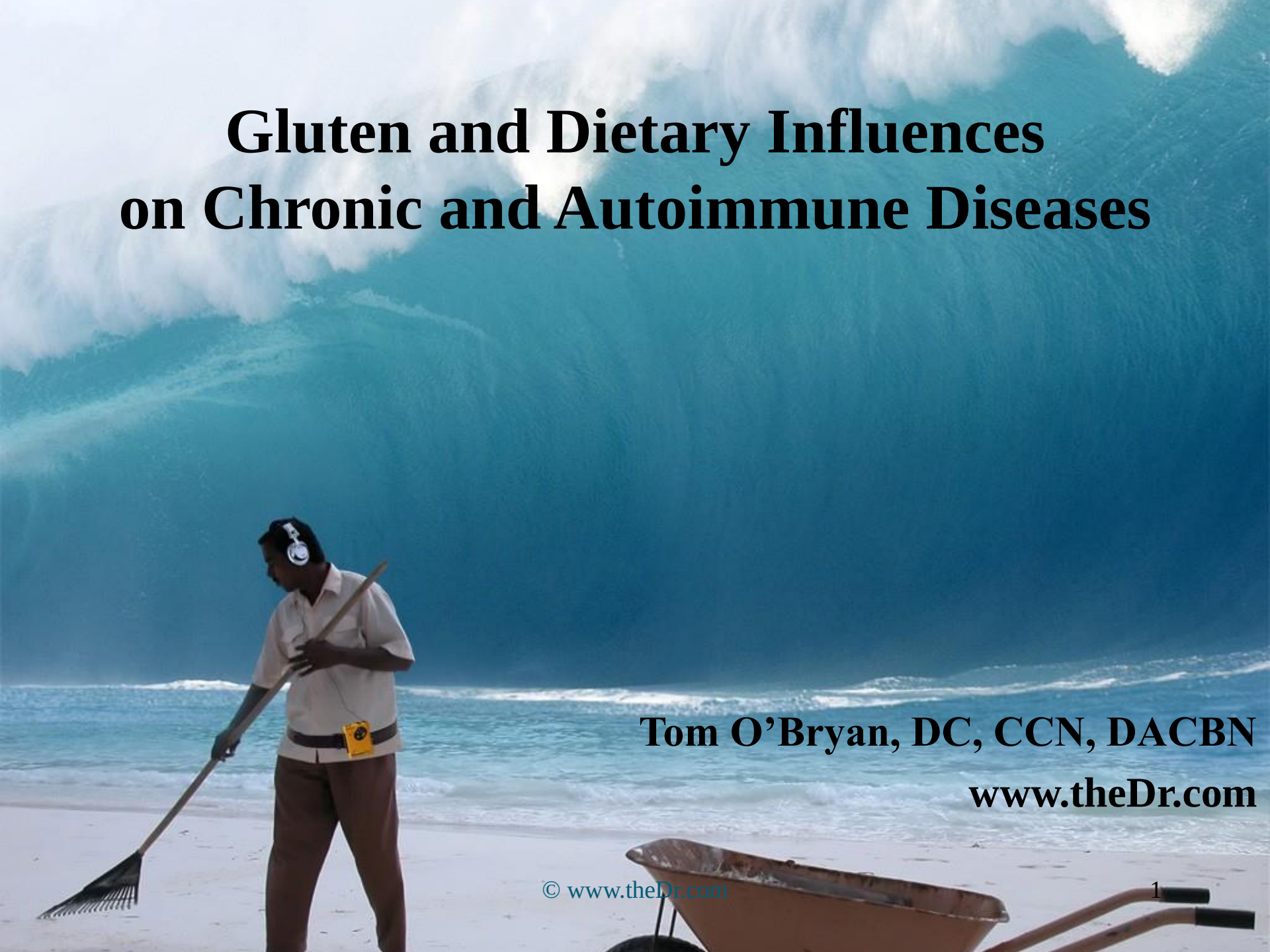
Gluten and Dietary Influences on Chronic and Autoimmune Diseases

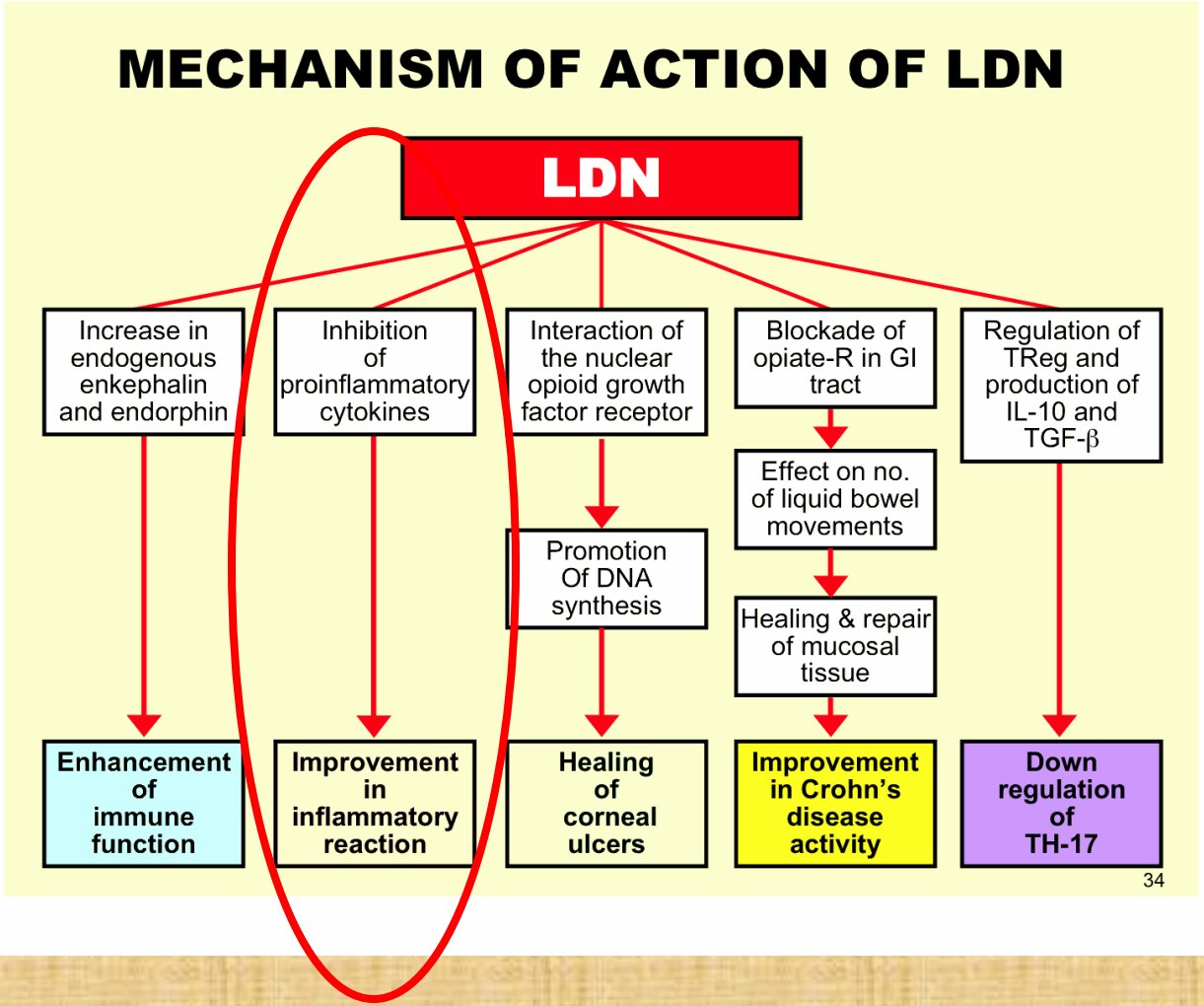


Tom O'Bryan, DC, CCN, DACBN

www.theDr.com

Tom O'Bryan, DC holds:

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



Vojdani, LDN Conference 2008


7 Premises To Look At

Premise #1

Incompletely digested peptides of wheat (exorphins) modulate opiod receptor activity

Detective Adrian Monk

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SCHRES-04003; No of Pages 8
Schizophrenia Research xx:

Schizophr Res. 2010 May;118(1-3):248-55.

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Novel immune response to gluten in individuals with schizophrenia

Diana Samaroo[a], Faith Dickerson[b], Donald D. Kasarda[c], Peter H.R. Green[d], Chiara Briani[e], Robert H. Yolken[f], Armin Alaedini[a,*]

[a] Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY, United States
[b] Sheppard Pratt Health System, Baltimore, MD, United States
[c] Western Regional Research Center, U.S. Department of Agriculture, Albany, CA, United States
[d] Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, United States
[e] Department of Neurosciences, University of Padova, Padova, Italy
[f] The Stanley Laboratory of Developmental Neurovirology, Department of Pediatrics, Johns Hopkins University Medical Center, Baltimore, MD, United States

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celiac disease and is independent of the action of transglutaminase enzyme and HLA-DQ2/DQ8. Meanwhile, the presence of elevated levels of antibodies to specific gluten proteins points to shared immunologic abnormalities in a subset of schizophrenia patients. Further characterization and understanding of the immune response to gluten in schizophrenia may provide novel insights into the etiopathogenesis of specific disease phenotypes.

