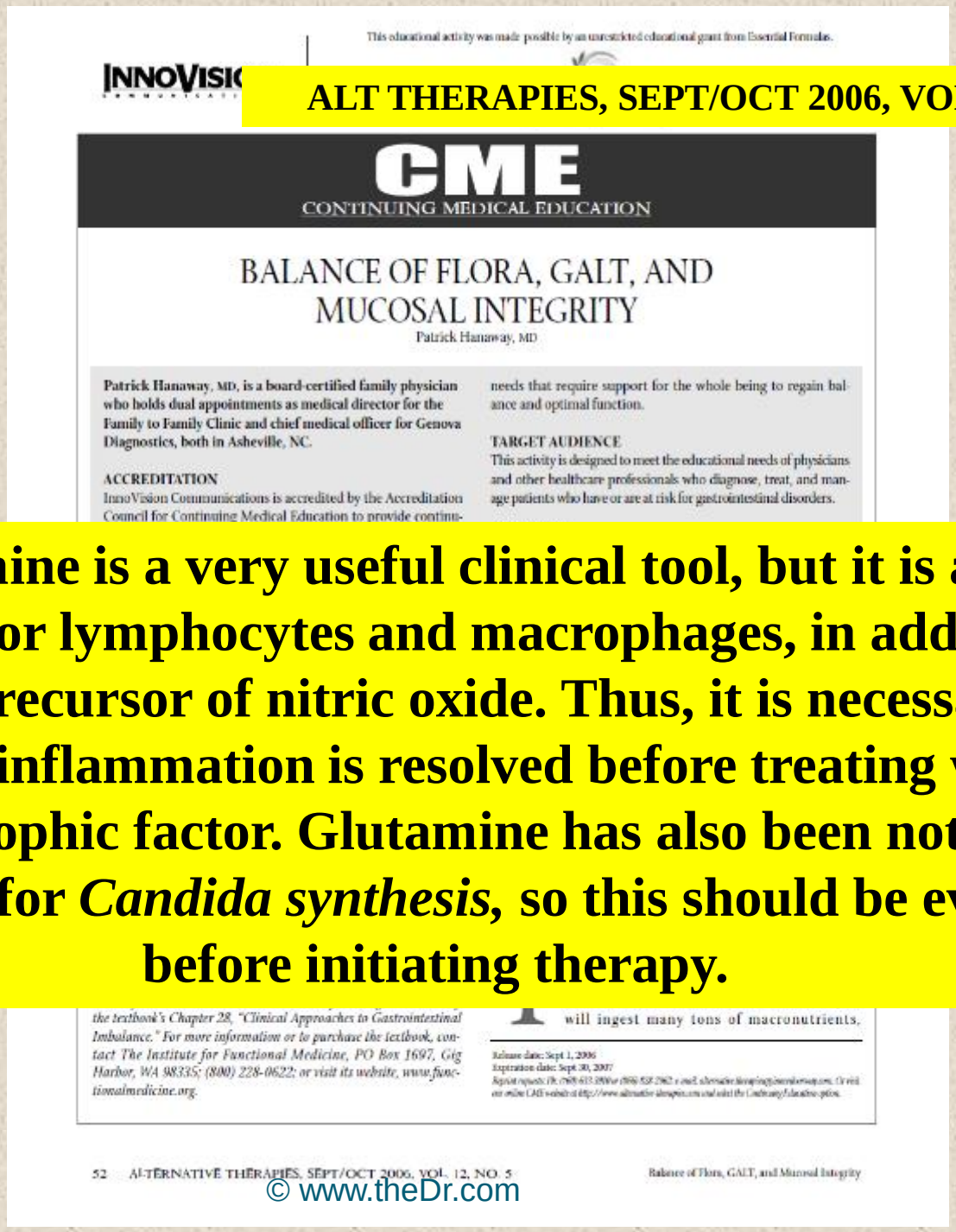

This educational activity was made possible by an unrestricted educational grant from Essential Formulas.

INNOVISION COMMUNICATIONS

ALT THERAPIES, SEPT/OCT 2006, VOL. 12, NO. 5

CME
CONTINUING MEDICAL EDUCATION

BALANCE OF FLORA, GALT, AND MUCOSAL INTEGRITY

Patrick Hanaway, MD

Patrick Hanaway, MD, is a board-certified family physician who holds dual appointments as medical director for the Family to Family Clinic and chief medical officer for Genova Diagnostics, both in Asheville, NC.

ACCREDITATION

InnoVision Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continu-

needs that require support for the whole being to regain balance and optimal function.

TARGET AUDIENCE

This activity is designed to meet the educational needs of physicians and other healthcare professionals who diagnose, treat, and manage patients who have or are at risk for gastrointestinal disorders.

the textbook's Chapter 28, "Clinical Approaches to Gastrointestinal Imbalance." For more information or to purchase the textbook, contact The Institute for Functional Medicine, PO Box 1697, Gig Harbor, WA 98335; (800) 228-0622; or visit its website, www.functionalmedicine.org.

will ingest many tons of macronutrients.

