Dietary Influences on Chronic and Autoimmune Thyroid Disease

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- **Medical Advisory Board National Association of Nutritional Professionals**

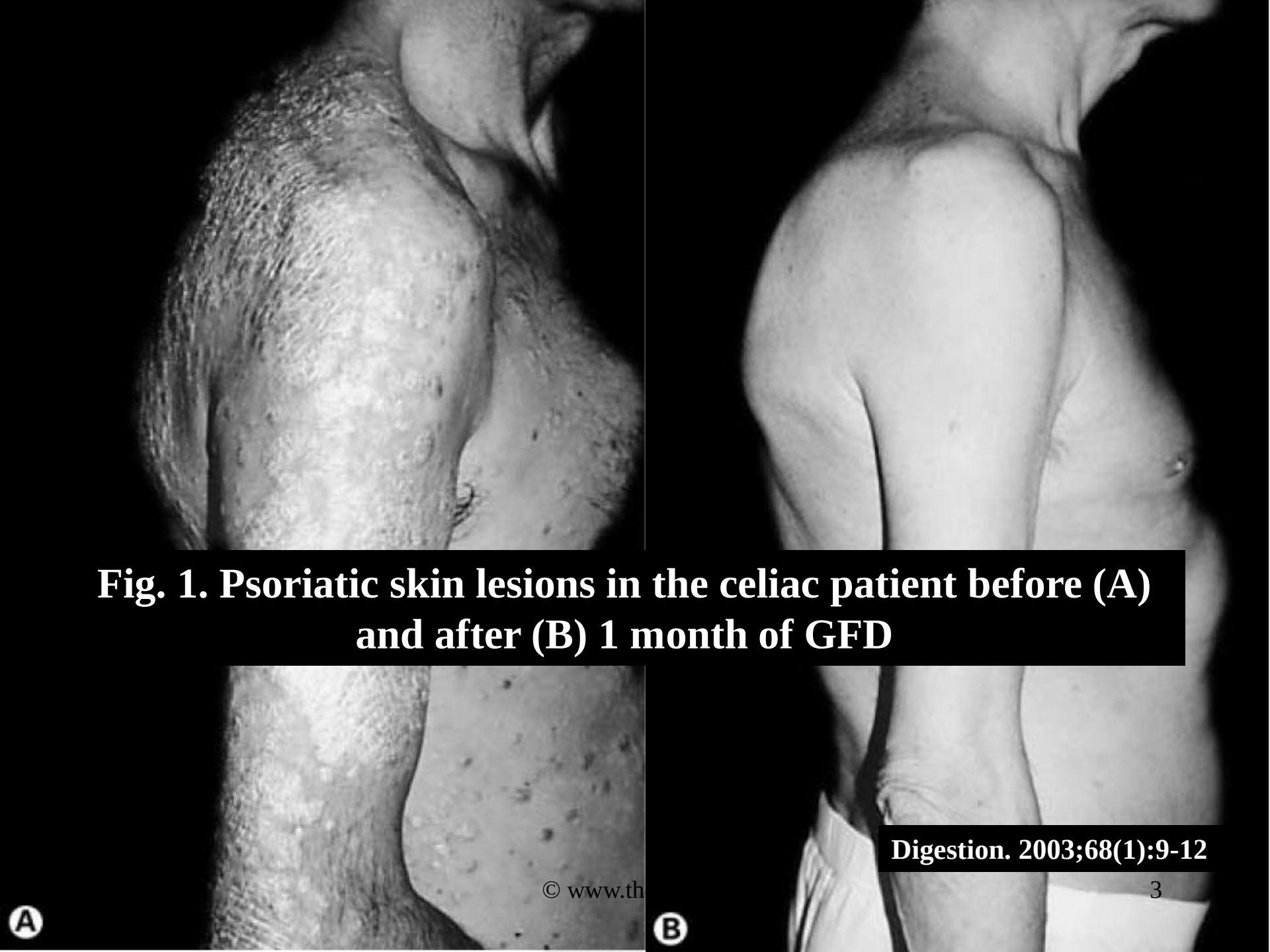


Fig. 1. Psoriatic skin lesions in the celiac patient before (A) and after (B) 1 month of GFD

Digestion. 2003;68(1):9-12

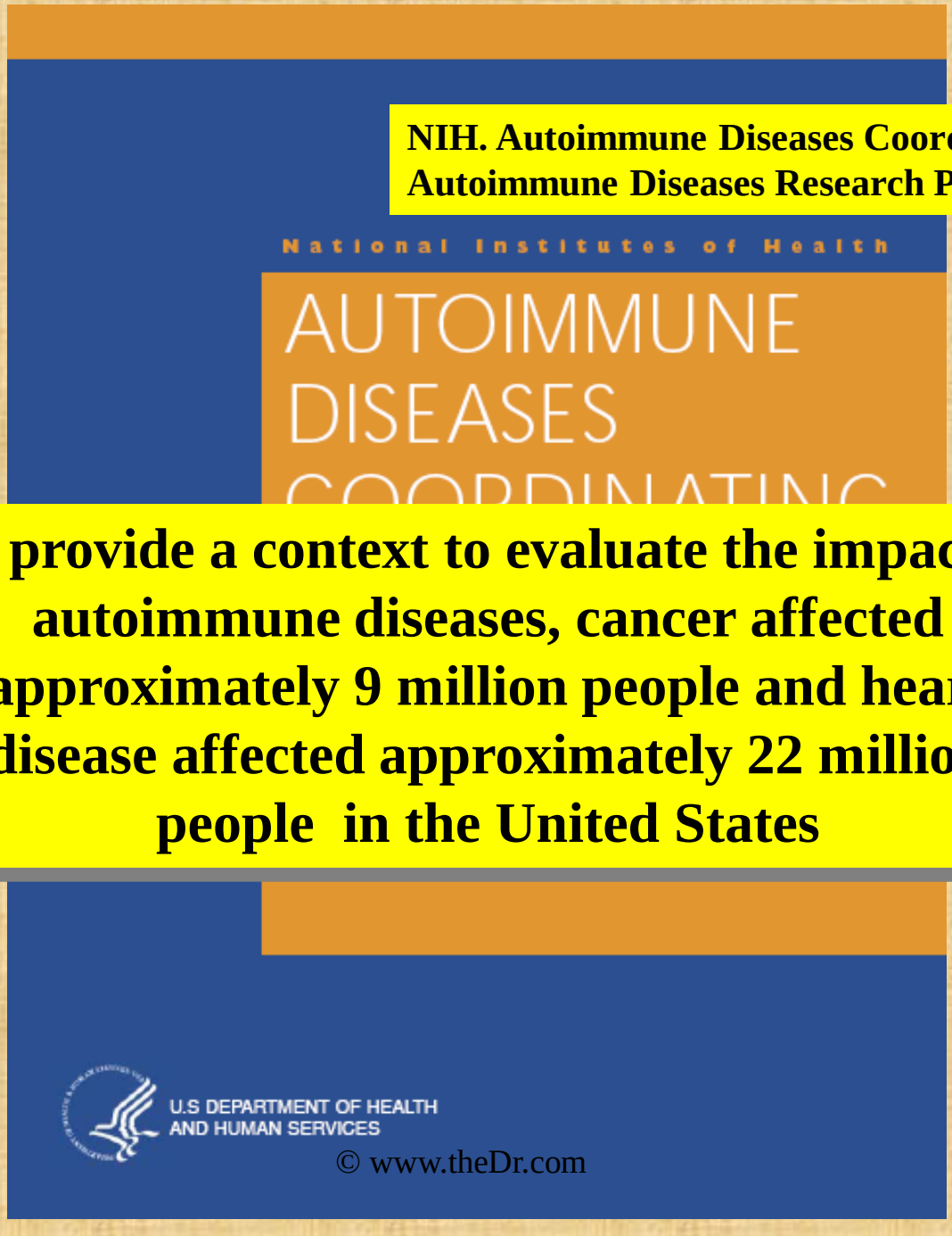

9 Premises To Look At

Premise #1

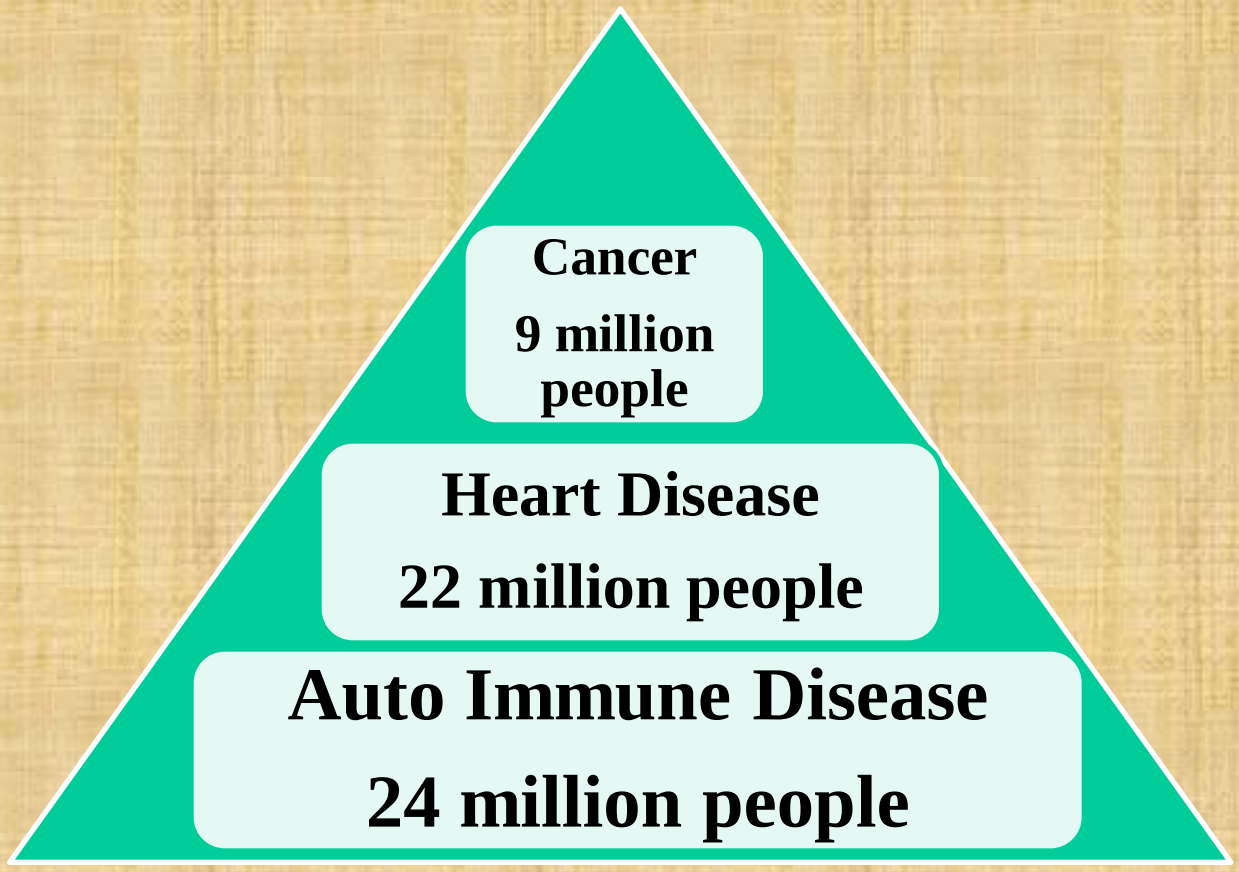
What is the Most Common Cause of Morbidity and Mortality in the Industrialized World?

Detective Adrian Monk

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



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



REVIEW

Vitamin D and autoimmunity: new aetiological and therapeutic considerations

Yoav Arnson, Howard Amital, Yehuda Shoenfeld

Ann Rheum Dis

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

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]

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 ultraviolet B light. Vitamin D 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 ($1,25(OH)_2D$). $1,25(OH)_2D$ 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

expressed in activated macrophages and dendritic cells.[16 17] However, in contrast to the renal cells, in antigen presenting cells the enzyme is non-responsive to suppression by either parathyroid hormone or $1,25(OH)_2D$. 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.[18]

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.[19] 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),[20–22] 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

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Abbreviations: 1, $25(OH)_2D$, 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

AND

Detective Adrian Monk

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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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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.

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

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

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Perhaps if We Open to More Current Information…..

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Nicolas Vuilleumier, Fabrizio Montecucco, Oliver Hartley

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

Oliver Hartley, Department of Immunology and Pathology, Faculty of Medicine, 1211 Geneva, Switzerland
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.

Vuilleumier N, Montecucco F, Hartley O. Autoantibodies to apo-

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 presence of macrophages and activated lymphocytes within ath-

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 interleukins as well as tumor necrosis factor-α and platelet-derived

folds, but also might be the result of other autoimmune and 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.[3] 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

tor–deficient mice into syngeneic mice, the recipients exhibited 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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Correspondence to Yehuda Shoenfeld, MD, FRCP (Hon.), Head, Department of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center, 52621 Tel-Hashomer, Israel. E-mail shoenfel@post.tau.ac.il
(*Circulation.* 2005;112:3337-3347.)

Circulation is available at http://www.circulationaha.org DOI: 10.1161/CIRCULATIONAHA.104.507996

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.

ATHEROSCLEROTIC PLAQUE FORMATION: THE ROLE OF LIPIDS AND INFLAMMATION

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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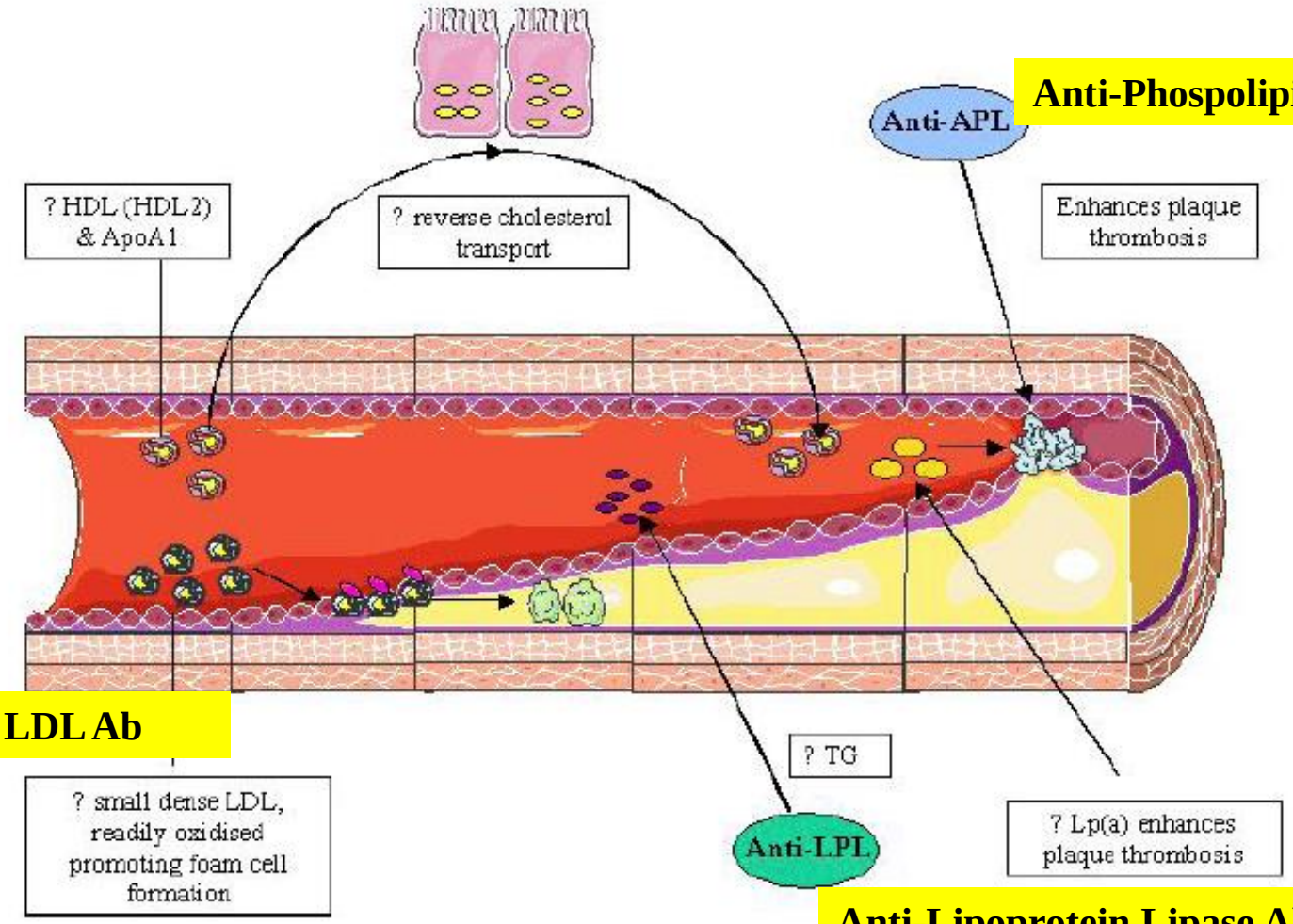

Fig. (5). Common changes in the lipid profile amongst the autoimmune rheumatic disease and their impact on atherosclerotic plaque formation. LDL: Low density lipoproteins, TG: Triglycerides, Lp(a): Lipoprotein (a), Anti-LPL: anti-Lipoprotein Lipase, HDL: high density lipoproteins, ApoA1: Apolipoprotein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

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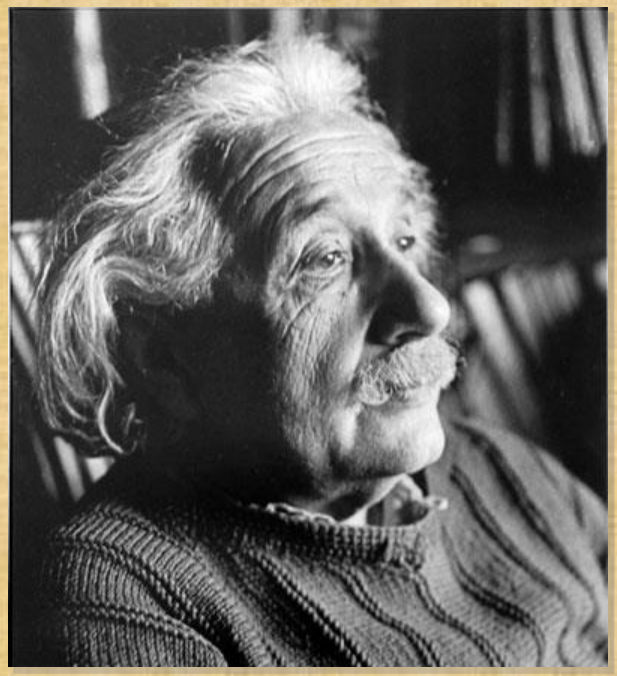
1874-1932/11 2011 Bentham Open

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-

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



Silently
Point to 2 People
Close By

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

Detective Adrian Monk

National Institutes of Health

THE AUTOIMMUNE DISEASES COORDINATING COMMITTEE

Prevention of Autoimmune Diseases:

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

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

National Institute of Allergy and Infectious Diseases

March 2005

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

Dyslipidaemia in Rheumatological Autoimmune Diseases

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

THERAPEUTIC TARGET

tions, 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

dyslipidaemia, and the potential impact this has on cardiovascular risk, in particular atherosclerotic plaque formation.

ATHEROSCLEROTIC PLAQUE FORMATION: THE ROLE OF LIPIDS AND INFLAMMATION

Coronary artery disease develops due to the formation and rupture of atherosclerotic plaques. The term atherosclerosis covers a spectrum of disease ranging from endothelial

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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

factorial 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-

Intersection Of The Origin Of Autoimmune Disease

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

Premise #2

Genes Control Function

Detective Adrian Monk

Reproductive Toxicology 23 (2007) 297–307

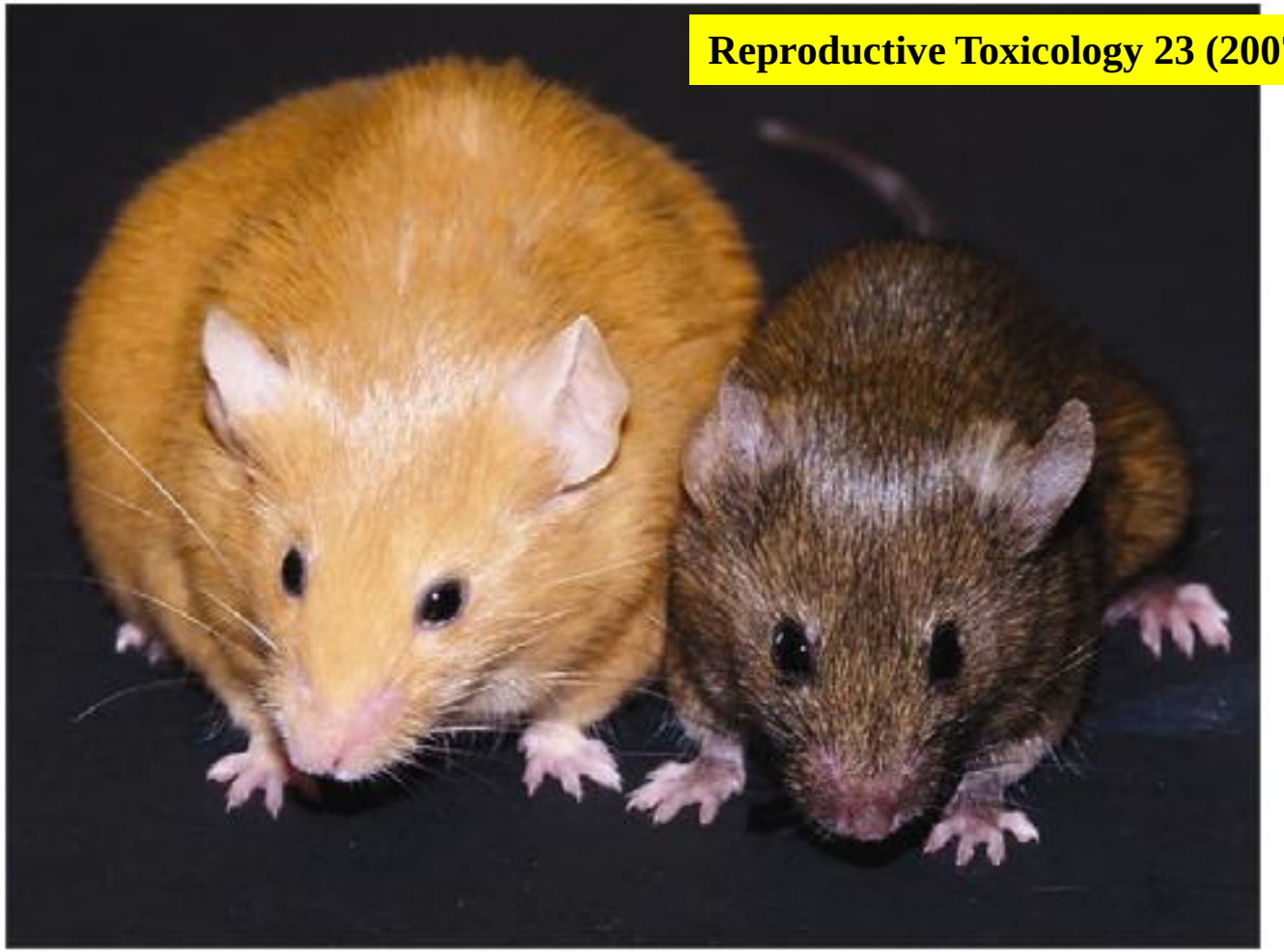


Fig. 1. One-year-old female genetically identical viable yellow agouti mice (A^{vy}). Maternal dietary supplementation with methyl donors such as folic acid, choline, and betaine [34] or the phytoestrogen, genistein [32], shifts the coat color of the offspring from yellow to brown, and reduces the incidence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

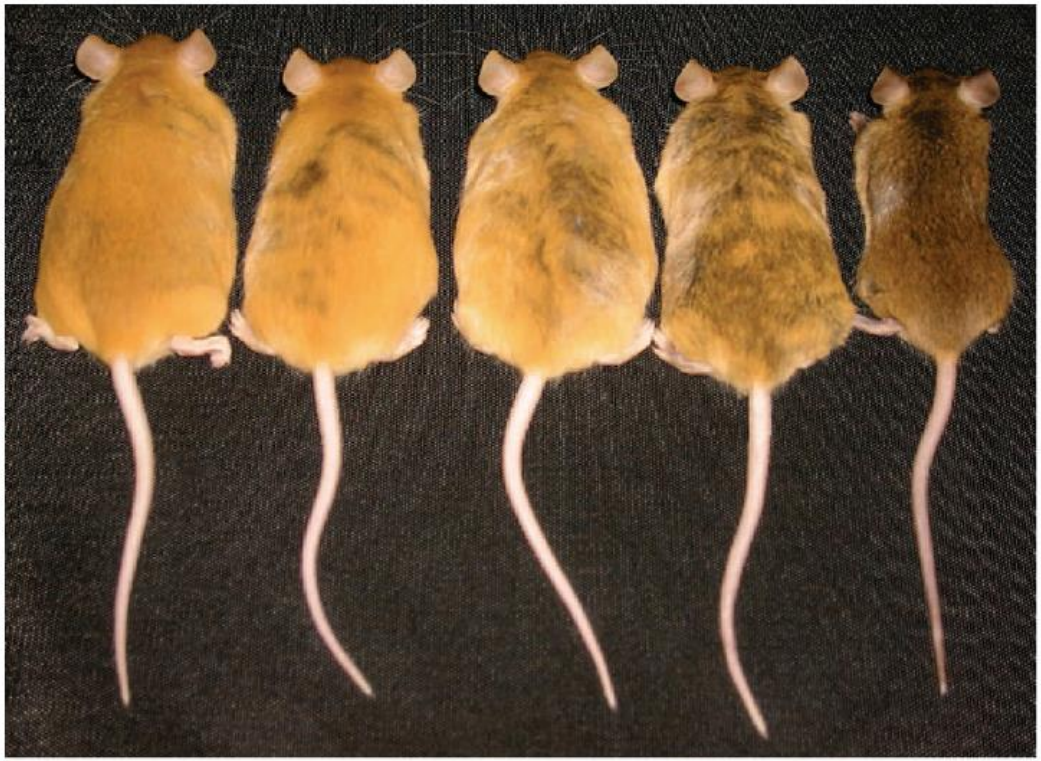


Figure 1. Genetically identical 3-mo-old A^{vy} mice representing the five coat color phenotypes. Yellow mice are hypomethylated at the transposable element upstream of the *Agouti* gene allowing maximal ectopic expression, whereas hypermethylation of this site silences ectopic Agouti expression in the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

Pediatr Res. 2007;61:30R–37R.

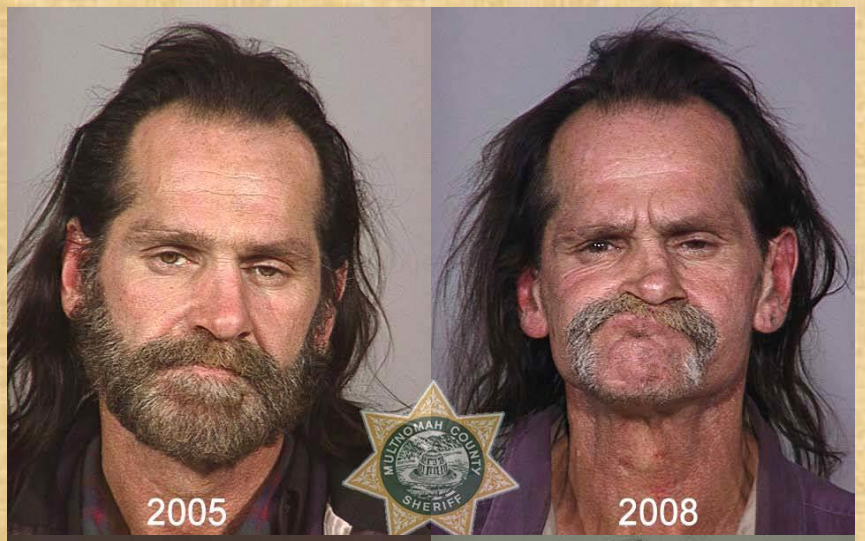
Algae are high in the beta-carotene Astaxanthine
Shrimp eat the Algae
Flamingos eat the Shrimp

The Epigenetics Revolution

Which Genes Do YOU Want To Turn On?

Which Genes Do YOU Want To Turn On?

What Epigenetics Really Means



How are you Feeding Your Genes

8 months later

POTENTIAL TRIGGER #1

Article

Am J P sychiatry 2012 ;169:625–632

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

Håkan Karlsson, Ph.D.

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Objective: The authors analyzed archival dried blood spots obtained from newborns to assess whether levels of immunoglobulin G (IgG) directed at dietary antigens were associated with a later diagnosis of a nonaffective psychotic disorder.

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Results: Levels of anti-gliadin IgG (but not anti-casein IgG) above the 90th percentile of levels observed among comparison subjects were associated with nonaffective psychosis (odds ratio=1.7, 95% CI=1.1–2.8). This association was not

in order to develop preventive strategies.

(Am J Psychiatry 2012; 169:625–632)

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

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A number of studies have also indicated immune activation or dysregulation in patients at the time of the first manifestations of schizophrenia and other nonaffective psychoses. Such studies include reports of altered levels of chemokines and cytokines (6, 7) and of antibodies directed at immune targets derived from infectious agents (8, 9), dietary proteins (10, 11), and self-antigens (12).

Recent studies have illustrated the usefulness of archival dried blood samples collected prospectively during neonatal screening for metabolic disorders (e.g., phenylketonuria) as a source of information on early life exposures that may be associated with diseases that have an adult onset. Such studies have reported an association between high levels of immunoglobulin G (IgG) directed at the protozoan *Toxoplasma gondii* (13) and at herpes simplex virus type 2 (14) and the future development of schizophrenia. IgG is actively transported across the placenta during the later stages of pregnancy to provide passive immunization of the fetus (15), and hence such antibodies reflect maternal exposures and immune responses to specific antigens. Using dried blood spots obtained from newborns, we investigated whether levels of IgG directed at food-derived

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

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A significantly elevated risk for nonaffective psychoses was associated with high levels (90th percentile) of IgG anti-gliadin antibodies (odds ratio=1.7), but not anti-casein antibodies (odds ratio=0.8).