1. Introduction

There is increasing evidence for the involvement of immunologic factors in schizophrenia (Patterson, 2008; Torrey and Yolken, 2001). Among the various reported immunologic abnormalities, increased immune sensitivity to gluten and association with celiac disease have been described in several reports (Bender, 1953; Cascella et al., 2009; Dohan et al., 1972; Graff and Handford, 1961; Jin et al., 2008; Reichelt and Landmark, 1995). Glutens, made up of two main fractions, gliadins and glutenins, are the main storage proteins of wheat and are comprised of about 100 different proteins in a given wheat cultivar (variety). When the various wheat cultivars are considered, the number of different gluten proteins is even greater, although almost all cultivars are made up of the same main types, α-type (also known as α/β type), γ-type, ω-type,

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Schizophrenia
Gluten sensitivity
Celiac disease
Antibody

characterized through examination of reactivity towards chromatographically separated gluten proteins. Target proteins of interest were identified by peptide mass mapping. In contrast to celiac disease patients, an association between the anti-gliadin immune response and anti-TG2 antibody or HLA-DQ2 and -DQ8 markers was not found in individuals with schizophrenia. In addition, the majority of individuals with schizophrenia and anti-gliadin antibody did not exhibit antibody reactivity to deamidated gliadin peptides. Further characterization of the antibody specificity revealed preferential reactivity towards different gluten proteins in the schizophrenia and celiac disease groups. These findings indicate that the anti-gliadin immune response in schizophrenia has a different antigenic specificity from that in celiac disease and is independent of the action of transglutaminase enzyme and HLA-DQ2/DQ8. Meanwhile, the presence of elevated levels of antibodies to specific gluten proteins points to shared immunologic abnormalities in a subset of schizophrenia patients. Further characterization and understanding of the immune response to gluten in schizophrenia may provide novel insights into the etiopathogenesis of specific disease phenotypes.

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Increased urinary excretion of gluten peptides in patients with schizophrenia has been observed previously.

Keywords:
Gluten
Gliadin
Schizophrenia
Gluten sensitivity
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including antibodies to transglutaminase 2 (TG2) enzyme and deamidated gliadin peptides, as well as the HLA-DQ2 and -DQ8 MHC genes. The anti-gliadin antibody response was further characterized through examination of reactivity towards chromatographically separated gluten proteins. Target proteins of interest were identified by peptide mass mapping. In contrast to celiac disease patients, an association between the anti-gliadin immune response and anti-TG2 antibody or HLA-DQ2 and -DQ8 markers was not found in individuals with schizophrenia. In addition, the majority of individuals with schizophrenia and anti-gliadin antibody did not exhibit antibody reactivity to deamidated gliadin peptides. Further characterization of the antibody specificity revealed preferential reactivity towards different gluten proteins in the schizophrenia and celiac disease groups. These findings indicate that the anti-gliadin immune response in schizophrenia has a different antigenic specificity from that in celiac disease and is independent of the action of transglutaminase enzyme and HLA-DQ2/DQ8. Meanwhile, the presence of elevated levels of antibodies to specific gluten proteins points to shared immunologic abnormalities in a subset of schizophrenia patients. Further characterization and understanding of the immune response to gluten in schizophrenia may provide novel insights into the etiopathogenesis of specific disease phenotypes.

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Referred to as gluten exorphins, these peptides have been shown to have potent opioid-like properties and to affect hormonal balance, behavior, and learning in animal models

antibody did not exhibit antibody reactivity to deamidated gliadin peptides. Further characterization of the antibody specificity revealed preferential reactivity towards different gluten proteins in the schizophrenia and celiac disease groups. These findings indicate that the anti-gliadin immune response in schizophrenia has a different antigenic specificity from that in celiac disease and is independent of the action of transglutaminase enzyme and HLA-DQ2/DQ8. Meanwhile, the presence of elevated levels of antibodies to specific gluten proteins points to shared immunologic abnormalities in a subset of schizophrenia patients. Further characterization and understanding of the immune response to gluten in schizophrenia may provide novel insights into the etiopathogenesis of specific disease phenotypes.

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Opioid Peptides Derived from Food Proteins

THE EXORPHINS*

(Received for publication, October 20, 1978)

Christine Zioudrou,‡ Richard A. Streaty, and Werner A. Klee

From the Laboratory of General and Comparative Biochemistry, National Institute of Mental Health, Bethesda, Maryland 20014

Peptides with opioid activity are found in pepsin hydrolysates of wheat gluten and α-casein. The opioid activity of these peptides was demonstrated by use of the following bioassays: 1) naloxone-reversible inhibition of adenylate cyclase in homogenates of neuroblastoma X-glioma hybrid cells; 2) naloxone-reversible inhibition of electrically stimulated contractions of the mouse vas deferens; 3) displacement of [^{3}H]dihydro-

Peptides with activity similar to that of morphine and other opioids have been isolated from the brain and other sources such as the pituitary. These peptides, the endorphins and enkephalins, are synthesized in vivo and may function both as hormones and neurotransmitters.

their exogenous origin and morphine-like activity. Also present in pepsin digests of wheat gluten are stimulatory materials which exhibit activities opposed to those of the exorphins.

MATERIALS AND METHODS

Opiate Assays

Adenylate Cyclase Activity—The opiate-sensitive adenylate cyclase activity of homogenates of neuroblastoma X-glioma NG108-15 hybrid cells was measured as described by Sharma *et al.* (11). In routine assays, samples were tested in the presence and absence of the specific morphine antagonist (−)-naloxone (a gift of Endo Laboratories) at 10^{-4} M. Inhibitory activity which is reversed by naloxone is considered to be opiate-like. Naloxone alone has no effect upon the activity of the enzyme. Maximal inhibition of adenylate cyclase by morphine and other opioids varies from 30 to 50% depending upon the enzyme preparation.

Mouse Vas Deferens—Opioid inhibition of the electrically stimulated contraction of the mouse vas deferens was performed as described by Henderson *et al.* (12). Tests were performed in a 5-ml organ bath filled with Ca^{2+}-free Ringers solution at 37°C. Electrical stimulation was 90 V at 0.1 Hz for 1 ms. Isotonic contraction size was recorded on a Brush recorder through a Statham transducer. (−)-Naloxone (200 nM) reversed opioid inhibition of contractions. (+)-Naloxone (200 nM) had no effect.

Gluten stimulatory fraction was also assayed for its effect on

stirred with 100 g of XAD-2 polystyrene beads for 30 min and filtered, and the resin was washed with 10 liters of water. The materials adsorbed on the resin were eluted with 5 liters of 90% 2-propanol, and the eluate was taken to dryness. The residue was dissolved in water and lyophilized to yield 3.7 g of powder. This material (3.2 g in 50 ml H_2O) was applied to an AG50W-X 2 column (H^+ form, 2.5 × 21 cm in water) which was then washed with 200 ml H_2O and eluted with a linear gradient from 0 to 4 M pyridine/acetate, pH 6.3 (1200 ml). Early fractions, eluting between 0 and 260 ml, were found to stimulate adenylate cyclase and were pooled and lyophilized to yield 7 mg (by A_{210nm}) of material which is the "gluten stimulatory fraction." Fractions eluting between 360 and 660 ml had opioid activity and were lyophilized to yield 0.4 g of material which was further purified in two batches, by preparative thin layer chromatography on 2-mm-thick silica gel plates (Merck) using 1-butanol, methanol, 20% NH_3 (4/1/1) as solvent. The silica gel was divided into 10 fractions which were extracted by shaking overnight with 90% methanol. After centrifugation and filtration, the extracts were taken to dryness and assayed. Opioid activity was found in all fractions, but was concentrated in those migrating with an R_F between 0.15 and 0.26, and these were pooled to yield 15 mg of material of which 10 mg, in 1 ml H_2O, was applied to a μBondapak C_{18} reversed phase column (0.4 × 30 cm) (Waters Associates) which was eluted with a linear gradient between 0 to 70% acetonitrile at 2.5 ml/min over 15 min. Fractions (2.5 ml) were dried under vacuum, dissolved in H_2O, and assayed. The highest specific activity fraction (14) is approximately 10,000 times more

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The results presented here have shown that peptides with morphine-like activities, which we call exorphins, can be isolated from some food proteins (wheat and casein).

tion both as hormones and neurotransmitters.

An alternate source of peptides, some of which may have biological activities, is dietary protein. Because of reports linking wheat gluten (7–9) with mental disorders, we tested pepsin digests of wheat gluten for opioid activity. The present report describes the isolation of some purified peptides with opioid activity from pepsin digests of wheat gluten and α-casein. These peptides are called exorphins (10) because of their exogenous origin and morphine-like activity. Also present in pepsin digests of wheat gluten are stimulatory materials which exhibit activities opposed to those of the exorphins.

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were a gift from Dr. J. S. Wall, United States Department of Agriculture, Northern Regional Research Laboratory, Peoria, Ill. XAD-2 (Applied Science Labs) was washed exhaustively with isopropyl alcohol and then water prior to use.