Release date: Sept 1, 2006
Expiration date: Sept 30, 2007

52 ALTERNATIVE THERAPIES, SEPT/OCT 2006, VOL. 12, NO. 5

Balance of Flora, GALT, and Mucosal Integrity

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

Treatment Protocols
(personal recommendations-Glutamine)

Therapeutic dosages:

Dosages vary greatly depending on the clinical situation

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

0148-6071/06/3001-0045$03.00/0
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Vol. 30, No. 1
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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

Stig Bengmark, MD, PhD, FRACS (hon), F

From the Institute of Hepatology, University College, London Medical Sch

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

ABSTRACT. *Background:* The world suffers a tsunami of chronic diseases, and a typhoon of acute illnesses, many of which are associated with the inappropriate or exaggerated activation of genes involved in inflammation. Finding thera-

oxide synthase (iNOS). Significant preventive and/or curative effects have been observed in experimental animal models of a number of diseases, including arteriosclerosis, cancer, diabetes, respiratory, hepatic, pancreatic, intestinal and gas-

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.

collapse of the system, preventive measures will be increasingly necessary.

The cost of medication is a large and growing part of health expenditure. This is one of many reasons why

berries, quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine, and various curcumenoids found in turmeric (TU) curry.

Curcumin (CU): A Promising Tool

Interest in polyphenols, and especially in CU as a chemoproctive agent, has dramatically increased in recent years. CU, the most explored of the curcumenoids, has received increasing interest in recent years. The majority of studies reported thus far are

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With all the focus on drug development and marketing, it is easy to forget that nutrition represents the world's earliest medicinal therapy. In the

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).

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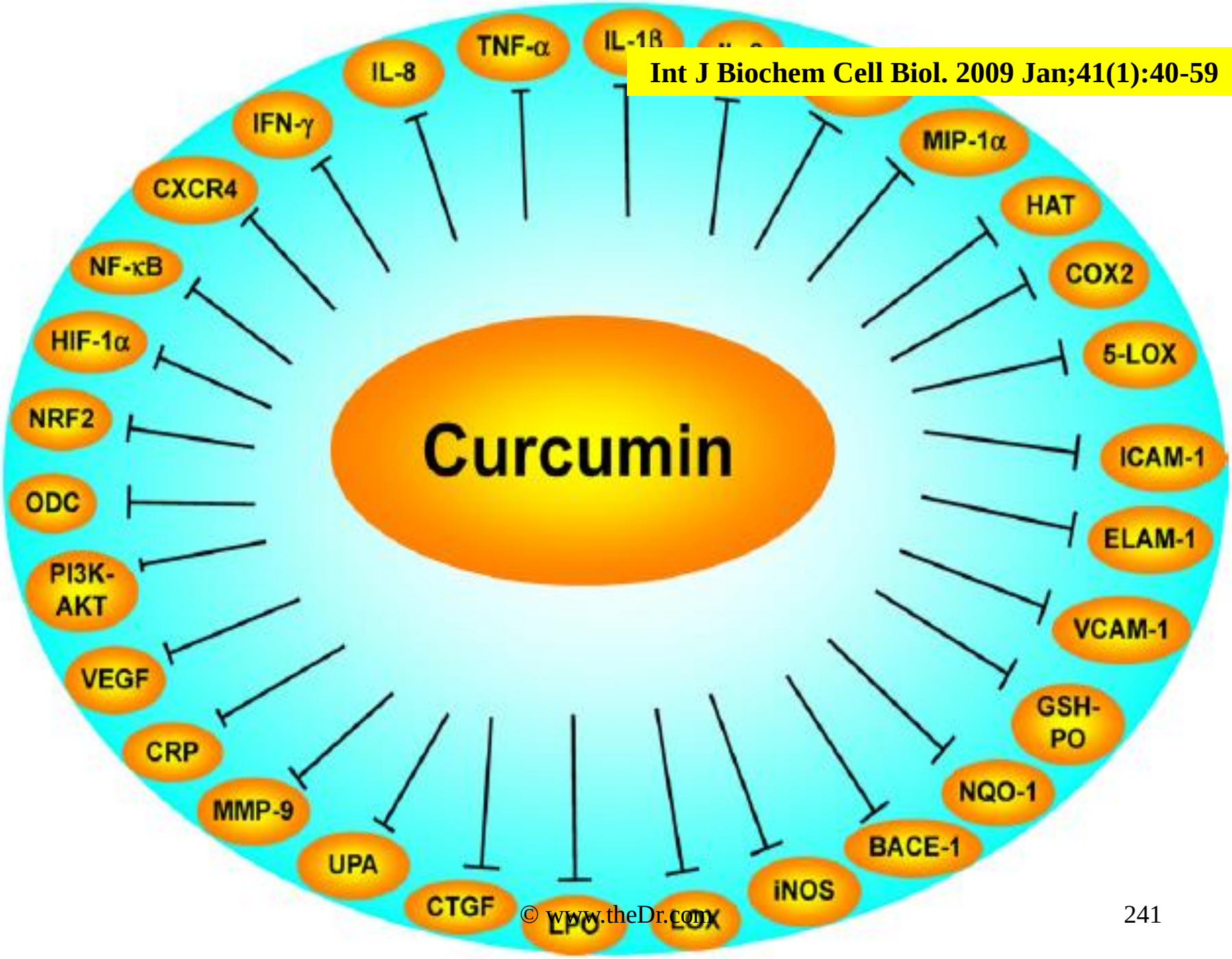