A number of adverse exposures in utero or in the neonatal period have been associated with the later development of schizophrenia and other nonaffective psychoses. These include exposures to maternal malnutrition or infections and complications of pregnancy and birth (1). The mechanisms underlying these associations are unknown, and a variety of hypotheses have been tested experimentally. For example, animal studies suggest that activation of maternal immune responses during fetal development can cause behavioral deficits involving both cognitive and emotional domains in adult offspring (2). Indeed, reports of an elevated risk for schizophrenia among offspring of women with high blood levels of interleukin-8 (3) or tumor necrosis factor-α (4) during pregnancy support this notion. A register-based study by Eaton et al. (5) indicated that chronic inflammatory or autoimmune conditions, such as celiac disease, are more common among parents of patients with schizophrenia than among comparison parents.

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The risk for future nonaffective psychosis increased further with levels of anti-gliadin antibodies at the 95th percentile (odds ratio=2.5)

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

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ated with an elevated risk for the development of a nonaffective psychosis in offspring. Research is needed to identify the mechanisms underlying this association in order to develop preventive strategies.

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

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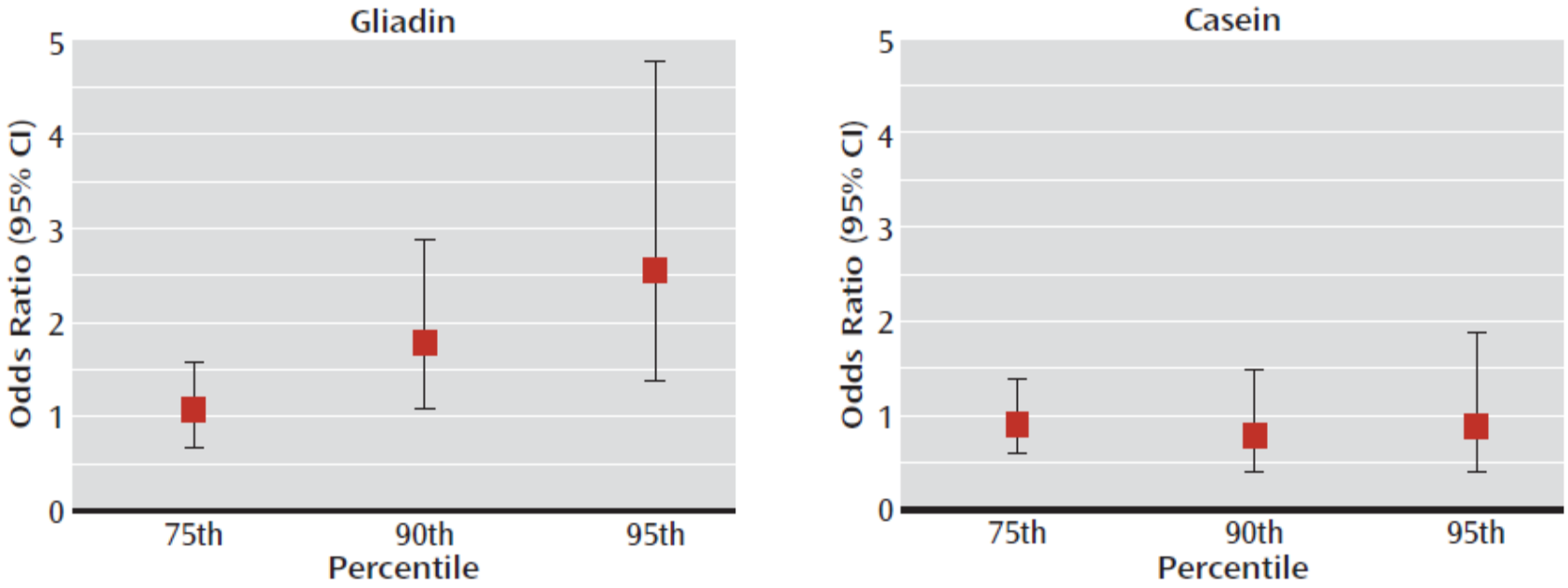
FIGURE 1. Levels of IgG Directed at Gliadin and Casein and Odds of Developing Nonaffective Psychosis



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(Am J Psychiatry 2012; 169:625–632)

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

A number of adverse exposures in utero or in the neonatal period have been associated with the later development of schizophrenia and other nonaffective psychoses. These include exposures to maternal malnutrition or infections and complications of pregnancy and birth (1). The mechanisms underlying these associations are unknown, and a variety of hypotheses have been tested experimentally. For example, animal studies suggest that activation of maternal immune responses during fetal development can cause behavioral deficits involving both cognitive and emotional domains in adult offspring (2). Indeed, reports of an elevated risk for schizophrenia among offspring of women with high blood levels of interleukin-8 (3) or tumor necrosis factor-α (4) during pregnancy support this notion. A register-based study by Eaton et al. (5) indicated that chronic inflammatory or autoimmune conditions, such as celiac disease, are more common among parents of patients with schizophrenia than among comparison parents.

A number of studies have also indicated immune activation or dysregulation in patients at the time of the first manifestations of schizophrenia and other nonaffective psychoses. Such studies include reports of altered levels of chemokines and cytokines (6, 7) and of antibodies directed at immune targets derived from infectious agents (8, 9), dietary proteins (10, 11), and self-antigens (12).

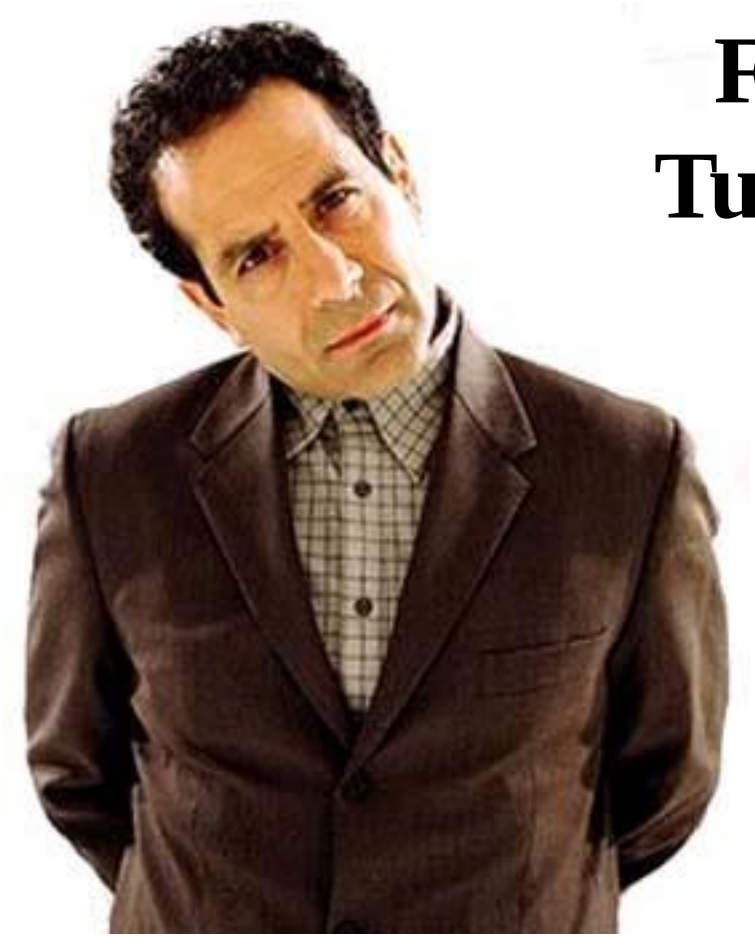
Recent studies have illustrated the usefulness of archival dried blood samples collected prospectively during neonatal screening for metabolic disorders (e.g., phenylketonuria) as a source of information on early life exposures that may be associated with diseases that have an adult onset. Such studies have reported an association between high levels of immunoglobulin G (IgG) directed at the protozoan *Toxoplasma gondii* (13) and at herpes simplex virus type 2 (14) and the future development of schizophrenia. IgG is actively transported across the placenta during the later stages of pregnancy to provide passive immunization of the fetus (15), and hence such antibodies reflect maternal exposures and immune responses to specific antigens. Using dried blood spots obtained from newborns, we investigated whether levels of IgG directed at food-derived

This article is discussed in an Editorial by Dr. Wisner (p. 554) and is the subject of a CME course (p. 671)

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

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

Premise #3



Food Turns On and Turns OFF Our Genes

Detective Adrian Monk

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

See corresponding editorial on page 1169.

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

Petteri Kallio, Marjukka Kolehmainen, David E Laaksonen, Jani Kekäläinen, Titta Salopuro, Katariina Sivenius, Leena Pulkkinen, Hannu M Mykkänen, Leo Niskanen, Matti Uusitupa, and Kaisa S Poutanen

ABSTRACT

Background: Diets rich in whole-grain cereals and foods with a low glycemic index may protect against type 2 diabetes, but the underlying molecular mechanisms are unknown.

Objective: The main objective was to test whether 2 different car-

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or oat, wheat, and potato differentially modulates the gene expression profile in abdominal subcutaneous adipose tissue, even in the absence of weight loss. *Am J Clin Nutr* 2007;85:1417–27.

KEY WORDS Gene-nutrient interactions, metabolic syndrome, insulin resistance, microarray, adipose tissue, diet intervention, insulinemic response, rye, oat, wheat

INTRODUCTION

The pathogenesis of the metabolic syndrome is not well understood, but lifestyle, including diet, and genetic factors clearly interact in its development and progression. These interactions are likely to be reflected in gene expression. The metabolic syndrome, characterized by central obesity, abnormal insulin and glucose metabolism, dyslipidemia, and hypertension, predisposes to cardiovascular diseases and especially type 2 diabetes (T2DM) (1–3).

Abdominal obesity and insulin resistance are the core features of the metabolic syndrome; associated abnormalities include inflammation, endothelial function, sex hormone metabolism, and cortisol metabolism (4–6). Impaired first-phase insulin secretion is also an inherent feature in those who have impaired

…

content of the diet.

Abdominal subcutaneous adipose tissue (SAT) produces a variety of secretory factors that have an important role in inflammation and insulin resistance via endocrine, paracrine, or autocrine signals (18, 19). Impaired insulin signaling occurs in

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

[1] From the Department of Clinical Nutrition, Food and Health Research Centre (PK, MK, and KSP), Department of Medicine (DEL and LN), Department of Computer Science (JK), and Department of Clinical Nutrition (TS, KS, LP, HMM, and MU), University of Kuopio, Kuopio, Finland, and VTT, Espoo, Finland (KSP).

[2] PK and MK contributed equally to this work.

[3] Supported by Fazer Bakeries Ltd, Vaasan & Vaasan Oy, the Technology Development Center of Finland, the Academy of Finland (no. 209445), the Sigrid Juselius Foundation, and the ABS graduate school.

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

pasta-based carbohydrate modification can enhance early insulin secretion in persons with the metabolic syndrome (17), although no changes in glucose tolerance or insulin resistance were observed. This effect was found to be independent of the fiber content of the diet.

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Conclusions: Dietary carbohydrate modification with rye and pasta or oat, wheat, and potato differentially modulates the gene expression profile in abdominal subcutaneous adipose tissue, even in the absence of weight loss. *Am J Clin Nutr* 2007;85:1417–27.

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early insulin secretion over the long term (15). In line with this hypothesis, we found that high-fiber rye bread increased the acute insulin response, but insulin sensitivity remained unchanged (16). Furthermore, we recently showed that rye and pasta-based carbohydrate modification can enhance early insulin secretion in persons with the metabolic syndrome (17), although no changes in glucose tolerance or insulin resistance were observed. This effect was found to be independent of the fiber content of the diet.

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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 interaction between the gastrointestinal cells and the commensal bacteria fosters immunological tolerance, whereas the interaction with pathogens triggers inflammatory responses.

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 spe-

nize the newborn's gastrointestinal tract, forming the intestinal microbiome, a complex ecosystem with a number of cells that are greater than all the somatic cells of the human by an order of magnitude and harboring 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.[7-9] The combination of emerging microbial genomic technologies with metabolic and immunologic analyses is revealing important diseases (such as inflammatory bowel disease and necrotizing enterocolitis) and autoimmune diseases (such as type 1 diabetes, allergies, and asthma).

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

Nature. 2014 Sep 17

Nature. 2014 Sep 17. doi: 10.1038/nature13793. [Epub ahead of print]

Artificial sweeteners induce glucose intolerance by altering the gut microbiota.

Suez J[1], Korem T[2], Zeevi D[2], Zilberman-Schapira G[3], Thaiss CA[1], Maza O[1], Israeli D[4], Zmora N[5], Gilad S[6], Weinberger A[7], Kuperman Y[8], Harmelin A[8], Kolodkin-Gal I[9], Shapiro H[1], Halpern Z[10], Segal E[7], Elinav E[1].

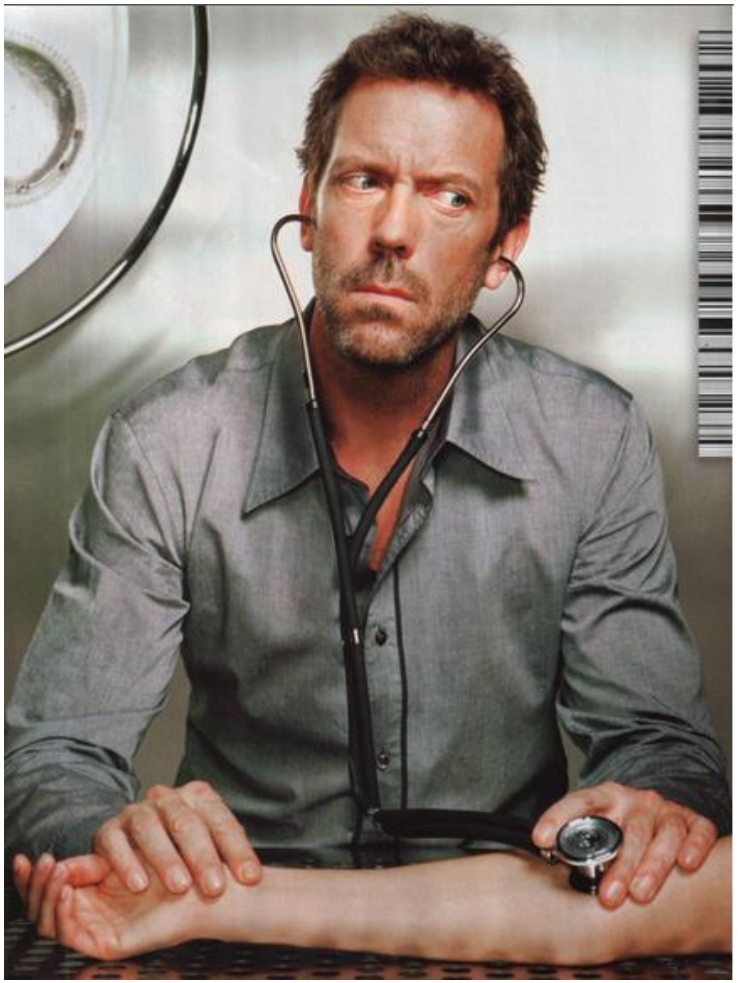
Author information

Abstract

Altered Function in 115 microbial metabolic pathways with saccharin exposure inducing glucose intolerance

transferrable to germ-free mice upon faecal transplantation of microbiota configurations from NAS-consuming mice, or of microbiota anaerobically incubated in the presence of NAS. We identify NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.

PMID: 25231862 [PubMed - as supplied by publisher]



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

Premise #4

Where Does the Persisting Inflammation Come From?

The American Journal of Pathology, Vol. 169, No. 6, December 2006

DOI: 10.2353/ajpath.2006.060681

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 Patbol 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.

Address reprint requests to Jerrold R. Turner, Department of Pathology, The University of Chicago, 5841 South Maryland Ave., MC 1089, Chicago, IL 60637. E-mail: jturner@bsd.uchicago.edu.

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From Basic Mechanisms to Clinical Application

Examples include the skin, which maintains a barrier that supports overall homeostasis and prevents systemic infection, and the renal tubule, which forms a barrier that maintains gradients between the renal interstitium and the sterile tubular lumen to allow active and passive transport to regulate urine composition

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)***

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Gastroenterol Clin N Am 37 (2008) 411–428
GASTROENTEROLOGY CLINICS OF NORTH AMERICA

Celiac Disease and Autoimmunity in the Gut and Elsewhere

Susan H. Barton, MD, Joseph A. Murray, MD*
Division of Gastroenterology and Hepatology
Rochester, MN 55905, USA

Gastroenterol Clin N Am 37 (2008) 411–428

Celiac disease is a common immune-mediated enteropathy with a prevalence of approximately 1% within the US and European populations. There is a worldwide disease distribution including Mexico, South America, the Middle East, parts of India, and specific regions of Africa.

Proposed mechanisms of association (in AID development) include abnormal regulation of intestinal permeability and increased autoantibody production in the setting of chronic gut inflammation.

for serologic screening may decrease the time to diagnosis and lessen the complications of untreated disease.

Several studies have demonstrated the cost-effectiveness of screening the population with irritable bowel syndrome for celiac disease. The results from one recent study addressed the possibility of immunologically based mechanisms following gluten exposure contributing to irritable bowel syndrome symptoms that may represent a celiac-like disorder. This study showed decreases in stool frequency and improvement in the gastrointestinal symptoms score among 60% of patients with diarrhea-predominant irritable bowel

Work for this article was supported by NIH training grant T32 DK07198 (SHB) and NIH grants DK57892 and 071003 (JAM). Dr. Murray has been a consultant to Astra Zeneca, Alvine, and Novartis and an investigator for Alba Therapeutics and Dynagen.

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0889-8553/08/$ – see front matter
doi:10.1016/j.gtc.2008.02.001

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The Gluten Summit
A Grain of Truth

Alessio Fasano, MD

Currently Chairs Harvard's Mass General Hospital for Children where he heads the Department of Pediatric Gastroenterology

Why Creating the Healthiest Intestinal Environment Possible Can Arrest Your Vulnerability to the #3 Cause of Getting Sick and Dying

- **Understanding autoimmunity and gluten sensitivity**
- **The evolution of wheat and gluten**
- **Epigenetics and the development of disease**
- **The three mechanisms that contribute to autoimmunity**
- **What triggers celiac disease?**
- **Why no human can digest gluten**

Alessio Fasano, MD

Dr. Fasano, Could you tell us, what is the importance of pathogenic intestinal permeability?

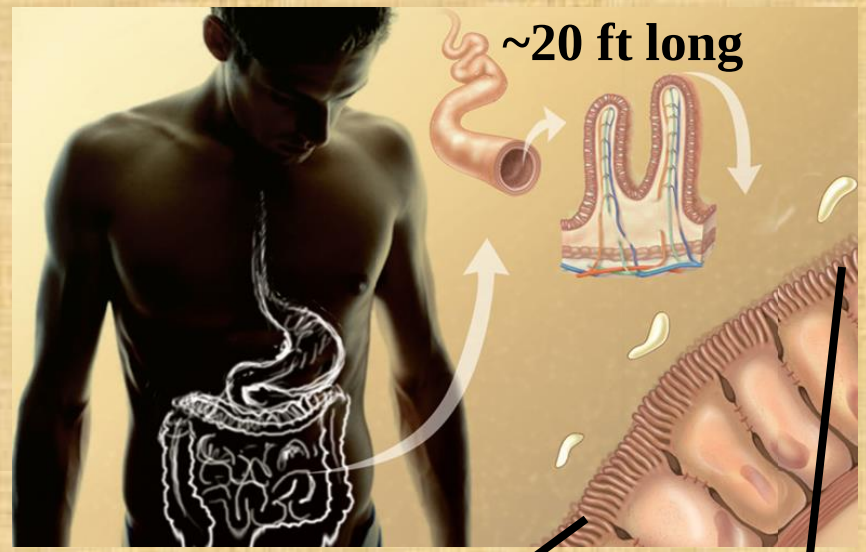
Alessio Fasano, MD

It's one of the key functions of the intestine that I probably think has been the most overlooked over human biology. So, we always were under the impression that the key function of the intestine is to digest and absorb foodstuffs. And, that, of course, is an important function. But, it's not just that. It's much more than that.

Alessio Fasano, MD

If we just pay attention to what nature has done in engineering this wonderland system that is the gut's intestinal system, you start to wonder why the anatomy and the physiology is built in that way. And, you start to see, the amplified surface. That means we want to interface with the environment as much as we can.

Intestine: Interesting Facts



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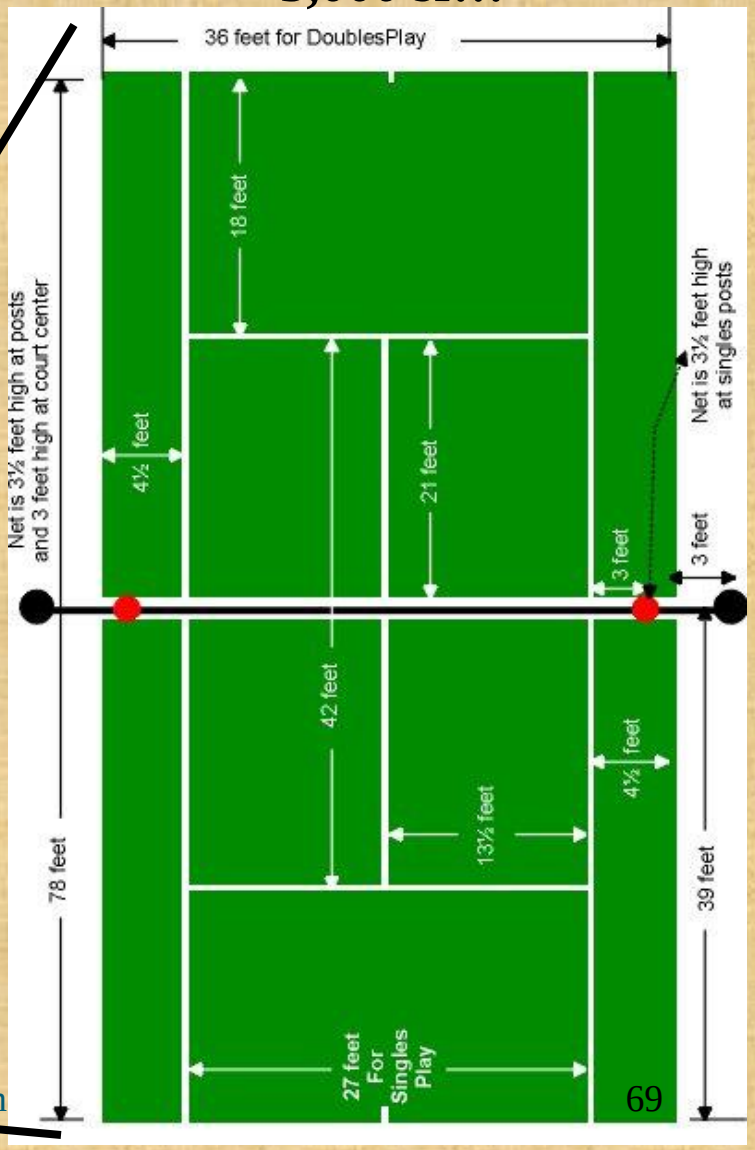


Alessio Fasano, MD

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

Alessio Fasano, MD

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

Alessio Fasano, MD

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

Alessio Fasano, MD

And, the bottom line, the modern biology seems to suggest that the state of health or the state of disease is the combination between what we are-meaning what genetically makes us, the way that we're engineered--and the environment that's around us.

Alessio Fasano, MD

And, the gut is the point of entry in which these two elements, they really meet. And, the way that, again, this exchange happens, it really is totally controlled by the permeability of the gut. They allow--if and when allowed--molecules to come through. And, on a specific genetic background, this brings us to the outcome of the overall picture of what, biologically, we are.

Alessio Fasano, MD

And, if everything goes fine and this traffic is tightly controlled...And, again if you look at what nature did, you realize that this is an extremely important function of this intestinal permeability, we stay in a state of health. But, if this tightly-controlled trafficking is, for whatever reason, jeopardized because of an infection, because of a change of the composition of bacteria in our gut--i.e. dysbiosis because we're abusing antibiotics--because, again, we're exposed to pollutants, chemicals, or genetically engineered foodstuffs, in other words, stuff that (will cause) dysfunction, we will pay a price.

Alessio Fasano, MD

"The state of health or the state of disease is the combination between what we are-meaning what genetically makes us the way that we're engineered-and the environment that's around us".

Alessio Fasano, MD

So, with Intestinal Permeability, we don't have this tightly-controlled trafficking anymore. But, this uncontrolled trafficking of these molecules. And, depending who we are, on what kind of genetic background we have, we can develop different problems.

Alessio Fasano, MD

For example, we can develop food allergies if we are skewed to develop allergies. We can develop autoimmune diseases. We can develop chronic inflammation that can lead to a stroke, Alzheimer's, you name it, cancer. And, all this depends, again, on who we are genetically speaking, and what kind of environment is surrounding us.

Alessio Fasano, MD

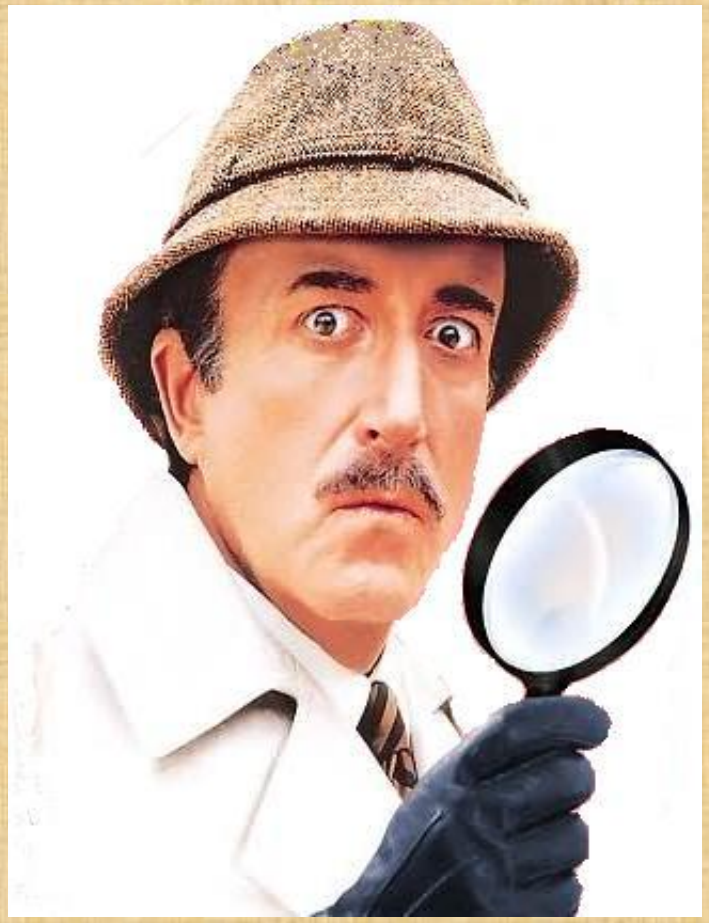
So, I think that to make this in even more in simple terms, when we're born, and, therefore, we have the entire genetic potentials, we are like a very precious single marble block. But, what is going to end up on this marble block in terms of what kind of sculpture, it depends on the environment. So, it can be an environment that you can become the painter Michelangelo's David.

Alessio Fasano, MD

Or, you can be in a different environment and the outcome will not be so wonderful. And, that's pretty much the story.

The result of the interface of our environment with our genes

Premise #5
What is the Impact of Intestinal Permeability?



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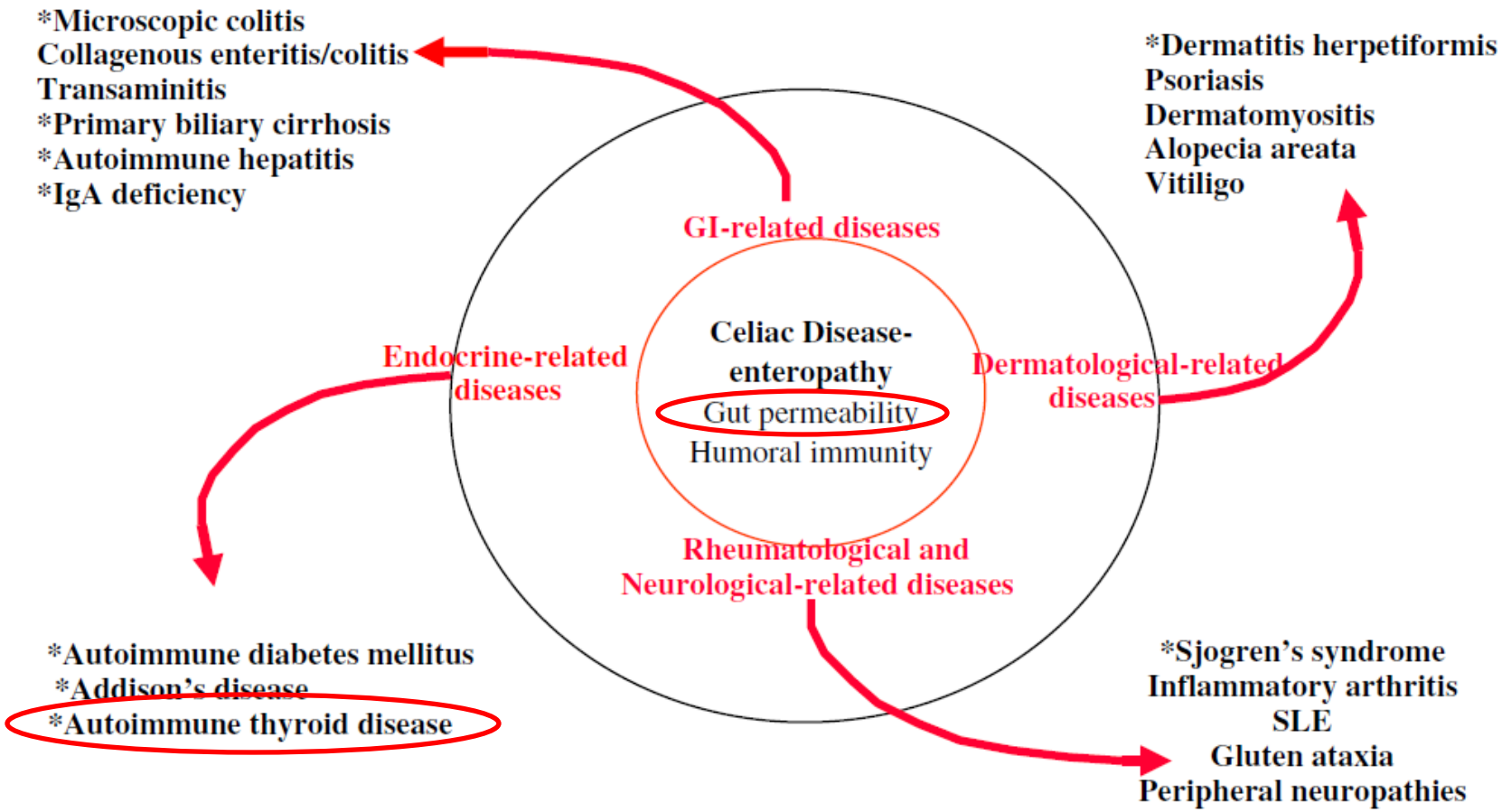

Fig. 1. Autoimmune and inflammatory diseases in relation to celiac disease. *Strongest associations.