Peptide Purification

Gluten (100 g) suspended in 2 liters of 0.1 N HCl was treated with pepsin, 2.5 g, with vigorous stirring for 1 h at 37°C. The pH of the hydrolysate was adjusted to 7.5 with 10 N NaOH, the suspension was stirred with 100 g of XAD-2 polystyrene beads for 30 min and filtered, and the resin was washed with 10 liters of water. The materials adsorbed on the resin were eluted with 5 liters of 90% 2-propanol, and the eluate was taken to dryness. The residue was dissolved in water and lyophilized to yield 3.7 g of powder. This material (3.2 g in 50 ml H_2O) was applied to an AG50W-X 2 column (H^+ form, 2.5 × 21 cm in water) which was then washed with 200 ml H_2O and eluted with a linear gradient from 0 to 4 M pyridine/acetate, pH 6.3 (1200 ml). Early fractions, eluting between 0 and 260 ml, were found to stimulate adenylate cyclase and were pooled and lyophilized to yield 7 mg (by A_{210nm}) of material which is the "gluten stimulatory fraction." Fractions eluting between 360 and 660 ml had opioid activity and were lyophilized to yield 0.4 g of material which was further purified in two batches, by preparative thin layer chromatography on 2-mm-thick silica gel plates (Merck) using 1-butanol, methanol, 20% NH_3 (4/1/1) as solvent. The silica gel was divided into 10 fractions which were extracted by shaking overnight with 90% methanol. After centrifugation and filtration, the extracts were taken to dryness and assayed. Opioid activity was found in all fractions, but was concentrated in those migrating with an R_F between 0.15 and 0.26, and these were pooled to yield 15 mg of material of which 10 mg, in 1 ml H_2O, was applied to a μBondapak C_{18} reversed phase column (0.4 × 30 cm) (Waters Associates) which was eluted with a linear gradient between 0 to 70% acetonitrile at 2.5 ml/min over 15 min. Fractions (2.5 ml) were dried under vacuum, dissolved in H_2O, and assayed. The highest specific activity fraction (14) is approximately 10,000 times more

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Journal of Nutritional Biochemistry

Food-derived opioid peptides inhibit cysteine uptake with redox and epigenetic consequences☆

Malav S. Trivedi[a], Jayni S. Shah[a], Sara Al-Mughairy[a], Nathaniel W. Hodgson[a], Benjamin Simms[a], Geert A. Trooskens[b], Wim Van Criekinge[b], Richard C. Deth[a,*]

Dietary interventions like gluten-free and casein-free diets have been reported to improve intestinal, autoimmune and neurological symptoms in patients with a variety of conditions

results illustrate the potential of milk- and wheat-derived peptides to exert antioxidant and epigenetic changes that may be particularly important during the postnatal transition from placental to GI nutrition. Differences between peptides derived from human and bovine milk may contribute to developmental differences between breastfed and formula-fed infants. Restricted antioxidant capacity, caused by wheat- and milk-derived opioid peptides, may predispose susceptible individuals to inflammation and systemic oxidation, partly explaining the benefits of gluten-free or casein-free diets.

Keywords: Glutathione; Casomorphin; Gliadin; Autism spectrum disorder; Schizophrenia; Celiac disease; Gluten-free/casein-free diet

1. Introduction

Gluten-free or casein-free diets have been reported to improve intestinal, autoimmune and neurological symptoms in celiac disease [1,2], autism [3,4] and schizophrenia [5,6], but the underlying mechanism of benefit for such diets remains unclear. Emerging evidence from biochemical investigations indicate that neurological disorders like schizophrenia and autism spectrum disorder (ASD) might have underlying defects in prenatal and early postnatal neurodevelopment as a contributing factor to the etiology of these disorders. Especially, systemic oxidative stress has been strongly reported in schizophrenic [7] and ASD [8] patients, associated with significantly lower levels of the antioxidant glutathione (GSH), whose synthesis is limited by cysteine availability. Consistently, brain GSH levels are also reported to be decreased in autism [9] and schizophrenia [10], strongly supporting the proposal that a deficit in this specific antioxidant, namely GSH, might contribute to neurodevelopmental and neuropsychiatric disorders. Notably, intestinal mucosa and plasma levels of GSH are also reduced in pediatric celiac disease patients [11]. Moreover, in few cases, patients with neurological conditions [12] like autism [13] and schizophrenia [14] also report a co-morbid problem of celiac disease and/or gut inflammation.

Oxidative stress and DNA methylation changes are metabolically coupled via the transsulfuration pathway and one-carbon metabolism. DNA methylation is carried out by a class of enzymes called DNA methyltransferases DNMTs, which depend on the levels of *S*-adenosylmethionine (SAM) [15], which in turn are dependent on the action of the enzyme methionine synthase (MS) and the redox status of the cell [16]. SAM acts a methyl donor for over 200 methylation reactions and is converted to *S*-adenosylhomocysteine (SAH), an inhibitor of methylation reactions. Hence, the ratio SAM/SAH is termed as the methylation capacity of the cell. Several studies report decreased

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* Corresponding author. Room #169, 140 The Fenway, Northeastern University, 360 Huntington Avenue, Boston, MA 02115, USA. Tel.: +1-617-678-0147.
E-mail address: r.deth@neu.edu (R.C. Deth).

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Food-derived opioid peptides inhibit cysteine uptake with redox and epigenetic consequences☆

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however, the underlying mechanism of benefit for such diets remains unclear

Dietary interventions like gluten-free and casein-free diets have been reported to improve intestinal, autoimmune and neurological symptoms in patients with a variety of conditions; however, the underlying mechanism of benefit for such diets remains unclear. Epigenetic programming, including CpG methylation and histone modifications, occurring during early postnatal development can influence the risk of disease in later life, and such programming may be modulated by nutritional factors such as milk and wheat, especially during the transition from a solely milk-based diet to one that includes other forms of nutrition. The hydrolytic digestion of casein (a major milk protein) and gliadin (a wheat-derived protein) releases peptides with opioid activity, and in the present study, we demonstrate that these food-derived proline-rich opioid peptides modulate cysteine uptake in cultured human neuronal and gastrointestinal (GI) epithelial cells via activation of opioid receptors. Decreases in cysteine uptake were associated with changes in the intracellular antioxidant glutathione and the methyl donor *S*-adenosylmethionine. Bovine and human casein-derived opioid peptides increased genome-wide DNA methylation in the transcription start site region with a potency order similar to their inhibition of cysteine uptake. Altered expression of genes involved in redox and methylation homeostasis was also observed. These results illustrate the potential of milk- and wheat-derived peptides to exert antioxidant and epigenetic changes that may be particularly important during the postnatal transition from placental to GI nutrition. Differences between peptides derived from human and bovine milk may contribute to developmental differences between breastfed and formula-fed infants. Restricted antioxidant capacity, caused by wheat- and milk-derived opioid peptides, may predispose susceptible individuals to inflammation and systemic oxidation, partly explaining the benefits of gluten-free or casein-free diets.

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Oxidative stress and DNA methylation changes are metabolically coupled via the transsulfuration pathway and one-carbon metabolism. DNA methylation is carried out by a class of enzymes called DNA methyltransferases DNMTs, which depend on the levels of *S*-adenosylmethionine (SAM) [15], which in turn are dependent on the action of the enzyme methionine synthase (MS) and the redox status of the cell [16]. SAM acts a methyl donor for over 200 methylation reactions and is converted to *S*-adenosylhomocysteine (SAH), an inhibitor of methylation reactions. Hence, the ratio SAM/SAH is termed as the methylation capacity of the cell. Several studies report decreased

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E-mail address: r.deth@neu.edu (R.C. Deth).

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Journal of Nutritional Biochemistry

Food-derived opioid peptides inhibit cysteine uptake with redox and epigenetic consequences☆

Malav S. Trivedi[a], Jayni S. Shah[a], Sara Al-Mughairy[a], Nathaniel W. Hodgson[a], Benjamin Simms[a], Geert A. Trooskens[b], Wim Van Criekinge[b], Richard C. Deth[a,*]

Epigenetic programming, including CpG methylation and histone modifications, occurring during early postnatal development can influence the risk of disease in later life, and such programming may be modulated by nutritional factors such as milk and wheat.

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The hydrolytic digestion of casein (a major milk protein) and gliadin (a wheat-derived protein) releases peptides with opioid activity, and in the present study, we demonstrate that these food-derived proline-rich opioid peptides modulate cysteine uptake in human neuronal and gastrointestinal (GI) epithelial cells via activation of opioid receptors.

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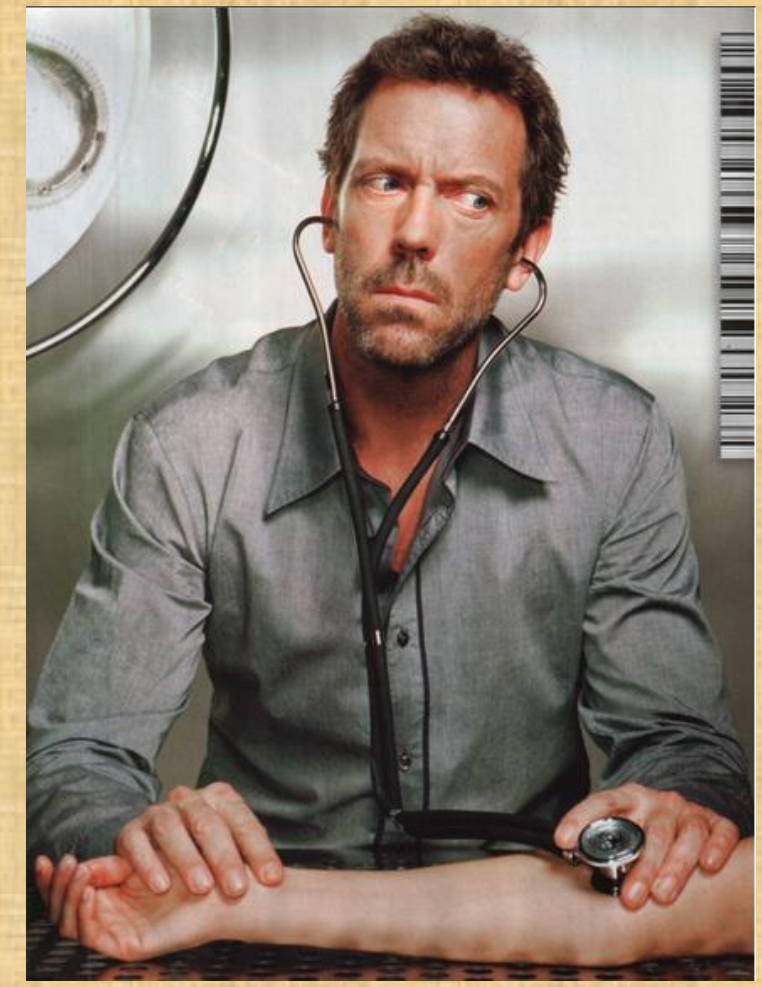


The inhibitory action of the exorphins in wheat has a specific opiate effect. This morphine-like psychoactive nature of the peptides results from the incomplete digestion of these dietary proteins binding to the opiate receptors in the brain, and offers a possible explanation for some of the reported psychiatric reactions to these gluten proteins, including the sense of 'brain fog' that often accompanies immune reactions to these foods and which may follow with panic attacks, depression, or other neurological complaints.