Int J Biochem Cell Biol. 2009 Jan;41(1):40-59

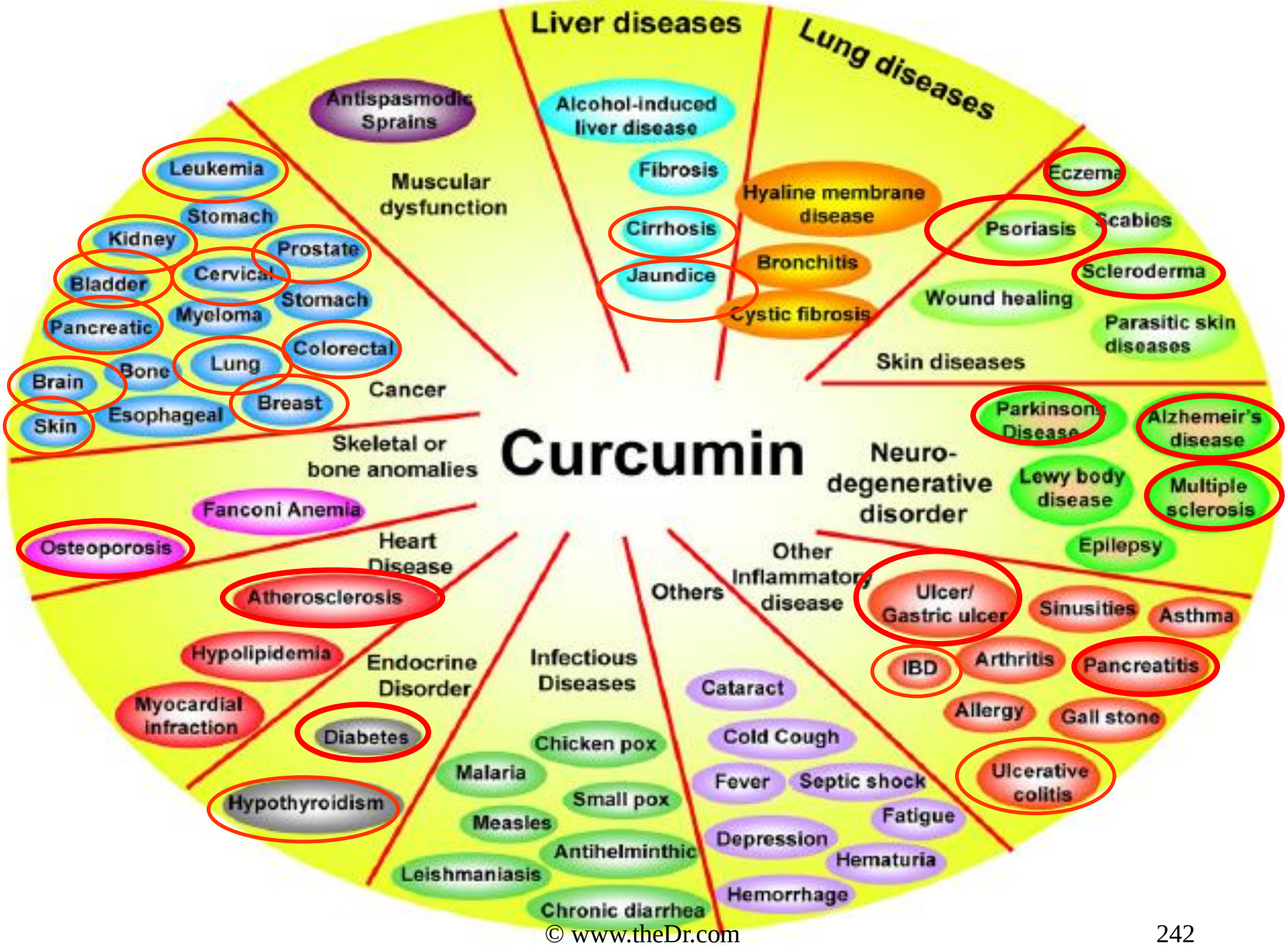
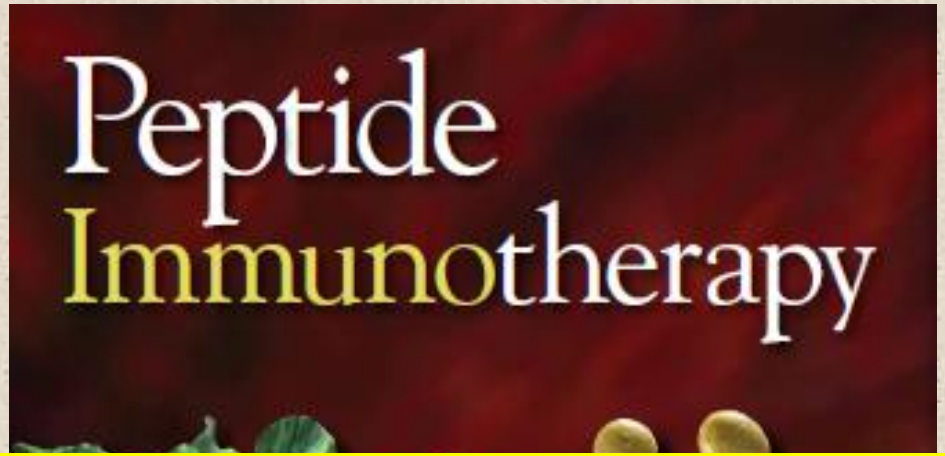


Fig. 2. Effect of curcumin on various proinflammatory diseases.