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"The Conundrum of Gluten Sensitivity"

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And 1 written by the Center for Celiac Research at Harvard

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- **Use the references:**
  - **For your personal review to increase your knowledge about the connection between food sensitivities and autoimmunity**
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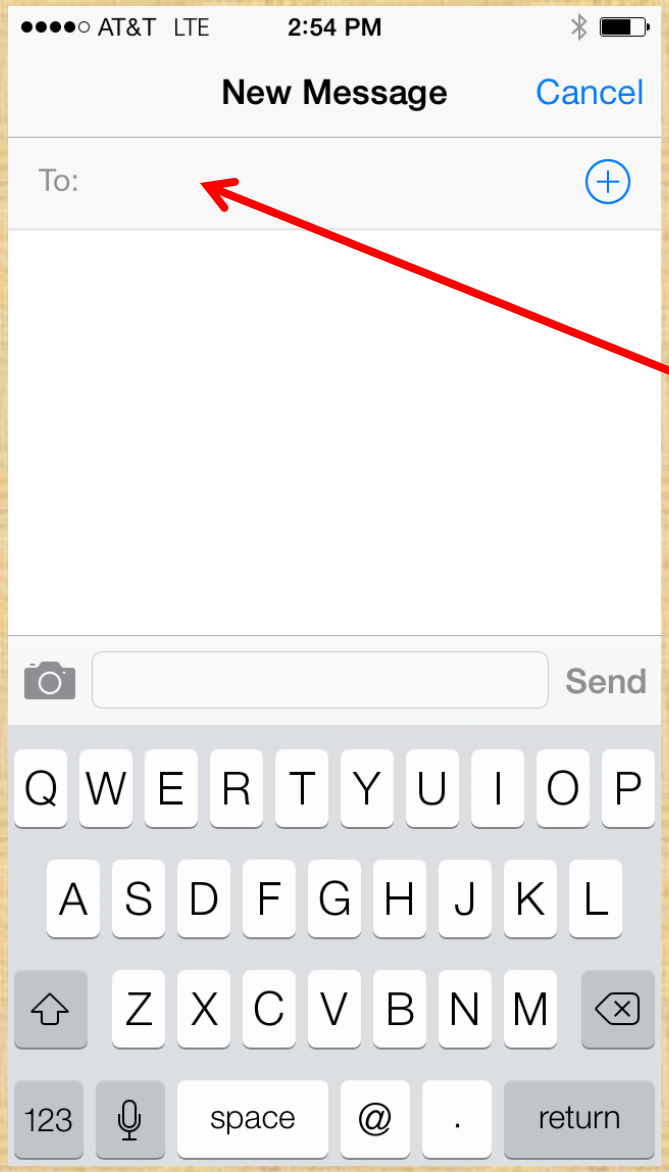
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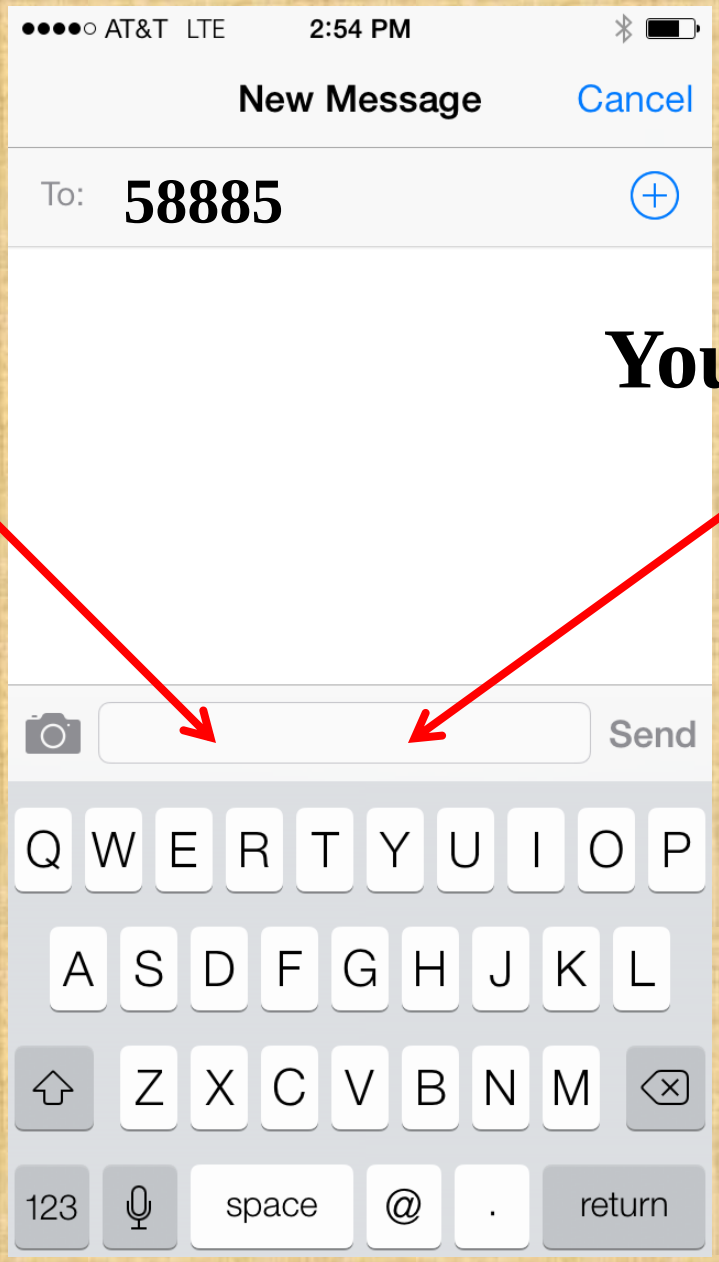

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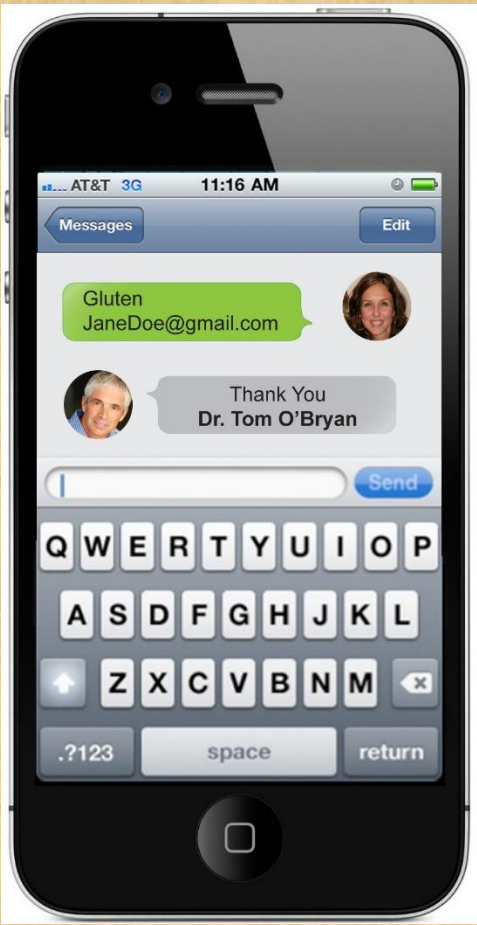
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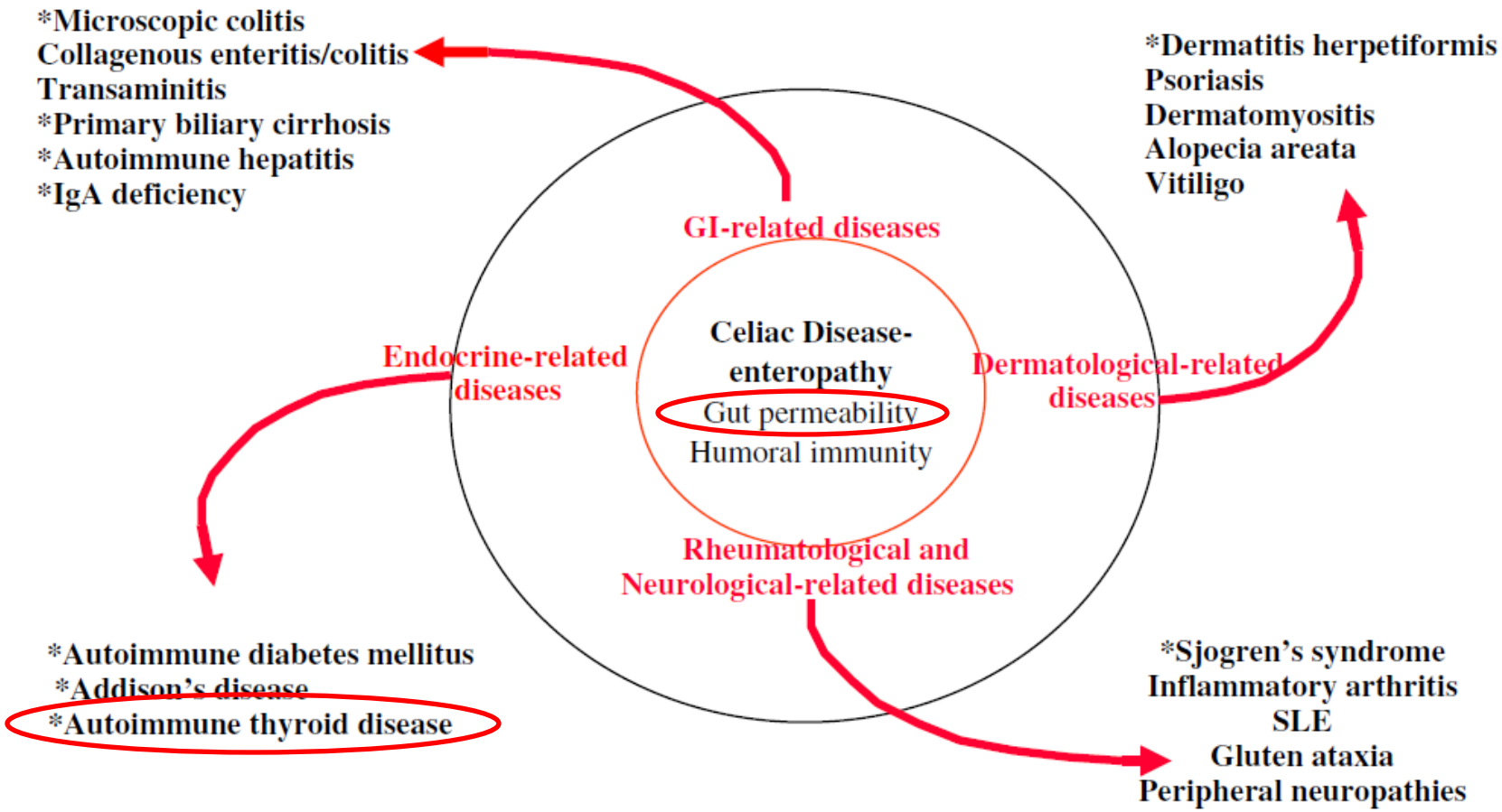

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REVIEW

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)

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Inflammatory bowel disease

Life and death in the gut: more killing, less Crohn's

A Sturm, C Fiocchi

Gut. 2002 Feb;50(2):148-9

The beneficial effects of infliximab, the tumour necrosis factor antibody, in Crohn's disease may be mediated by apoptosis of activated mucosal T cells

There is a constant state of balanced chronic inflammation present in the gastrointestinal tract. This physiologic inflammation is essential for the maturing of the immune system and development of the normal morphology of the intestinal mucosa.

The advent of new biological agents for the treatment of autoimmune and chronic inflammatory disorders is drastically altering the approach to management while setting higher standards for therapeutic expectations. Only a magic bullet against unyielding diseases causes all interest and resources to be shifted to more clinical trials. Although this reaction is understandable, all too often it comes at the expense of investigating mechanisms of action that would ultimately lead to a safer and more reliable use of the biological agent, or even the discovery of better biologicals. Thus the study of ten Hove *et al* in this issue of *Gut*, describing induction of mucosal T cell apoptosis during infliximab treatment of Crohn's disease, is a welcome and necessary complement to our still incomplete knowledge of the effect and manipulation of TNF-α in chronic intestinal inflammation **[see page 206]**.[3]

The in vivo action of infliximab has been more extensively explored in rheumatoid arthritis where blocking of TNF-α alters production of interleukin (IL)-6, IL-8, monocyte chemotactic protein 1, vascular endothelial growth factor, matrix metalloproteinases 1 and 3, angiogenesis, and the recruitment of inflammatory cells.[4] Targeting of these and other activities is also of obvious importance in Crohn's disease in view of the broad role of TNF

apoptotic stimuli and have a reduced expression of the proapoptotic Bax protein, while an imbalance between Bax and the antiapoptotic Bcl-2 protein is present in the inflamed mucosa.[9–11] Therefore, it is reasonable to assume that eliminating excessive T cells could restore the gut to its normal state of physiological inflammation or, at least, a state of controlled inflammation (fig 1). Strong evidence for this effect is provided by animal models where experimental colitis is abrogated by induction of increased T cell apoptosis with IL-12 antibodies, blockade of IL-6 trans signalling, or deletion of CD44v7+ cells.[12–14]

Based on the above reasoning and experimental evidence, ten Hove *et al* hypothesised that infliximab, in addition to neutralising soluble TNF-α, could improve Crohn's disease by inducing apoptosis of mucosal T cells.[3] To test this

ers of activ
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tients with c
ease receiving
infliximab. In patients with a clinical response they found only minor changes in the properties and apoptosis of circulating T cells while the number of apoptotic cells, primarily CD3+ T cells, significantly increased in mucosal biopsies taken 24 hours after the start of treatment. They complemented these observations by demonstrating that infliximab could induce in vitro apoptosis of activated but not resting Jurkat T cells. As mucosal T cells in active Crohn's disease are in an enhanced state of activation, the authors concluded that the beneficial effects of infliximab may be mediated by killing of activated mucosal T cells (fig 1). This conclusion is warranted even though in vitro studies on infliximab mediated apoptosis of resting and acti-

of action should be ascertained in the near future once studies similar to the one reported in this issue of *Gut* are repeated in other diseases that also benefit from TNF-α blockade. Finally, if indeed killing of activated T cells is the *modus operandi* of infliximab, this could have broad therapeutic implications. In fact, any condition characterised by increased numbers of activated T cells may profit from killing of these cells in the affected organs. There is preliminary evidence that infliximab provides clinical benefit for some patients with steroid refractory ulcerative colitis,[16] which is also characterised by high numbers of activated T cells in the mucosa. Expansion of the ten Hove study to ulcerative colitis and other chronic inflammatory conditions should provide rather interesting answers to the questions and speculation raised in this commentary.

REVIEW

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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

The primary functions of the gastrointestinal tract have traditionally been perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis.

tight junction, toll-like receptor

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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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CLASSICAL THEORIES ON THE

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.

"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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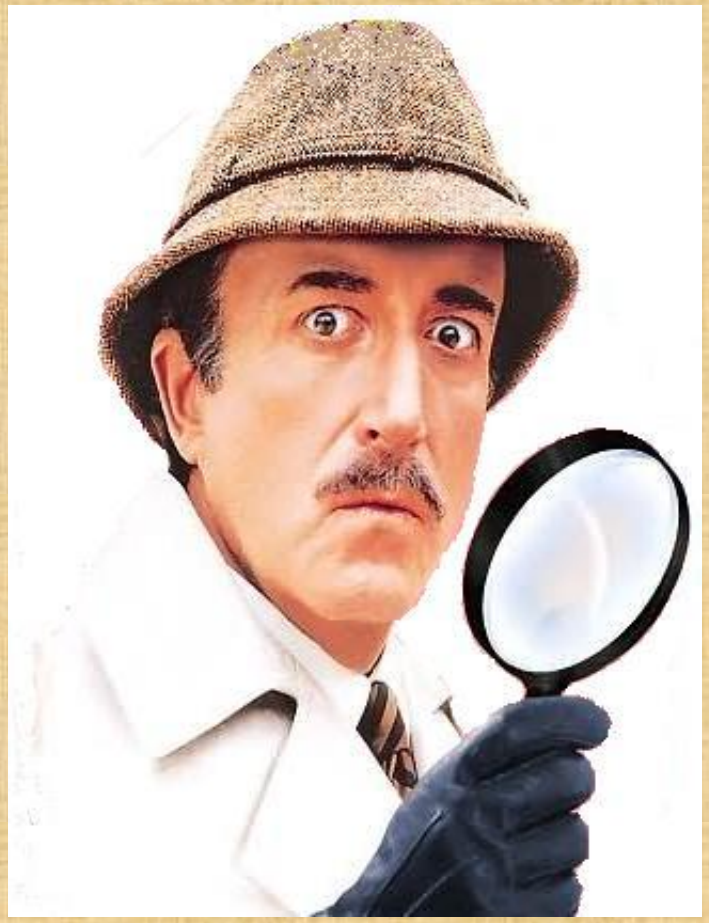
The autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier function.

Premise #6

What is the Mechanism of Intestinal Permeability?



CLINICA

CLIN GASTRO AND HEP 2012;10:1096–1100

ADVANCES IN TRANSLATIONAL SCIENCE

Joseph H. Sellin, Section Editor

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

ALESSIO FASANO

Mucosal Biology Research Center and Center for Celiac Research, University of Maryland School of Medicine, Baltimore, Maryland

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

Keywords: Autoimmune Disease; Bacterial Overgrowth; Gluten; Gut Inflammation; Obesity.

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

Enteric infections have been implicated in the pathogenesis of several pathologic conditions, including allergic, autoimmune, and inflammatory diseases, by causing impairment of the intestinal barrier. We have generated evidence that small 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.[4] 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.[5] 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.[5]

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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http://dx.doi.org/10.1016/j.cgh.2012.08.012

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

A Fasano is Professor of Pediatrics, Medicine, and Physiology, and Director of the Mucosal Biology Research Center and the Center for Celiac Research, and T Shea-Donohue is Professor of Medicine and Physiology and a member of the Mucosal Biology Research Center, at the University of Maryland School of Medicine, Baltimore, MD, USA.

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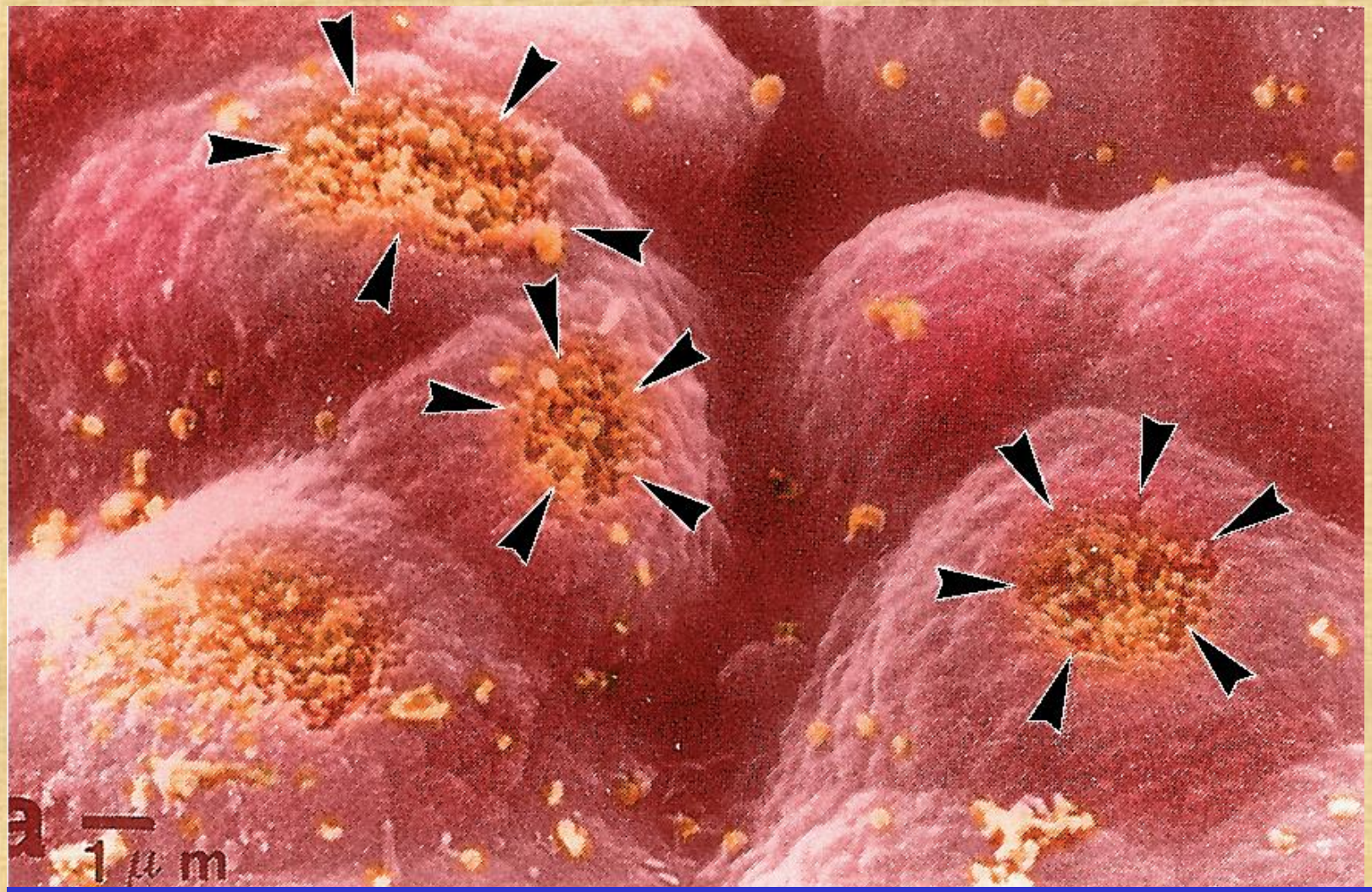
means that they are the third most common category of diseases in the US after cancer and heart disease. They can affect virtually every site in the body, including the gastrointestinal tract. At least 15 diseases are known to be the direct result of an autoimmune response, and circumstantial evidence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

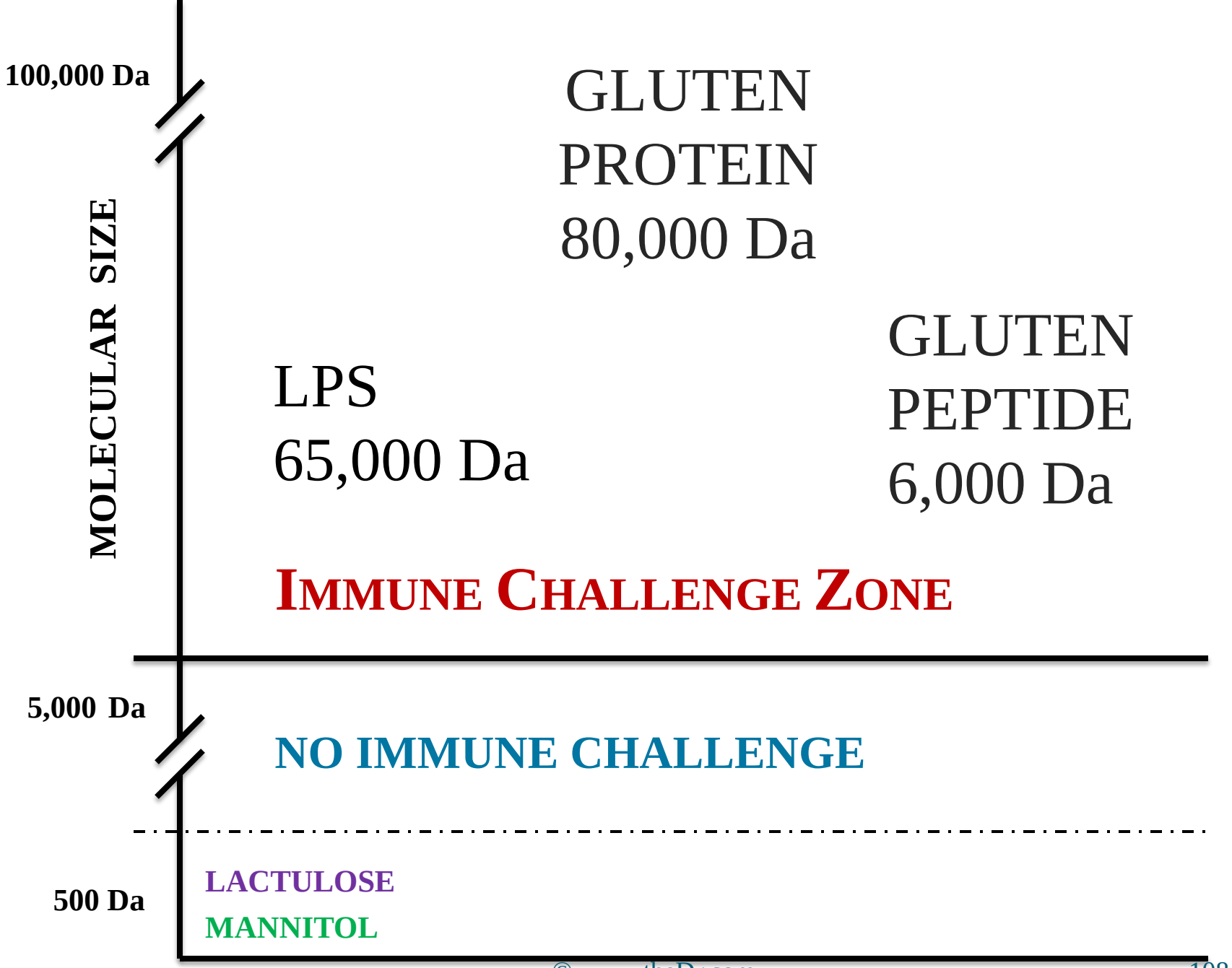
specifically, EPITOPES) are postulated to resemble self-antigens.[2] The induction of an immune response to the microbial antigens results in a cross-reaction with the self-antigens and the induction of autoimmunity. According to this theory, once the autoimmune process is activated it becomes independent 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]

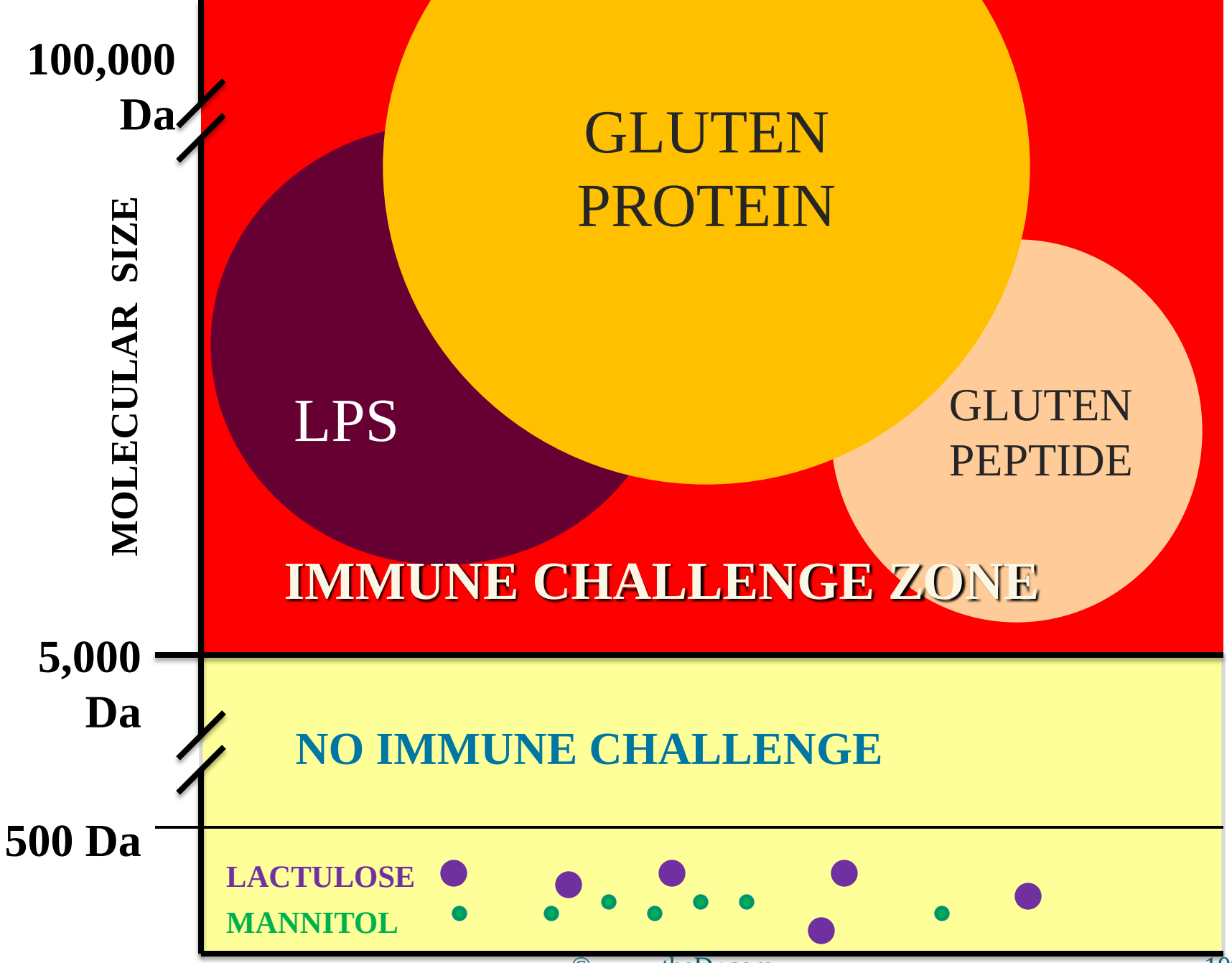
Another theory suggests that microorganisms expose self-antigens to the immune system by directly damaging tissues during active infection, and that this leads to the development of autoimmunity. This mechanism has been referred to as the 'bystander effect', and it occurs only when the new antigen is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

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



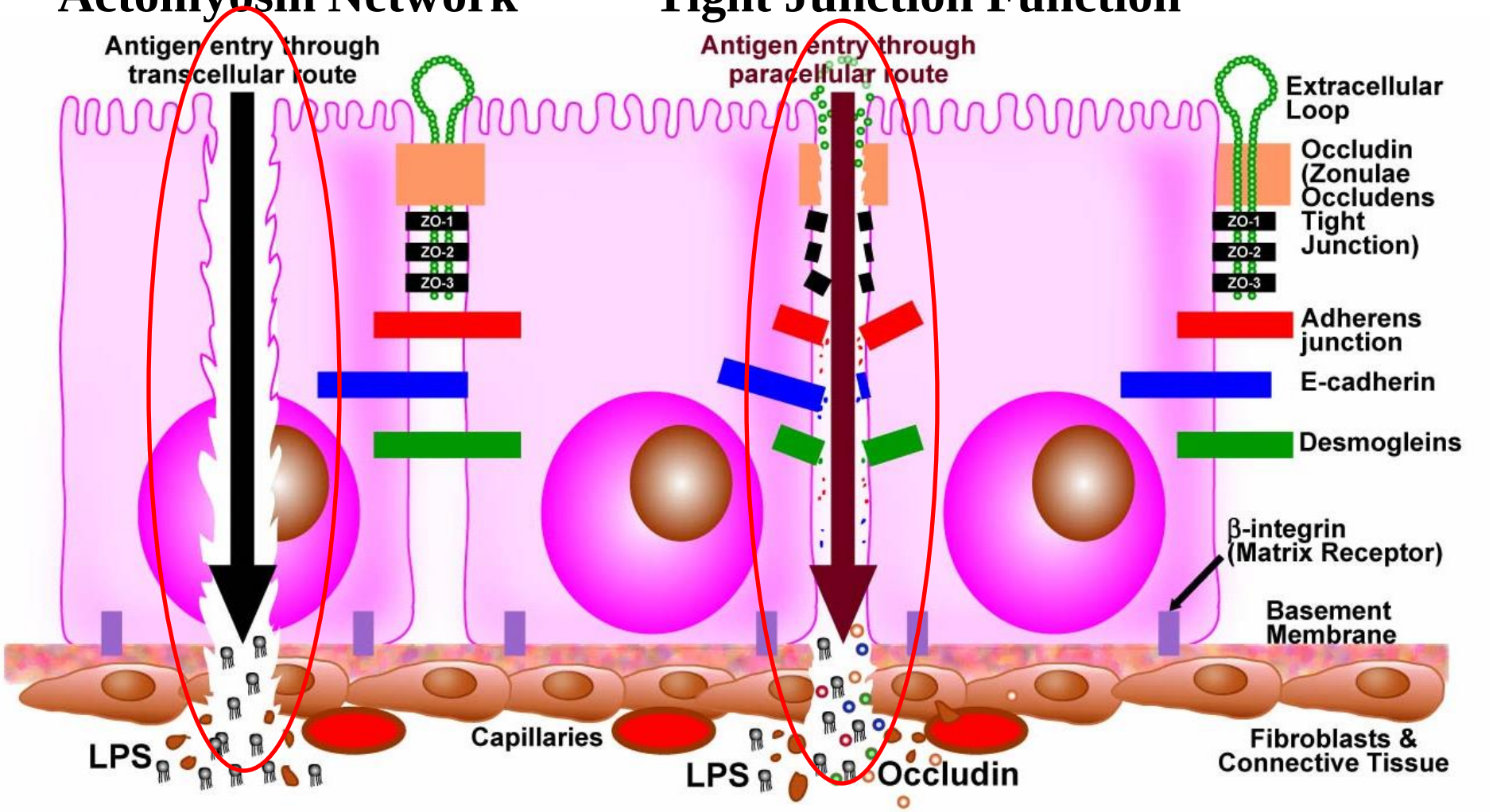
Identifying Antigenic Intestinal Permeability





Breakdown of Actomyosin Network

Breakdown of Tight Junction Function



The pathways of antigen invasion through <u>Transcellular</u> and <u>Paracellular</u> routes.