- **Schizophr Bull. 14(4):489-94.**
- **Biol. Psychiatry 20(3):245-56.**
- **Interchange. 28(2/3):183-189.**

Premise #2

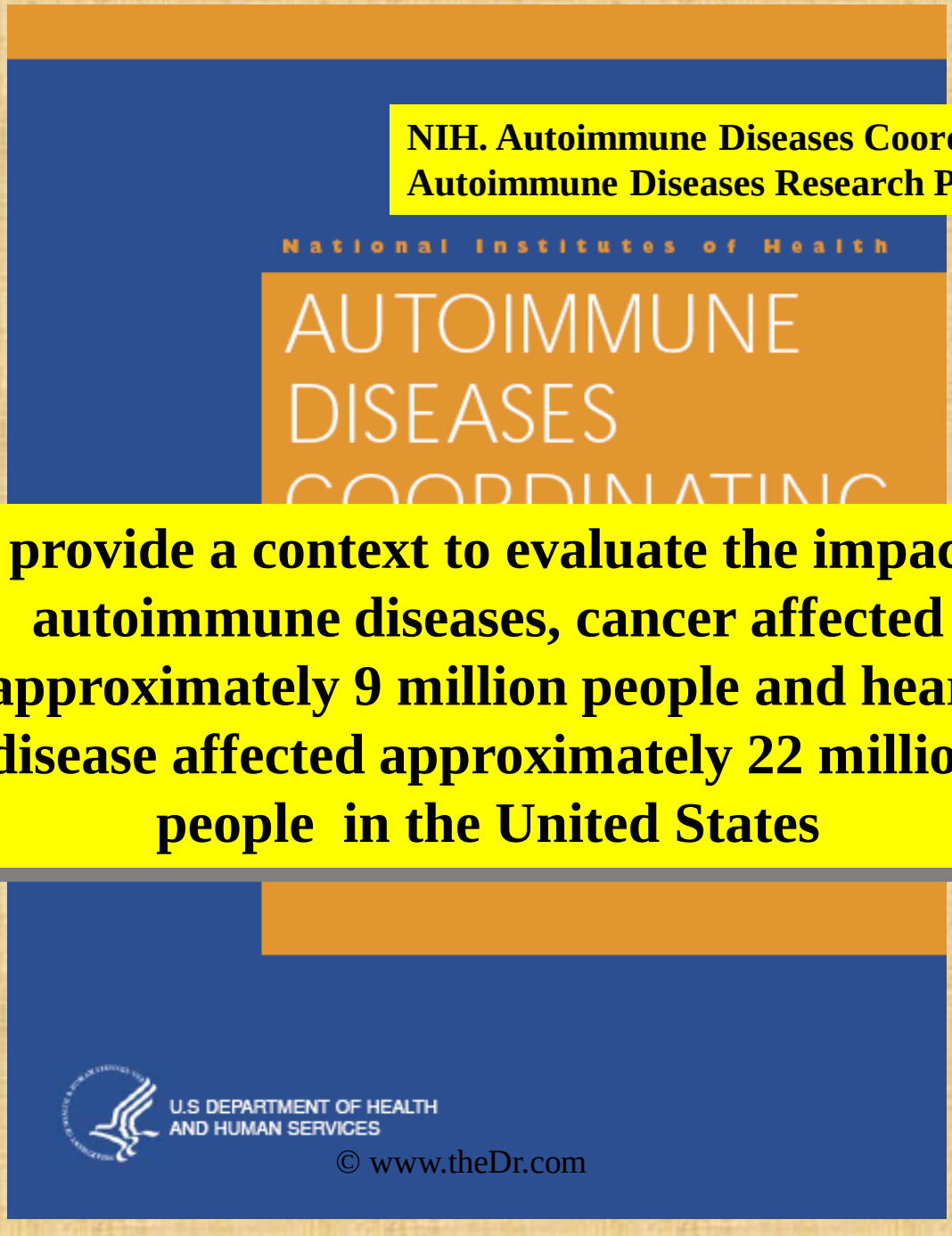
What is the Most Common Cause of Morbidity and Mortality in the Industrialized World?

Detective Adrian Monk

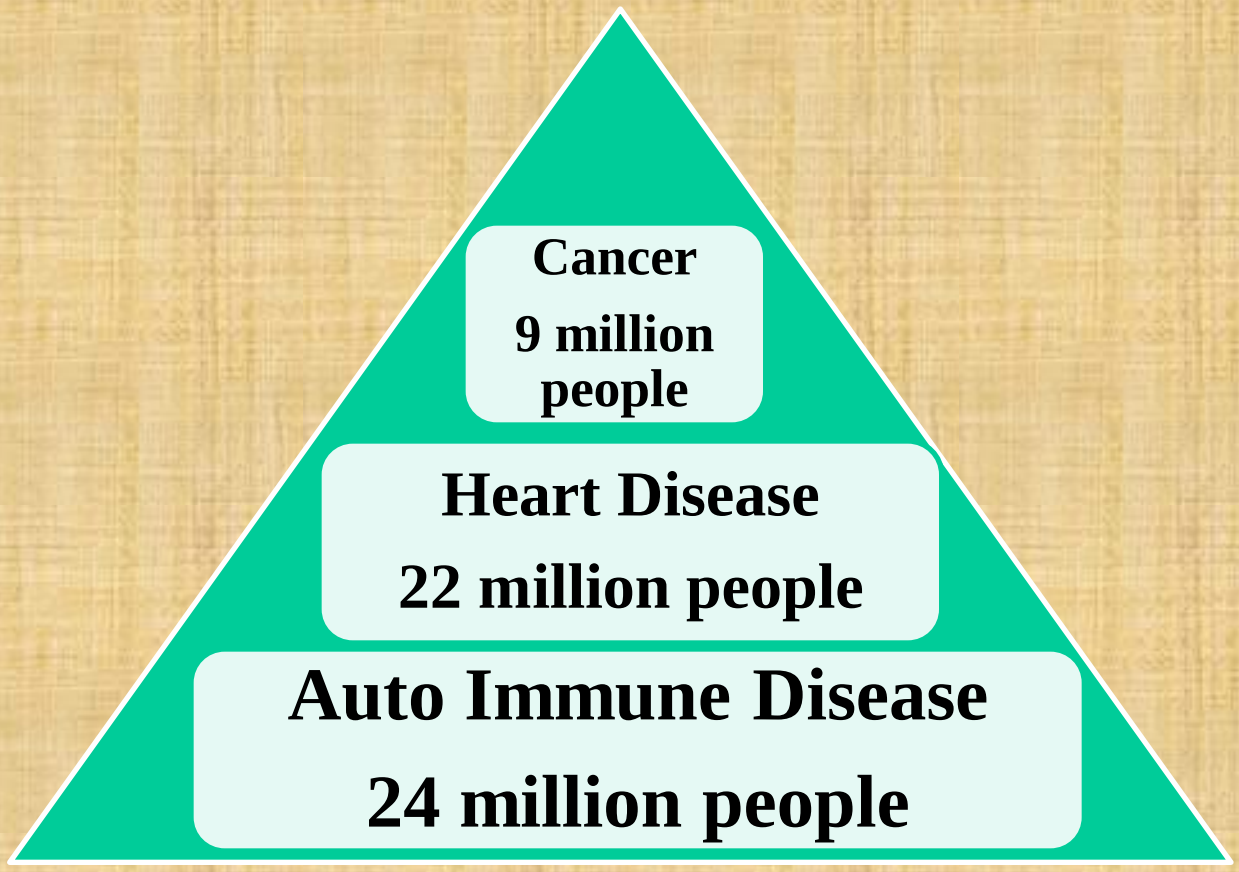
NIH. Autoimmune Diseases Coordinating Comm. Autoimmune Diseases Research Plan. 2006

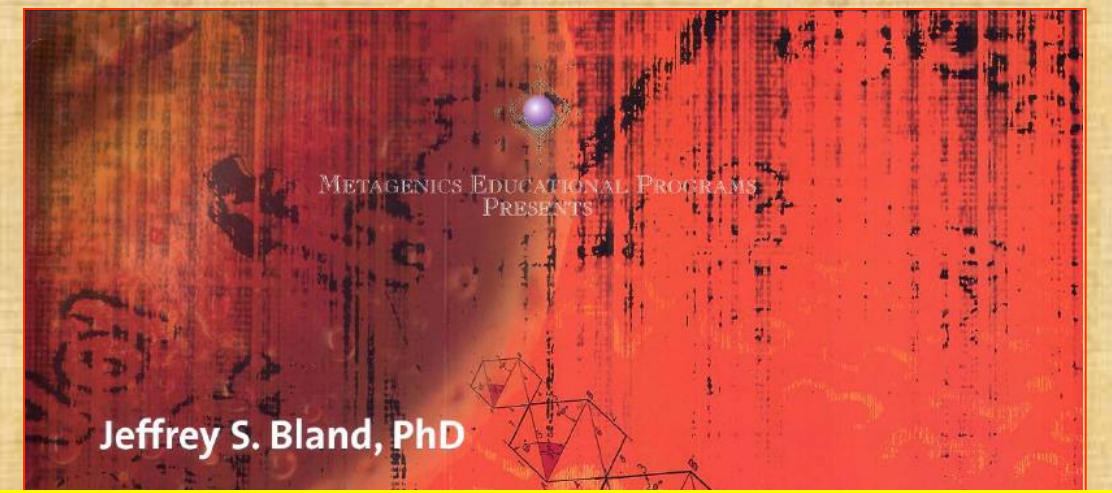
While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 8 percent of the United States population – 24 million persons.