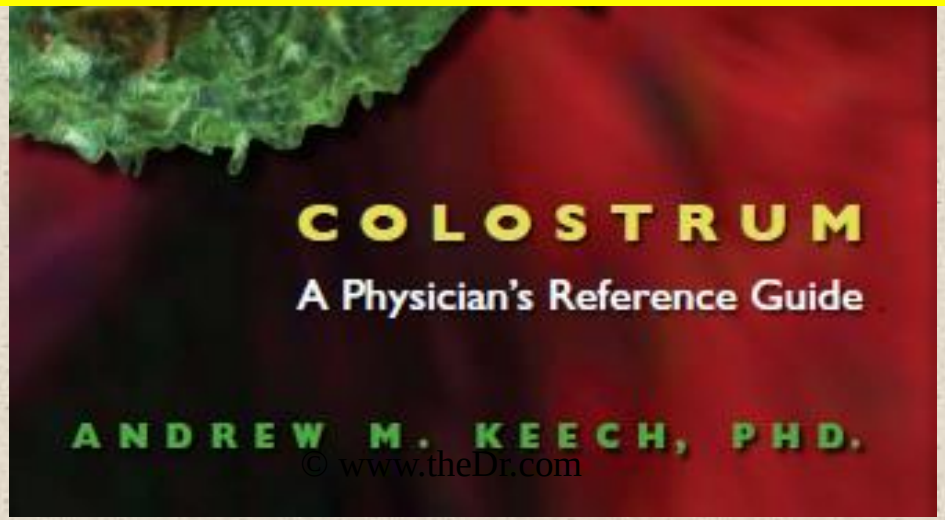
Treatment Protocols
(personal recommendations-Curcumin)

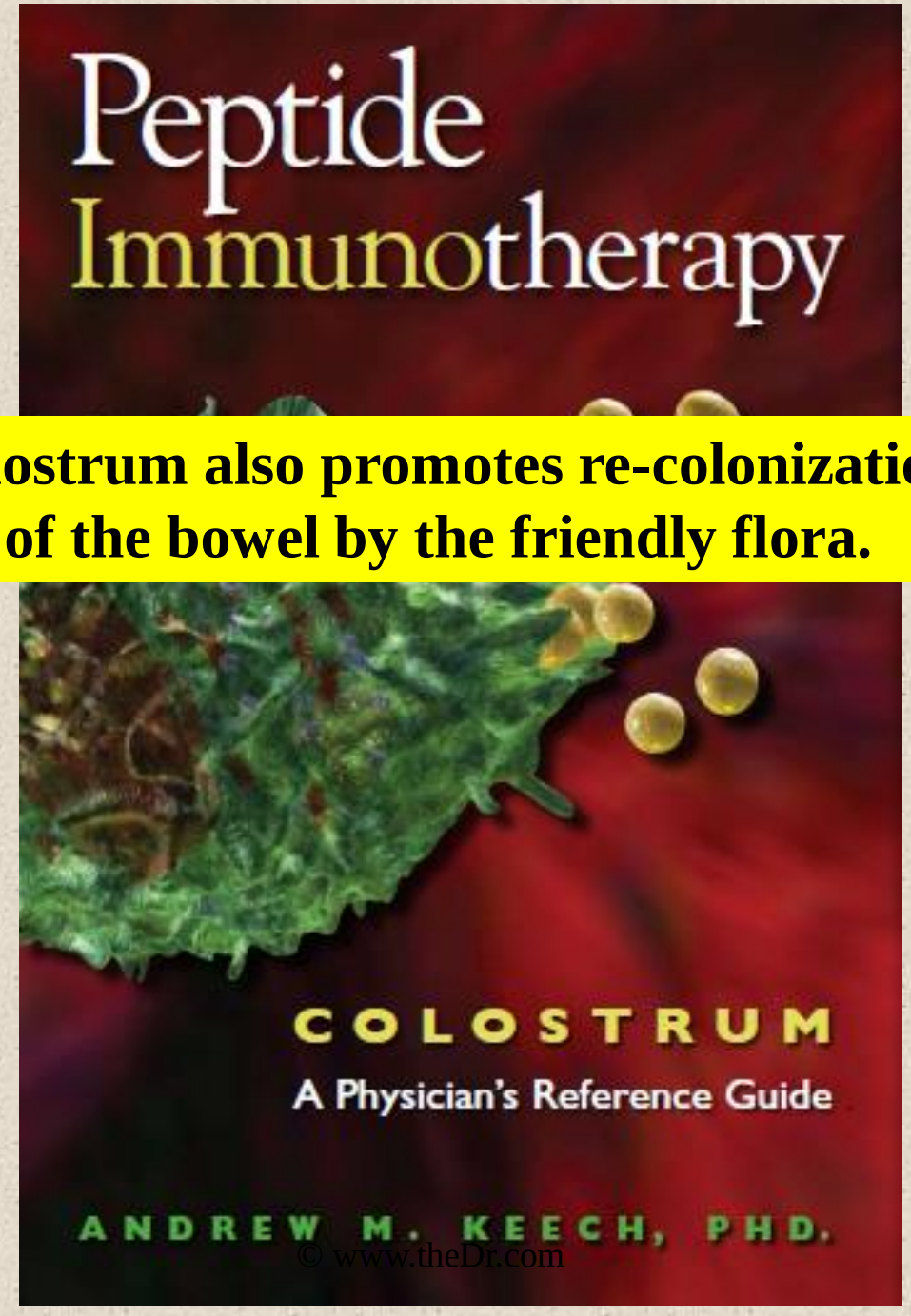
Therapeutic dosages:

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

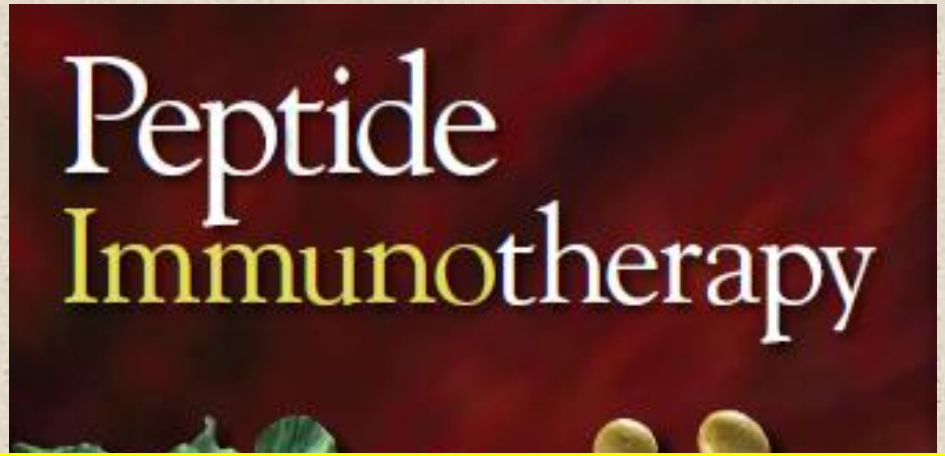


High intestinal permeability is a normal feature of newborn gut ecology. Colostrum functions to reduce inflammation protect against irritation from toxins and check any potential infection, while promote epithelial growth and repair.

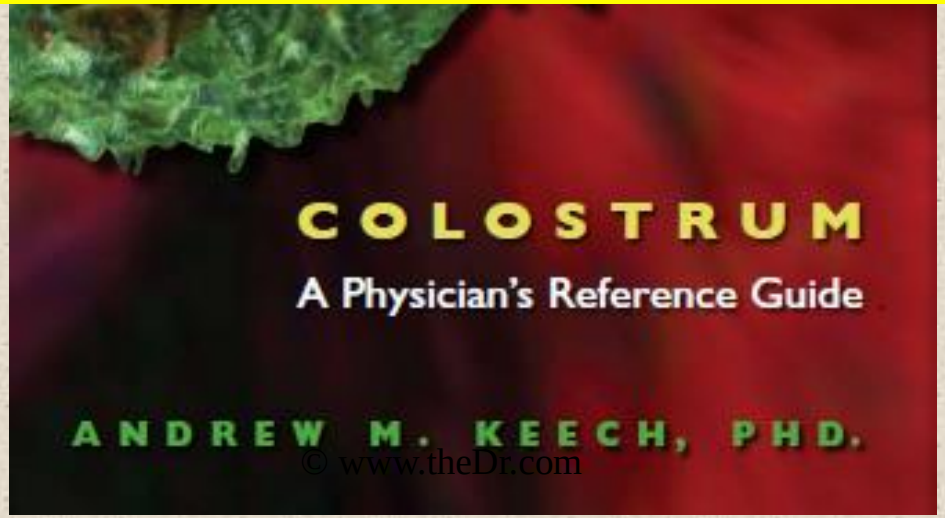


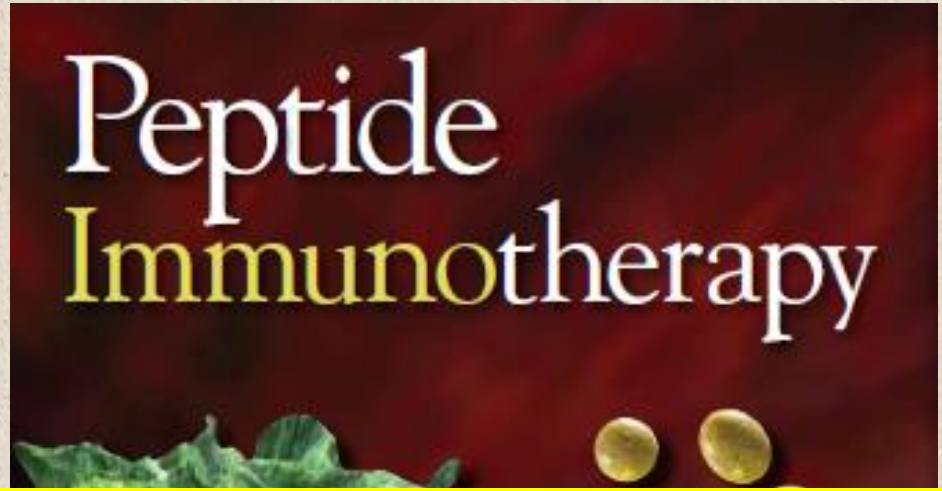


Colostrum also promotes re-colonization of the bowel by the friendly flora.