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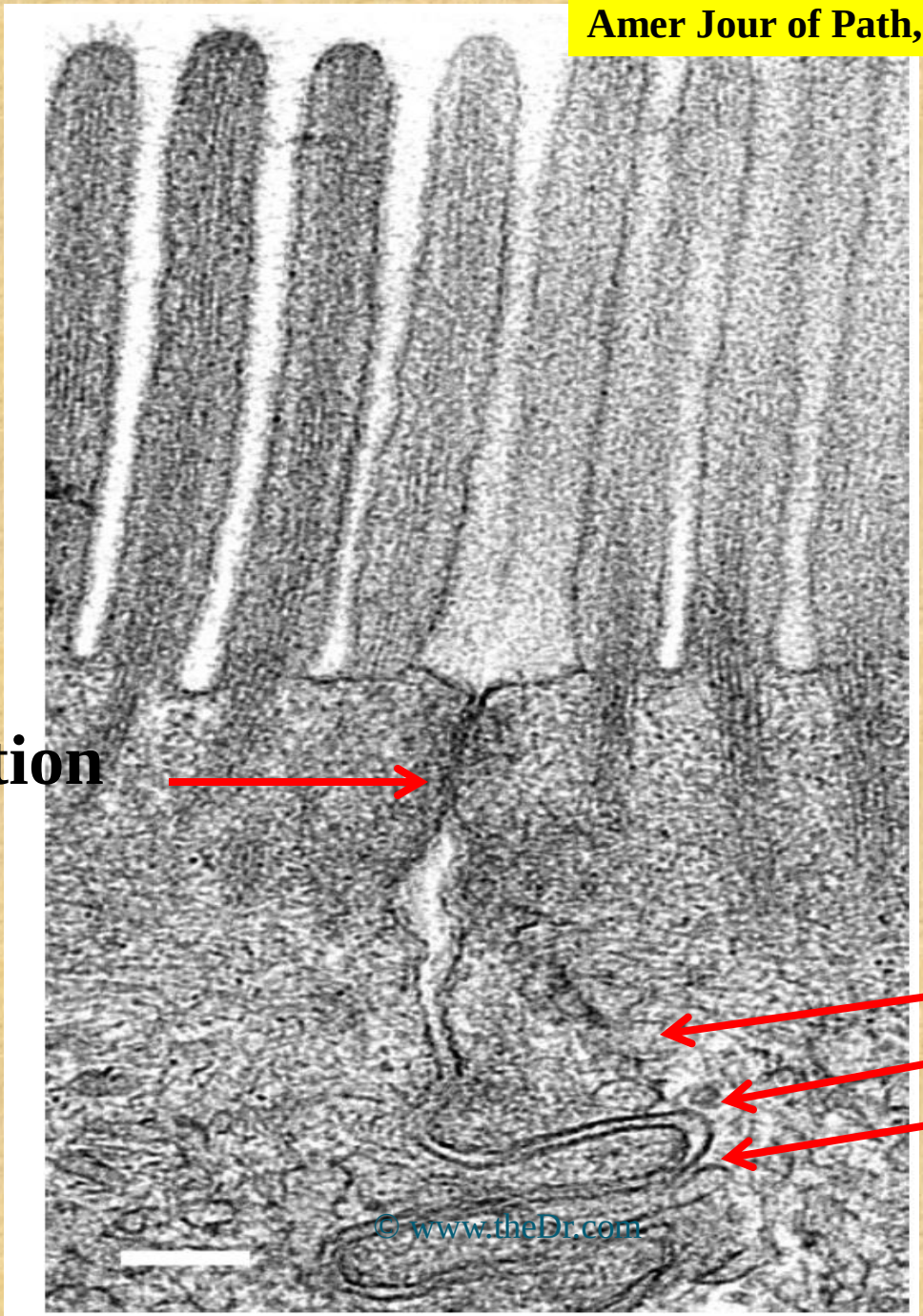
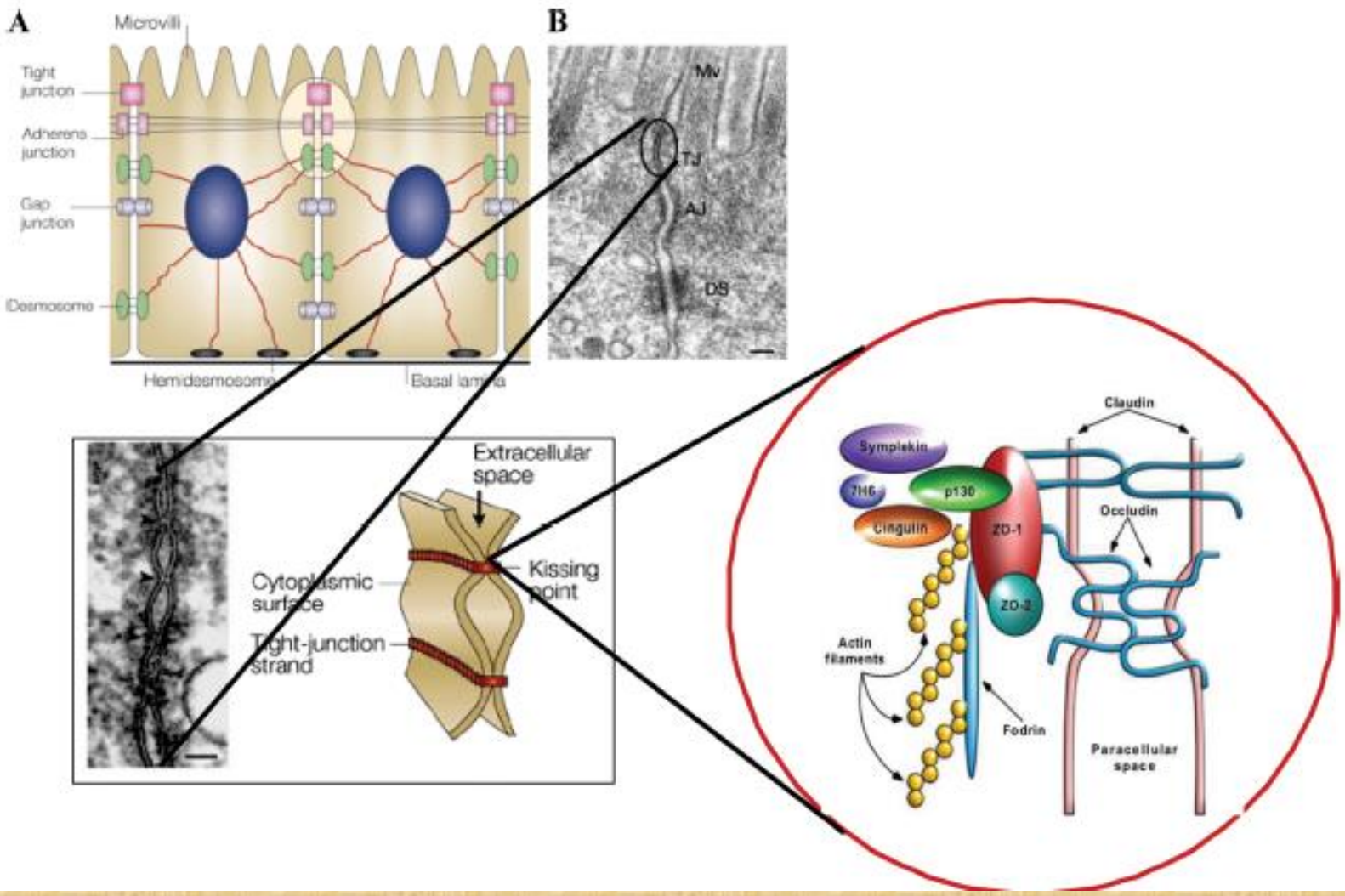
Amer Jour of Path, Vol. 169, No. 6, Dec 2006



Tight Junction

Actomyosin Network

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



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

Received 13 Nov 2008; first review completed 26 Nov 2008; accepted in final form 29 Jan 2009

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,

Address reprint requests to Falco Hietbrink, MD, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: F.Hietbrink@umcutrecht.nl.

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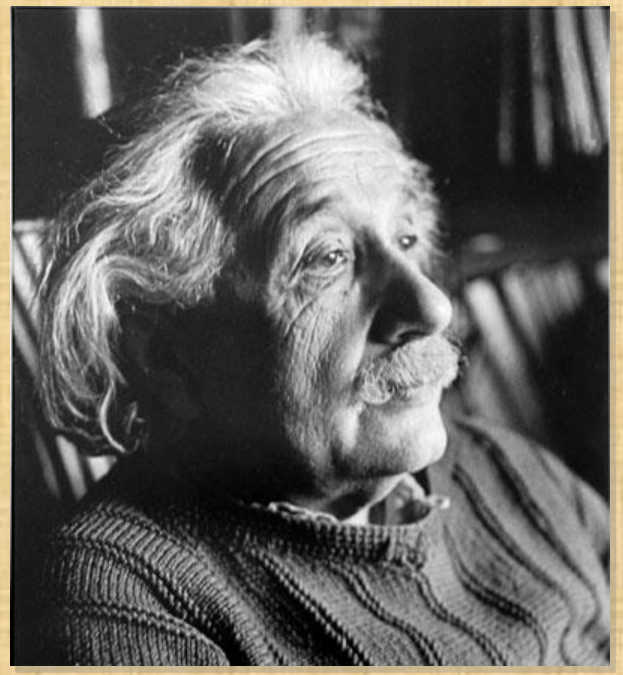
DOI: 10.1097/SHK.0b013e3181a2bcd6

Premise #7
Immunological Markers in Screening for Antigenic Intestinal Permeability



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

Immunological Markers in Screening for Antigenic Intestinal Permeability

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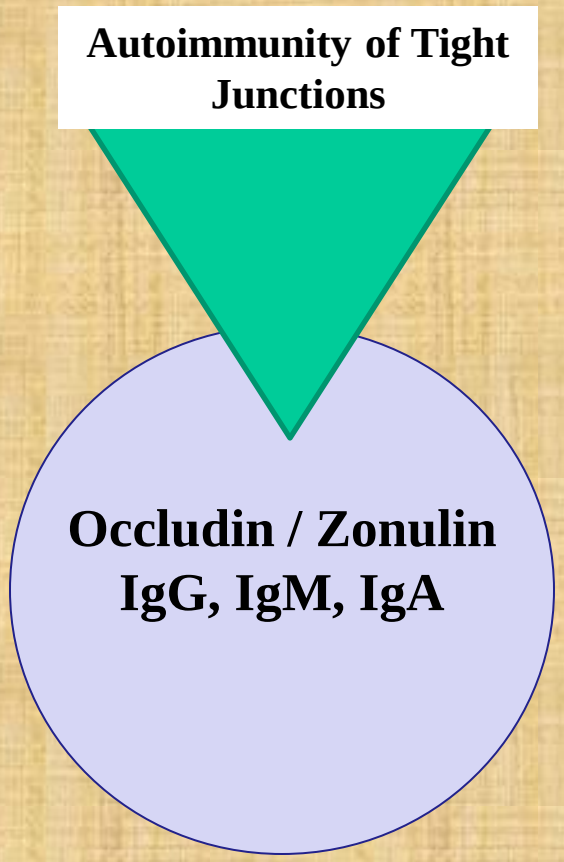
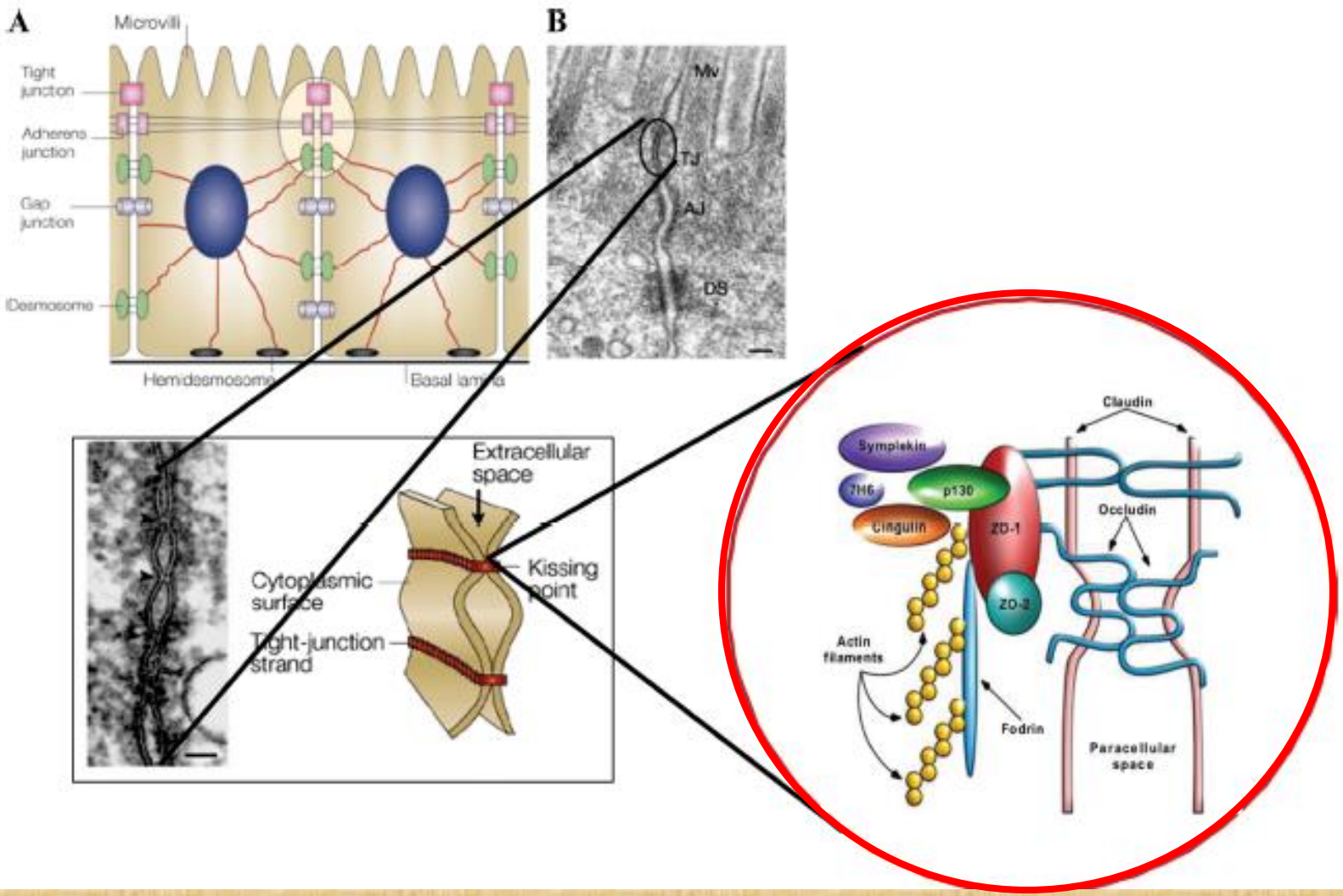


Ann. N.Y. Acad. Sci. 1165: 195–205 (2009)



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 immediate reduction of intestinal barrier function and passage of gliadin into the subepithelial compartment.

think polymerase chain reaction (PCR). ***Results***. When exposed to gliadin, zonulin receptor-positive IEC6 and Caco2 cells 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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Immunological Markers in Screening for Antigenic Intestinal Permeability

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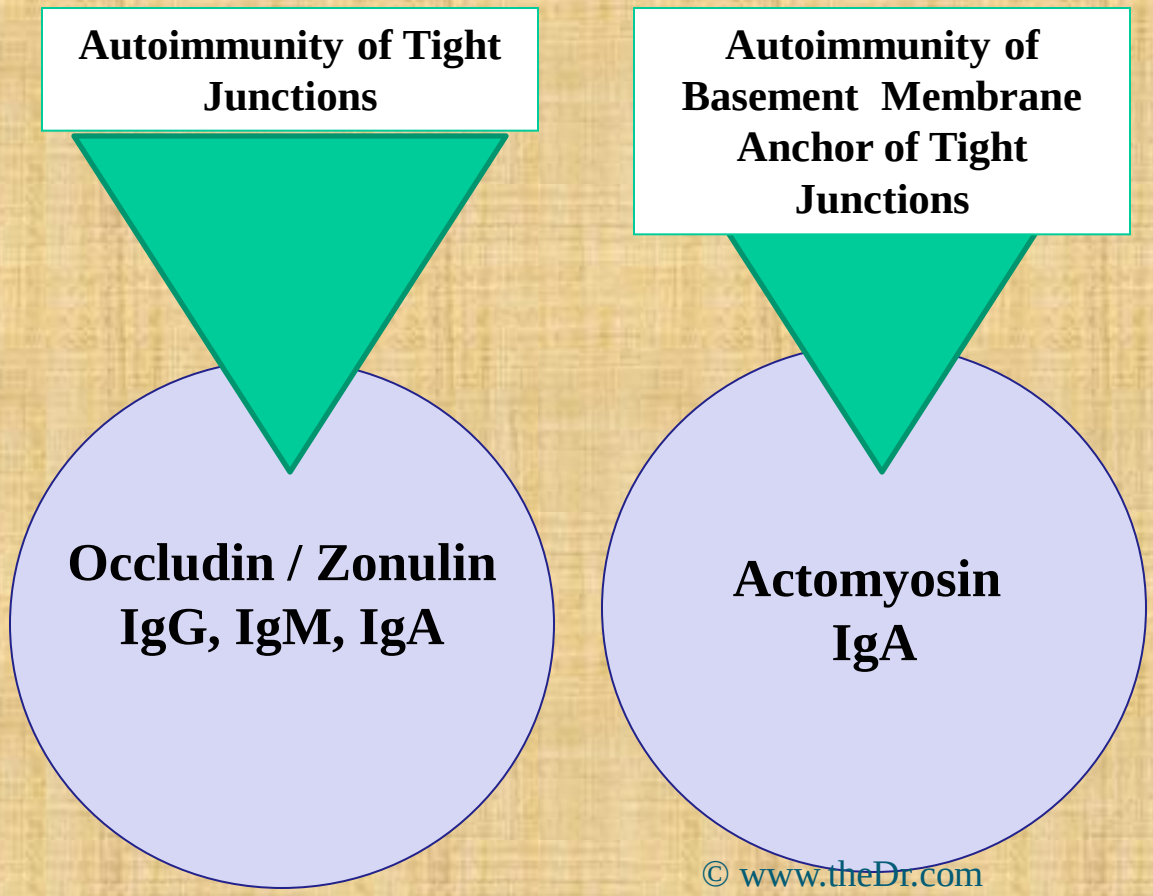

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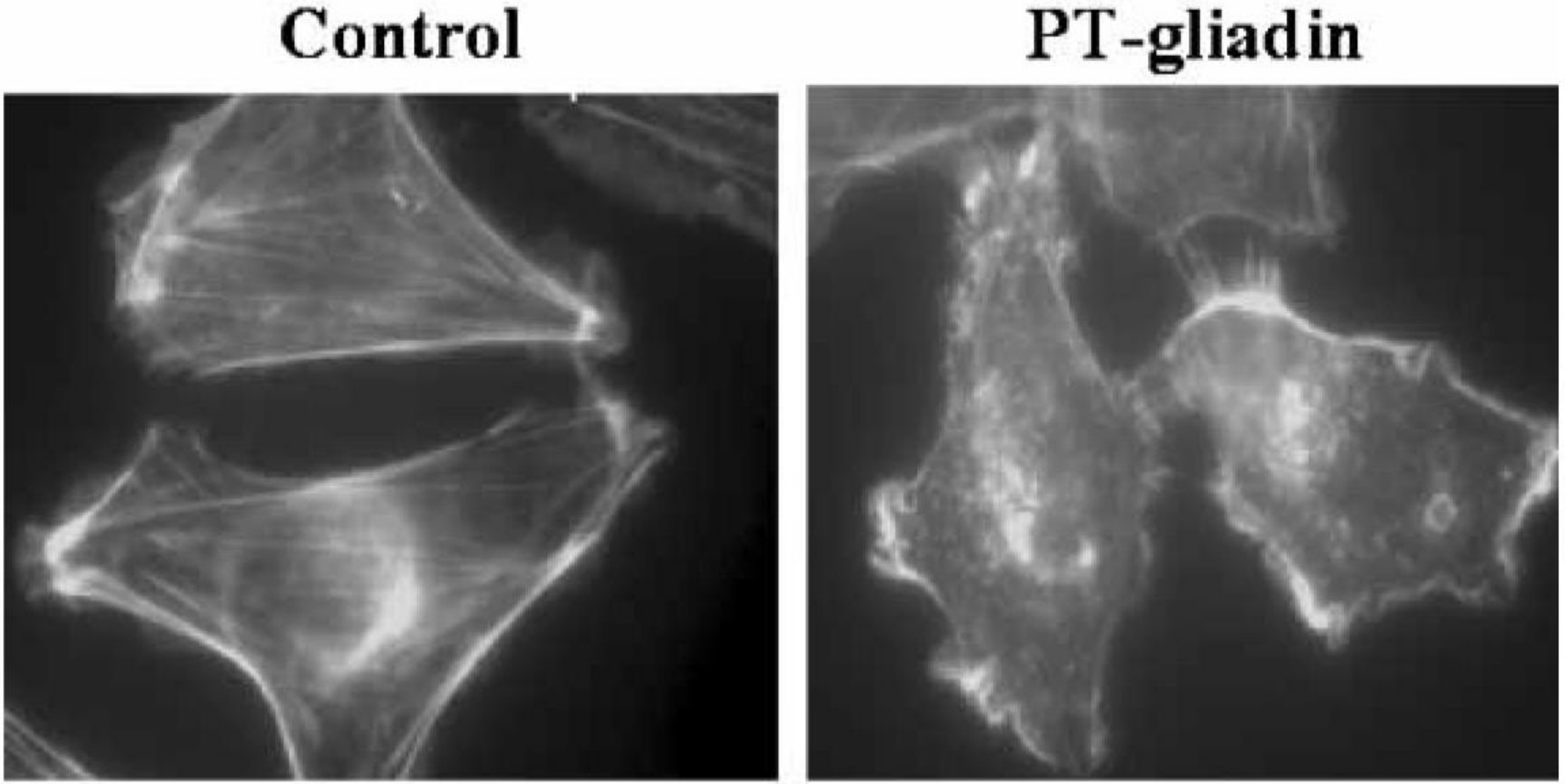

Figure 2. Effect of gliadin on intestinal epithelial cells cytoskeleton leads to a reorganization of actin filaments

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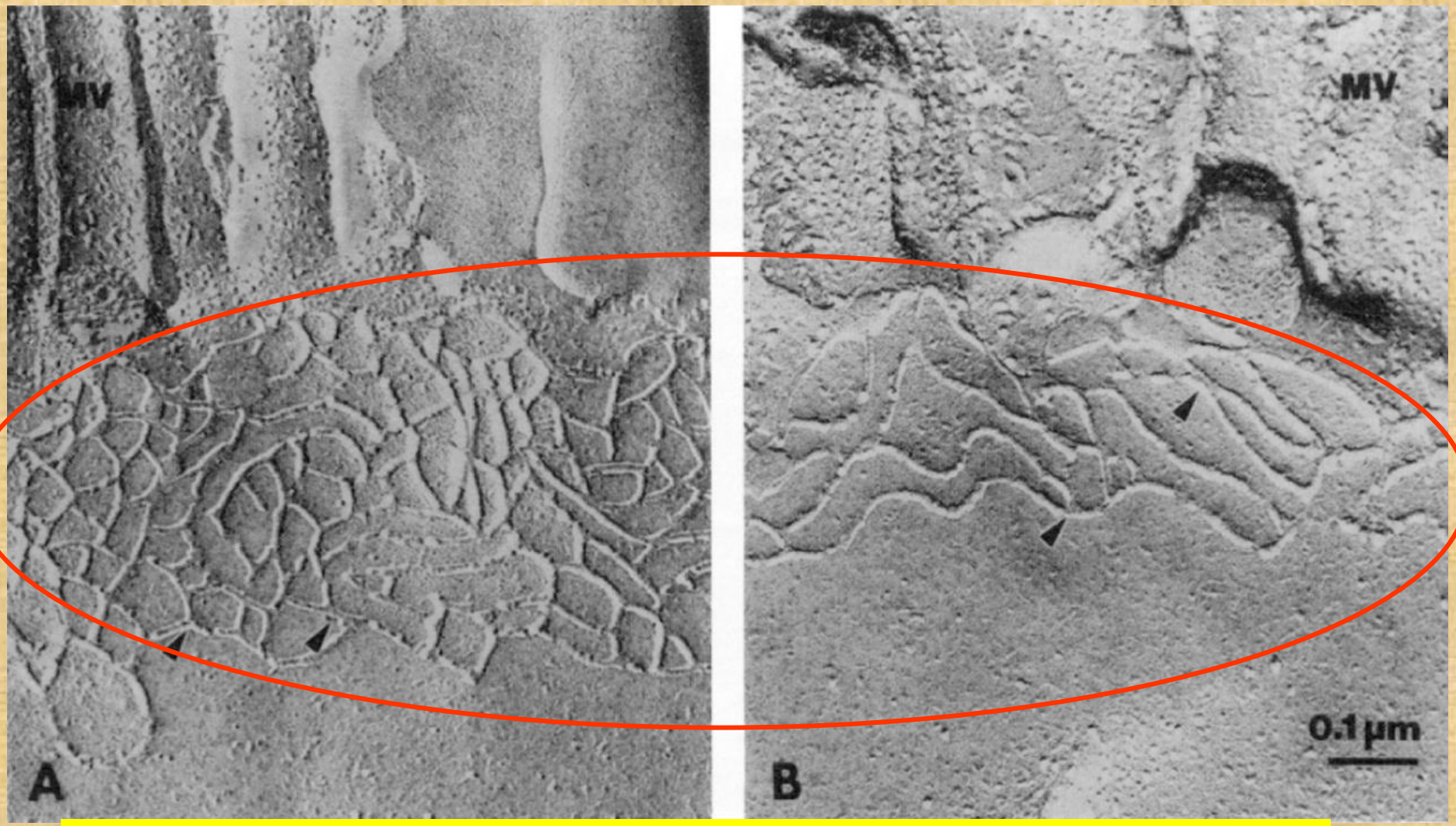

The rearrangement of the filaments of actin and the subsequent displacement of proteins (including ZO-1) from the junctional complex

CLINICA

CLIN GASTRO AND HEP 2012;10:1096–1100

ADVANCES IN TRANSLATIONAL SCIENCE

Joseph H. Sellin, Section Editor

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ALESSIO FASANO

Mucosal Biology Research Center and Center for Celiac Research, University of Maryland School of Medicine, Baltimore, Maryland

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Keywords: Autoimmune Disease; Bacterial Overgrowth; Gluten; Gut Inflammation; Obesity.