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





"Collectively Auto-immune Diseases have been identified in about 24 million people in the US, and only 1/3rd are diagnosed. That means about 72 million people have an AI Disease. It's not looked for. Our system waits until the signs and symptoms are severe enough with organ failure and irreversible damage before we identify it."

REVIEW

Vitamin D and autoimmunity: new aetiological and therapeutic considerations

Yoav Arnson, Howard Amital, Yehuda Shoenfeld

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

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

See end of article for authors' affiliations

Correspondence to: Dr Howard Amital, Head of Department of Medicine 'D', Meir Medical Center, Tshernichovsky 59, Kfar-Saba, 95847, Israel; hamital@netvision.net.il

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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

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

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DOI: 10.4330/wjc.v6.i5.314

World J Cardiol 2014 May 26; 6(5): 314-326
ISSN 1949-8462 (online)

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.

Correspondence to: Dr. Nicolas Vuilleumier, MD, PD, Head of Laboratory Medicine Division, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland. nicolas.vuilleumier@hcuge.ch
Telephone: +41-22-3729150 Fax: +41-22-3827245
Received: December 23, 2013 Revised: February 5, 2014
Accepted: March 17, 2014
Published online: May 26, 2014

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.

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

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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
Correspondence to: Dr. Nicolas Vuilleumier, MD, PD, Head of Laboratory Medicine Division, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland. nicolas.vuilleumier@hcuge.ch
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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*

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Perhaps if We Open to More Current Information…..

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

Oliver Hartley, Department of Immunology and Pathology, Faculty of Medicine, 1211 Geneva, Switzerland
Author contributions: All the authors contributed to this manuscript.
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Correspondence to: Dr. Nicolas Vuilleumier, MD, PD, Head of Laboratory Medicine Division, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland. nicolas.vuilleumier@hcuge.ch
Telephone: +41-22-3729150 Fax: +41-22-3827245
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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

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 interleu-kins 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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From the Department of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center Tel-Hashomer, Sackler Faculty of Medicine, Tel-Aviv University, Israel (Y. Shoenfeld, Y. Sherer); the Center for Study of Rheumatic Diseases, Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy (R.G.); the Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Padova, Italy (A.D.); the Department of Cell Chemistry, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan (E.M.); the Department of Medicine, Division of Rheumatology, University of Florence, Firenze, Italy (M.M.C.); the Dipartimento di Clinica Medica, Nefrologia e Scienze della Prevenzione, Università degli Studi di Parma, Parma, Italy (N.R.); the Clinical Research Unit, Hospital de Especialidades, Centro Medico La Raza, and Universidad Nacional Autónoma de México, Mexico City, Mexico (L.J.J.); the Autoimmune Rheumatic Diseases Unit, Department of Medicine, Soroka Medical Center and Ben-Gurion University, Beer-Sheva, Israel (M.A.-S.); and the Department of Internal Medicine, University of Milan, Allergy and Clinical Immunology Unit, IRCCS Istituto Auxologico Italiano, Milano, Italy (P.L.M.).
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
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The Open Cardiovascular Medicine Journal, 2011, 5, 64-75

Dyslipidaemia in Rheumatological Autoimmune Diseases

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

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

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

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

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

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

INTRODUCTION

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

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-

*Address correspondence to this author at the Department of Rheumatology, Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Pensnett Road, Dudley, West Midlands, DY1 2HQ, United Kingdom;
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E-mail: gd.kitas@dgoh.nhs.uk or g.d.kitas@bham.ac.uk

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REVIEW

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

Nicolas Vuilleumier, Fabrizio Montecucco, Oliver Hartley

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

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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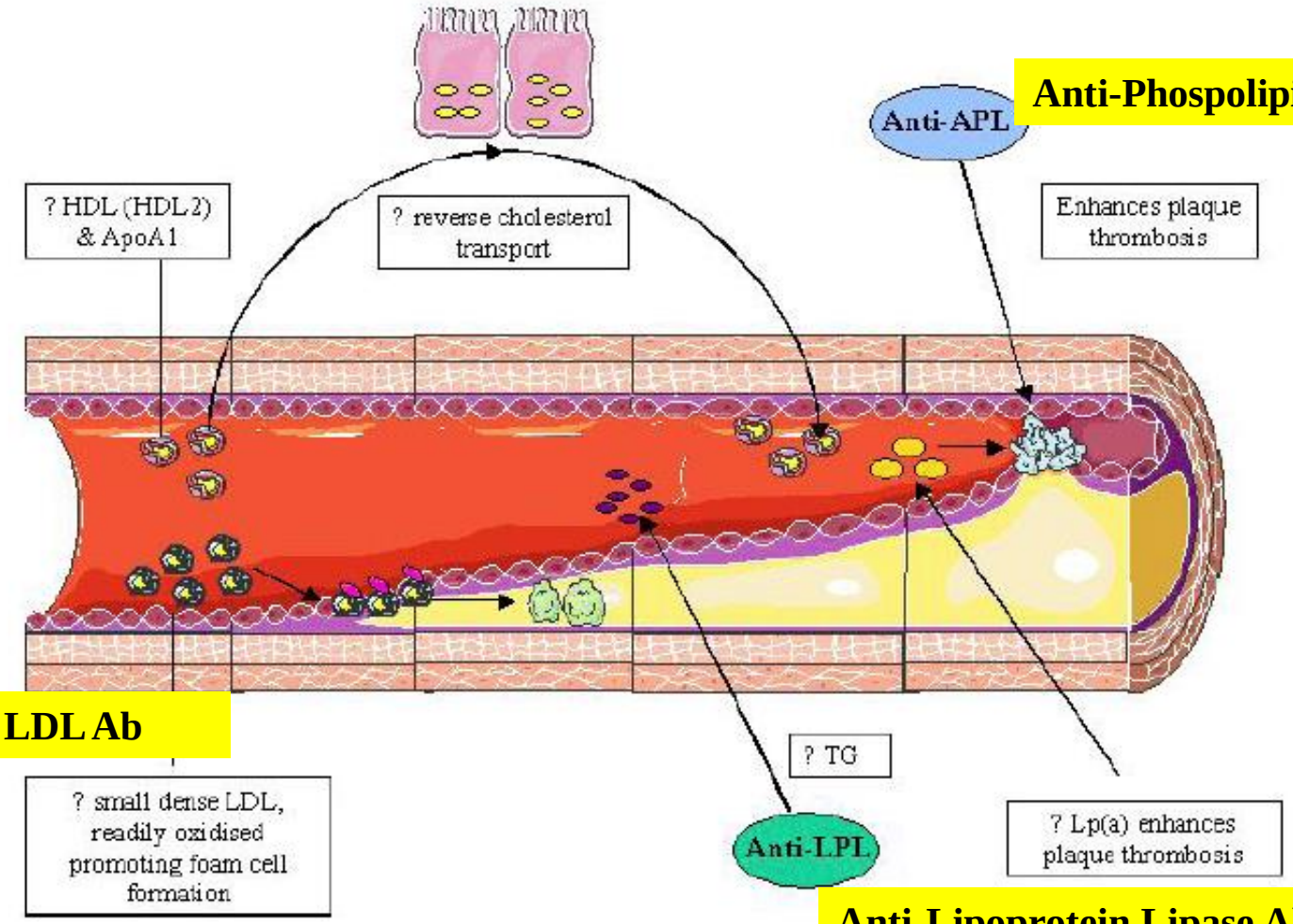

Fig. (5). Common changes in the lipid profile amongst the autoimmune rheumatic disease and their impact on atherosclerotic plaque formation. LDL: Low density lipoproteins, TG: Triglycerides, Lp(a): Lipoprotein (a), Anti-LPL: anti-Lipoprotein Lipase, HDL: high density lipoproteins, ApoA1: Apolipoprotein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

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

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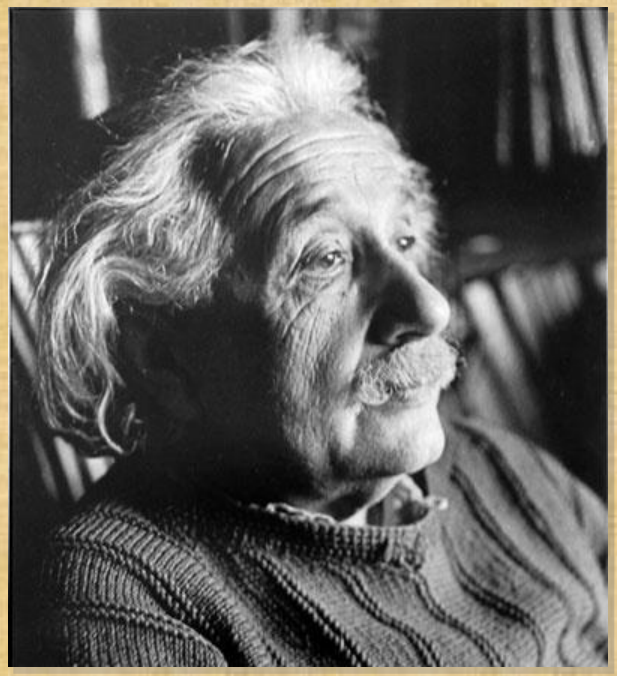
1874-1932/11 2011 Bentham Open

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 2003

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THERAPEUTIC TARGET

Identifying antibodies and Preventive interactions

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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 #3

Genes Control Function

Detective Adrian Monk

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.