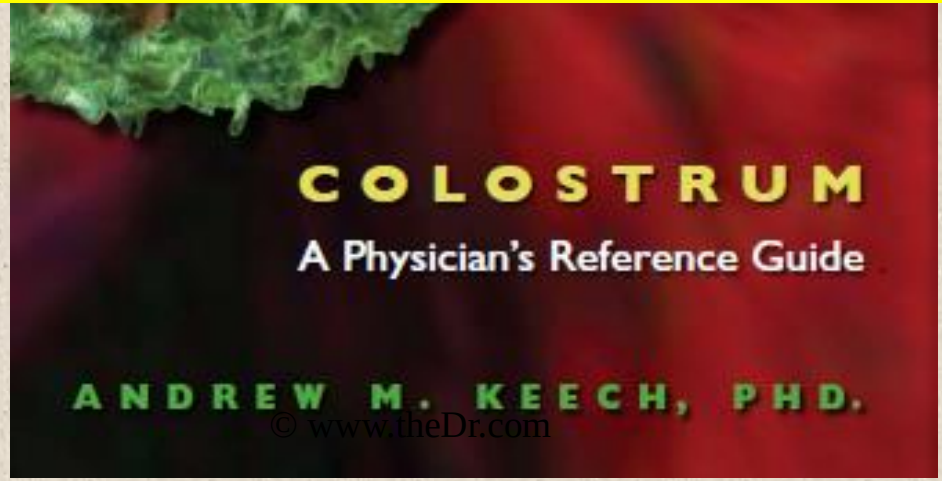


Colostrum is the best remedy known for all-around gut health. Colostrum restores leaky gut to normal permeability levels. It contains growth factors and hormones to help repair damage to the intestinal lining, and restore gut integrity.





Colostrum is unmatched as an immune system stimulant and modulator. There are numerous "one note" products lining the shelves of natural food stores that claim to stimulate the immune system. Only colostrum, however, plays the whole symphony.



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 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.

inflammation (de Jonge and Ullola, 2007). Furthermore, the gut microbiome emerges as a major player not only in the maturation of GIT tissue and the gut brain axis but also in brain maturation, through its effect on both the immune and endocrine systems. Many toxins, toxicants, infectious agents, diet or stress, affect an individual's gut microbiome, which may be especially sensitive during the critical developmental period. Disruption of the developing microbiome may have profound consequences on the developing gut-brain axis including the brain as well as long-term effects on both the physical and psychological development.

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

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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 Ullola, 2007). Furthermore, the gut microbiome emerges as a major player not only in the maturation of GIT tissue and the gut brain axis but also in brain maturation, through its effect on both the immune and endocrine systems. Many toxins, toxicants, infectious agents, diet or stress, affect an individual's gut microbiome, which may be especially sensitive during the critical developmental period. Disruption of the developing microbiome may have profound consequences on the developing gut-brain axis including the brain as well as long-term effects on both the physical and psychological development.

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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

Premise #1

Just How Prevalent is the Development of Autoimmune Disease?

Detective Adrian Monk

Premise #2

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

Detective Adrian Monk

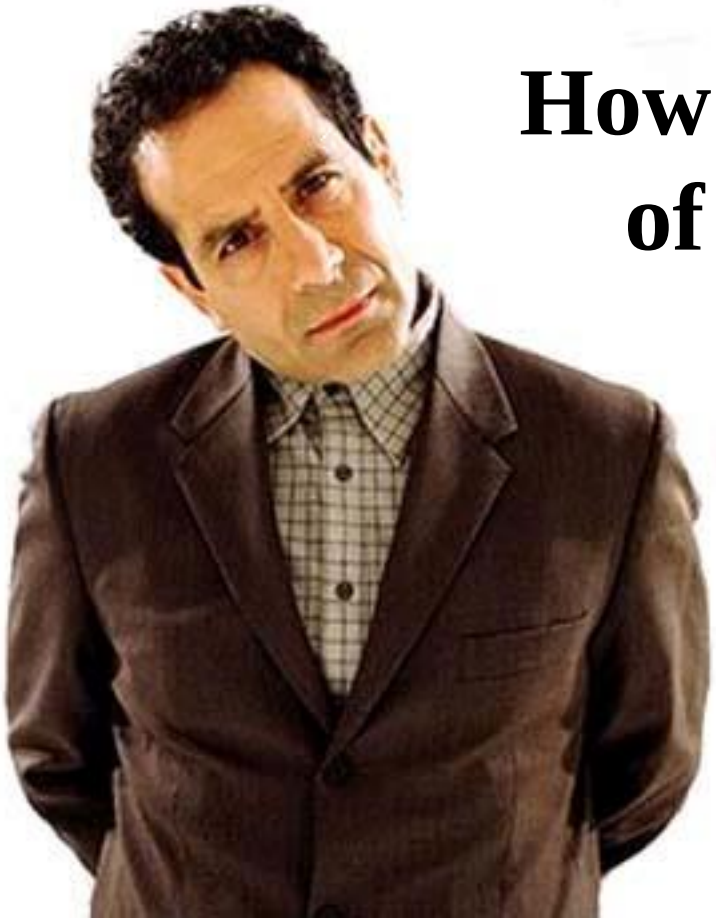
Premise #3
How does Autoimmunity Develop?

Detective Adrian Monk

Premise #4
Can Foods Trigger Pathogenic Intestinal Permeability

Detective Adrian Monk

Premise #5



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

Detective Adrian Monk

Premise #6

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

Detective Adrian Monk

Premise #7

How Does the Inflammatory Cascade Begin That Causes Intestinal Permeability?