Technological Primer

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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

Enteric infections have been implicated in the pathogenesis of several pathologic conditions, including allergic, autoimmune, and inflammatory diseases, by causing impairment of the intestinal barrier. We have generated evidence that small 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.[4] 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.[5] 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.[5]

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

TOM VAN DER POLL,[1,2] ERIK ENDERT,[3] SUSETTE M. COYLE,[1]
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Am J Physiol Regul Integr Comp Physiol 276:R357-R362, 1999.

Van Der Poll, Tom, Erik Endert, Susette M. Coyle, Jan M. Agosti, and Stephen F. Lowry. Neutralization of TNF does not influence endotoxin-induced changes in thyroid hormone metabolism in humans. *Am. J. Physiol.* 276 (*Regulatory Integrative Comp. Physiol.* 45): R357–R362, 1999.—To determine the role of tumor necrosis factor (TNF) in endotoxin-induced changes in plasma thyroid hormone and thyroid-stimulating hormone (TSH) concentrations, 24 healthy postabsorptive humans were studied on a control study day ($n = 6$), after infusion of a recombinant TNF receptor IgG fusion

healthy subjects reproduced a number of changes in the plasma concentrations of thyroid hormones and TSH commonly seen in NTI, including reduced T_4, T_3, and TSH concentrations, and increased rT_3 levels. We used this model to determine the role of IL-1 in LPS-induced changes in thyroid hormone metabolism by blocking endogenous IL-1 activity through treatment with recombinant IL-1 receptor antagonist. It was found that IL-1 receptor blockade did not affect the alterations in

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

cally euthyroid (8, 34). Characteristically this syndrome involves a decrease in the serum concentrations of 3,5,3 -triiodothyronine (T_3) and an increase in 3,3 ,5 -triiodothyronine (rT_3). L-Thyroxine (T_4) and thyroid-stimulating hormone (TSH) levels usually remain normal but can be decreased in severe NTI (8, 21, 35). Many systemic NTIs are associated with enhanced production of proinflammatory cytokines, among which interleukin (IL)-1 and tumor necrosis factor (TNF) are the most potent (5, 39). Increased activity of these mediators has been implicated in the development of altered thyroid hormone metabolism in NTI.

Recently, we established a human model of the euthyroid sick syndrome (31). Intravenous administration of low-dose endotoxin (lipopolysaccharide, LPS) to

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MATERIALS AND METHODS

Study design. The present study was performed simultaneously with an investigation examining the effect of TNF neutralization on LPS-induced clinical, leukocyte, and cytokine responses, of which the results have been reported in detail (27, 28). Twenty-four adult male subjects, aged 27 ± 1 (mean ± SE) yr, were admitted to the Adult Clinical Research Center after documentation of good health by history, physical examination, and hematologic and biochemical screening. The study was approved by the Institutional Review Board, and written informed consent was obtained from all subjects before enrollment in the study. Subjects were allowed no intake of food from 10:00 PM on the night before the study until 12 h after endotoxin or placebo administration (9:00 PM). During this time they had free access to water. Twelve subjects received an intravenous injection with LPS [National Reference Endotoxin, *Escherichia coli* 0113 (lot EC-5), generously provided by Dr. H. D. Hochstein, the Bureau of Biologics, Food and Drug Administration, Bethesda, MD] at a dose of 2 ng/kg body wt at 9:00 AM. These 12 subjects were

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

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tions induced by mild endotoxemia in healthy humans.

lipopolysaccharide; cytokines; thyrotropin

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

THE EUTHYROID SICK SYNDROME is characterized by changes in thyroid hormone metabolism in patients with systemic nonthyroidal illness (NTI) who are clinically euthyroid (8, 34). Characteristically this syndrome involves a decrease in the serum concentrations of 3,5,3 -triiodothyronine (T_3) and an increase in 3,3 ,5 -triiodothyronine (rT_3). L-Thyroxine (T_4) and thyroid-stimulating hormone (TSH) levels usually remain normal but can be decreased in severe NTI (8, 21, 35). Many systemic NTIs are associated with enhanced production of proinflammatory cytokines, among which interleukin (IL)-1 and tumor necrosis factor (TNF) are the most potent (5, 39). Increased activity of these mediators has been implicated in the development of altered thyroid hormone metabolism in NTI.

Recently, we established a human model of the euthyroid sick syndrome (31). Intravenous administration of low-dose endotoxin (lipopolysaccharide, LPS) to

determine the role of endogenous TNF activity in the changes in plasma thyroid hormone and TSH concentrations elicited by intravenous LPS in humans. For this purpose we performed a placebo-controlled study in healthy humans exposed to a single intravenous dose of LPS in conjunction with a (TNF neutralizing) recombinant dimeric TNF receptor IgG fusion protein (TNFR:Fc).

MATERIALS AND METHODS

Study design. The present study was performed simultaneously with an investigation examining the effect of TNF neutralization on LPS-induced clinical, leukocyte, and cytokine responses, of which the results have been reported in detail (27, 28). Twenty-four adult male subjects, aged 27 ± 1 (mean ± SE) yr, were admitted to the Adult Clinical Research Center after documentation of good health by history, physical examination, and hematologic and biochemical screening. The study was approved by the Institutional Review Board, and written informed consent was obtained from all subjects before enrollment in the study. Subjects were allowed no intake of food from 10:00 PM on the night before the study until 12 h after endotoxin or placebo administration (9:00 PM). During this time they had free access to water. Twelve subjects received an intravenous injection with LPS [National Reference Endotoxin, *Escherichia coli* 0113 (lot EC-5), generously provided by Dr. H. D. Hochstein, the Bureau of Biologics, Food and Drug Administration, Bethesda, MD] at a dose of 2 ng/kg body wt at 9:00 AM. These 12 subjects were

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

TOM VAN DER POLL,[1,2] ERIK ENDERT,[3] SUSETTE M. COYLE,[1]
JAN M. AGOSTI,[4] AND STEPHEN F. LOWRY[1]
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Am J Physiol Regul Integr Comp Physiol 276:R357-R362, 1999.

Van Der Poll, Tom, Erik Endert, Susette M. Coyle, Jan M. Agosti, and Stephen F. Lowry. Neutralization of TNF does not influence endotoxin-induced changes in thyroid hormone metabolism in humans. *Am. J. Physiol.* 276 (*Regulatory Integrative Comp. Physiol.* 45): R357–R362, 1999.—To determine the role of tumor necrosis factor (TNF) in endotoxin-induced changes in plasma thyroid hormone and thyroid-stimulating hormone (TSH) concentrations, 24 healthy postabsorptive humans were studied on a control study day ($n = 6$), after infusion of a recombinant TNF receptor IgG fusion

healthy subjects reproduced a number of changes in the plasma concentrations of thyroid hormones and TSH commonly seen in NTI, including reduced T_4, T_3, and TSH concentrations, and increased rT_3 levels. We used this model to determine the role of IL-1 in LPS-induced changes in thyroid hormone metabolism by blocking endogenous IL-1 activity through treatment with recombinant IL-1 receptor antagonist. It was found that IL-1 receptor blockade did not affect the alterations in

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

cally euthyroid (8, 34). Characteristically this syndrome involves a decrease in the serum concentrations of 3,5,3 -triiodothyronine (T_3) and an increase in 3,3 ,5 -triiodothyronine (rT_3). L-Thyroxine (T_4) and thyroid-stimulating hormone (TSH) levels usually remain normal but can be decreased in severe NTI (8, 21, 35). Many systemic NTIs are associated with enhanced production of proinflammatory cytokines, among which interleukin (IL)-1 and tumor necrosis factor (TNF) are the most potent (5, 39). Increased activity of these mediators has been implicated in the development of altered thyroid hormone metabolism in NTI.

Recently, we established a human model of the euthyroid sick syndrome (31). Intravenous administration of low-dose endotoxin (lipopolysaccharide, LPS) to

MATERIALS AND METHODS

Study design. The present study was performed simultaneously with an investigation examining the effect of TNF neutralization on LPS-induced clinical, leukocyte, and cytokine responses, of which the results have been reported in detail (27, 28). Twenty-four adult male subjects, aged 27 ± 1 (mean ± SE) yr, were admitted to the Adult Clinical Research Center after documentation of good health by history, physical examination, and hematologic and biochemical screening. The study was approved by the Institutional Review Board, and written informed consent was obtained from all subjects before enrollment in the study. Subjects were allowed no intake of food from 10:00 PM on the night before the study until 12 h after endotoxin or placebo administration (9:00 PM). During this time they had free access to water. Twelve subjects received an intravenous injection with LPS [National Reference Endotoxin, *Escherichia coli* 0113 (lot EC-5), generously provided by Dr. H. D. Hochstein, the Bureau of Biologics, Food and Drug Administration, Bethesda, MD] at a dose of 2 ng/kg body wt at 9:00 AM. These 12 subjects were

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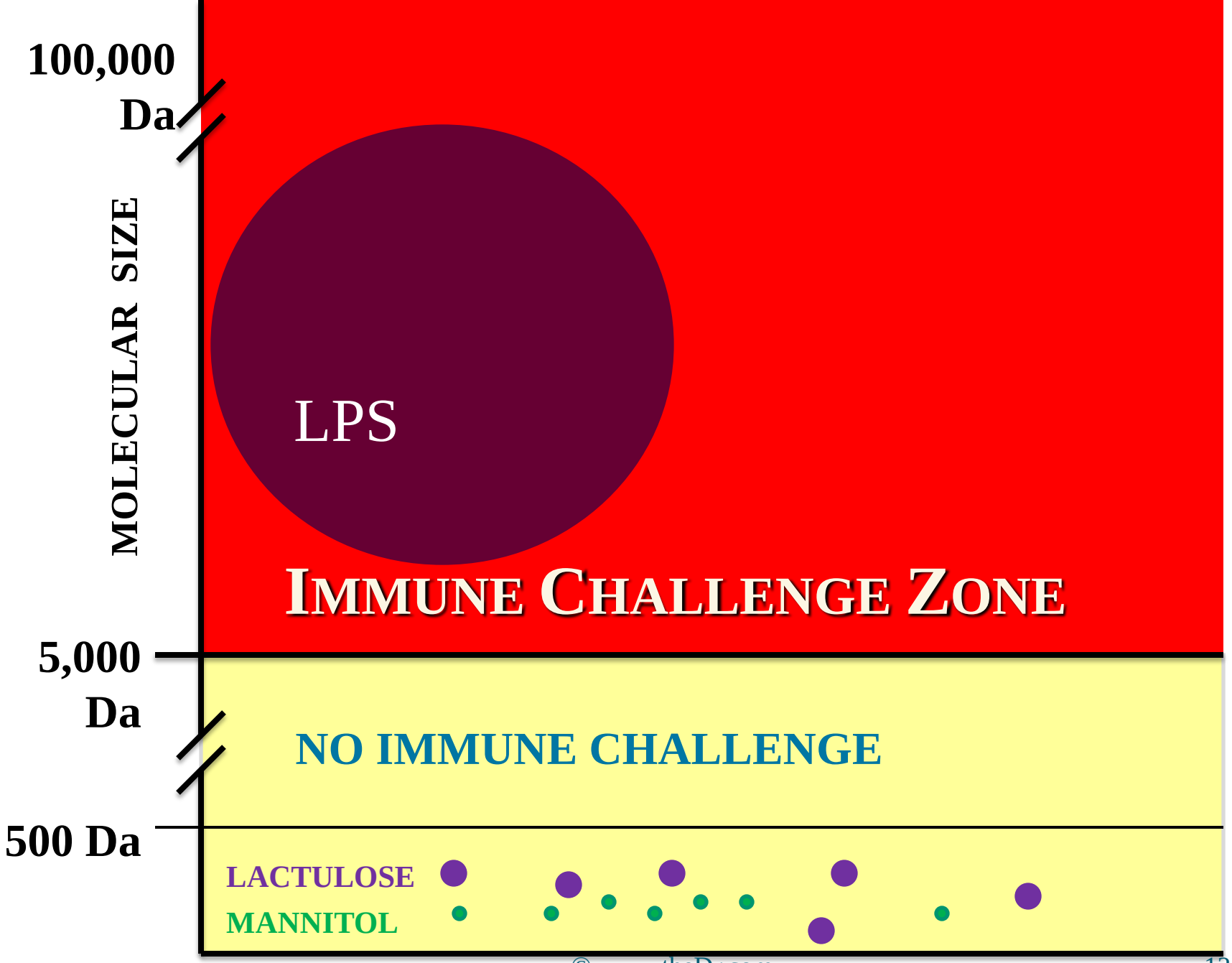
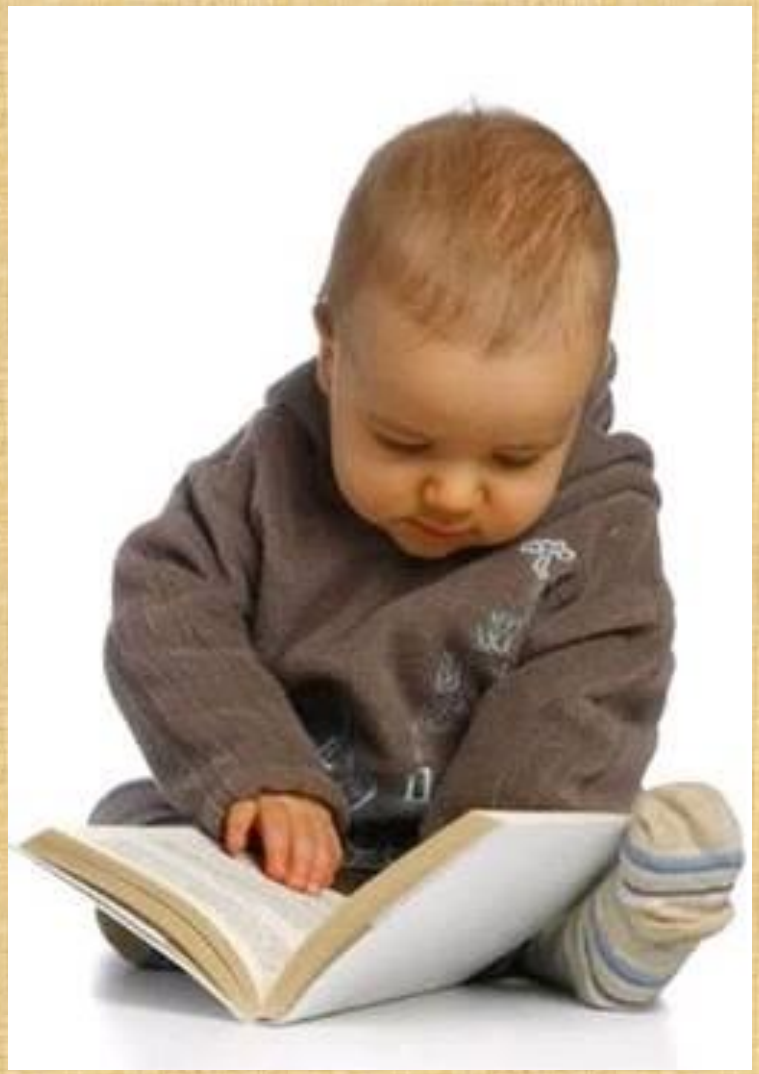

100,000 Da
MOLECULAR SIZE
LPS
IMMUNE CHALLENGE ZONE
5,000 Da
NO IMMUNE CHALLENGE
500 Da
LACTULOSE
MANNITOL

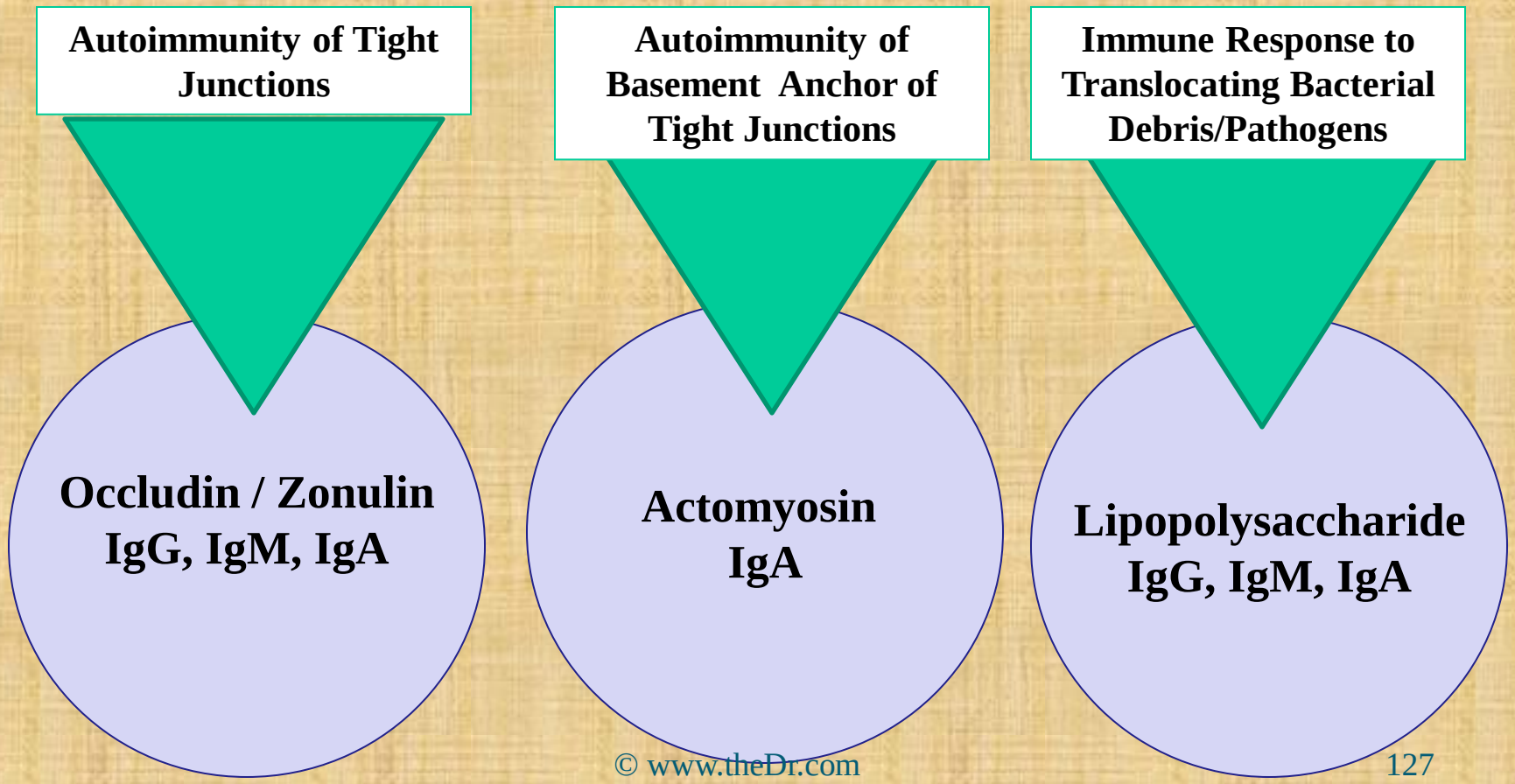
How does the Passage of LPS into the blood stream occur?



- through the oral cavity (gingivitis, peridontitis)
- through an open wound
- septicemia
- lipid raft transcytosis
- pathogenic Intestinal Permeability

Immunological Markers in Screening for Antigenic Intestinal Permeability

BLOOD



The Journal of Immunology, 2006, 176: 2512–2521.

Gliadin Stimulation of Murine Macrophage Inflammatory Gene Expression and Intestinal Permeability Are MyD88-Dependent: Role of the Innate Immune Response in Celiac Disease[1]

Karen E. Thomas,* Anna Sapone,†‡ Alessio Fasano,†‡ and Stefanie N. Vogel[2]*‡

Recent studies have demonstrated the importance of TLR signaling in intestinal homeostasis. Celiac disease (CD) is an autoimmune enteropathy triggered in susceptible individuals by the ingestion of gliadin-containing grains. In this study, we sought to test the hypothesis that gliadin initiates this response by stimulating the innate immune response to increase intestinal permeability and by up-regulating macrophage proinflammatory gene expression and cytokine production. To this end, intestinal permeability and the release of zonulin (an endogenous mediator of gut permeability) in vitro, as well as proinflammatory gene expression and cytokine release by primary murine macrophage cultures, were measured. Gliadin and its peptide derivatives, 33-mer and p31-43, were found to be potent inducers of both a zonulin-dependent increase in intestinal permeability and macrophage proinflammatory gene

The increased permeability, which occurs within 36 hrs (of exposure to the toxic gluten proteins in wheat) seems to be a very early response to gluten exposure…

other grains are the environmental stimuli responsible for the development of intestinal damage associated with CD (2, 3). The disease is associated with the HLA alleles DQA1*0501/DQB1*0201, and in the continued presence of gluten the disease is self-perpetuating (1). The typical intestinal damage in CD is characterized by the loss of absorptive villi and hyperplasia of the crypts that resolve upon the elimination of gluten-containing grains from the patient's diet (2).

It is now evident that CD is the end result of an inappropriate T cell-mediated immune response against ingested gluten (2). How-

as gluten (4). In healthy individuals, small but immunologically significant amounts of Ag cross the defensive epithelial barrier via one of two functional pathways. Most Ags are absorbed through the transcellular pathway, followed by lysosomal degradation that converts proteins into smaller peptides and/or constitutive amino acids. The remainder is transported in the form of intact proteins or their polypeptide by-products, resulting in Ag-specific immune responses in the submucosa. This latter phenomenon uses the paracellular pathway that involves a sophisticated regulation of intercellular tjs that leads, ultimately, to Ag presentation to the GALT. When the integrity of the tj system is compromised as it is in CD (5, 6), an inappropriate immune response to environmental Ags (i.e., gluten) may develop. The gliadin-induced release of zonulin, a recently described intestinal protein involved in tj regulation (7), seems to be responsible, in part, for the increased gut permeability that is characteristic of the early phase of CD (8). Zonulin was first described as a mammalian homologue of *Vibrio cholerae*-derived zonula occludens toxin (ZOT) (7, 9). Although zonulin has yet to be cloned, recent functional and biochemical characterizations strongly support the hypothesis that it is a preformed protease that is rapidly released into the luminal side of the intestine in response to gliadin or bacteria (10). Like ZOT, zonulin interacts with the intestinal epithelium to initiate a signaling pathway that results in phosphorylation of proteins within the zonula occludens and, in turn, a loss of intestinal tj integrity (11). Zonulin-mediated tj permeability may also be responsible for the increased incidence of other autoimmune disorders reported in untreated CD patients (8).

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[1] This work was supported by National Institutes of Health Grants AI-18797 (to S.N.V.) and DK-48373 and DK-66630 (to A.F.).

[2] Address correspondence and reprint requests to Dr. Stefanie N. Vogel, Department of Microbiology and Immunology, University of Maryland, 660 West Redwood Street 324, Baltimore, MD 21201. E-mail address: svogel@som.umaryland.edu

[3] Abbreviations used in this paper: CD, celiac disease; CHO, Chinese hamster ovary; CHX, cycloheximide; HPRT, hypoxanthine phosphoribosyltransferase; iNOS, inducible NO synthase; Pam3Cys, *S*-[2,3-bis(palmitoyloxy)-(2-*RS*)-propyl]-*N*-palmitoyl-(*R*)-Cys-(*S*)-Ser-Lys4-OH, trihydrochloride; PT-gliadin, pepsin/trypsin-digested gliadin; poly(I:C), polyinosinic-polycytidylic acid; TEER, transepithelial electrical resistance; tj, tight junction; WT, wild type; ZOT, zonula occludens toxin.

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Alimentary Tract

Intestinal permeability in patients with adverse reactions to food

M.T. Ventura[a,*], L. Polimeno[b], A.C. Amoruso[b], F. Gatti[b], E. Annoscia[b], M. Marinaro[d], E. Di Leo[a], M.G. Matino[a], R. Buquicchio[a], S. Bonini[c], A. Tursi[a], A. Francavilla[b]

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Impaired intestinal permeability is present in all subjects with adverse reactions to food. regardless of the type of immunogenic reaction (IgE- or non-IgE-mediated).

by using Spearman test, was statistically significant for food allergy ($p = 0.0195$) and hypersensitivity ($p = 0.005$) patients.

Conclusions. The present data demonstrate that impaired intestinal permeability, measured in our conditions, is present in all subjects with adverse reactions to food. In addition, for the first time, we report a statistically significant association between the severity of referred clinical symptoms and the increasing of Intestinal Permeability Index. These data reveal that intestinal permeability is not strictly dependent on IgE-mediated processes but could better be related to other mechanisms involved in early food sensitisation, as breast-feeding, or microbial environment that influence the development of oral tolerance in early infancy.

Keywords: Food allergy; Food hypersensitivity; Intestinal permeability

1. Introduction

Intestinal permeability (I.P.) is the mucosal capacity to allow the passage of molecules from the intestinal lumen to the blood stream. Recent laboratory techniques enable to evaluate the I.P. through urinary detection of sugars probes, administrated in couples that passively cross the intestinal epithelium. Recent studies suggest the use of Lactulose (La) and Mannitol (Ma) as probes; indeed these sugars cross the mucosal epithelium, are recovered in the urine and the ratio of their clearance is used as I.P. assessment [1,2]. Recently, it has demonstrated that the use of a highly dedicated chromatographic device permits to measure appropriately the presence of La and Ma in the urine, providing a good methodology to explore the I.P. in normal and pathological conditions [3]. Thanking to the availability of these technologies, many studies have been performed to determine the I.P. in diseases that involve the gastrointestinal tract, in which the gut integrity is altered, such as Crohn's disease [4,5] and coeliac disease [6,7]. In addition, our previous data on newborns [8] and researches on animal models [9–11] have demonstrated that, during the first months of life, when the intestinal mucosa is still immature, there is an incomplete gut integrity that

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When these analyses were carried out, all patients were on an allergen free diet a minimum of six months.

Methods. Intestinal permeability was evaluated by Lactulose/Mannitol ratio urinary detection determined by anion-exchange chromatography.

Results. Statistically significant different Lactulose/Mannitol ratio was evidenced in subjects with food allergy ($p = 0.003$) or hypersensitivity ($p = 0.0008$) compared to control patients. The correlation between Lactulose/Mannitol ratio and the seriousness of clinical symptoms, by using Spearman test, was statistically significant for food allergy ($p = 0.0195$) and hypersensitivity ($p = 0.005$) patients.

Conclusions. The present data demonstrate that impaired intestinal permeability, measured in our conditions, is present in all subjects with adverse reactions to food. In addition, for the first time, we report a statistically significant association between the severity of referred clinical symptoms and the increasing of Intestinal Permeability Index. These data reveal that intestinal permeability is not strictly dependent on IgE-mediated processes but could better be related to other mechanisms involved in early food sensitisation, as breast-feeding, or microbial environment that influence the development of oral tolerance in early infancy.

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Inflammation and Leaky Gut: A Primary Pathway and Therapeutic Target

Immune Response to Intestinal Antigen Presentation

- → **Intestinal Inflammation from antigen delivery (eating food)**
  - → **Loosening tight junction barrier proteins**
    - → **Antibody production to Barrier Proteins (zonulin,actomyosin)**
      - → **Leaky or Leaking gut, brain, bladder,…**
        - → **Intestinal Permeability (BBB permeability,…)**
          - → **Antigen translocation**
            - → **Antibody Production to antigen (gluten, dairy,…)**
              - → **Molecular Mimicry (Cross Reactivity)**
                - → **Autoimmune Syndromes**

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

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Received 13 Nov 2008; first review completed 26 Nov 2008; accepted in final form 29 Jan 2009

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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DOI: 10.1097/SHK.0b013e3181a2bcd6

Physiol Rev 91: 151–175, 2011

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

ALESSIO FASANO

Mucosal Biology Research Center and Center for Celiac Research, University of Maryland School of Medicine, Baltimore, Maryland

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

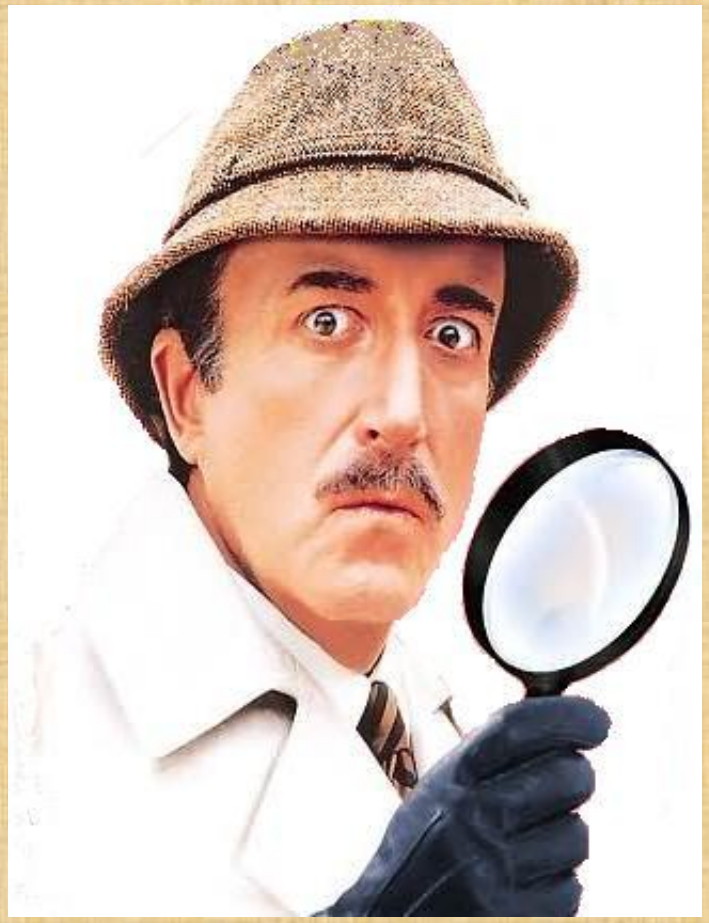
non-self antigens. Zonulin is the only physiological modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the finely tuned zonulin pathway is deregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune, inflammatory, and neoplastic disorders can occur. This new paradigm subverts traditional theories underlying the development of these diseases and suggests that these processes can be arrested if the interplay between genes and environmental triggers is prevented by reestablishing the zonulin-dependent intestinal barrier function. This review is timely given the increased interest in the role of a "leaky gut" in the pathogenesis of several pathological conditions targeting both the intestine and extraintestinal organs.