Åsa Blomström, M.D.

Susanne Wicks, Ph.D.

Shuojia Yang, M.Sc.

Robert H. Yolken, M.D.

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.

Method: The study population consisted of individuals born in Sweden between 1975 and 1985 with verified register-

spots by enzyme-linked immunosorbent assay. Odds ratios were calculated for levels of IgG directed at gliadin or casein for nonaffective psychosis.

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.

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)

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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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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.

Method: The study population consisted of individuals born in Sweden between 1975 and 1985 with verified register-

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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

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.

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)

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.

Åsa Blomström, M.D.

Susanne Wicks, Ph.D.

Shuojia Yang, M.Sc.

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in order to develop preventive strategies.

(Am J Psychiatry 2012; 169:625–632)

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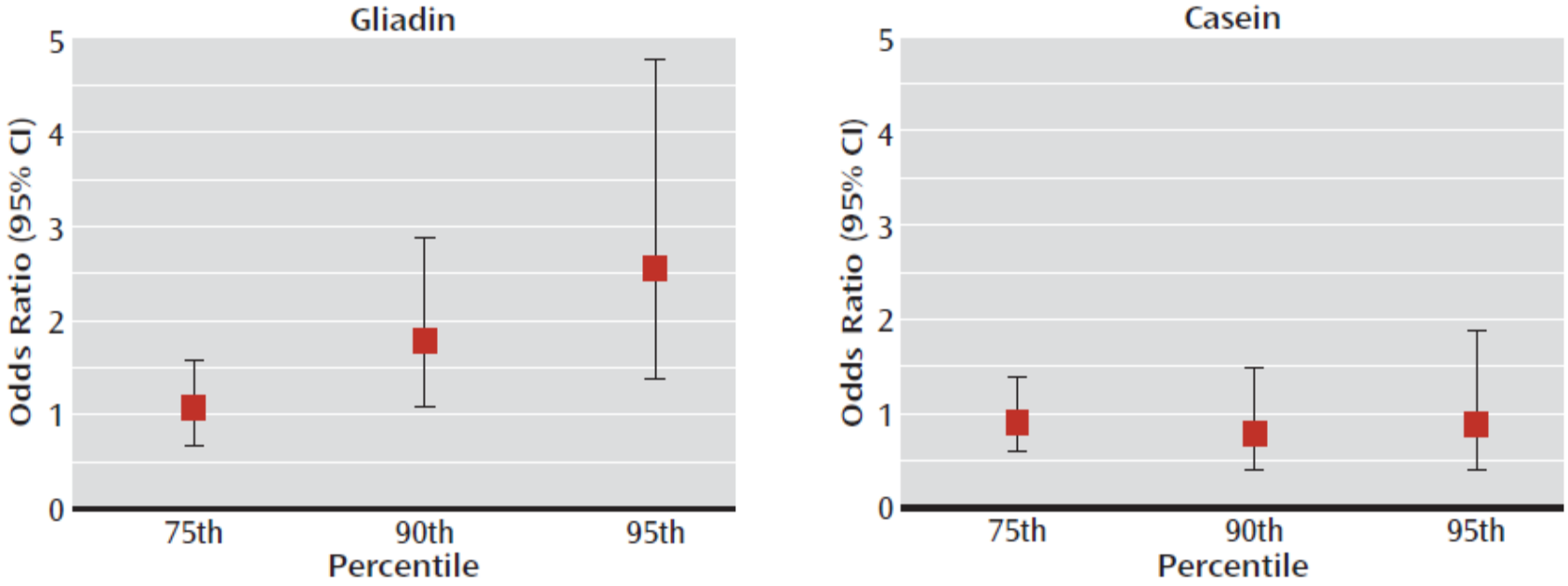
FIGURE 1. Levels of IgG Directed at Gliadin and Casein and Odds of Developing Nonaffective Psychosis



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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.

Note: These are Not Celiacs

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manifestations of schizophrenia and other nonaffective

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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

Latent celiac disease in reproductive performance of women

Ashok Kumar, M.D.,[a] *Mamta Meena, M.B.B.S.,*[a] *Ram Kumar Gupta, M.Sc.,*[a] *Sarita Aggarwal, M.D.*[b]

[a] Department of Obstetrics and Gynecology, Maulana Azad Medical College and Lok Nayak Hospital; [b] Department of Gastroenterology, Maulana Azad Medical College and GB Pant Hospital; and [c] Department of Biochemistry, Maulana Azad Medical College, New Delhi, India

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

Objective: To investigate the prevalence of positive serologic findings for celiac disease in Indian women with poor reproductive performance.
Design: Cross-sectional except that the women with intrauterine growth restriction were followed prospectively until delivery.
Setting: Department of Obstetrics and Gynecology of a tertiary teaching hospital, New Delhi.
Patient(s): Eight hundred ninety-three women (104 women with idiopathic recurrent abortion, 104 women with

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

and atypical and silent presentations are increasing. It may be associated with increased risk of adverse pregnancy-related events (1). The disorder is common, occurring in 0.5% to 1% of the general population in most countries (2). A prevalence of 0.5% to 1% has been reported in western Indian and Arabian populations (3). During the last few years, a large number of patients with celiac disease have been observed in many case studies in the Indian subcontinent, especially in northern India (4, 5) with a prevalence rate of 0.3% (6). Screening studies in different populations have shown that the prevalence of the disease is much higher than previously thought. With the availability of improved and more accessible diagnostic tools, the disease is being recognized more frequently among adults. Celiac disease often affects women in their fertile period, and malabsorption may interfere with embryogenesis and fetal nutrition and growth. Latent celiac disease has been found to be associated with

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Supported by the Indian Council of Medical Research, New Delhi.
Reprint requests: Ashok Kumar, M.D., 13 B, DDA Flats, Ber Sarai, New Delhi 110016, India (E-mail: ashkumar@eth.net, ash64kr@yahoo.com).

been neglected. It is possible that reproductive disorders are the first symptoms of celiac disease. Although there are a very few studies regarding the effect of latent celiac disease on reproductive performance, the association has never before been investigated in India. Hence, the present study attempts to learn the prevalence of positive serologic findings for identifying latent or subclinical celiac disease among a cohort of women with poor reproductive performance and to compare different serologic markers for celiac disease.

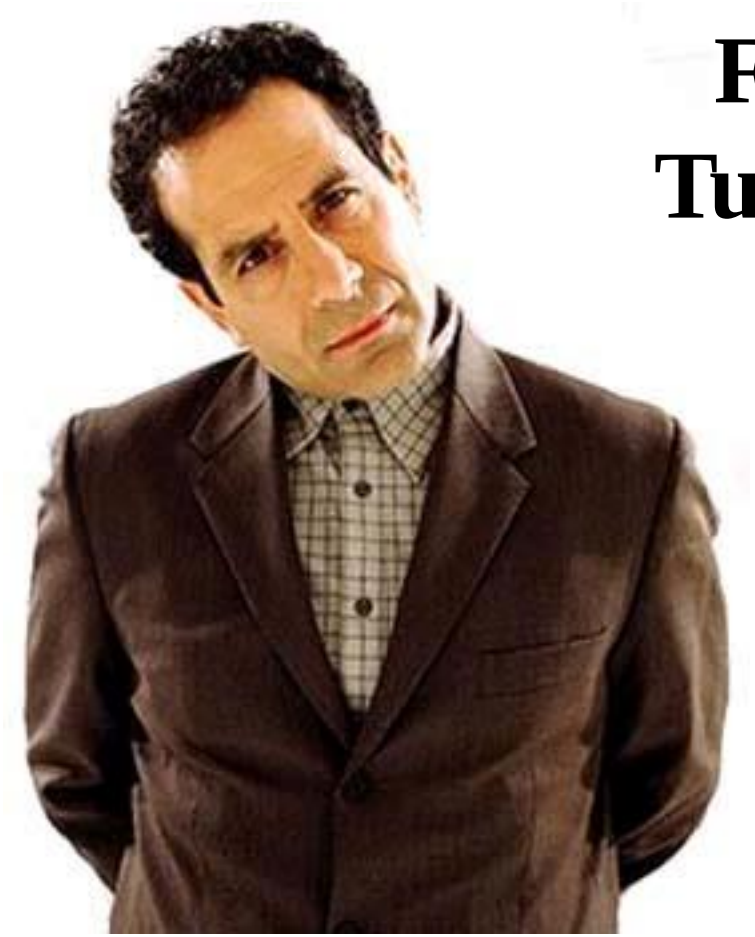
MATERIALS AND METHODS

All the consecutive women with a history of idiopathic recurrent spontaneous abortion, history of unexplained stillbirth, unexplained infertility, and idiopathic intrauterine growth restriction (IUGR) attending the Lok Nayak Hospital, a tertiary teaching hospital in New Delhi, were recruited from August 2006 to July 2009. Prevalence of celiac disease in women with pregnancy loss (recurrent spontaneous abortion and stillbirth) has been reported to be 10% (9, 10), in pregnant women with IUGR as 15% (9), and in infertile women as 6% (11, 12). Thus, to detect difference between cases and the control group, with the power of the study 90% and chance factor being 5%, the estimated sample size is 100 women each in the groups with recurrent abortion and stillbirth, 150 women in the group with IUGR, and 220 in the group with unexplained infertility.