Detective Adrian Monk

Premise #8
How do we Arrest Pathogenic Intestinal Permeability

Detective Adrian Monk

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

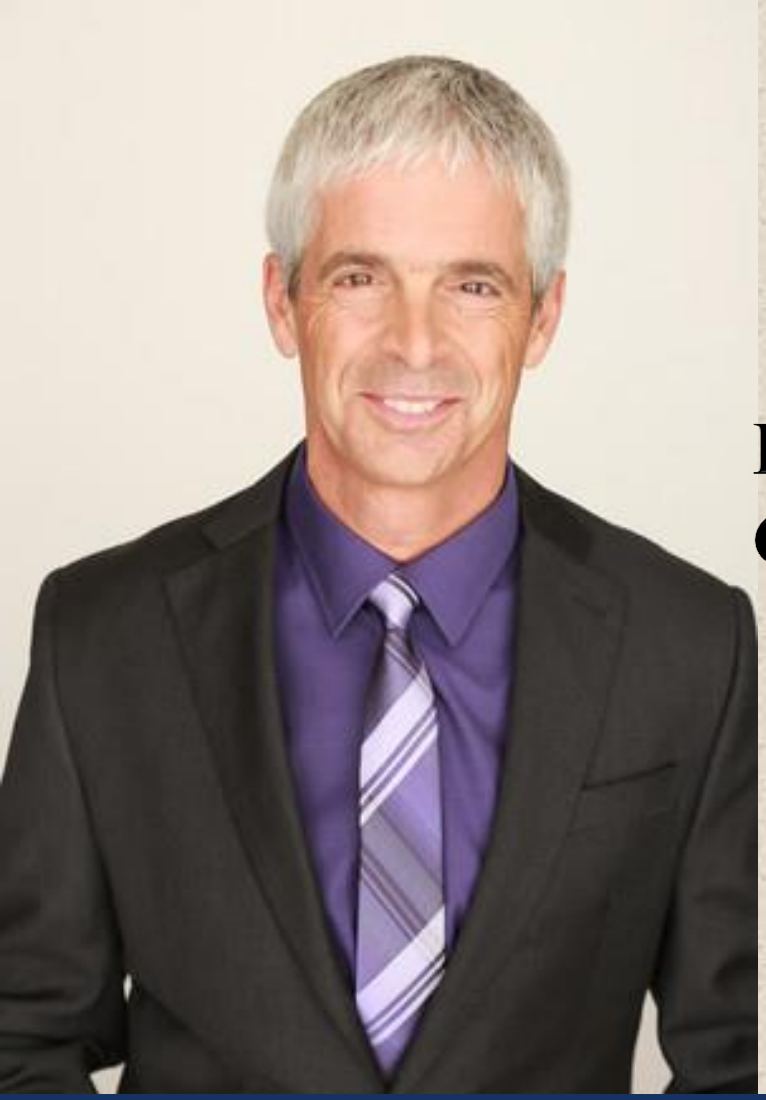
Increased load on liver detoxification pathways (food antigens, toxins, endotoxin)