I. INTRODUCTION

In recent years much has been discovered about the structure, function, and regulation of intercellular tight junctions (TJ). However, the precise mechanism(s) by which they operate is/are still incompletely understood. The discovery of zonula occludens toxin (Zot), an enterotoxin elaborated by *Vibrio cholerae* that affects the TJ competency, has shed light on the intricate mechanisms involved in the modulation of the intestinal paracellular pathway. Our Zot structure-functional analysis demonstrated that the COOH-terminal portion (that we called ΔG) of the toxin is involved in specific proteinase activating receptor $(PAR)_2$ binding and activation of intracellular signaling leading to reversible opening of intercellular TJ (47, 58). Taken collectively, our data suggested that Zot regulates TJ in a rapid, reversible, and reproducible fashion,

Premise #7

How Might The Impact of Intestinal Permeability Present?



CASE STUDY #1

Recurrent Miscarriages and Autoimmune Diseases

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

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 ISSN 1007-9327

• CASE REPORT •

Multiple immune disorders in unrecognized celiac disease: a case report

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Received: 2002-11-26 **Accepted:** 2002-12-22

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

Abstract

We reported a female patient with unrecognized celiac disease and multiple extra intestinal manifestations, mainly

CASE REPORT

A 34 years old, non drinker, non smoking woman, was admitted to the third Medical Clinic, Careggi University Hospital, Florence because of hyper-amilasemia and hyper-lipasemia of unknown origin. The patient had acute meningitis at the age of three. At age of 23, she was admitted to hospital because of syncope, referred to acute gastroenteritis complicated by metabolic acidosis; laboratory evaluation performed on that occasion showed iron deficient anemia, polyclonal hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), reduced C3 levels and circulating antinuclear antibodies (1:80), that led to suspicion of a not otherwise specified collagen disease. Iron deficiency was unresponsive

A 34 years old, non drinker, non smoking woman, was admitted because of hyper-amilasemia and hyper-lipasemia of unknown origin.

Celiac disease (CD), the most common life-long food sensitive enteropathy in humans, is characterized by malabsorption, chronic inflammation of small intestine mucosa, villous atrophy and crypt hyperplasia, which occur as a consequence of the ingestion of wheat gluten or related rye and barley proteins[1,2]. CD is strongly associated with HLA-DQ2, coded by the DQA1*0501 and DQB1*02 alleles, and/or the DQ8 (DQA1*03, DQB1*0302 alleles), but a role of non-HLA genes has also been postulated[2,3]. The current prevalence of celiac disease has increased from 1:1 000 to 1:300 inhabitants, or even more[4]. Typical symptoms include chronic diarrhea, abdominal distension, and failure to thrive[2,5]. However, only few patients with CD show clinical malabsorption, while most patients have subtle symptoms, if any[6]. Therefore, the disease is clearly under diagnosed[2,7]. The recent introduction of tests for IgA anti-endomysial antibodies and the anti-tissue transglutaminase test has proved promising with a sensitivity and specificity of over 95 %[2,8,9].

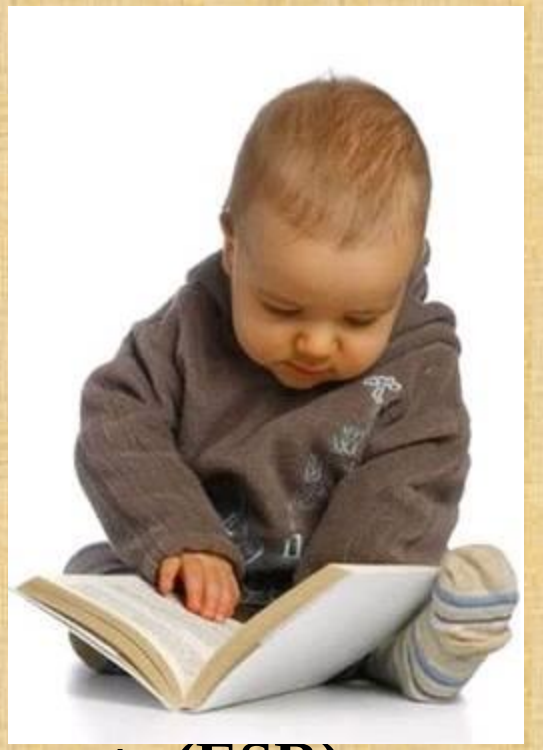
Celiac disease may be associated with a wide range of diseases[2,8], including thyroid, dermatological and lympho-proliferative disorders, mainly intestinal lymphomas[2]. Furthermore, there is a greater than expected prevalence of immune disorders in CD patients[2,10-12] as well as of CD in patients with autoimmune diseases[13-15].

The current report dealed with a female patient with unrecognized CD and recurrent miscarriage, [illegible] macrolipasemia, IgA nephropathy, and thyroiditis that

At the time of admission to our hospital unit, physical examination was completely negative. Routine blood analysis showed anemia (Ht: 32.8 %, Hb: 11.2 g/dL), thrombocytosis (452 000 platelets/mL), high ESR (124 mm/h), low plasma albumin (3.05 g/dL), and high levels of IgA (1 100 mg/dL) and IgM (369 mg/dL) with no monoclonal component. The patient also had low ferritin (<9 mg/mL) and tetrahydrofolate levels (1.9 ng/ml; normal range 3-17 ng/mL). A coagulation study showed the presence of lupus anticoagulant (Table 1). Enzyme studies confirmed a remarkable increase of serum amylase (1 196 IU/L), pancreatic isoamylase fraction (798 IU/L), and serum lipase (1 650 IU/L). On the other hand, urinary amylase excretion was normal (120, normal value <1 500 IU/day), and ultrasound examination of the pancreas was normal. A chromatographic assay was therefore performed at another Institution (Ospedali Riuniti, Padova, Italy), which demonstrated the presence of macroamylasemia and macrolipasemia.

Our patient had iron-deficient anemia, which was refractory to oral iron supplementation, a well known presenting sign of CD[2,6,16], together with low albumin and tetrahydrofolate levels. In addition, she had macroamylasemia and macrolipasemia which could be associated with CD[17]. Therefore, a search was performed for circulating anti-gliadin, anti-endomysial and anti-transglutaminase (TTG) antibodies. Detection of these antibodies (Table 1) led us to perform upper gastrointestinal [illegible] and duodenal biopsy, which confirmed the diagnosis of CD. A gluten free diet was therefore introduced.

Health History (since age 3)



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

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• CASE REPORT •

Multiple immune disorders in unrecognized celiac disease: a case report

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Iron deficiency was unresponsive to supplement of oral iron, while it improved following intravenous therapy.

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gluten-free diet.

La Villa G, Pantaleo P, Tarquini R, Cirami L, Perfetto F, Mancuso F, Laffi G. Multiple immune disorders in unrecognized celiac disease: a case report. *World J Gastroenterol* 2003; 9(6): 1377-1380
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The current report dealed with a female patient with unrecognized CD and recurrent miscarriage, [illegible] macrolipasemia, IgA nephropathy, and thyroiditis that

a thorough investigation was performed that was negative for potential causes of fetal demise, including fasting glucose, basal FSH, LH and estradiol levels on day 3 of a natural cycle, TSH and prolactin levels, antinuclear antibodies, antibodies against infectious agents, hysterosalpingography and genetic karyotyping of the couple. On that occasion, she was found to have hyperamilasemia and hyperlipasemia, together with the previously reported laboratory alterations; so further investigations were performed including CT, which turned out to be negative for any pancreatic disease.

At the time of admission to our hospital unit, physical examination was completely negative. Routine blood analysis showed anemia (Ht: 32.8 %, Hb: 11.2 g/dL), thrombocytosis (452 000 platelets/mL), high ESR (124 mm/h), low plasma albumin (3.05 g/dL), and high levels of IgA (1 100 mg/dL) and IgM (369 mg/dL) with no monoclonal component. The patient also had low ferritin (<9 mg/mL) and tetrahydrofolate levels (1.9 ng/ml; normal range 3-17 ng/mL). A coagulation study showed the presence of lupus anticoagulant (Table 1). Enzyme studies confirmed a remarkable increase of serum amylase (1 196 IU/L), pancreatic isoamylase fraction (798 IU/L), and serum lipase (1 650 IU/L). On the other hand, urinary amylase excretion was normal (120, normal value <1 500 IU/day), and ultrasound examination of the pancreas was normal. A chromatographic assay was therefore performed at another Institution (Ospedali Riuniti, Padova, Italy), which demonstrated the presence of macroamylasemia and macrolipasemia.

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The patient had two spontaneous abortions when aged 30 and 31 years, respectively, both at the 16th week of gestation

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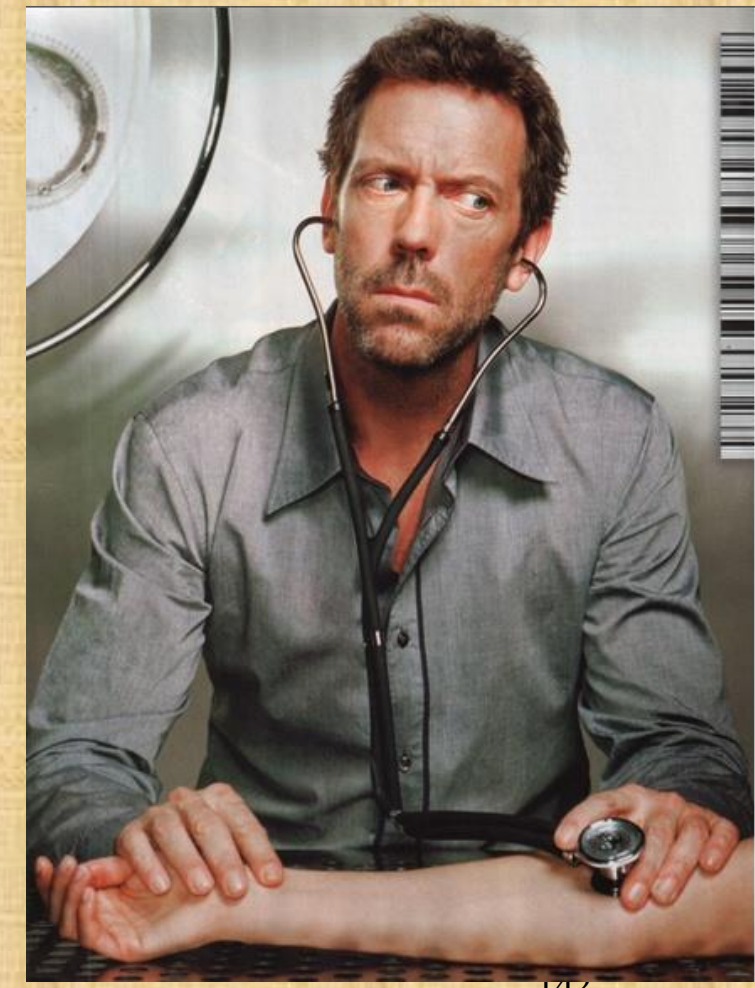
During admission because of the second abortion, a thorough investigation was performed that was negative for potential causes of fetal demise, including:

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

On that occasion, she was found to have:

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



On that occasion, she also was found to have:

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

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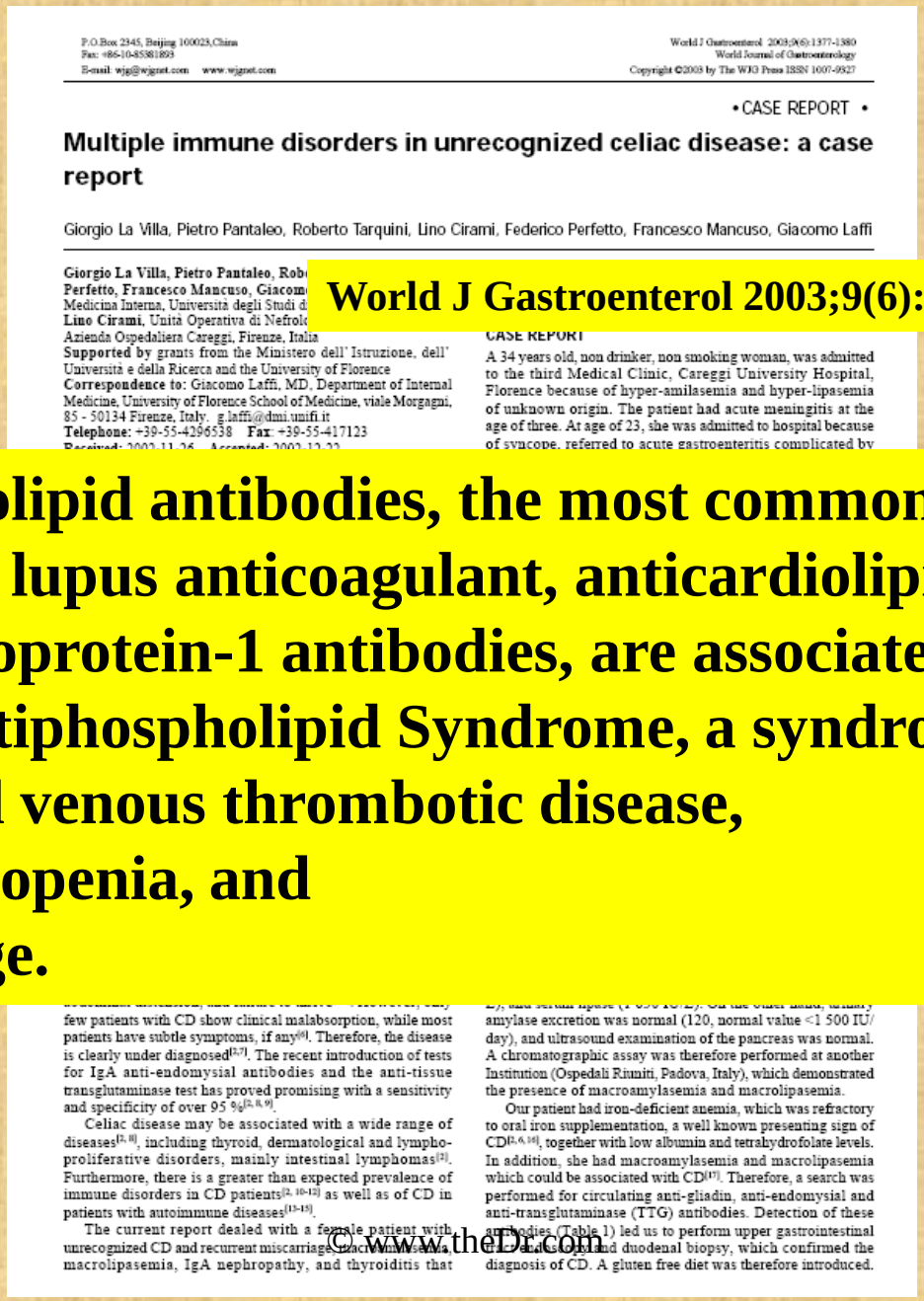
2003;9(6):13[illegible]



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

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

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

- body weight increased 12 kg

- laboratory rechecks demonstrated normalization of serum amylase, serum lipase and all immunoglobulin levels antigliadin, anti-b2-glicoprotein-1, anti-thyroglobulin antibodies were no longer detectable but <u>antiendomysial antibodies were still present</u>.

-Due to the persistence of proteinuria (2.3 g/day), microscopic hematuria and hyaline and granular casts, a kidney biopsy was positive for IgA nephropathy

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Repeat Endoscopy:
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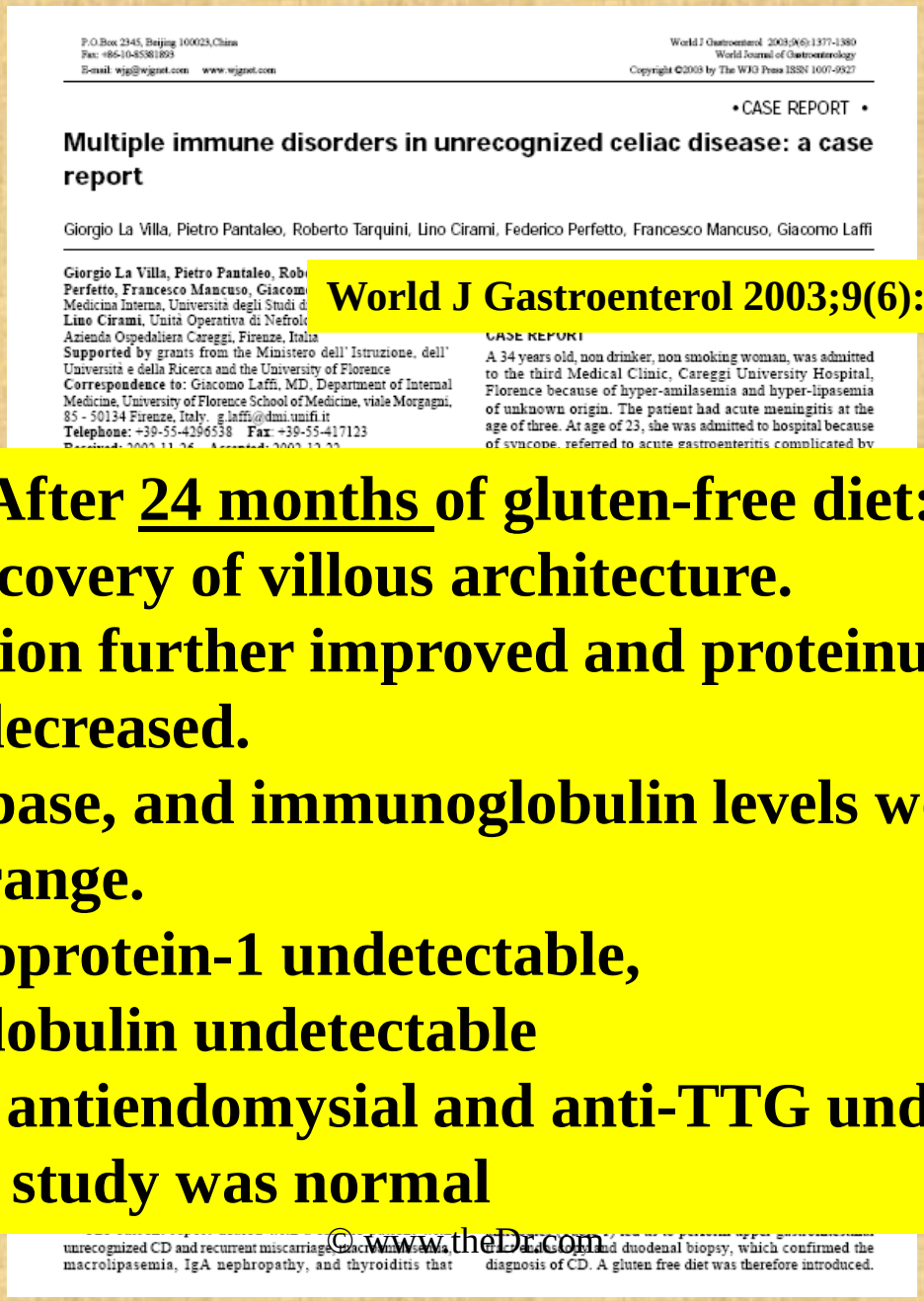
Recommendation to the patient???
“You’re improving. Stay the course”
“But Dr. It’s been SIX MONTHS”
“STAY THE COURSE”



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Supported by grants from the Ministero dell' Istruzione, dell' Università e della Ricerca and the University of Florence
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World J Gastroenterol 2003;9(6):1377-1380

CASE REPORT

A 34 years old, non drinker, non smoking woman, was admitted to the third Medical Clinic, Careggi University Hospital, Florence because of hyper-amilasemia and hyper-lipasemia of unknown origin. The patient had acute meningitis at the age of three. At age of 23, she was admitted to hospital because of syncope, referred to acute gastroenteritis complicated by

unrecognized CD and recurrent miscarriage, [illegible] and duodenal biopsy, which confirmed the diagnosis of CD. A gluten free diet was therefore introduced.

macrolipasemia, IgA nephropathy, and thyroiditis that

After <u>24 months</u> of gluten-free diet:

-complete recovery of villous architecture.

-Renal function further improved and proteinuria markedly decreased.

-Amylase, lipase, and immunoglobulin levels were within the normal range.

Anti-b2-glicoprotein-1 undetectable,

-anti-thyroglobulin undetectable

-antigliadin, antiendomysial and anti-TTG undetectable

-coagulation study was normal

Syncope

Acute gastroenteritis

Metabolic Acidosis

Anemia

Hypergammaglobulinemia

Elevated ESR

Positive ANA

Positive SLE indicators

Low Ferritin, Low Tetrahydrofolate

Total Villous Atrophy and Celiac Disease

Positive Pancreatic Hypersecretion

Positive Thyroid Antibodies

IgA Nephropathy

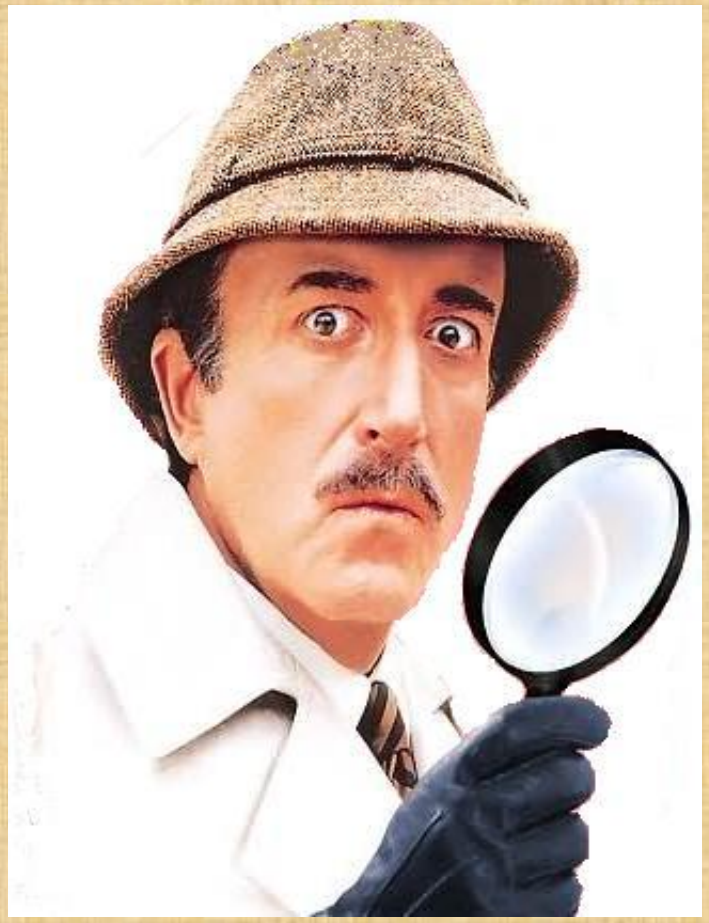
Loss of 2 pregnancies

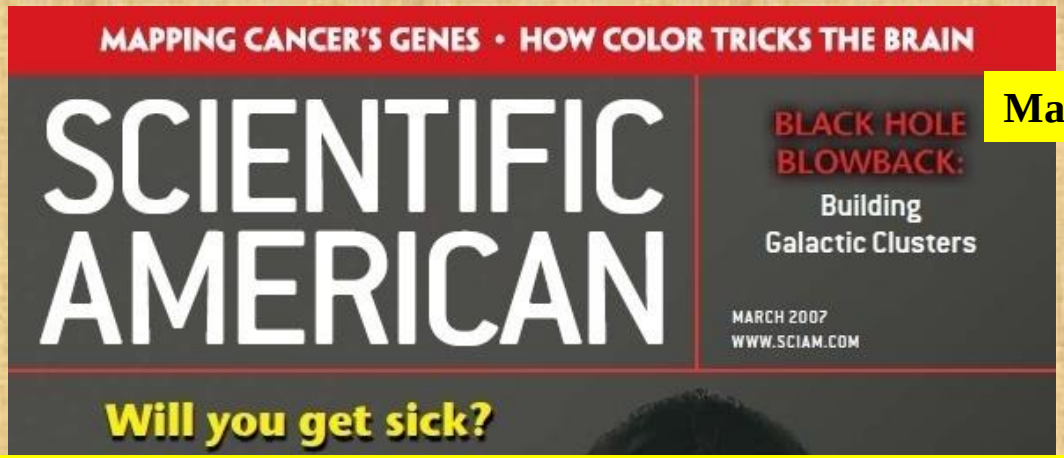
CAN SUPPOSEDLY GOOD FOODS ALL BE RESOLVED ON A GFD

REALLY DO THIS TO ME???

WITHIN 2 YEARS

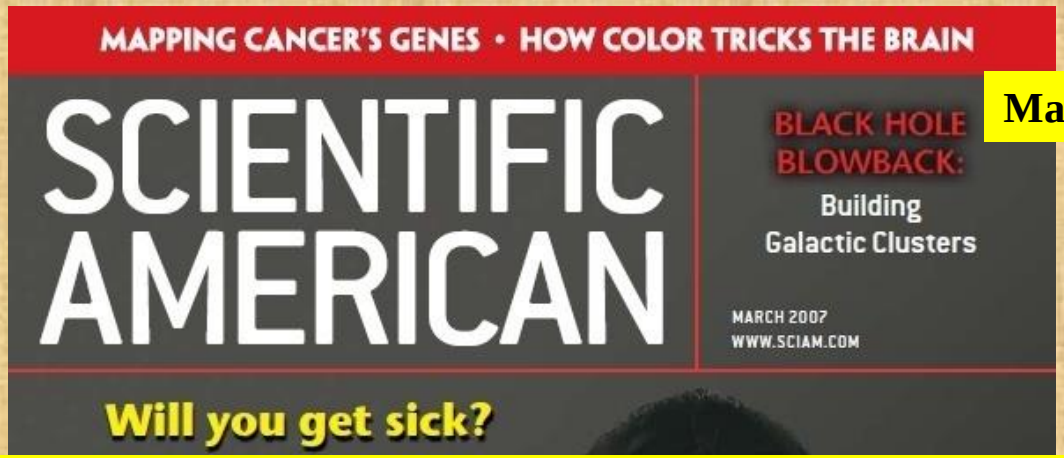
Premise #8
When Does Autoimmune Disease Begin?





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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus

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

NEJM:2003;349:1526-1533

ABSTRACT

BACKGROUND

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.