A total of 125 women with a history of recurrent spontaneous abortion, 118 women with a history of stillbirth attending the outpatient department, 170

0015-0282/$36.00
doi:10.1016/j.fertnstert.2010.11.005

Premise #4



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

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.

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

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[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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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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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).

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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 carbohydrate modifications with a low glycemic index would alter the gene expression profile in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome.

Results: We detected 71 down-regulated genes in the rye-pasta group, including genes linked to insulin signaling and apoptosis. In contrast, the 12-wk oat-wheat-potato diet up-regulated 62 genes related to stress, cytokine-chemokine–mediated immunity, and the interleukin pathway. The insulinogenic index improved after the rye-pasta diet ($P = 0.004$) but not after the oat-wheat-potato diet. Body weight was unchanged in both groups.

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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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Premise #5

Where Does the Persisting Inflammation Come From?

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

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.

*Corresponding author. *E-mail address*: murray.joseph@mayo.edu (J.A. Murray).

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

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Gastroenterol Clin N Am 37 (2008) 411–428

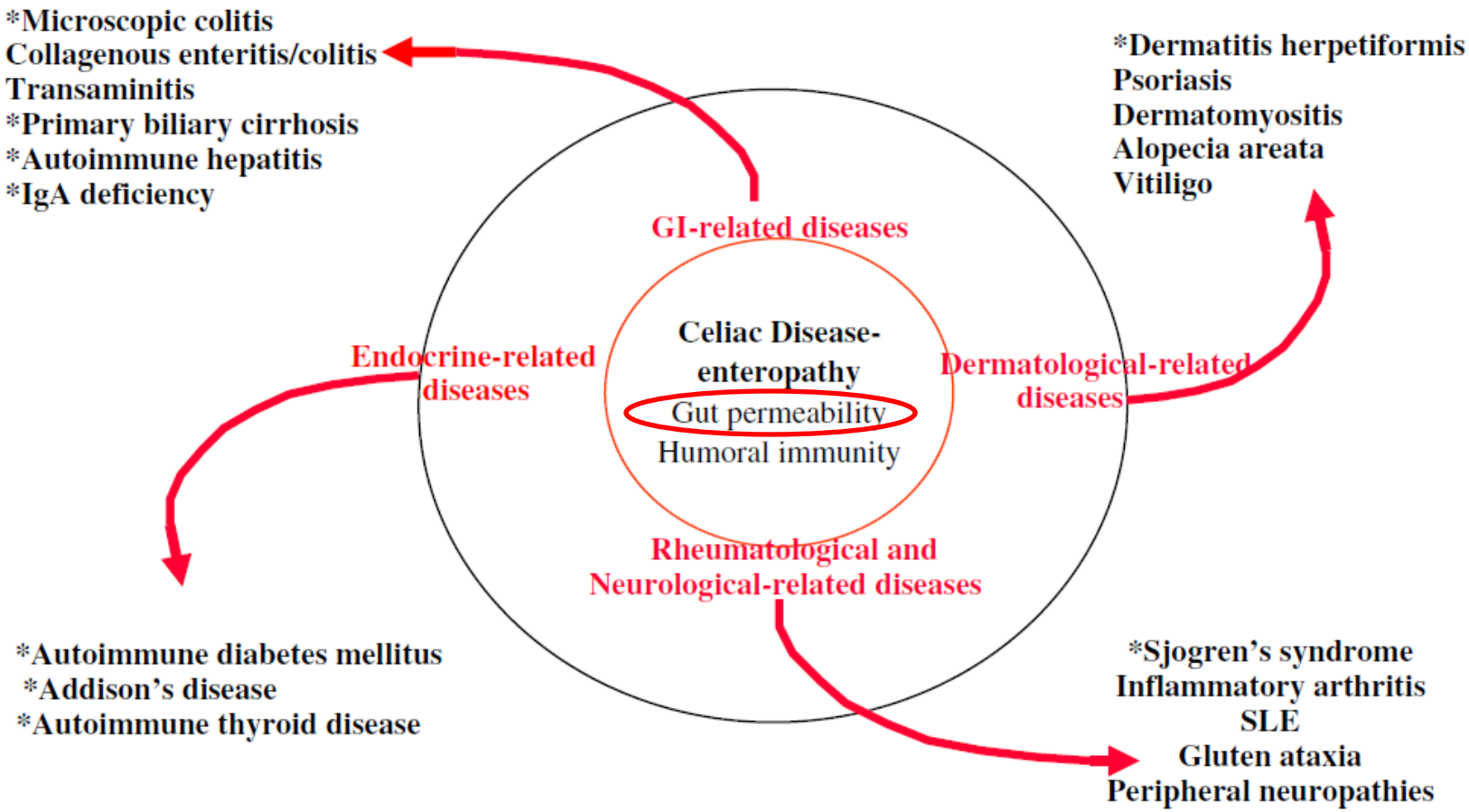

Fig. 1. Autoimmune and inflammatory diseases in relation to celiac disease. *Strongest associations.


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The Gluten Summit
A Grain of Truth

Alessio Fasano, MD

Currently at Harvard's Mass General Hospital for Children where he Chairs 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

Alessio Fasano, MD

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

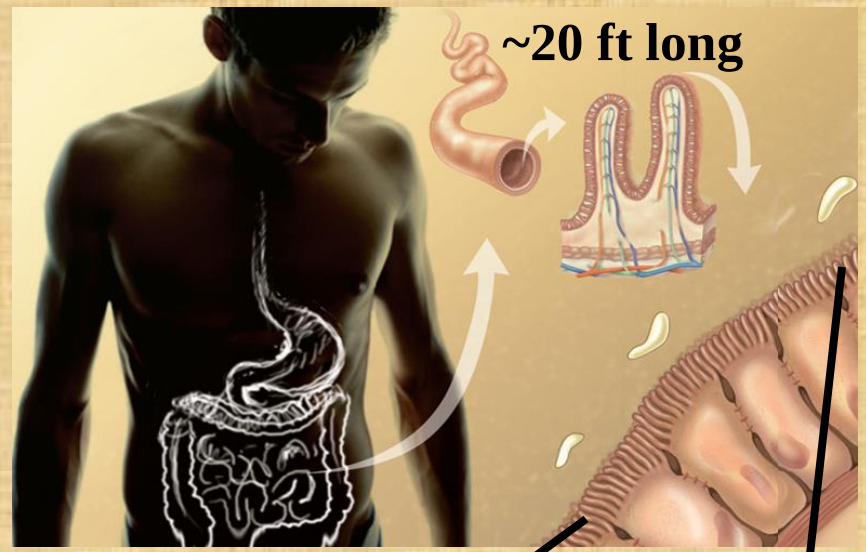
Alessio Fasano, MD

It's one of the key functions of the intestine that I probably think has been the most overlooked over human biology.

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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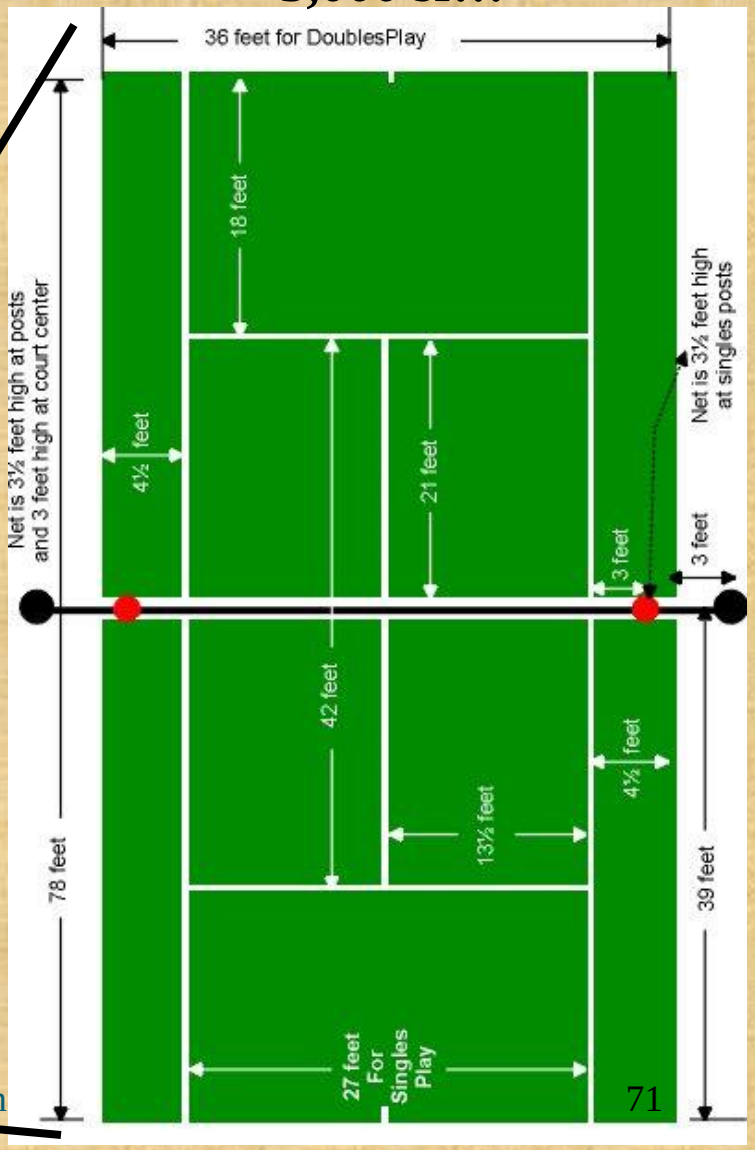

Alessio Fasano, MD

The key function is to interface with the environment and eventually exchange information, including molecules from the environment that comes in in a very tightly and coordinated and controlled manner.