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



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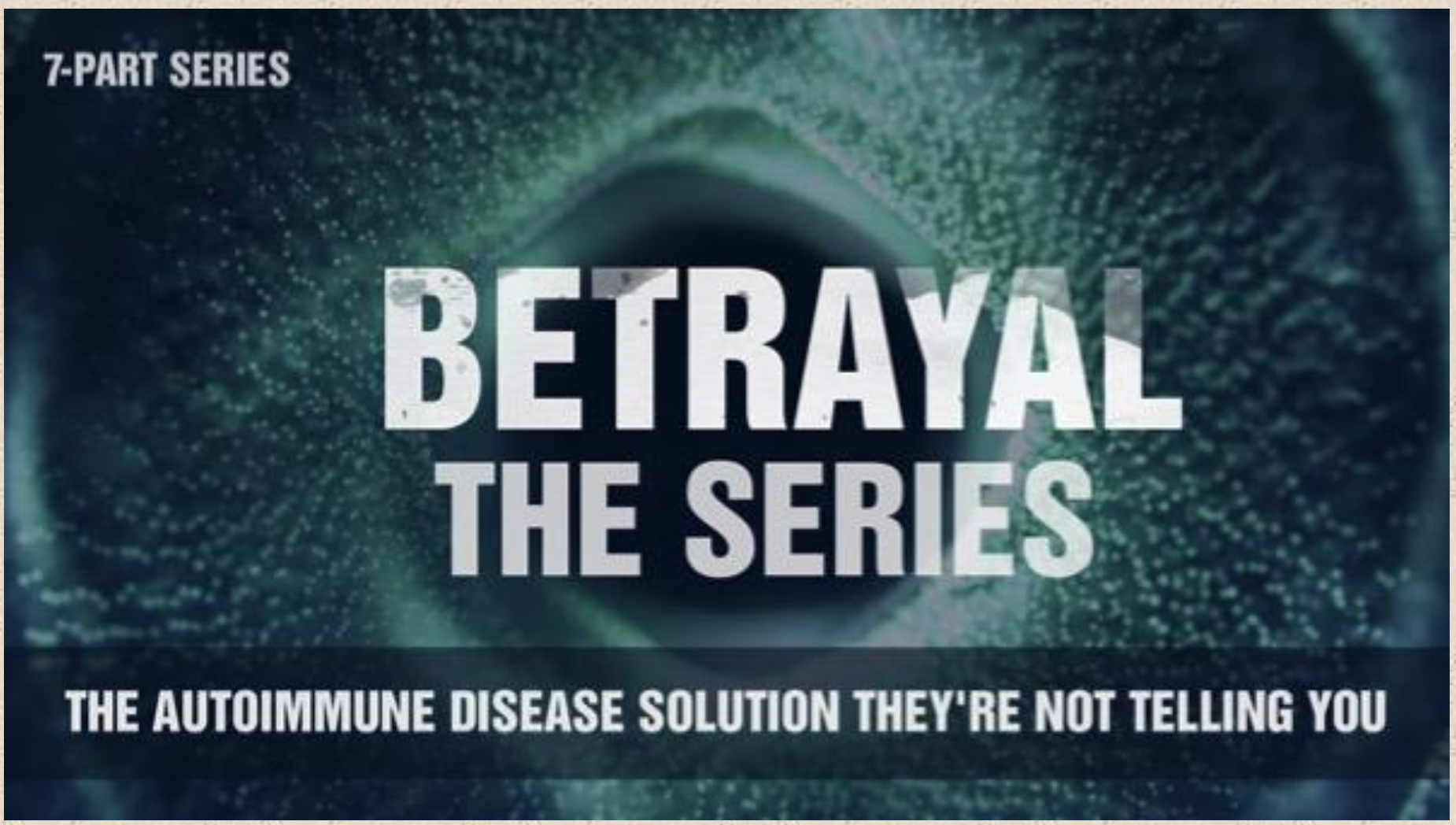
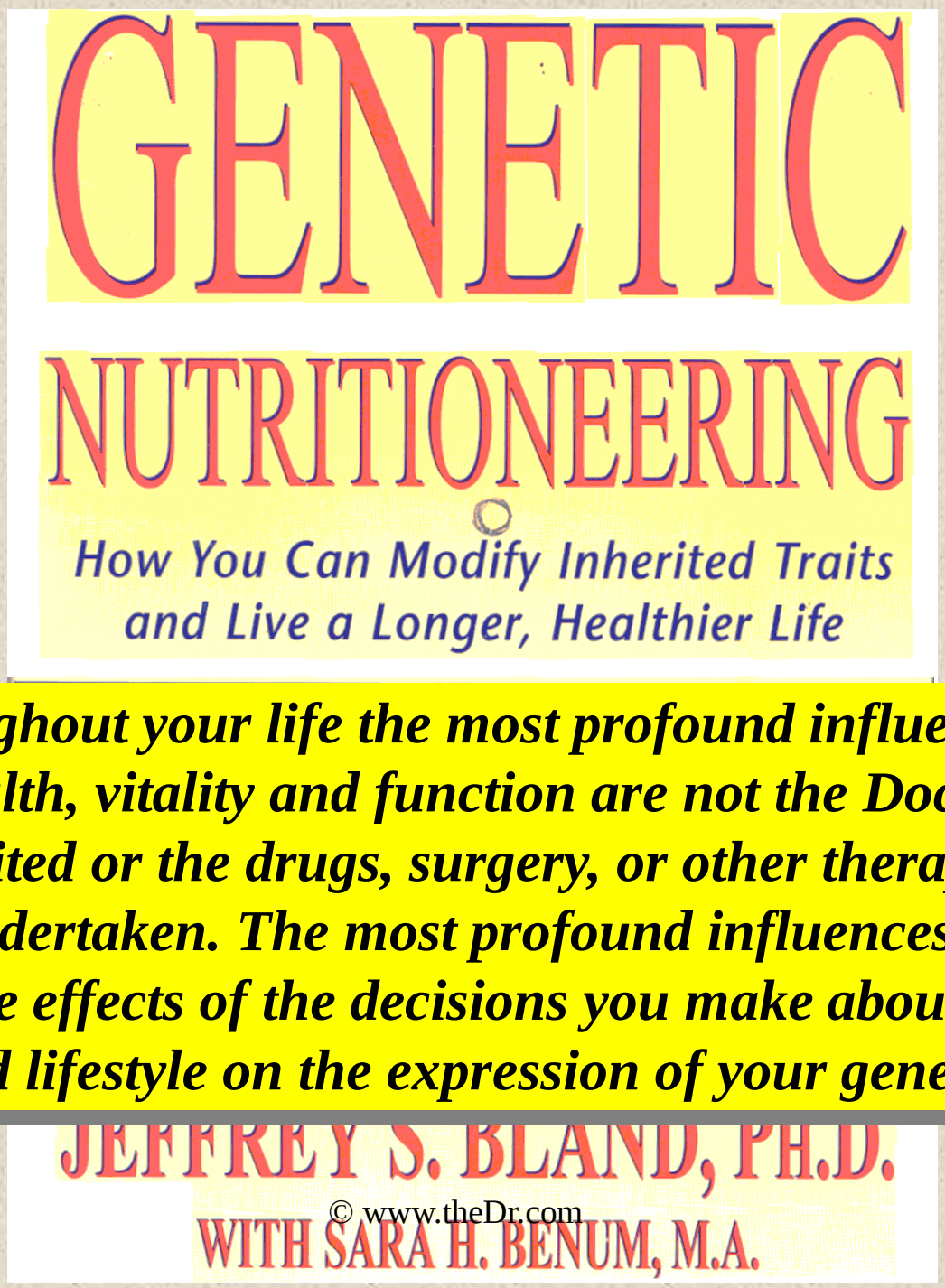

7-PART SERIES
BETRAYAL
THE SERIES
THE AUTOIMMUNE DISEASE SOLUTION THEY'RE NOT TELLING YOU

Take Care of Yourself

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



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


“Thank You for Your Kind Attention”


Wishing you Sunrises of Beauty throughout your life