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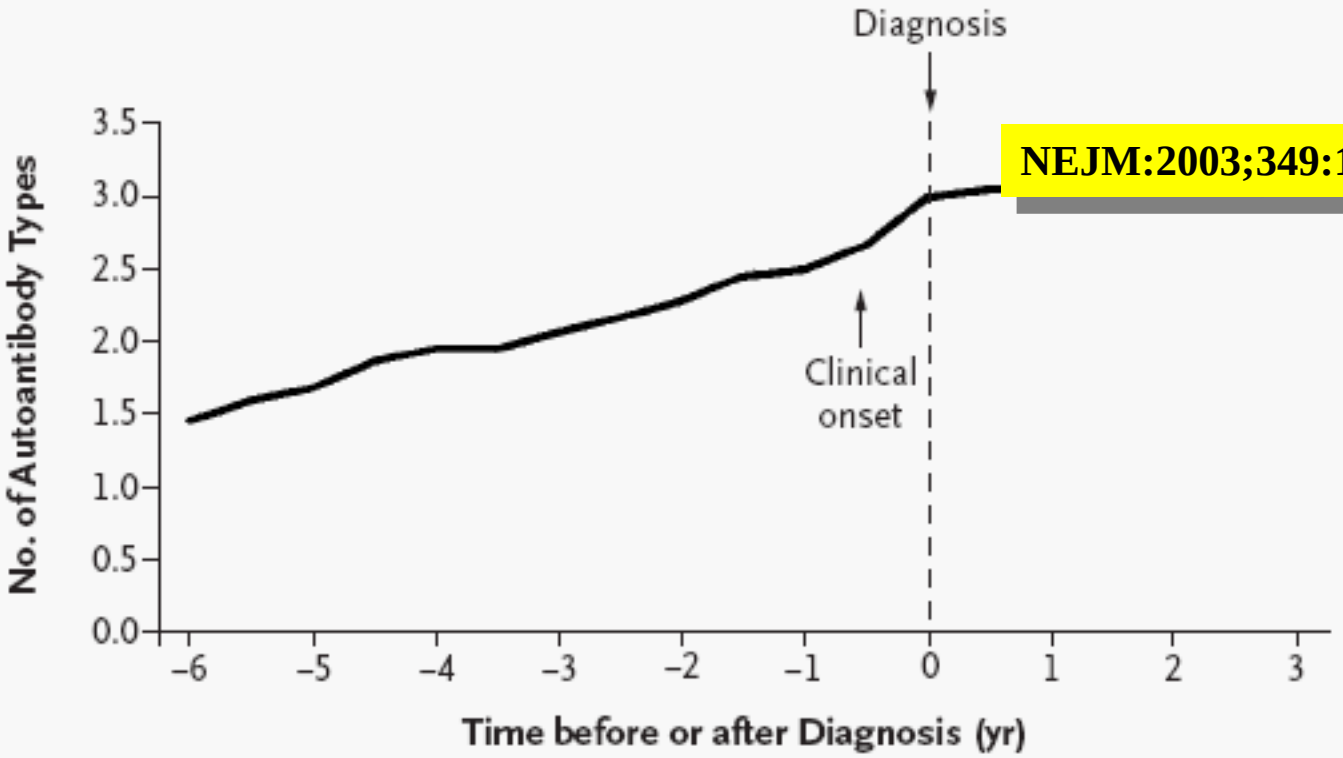
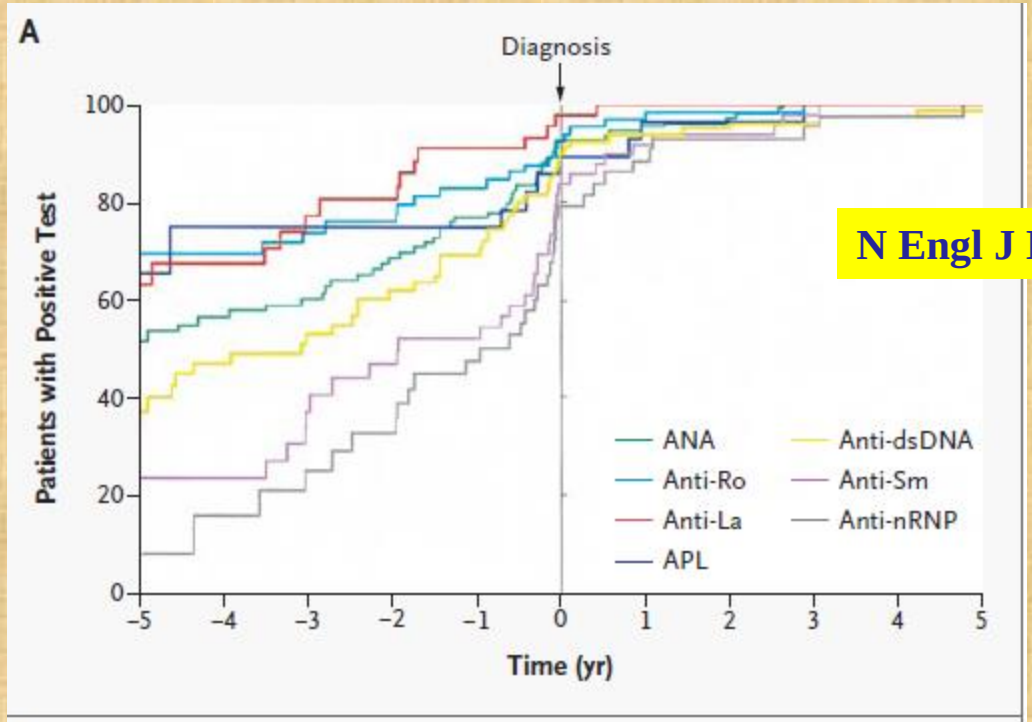


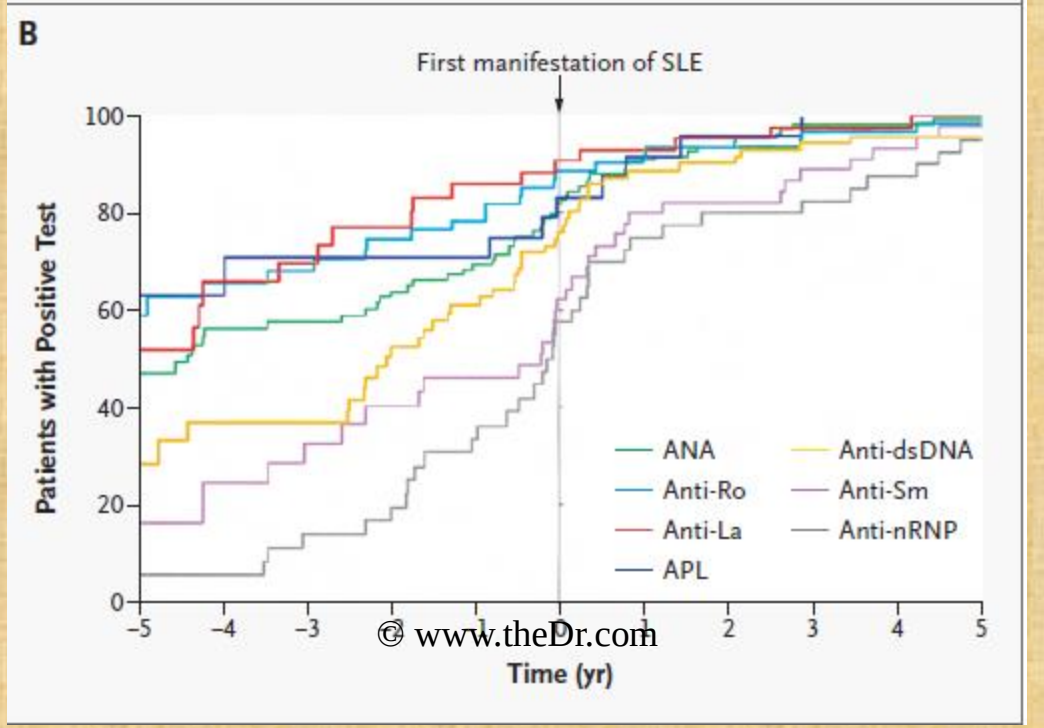
NEJM:2003;349:1526-1533

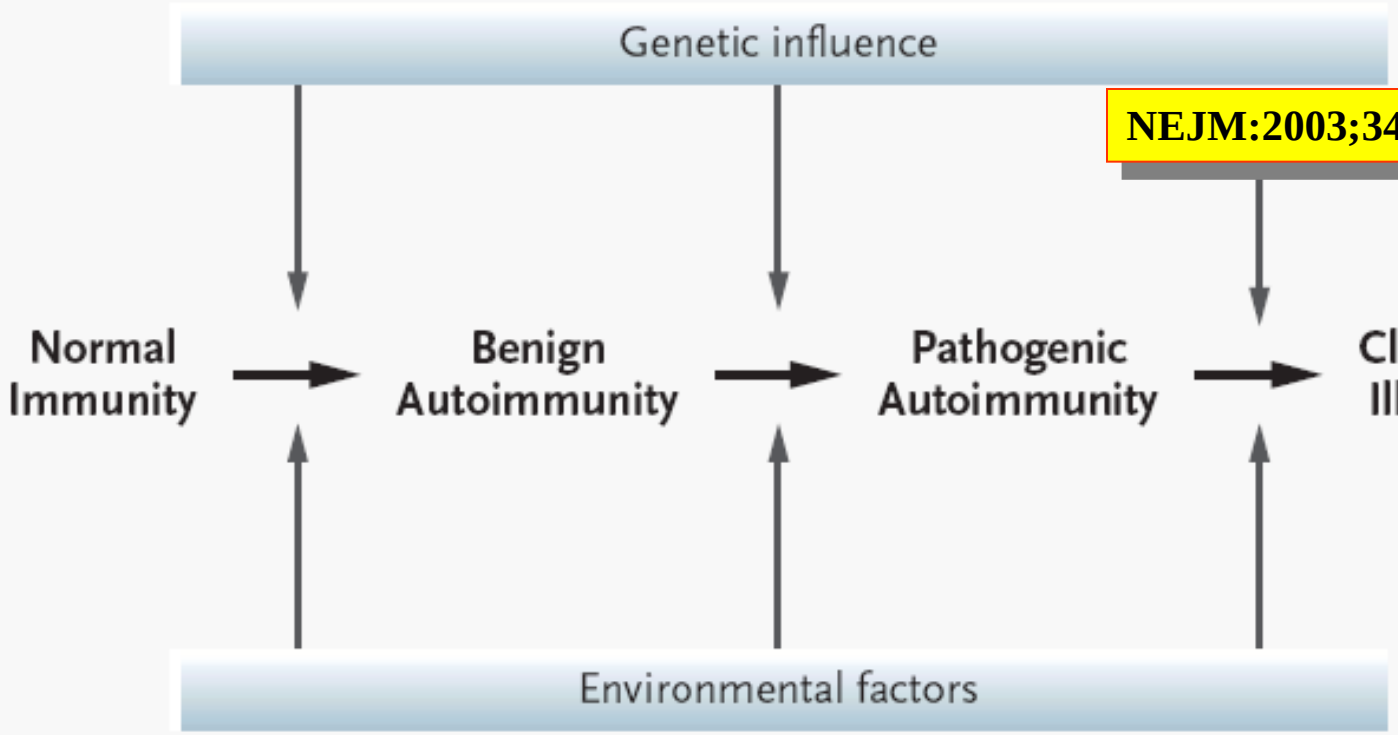
Figure 2. Accumulation of Systemic Lupus Erythematosus Autoantibodies.

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.





NEJM:2003;349:1526-1533

Figure 3. Phases in the Development of Pathogenic Autoimmunity.

Normal immunity progresses to benign autoimmunity through the influence of genetic composition and environment. Later, benign autoimmunity progresses to pathogenic autoimmunity. Symptoms of clinical illness appear soon after pathogenic autoimmunity develops.

Are You Developing an Autoimmune Disease Years Before Symptoms?

Prof. Yehuda Shoenfeld, MD, FRCP

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

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

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

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

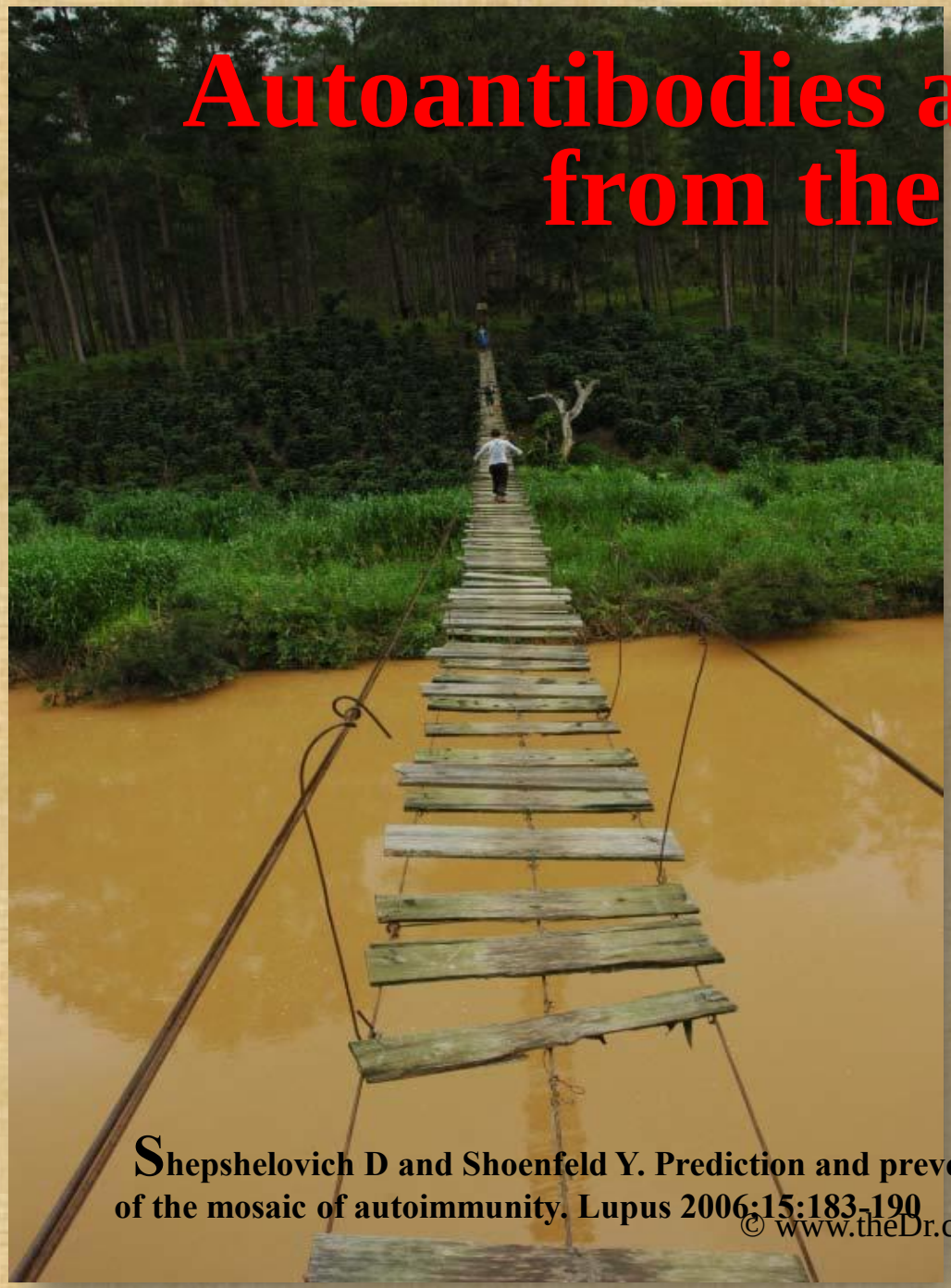
Dr. Shoenfeld: In some ways we do have some measurements. But I would like to refer to one of them, which is very simple, it's cheap, and it has no side effects whatsoever. And this is vitamin D.

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

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

The Mosaic of Autoimmunity: Prediction, Autoantibodies, and Therapy in Autoimmune Diseases – 2008

Yehuda Shoenfeld MD[1,2*], Miri Blank PhD[2], Mahmoud Abu-Shakra MD[3], Howard Amital MD[4], Ori I
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Yaniv Sherer MD[1,2], Elias Toubi MD[12] and M. Eric Gershwin MD[13]

[1] Department of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[2] Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Israel
[3] Rheumatic Diseases Unit, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[4] Department of Medicine D, Meir Medical Center, Kfar Saba, and Sackler Faculty of Medicine, Tel Aviv University, Israel
[5] Department of Pediatrics, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv

IMAJ 2008;10:13–19

The positive predictive value of anti-tissue transglutaminase and anti-endomysial antibodies for celiac disease onset is 50–60%

Key words: autoimmunity, prediction, autoantibodies, biological therapies, intravenous immunoglobulin, T regulatory cells, primary biliary cirrhosis

IMAJ 2008;10:13–19

The most significant development in our understanding of autoimmunity in the last 5 years relates to our ability to predict autoimmune diseases.

Predictivity of autoimmunity

For more than two decades, the detection of serum autoantibodies has been used for the diagnosis and classification of autoimmune diseases. In addition, some autoantibodies have a prognostic significance or are used as markers for disease activity. In recent years a new piece in the mosaic of autoimmunity has clearly emerged – namely, the predictive value of autoantibodies. Indeed, many autoantibodies can be detected in the preclinical phase of autoimmune diseases many years before the disease becomes apparent; furthermore, they have a high diagnostic positive predictive value [1].

Among autoimmune rheumatic diseases, antibodies to RNP, Sm, dsDNA, cardiolipin, Ro and La have a PPV for systemic lupus erythematosus of 94–100%. According to the type of antibody, the appearance can precede clinical diagnosis by 7–10 years with a frequency that varies from 32% to 78% at the moment of diagnosis [2]. In subjects with scleroderma, anti-centromere and anti-topoisomerase I antibodies are detectable, with a PPV of 100%, up to 11 years before clinical manifestations. In rheumatoid arthritis, the rheumatoid factor has a predictivity of 52–88%, depending on the study, while for anti-cyclic citrullinated peptide antibodies the predictivity is much higher, reaching 97%. If the rheumatoid factor and anti-CCP antibodies are both present, PPV rises to 100%. These two antibodies have even been detected in the serum up to 14 years before patients manifested the first symptoms of the disease.

Anti-Ro and anti-La antibodies were detected on average 5 years before the appearance of overt clinical signs and symptoms of Sjögren's disease in 73% of asymptomatic mothers who had given birth to a child with autoantibody-associated congenital heart block and who later developed Sjögren's syndrome.

Anti-nucleosome antibodies were found in 67% of patients with primary antiphospholipid syndrome up to 11 years before the development of SLE. Their PPV was 100%. Additionally, anti-cardiolipin antibodies may help to predict cases of SLE shifting to secondary APS [3].

* Incumbent of the Laura Schwartz-Kipp Chair for Research of Autoimmune Diseases, Tel Aviv University, Israel
PPV = positive predictive value

CCP = cyclic citrullinated peptide
SLE = systemic lupus erythematosus
APS = antiphospholipid syndrome

The Mosaic of Autoimmunity: Prediction, Autoantibodies, and Therapy in Autoimmune Diseases – 2008

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[5] Department of Pediatrics, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv

IMAJ 2008;10:13–19

If the patient carries the HLA-DQ2 or DQ8 antigens, known to be genetic markers for susceptibility to celiac disease, the PPV of the autoantibodies approaches 100%.

Key words: autoimmunity, prediction, autoantibodies, biological therapies, intravenous immunoglobulin, T regulatory cells, primary biliary cirrhosis

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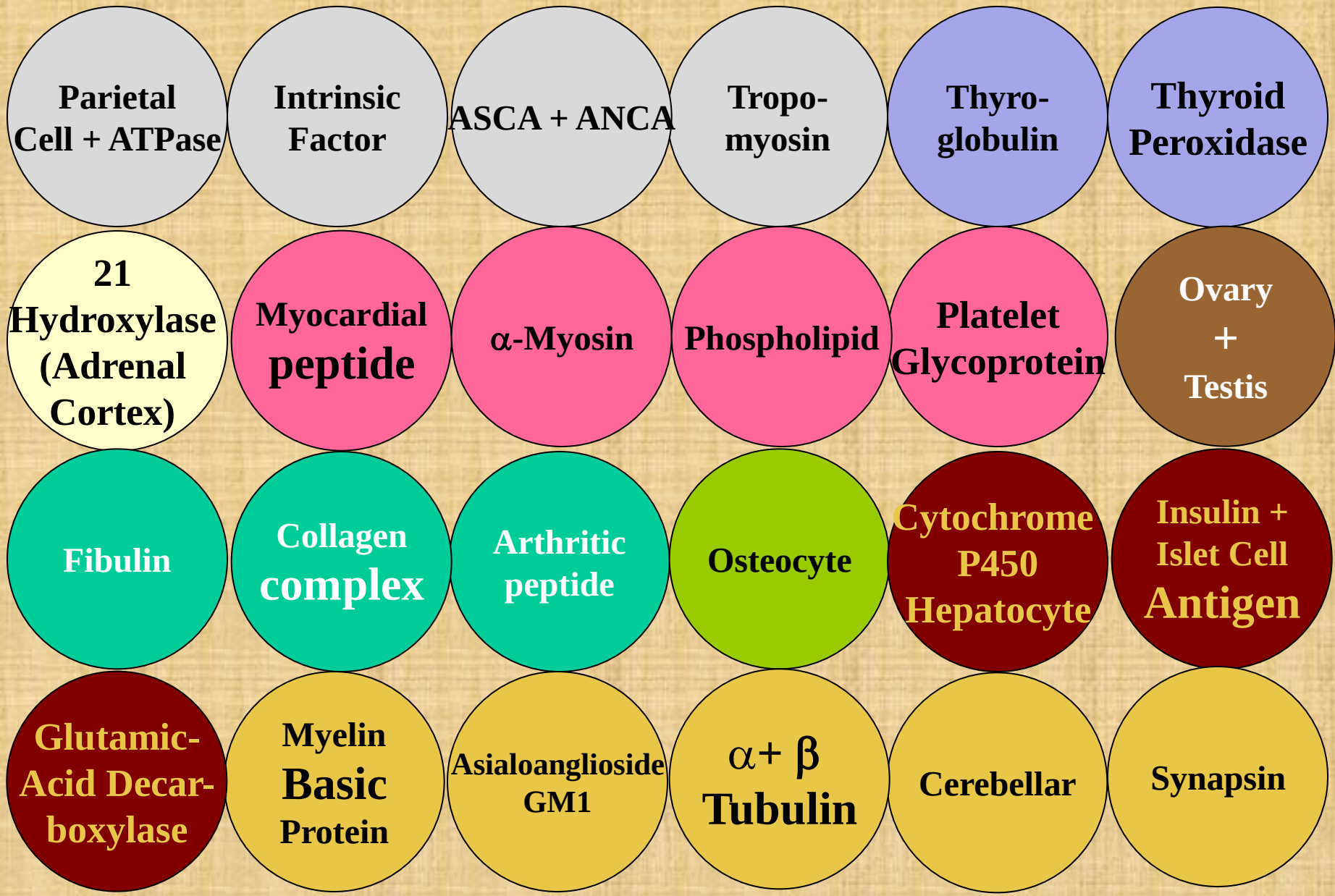
Array 5 – Multiple Autoimmune Reactivity Screen




9 Premises To Look At

Premise #1

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

Detective Adrian Monk

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

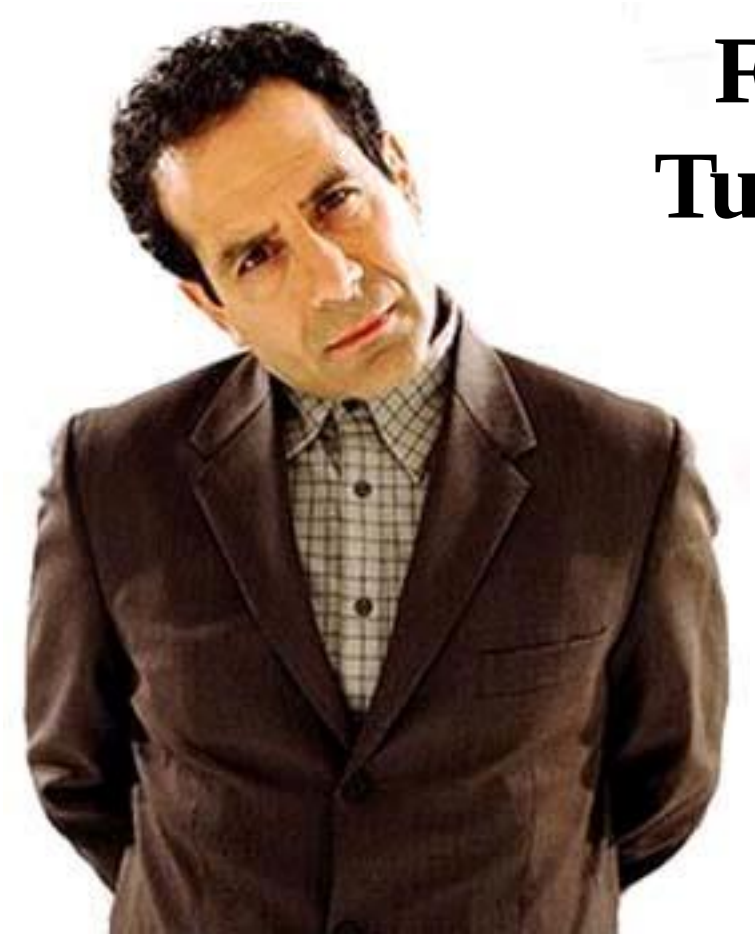
While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 8 percent of the United States population – 24 million persons.

Premise #2

Genes Control Function

Detective Adrian Monk

Premise #3

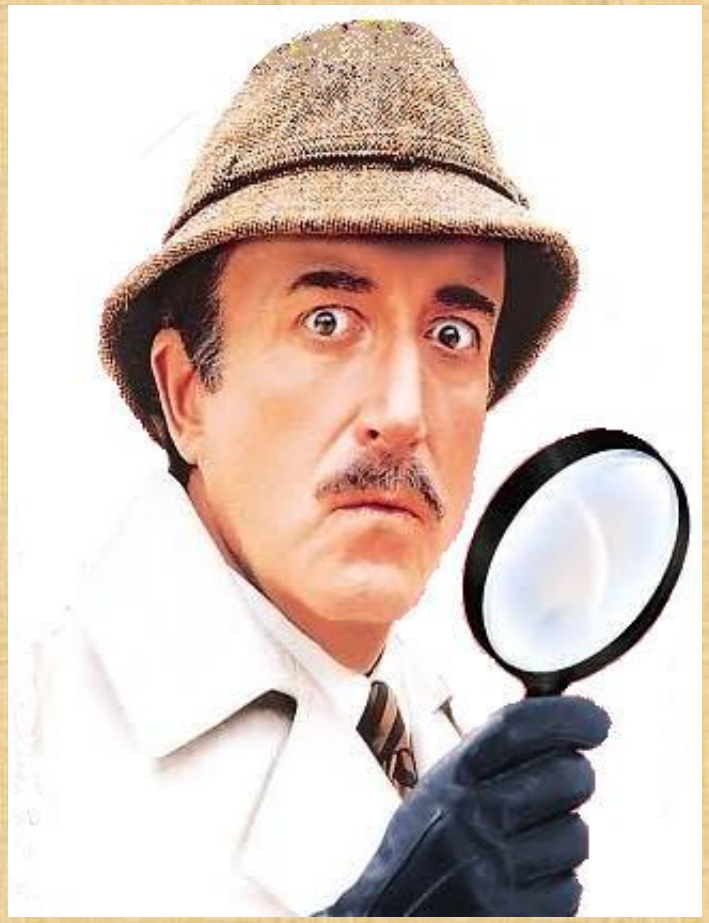


Food Turns On and Turns OFF Our Genes

Detective Adrian Monk

Premise #4

Where Does the Persisting Inflammation Come From?



Premise #5
What is the Impact of Intestinal Permeability?

Gastroenterol Clin N Am 37 (2008) 411–428

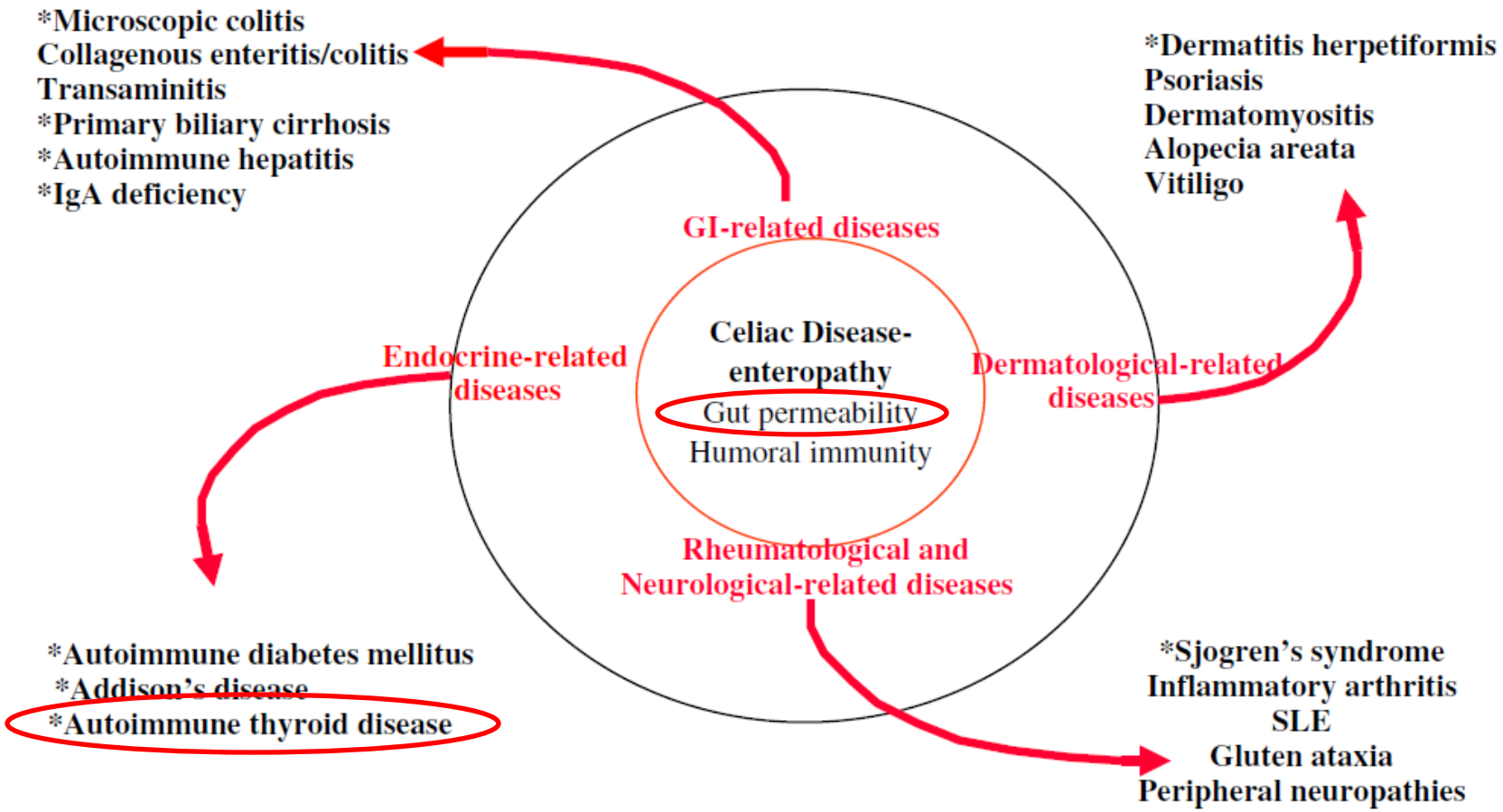
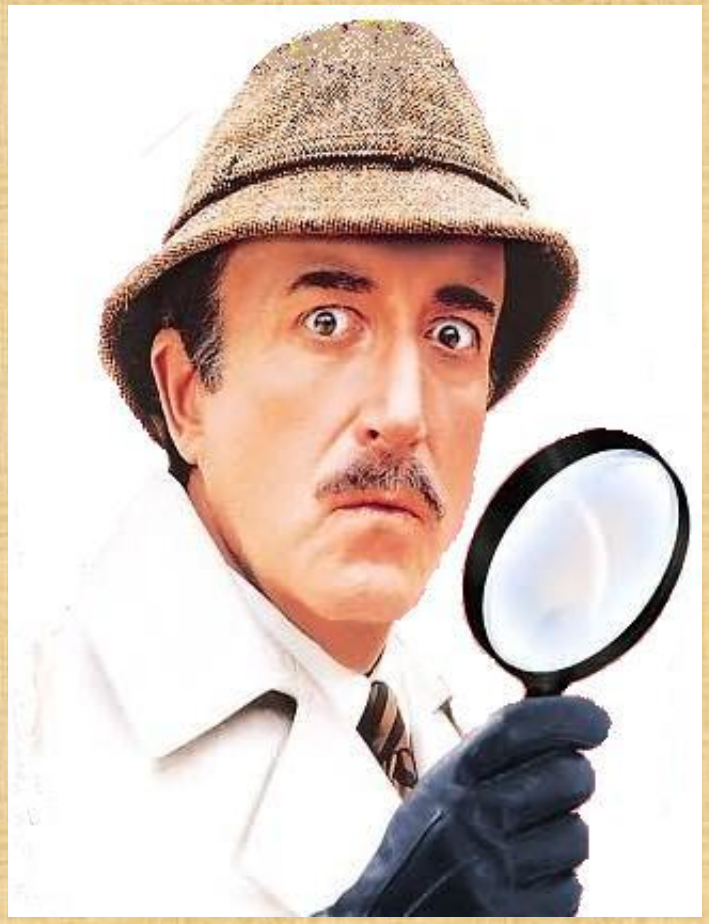


Fig. 1. Autoimmune and inflammatory diseases in relation to celiac disease. *Strongest associations.

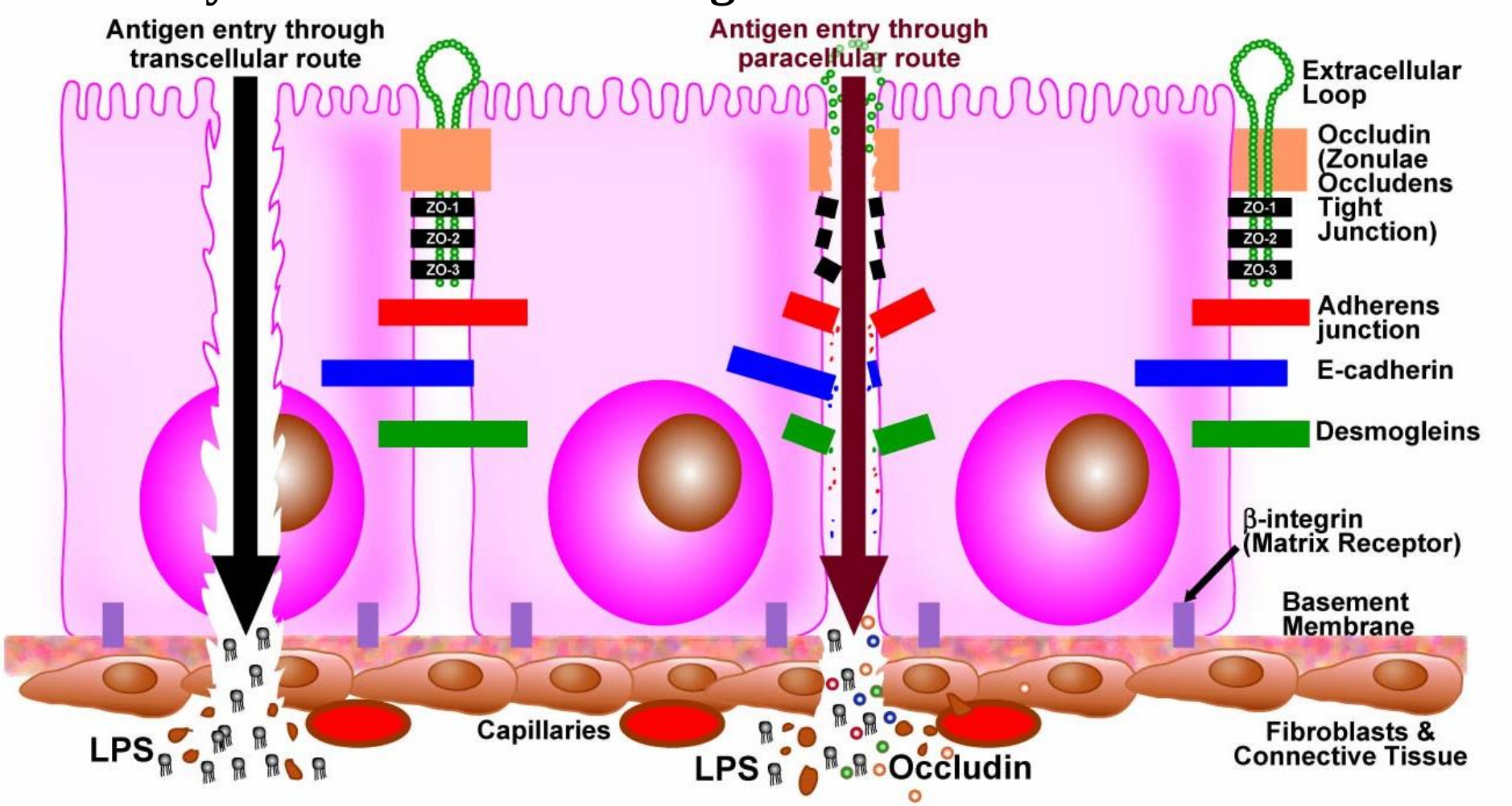
Premise #6

What is the Mechanism of Intestinal Permeability?



Breakdown of Actomyosin Network

Breakdown of Tight Junction Function

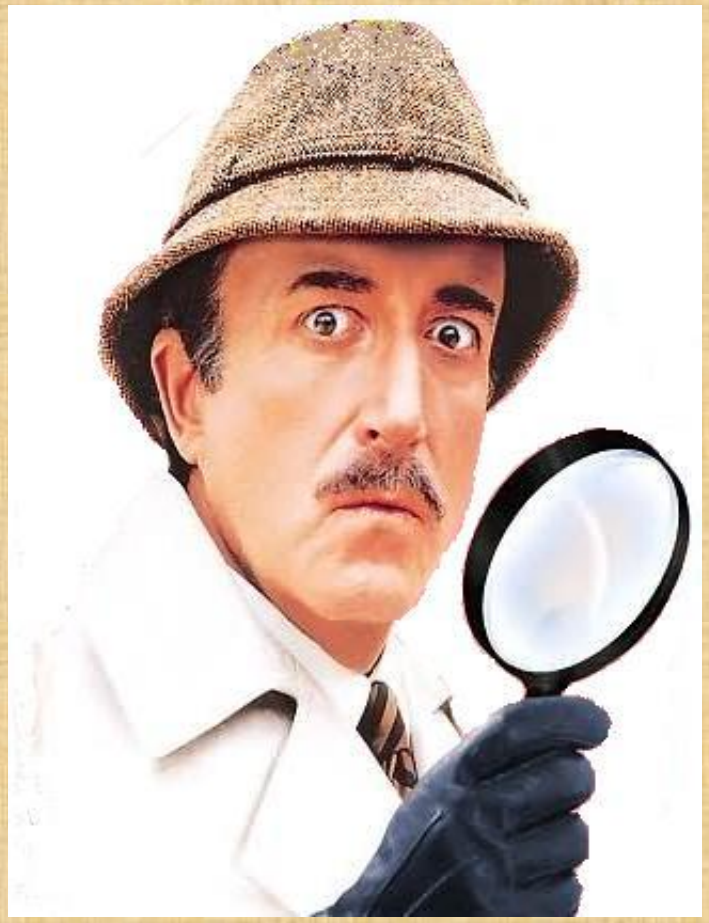


The pathways of antigen invasion through <u>Transcellular</u> and <u>Paracellular</u> routes.

186

Premise #7

How Might The Impact of Intestinal Permeability Present?

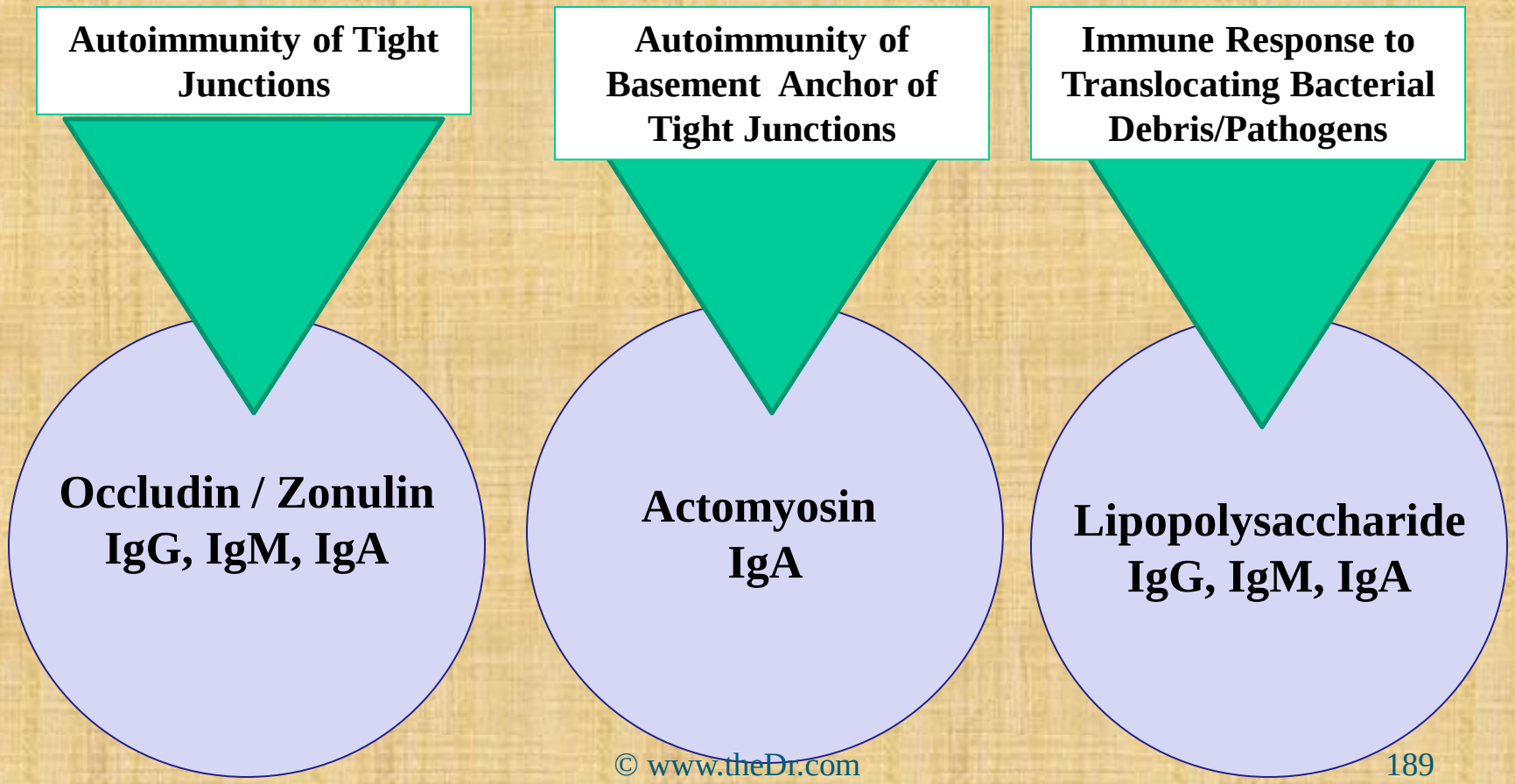


Premise #8
Immunological Markers in Screening for Antigenic Intestinal Permeability

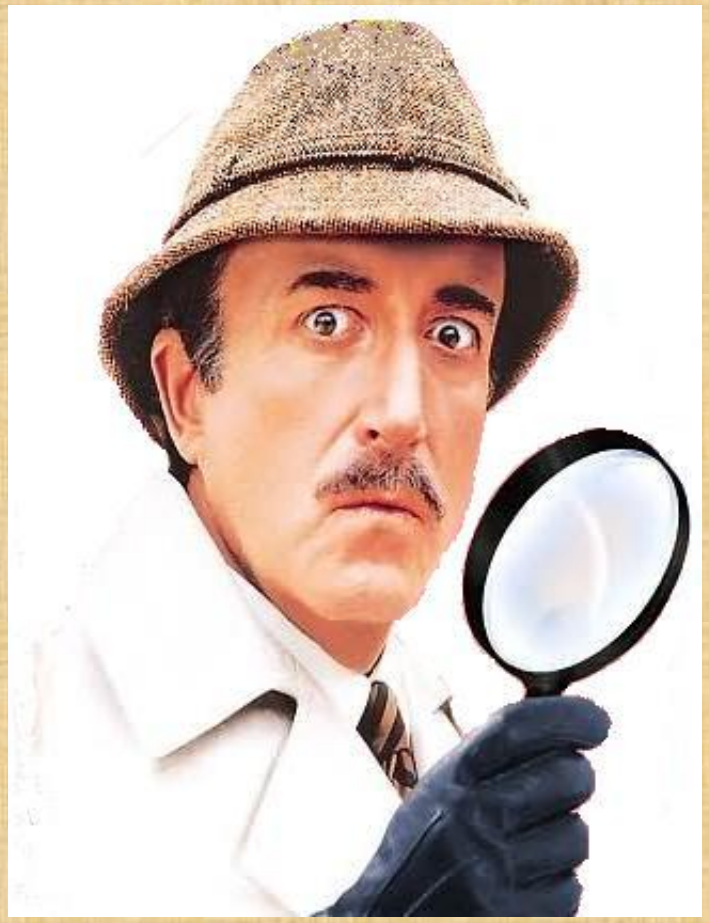
Mucosal Immunology Vol 3 No 3 | MAY 2010
Neuroendocrinology Letters Volume 29 No. 1 2008
J Affect Disord. 2007 Apr;99(1-3):237-40
Neuro Endocrinol Lett. 2007 Dec;28(6):739-44.

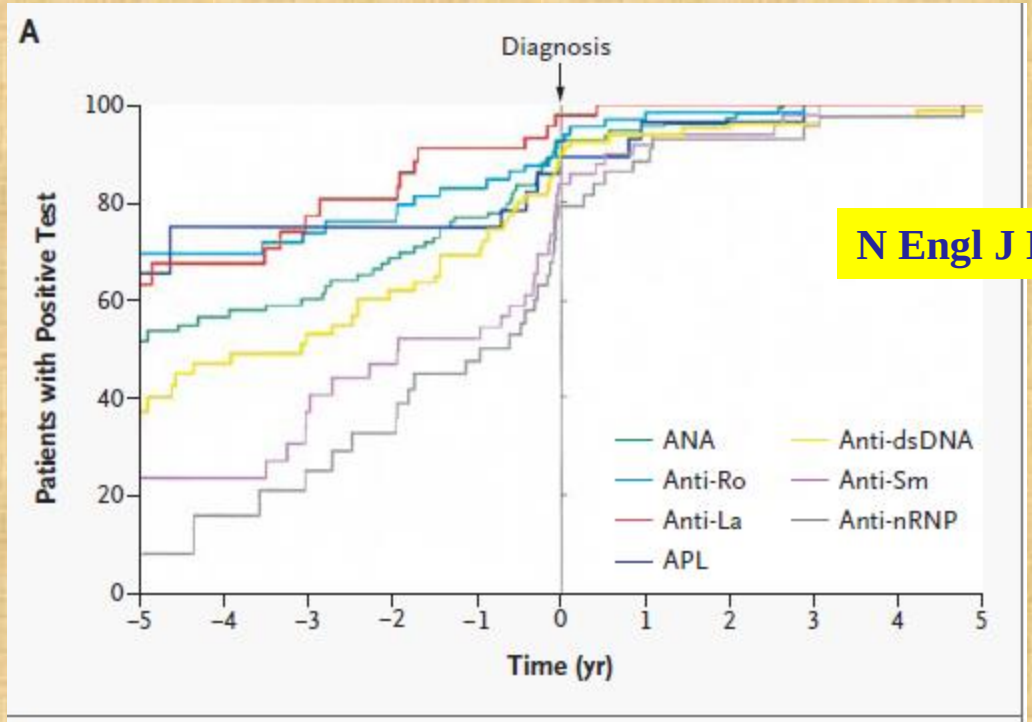
Immunological Markers in Screening for Antigenic Intestinal Permeability

BLOOD



Premise #9
When Does Autoimmune Disease Begin?





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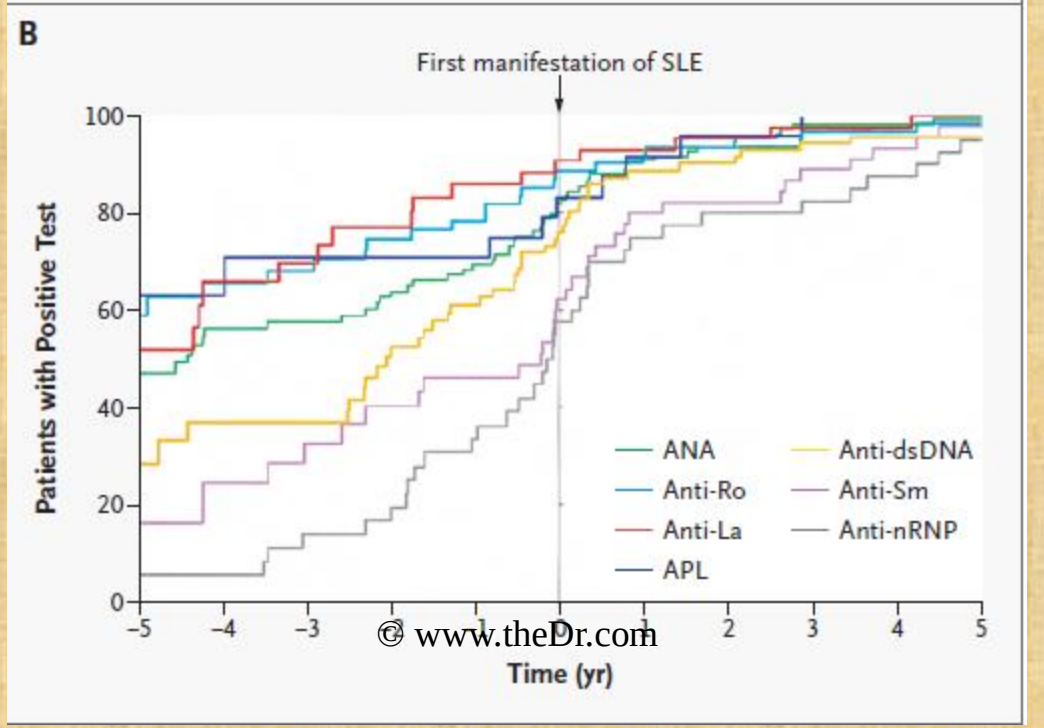

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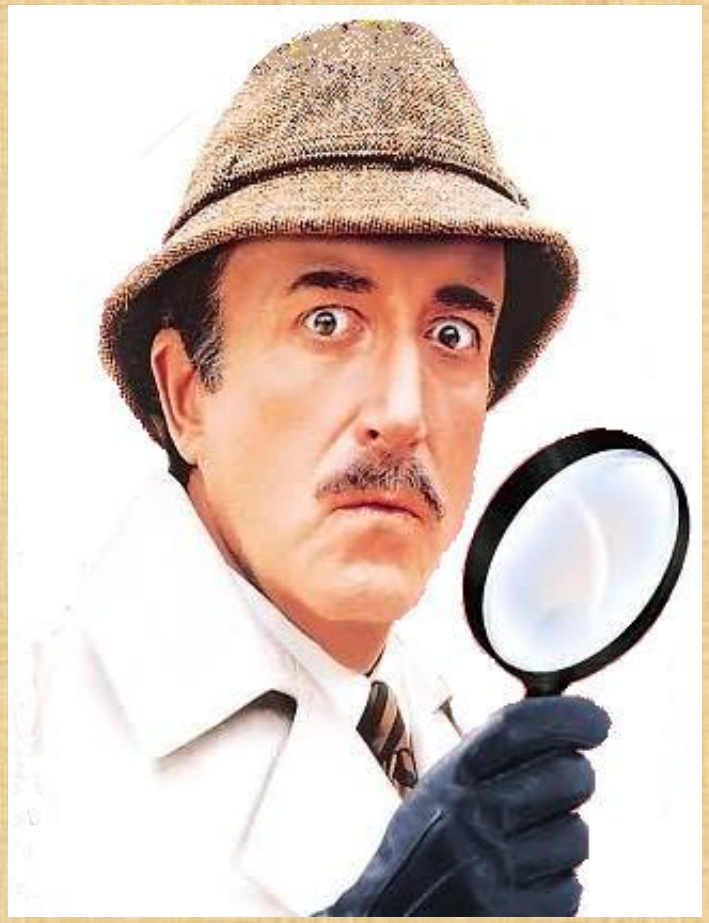
Premise #10
How Might The Impact of Intestinal Permeability Present?



CASE STUDY #1

Recurrent Miscarriages and Autoimmune Diseases

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

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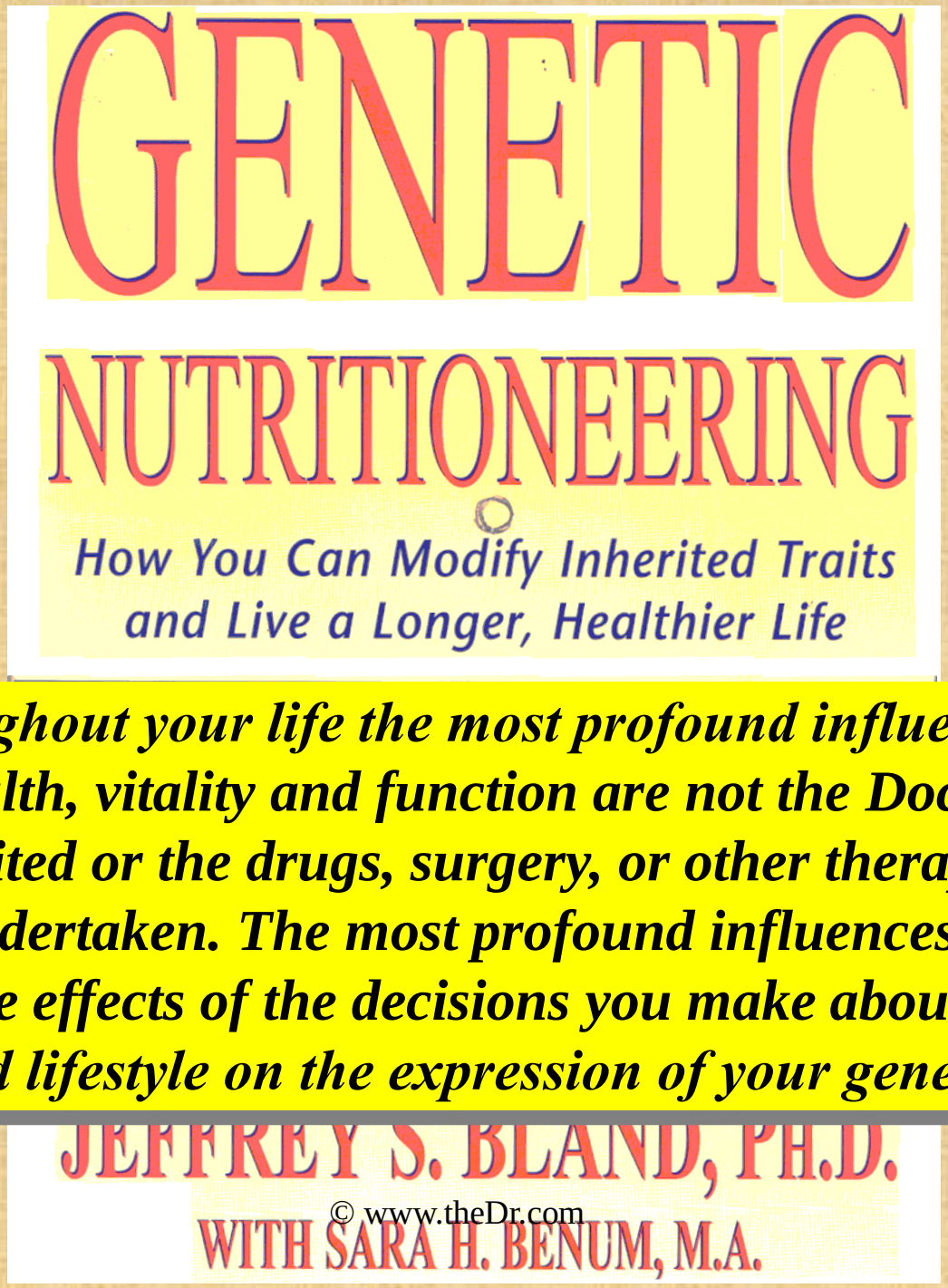
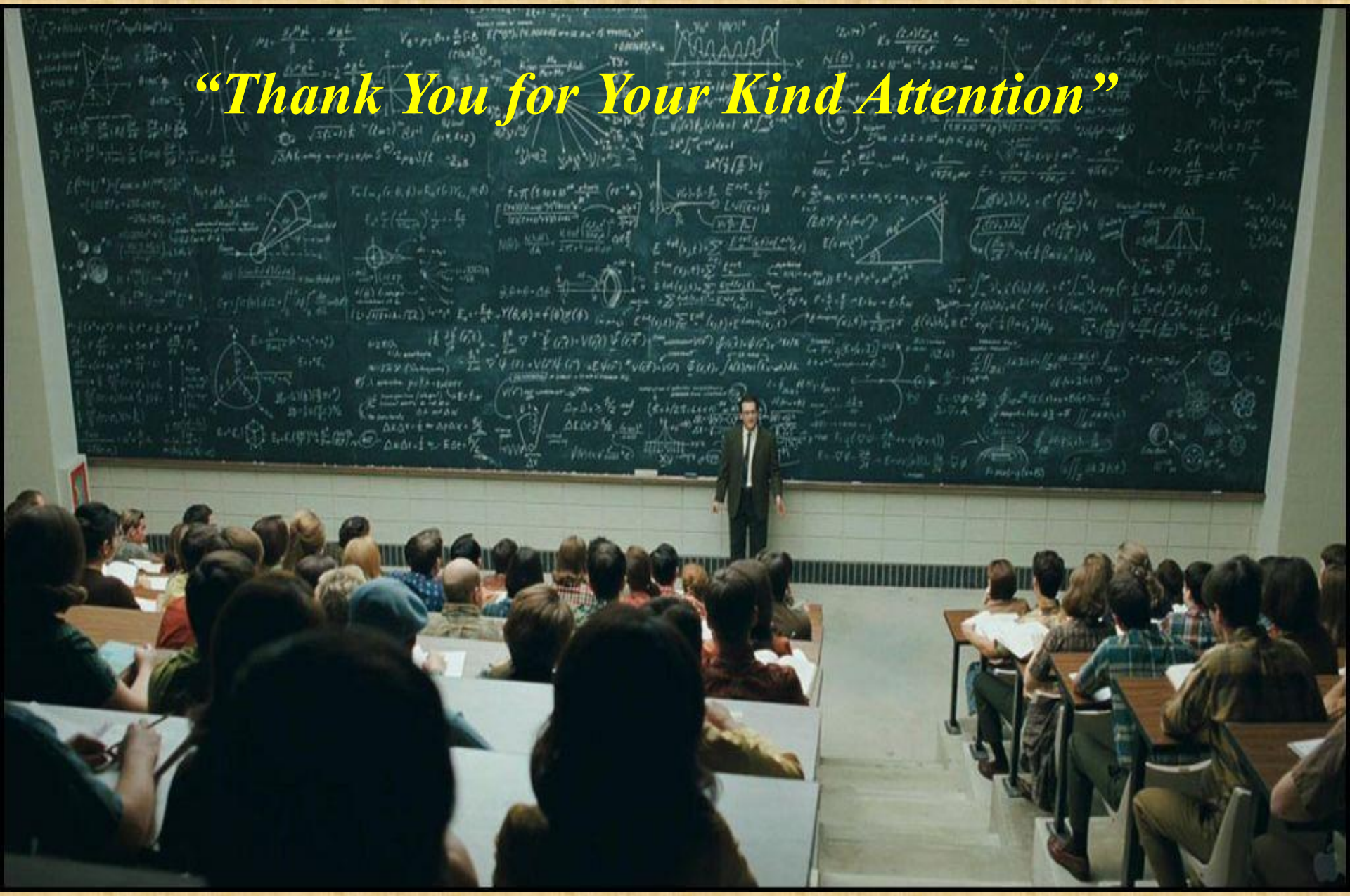
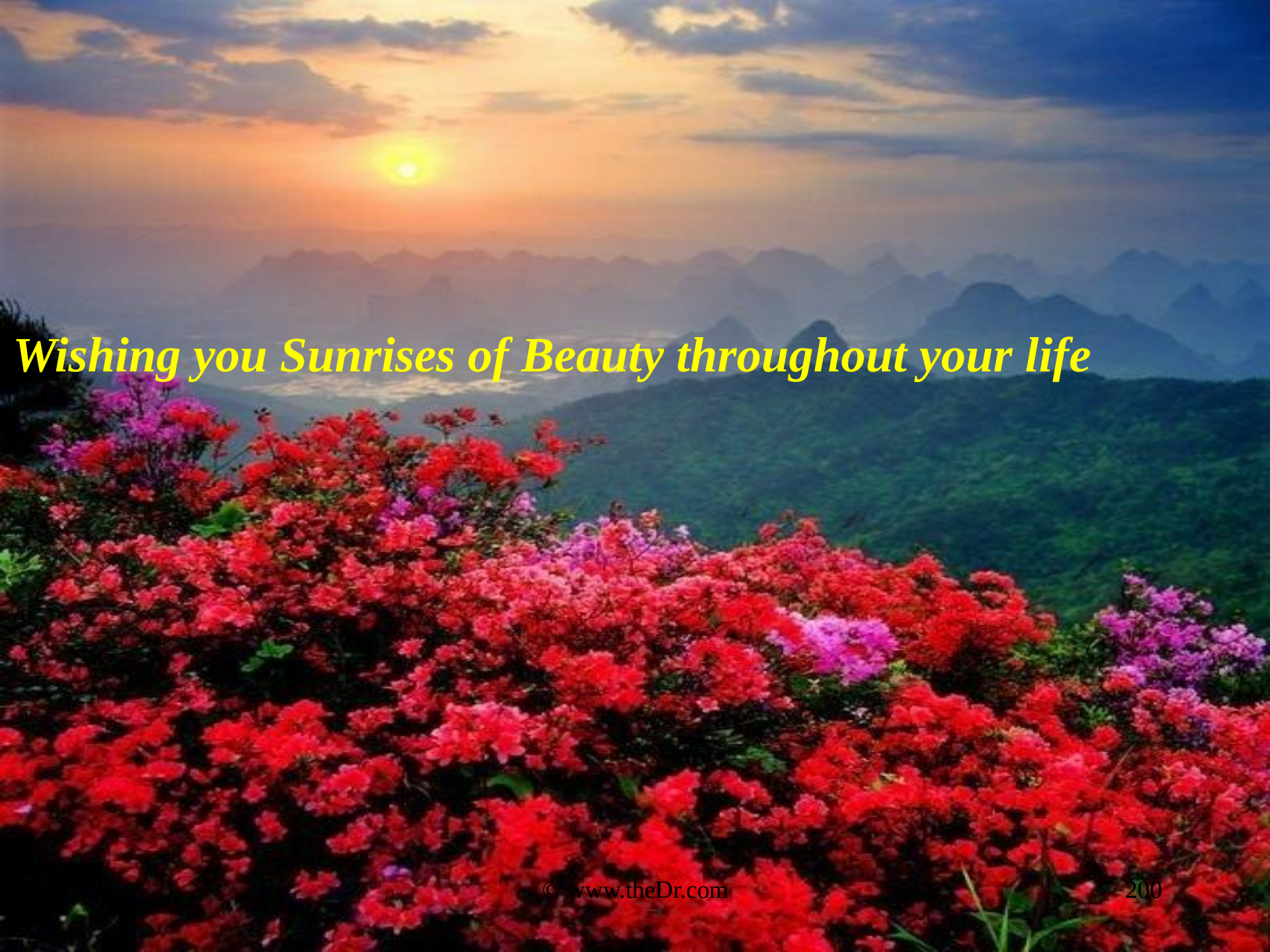
Take Care of Yourself

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