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, 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 have this uncontrolled trafficking of macromolecules. 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 #6
What is the Impact of Intestinal Permeability?

nature publishing group

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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REVIEW

www.nature.com/clinicalpractice/gasthep

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

Alessio Fasano* and Terez Shea-Donohue

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

SUMMARY

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

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

REVIEW CRITERIA

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Correspondence
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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 circum-

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

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

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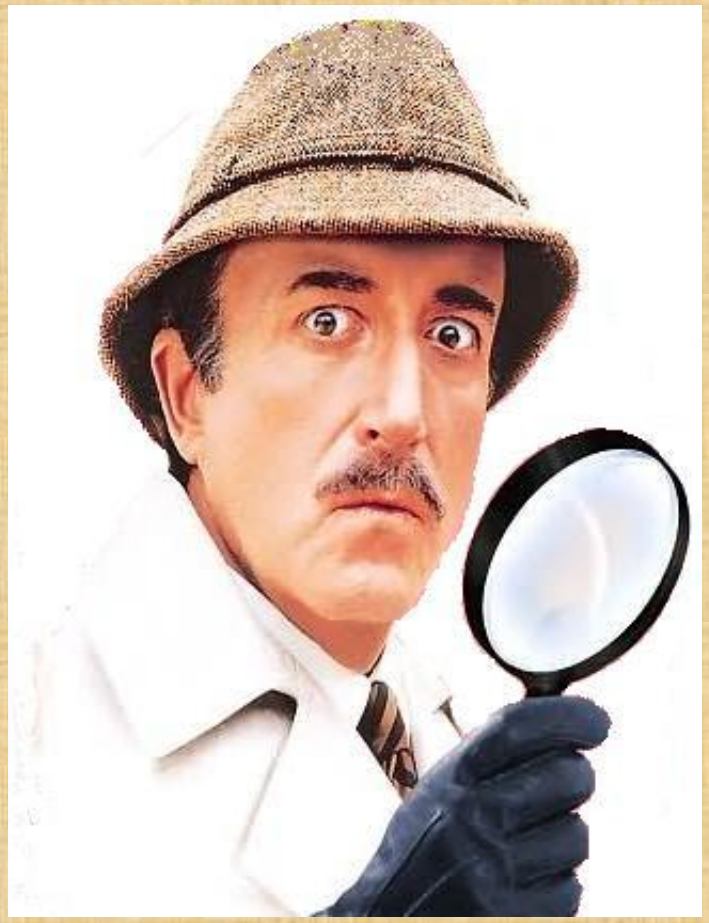
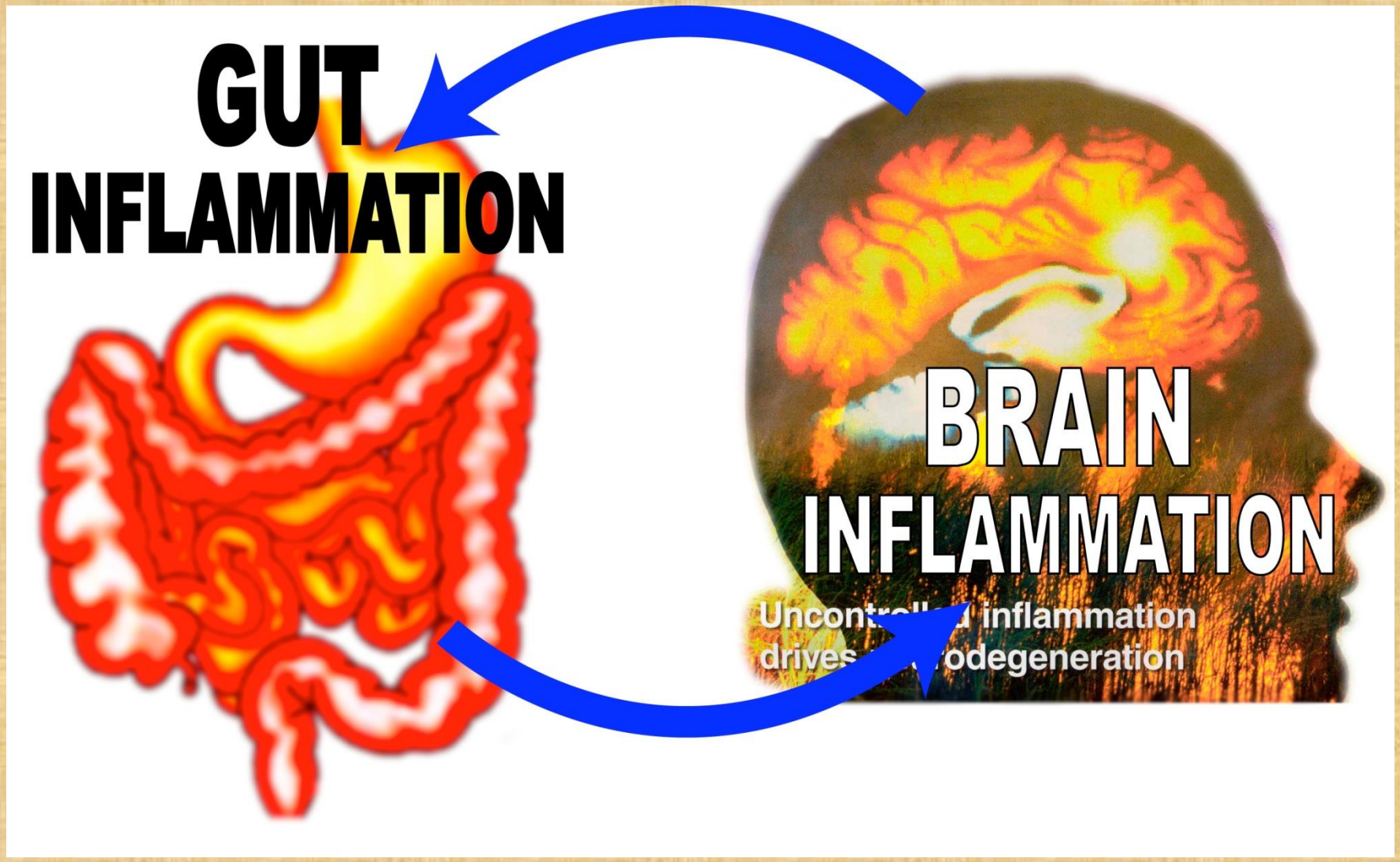
Premise #7

How Might The Impact of Intestinal Permeability Present?





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PLOS ONE

Markers of Celiac Disease and Gluten Sensitivity in Children with Autism

PLoS One. 2013 Jun 18;8(6):e66155

Nga M. Lau[1,2], Peter H. R. Green[1,2], Annette K. Taylor[3], Dan He
Barry E. Kosofsky[5,6], Joseph J. Higgins[6], Anjali M. Rajadhyak

1 Department of Medicine, Columbia University, New York, New York, United States of America, 2 Celiac Disease Center, Columbia University, New York, New York, United States of America, 3 Kimball Genetics, a Division of LabCorp, Denver, Colorado, United States of America, 4 Center for Clinical Research, Uppsala Univeristy, Falun, Sweden, 5 Department of Neurology & Neuroscience, Weill Cornell Medical College, New York, New York, United States of America, 6 Department of Pediatrics, Weill Cornell Medical College, New York, New York, United States of America, 7 Institute of Human Nutrition, Columbia University, New York, New York, United States of America

Abstract

Objective: Gastrointestinal symptoms are a common feature in children with autism, drawing attention to a potential association with celiac disease or gluten sensitivity. However, studies to date regarding the immune response to gluten in autism and its association with celiac disease have been inconsistent. The aim of this study was to assess immune reactivity to gluten in pediatric patients diagnosed with autism according to strict criteria and to evaluate the potential link between autism and celiac disease.

Methods: Study participants included children (with or without gastrointestinal symptoms) diagnosed with autism

Children with autism exhibited significantly elevated levels of IgG antibody to gliadin when compared with unrelated healthy controls or when compared with the combination of unaffected siblings and unrelated healthy controls (p,0.01).

Funding: This study was supported by a grant from the Department of Defense, award number W81XWH 10-1-0887, to Armin Alaedini (PI). The sponsor of the study had no role in the study design, collection, analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: aa819@columbia.edu

Introduction

Glutens are the major storage proteins of wheat and related cereals, comprising over 70 different molecules in any given wheat variety [1]. The main classes of gluten include α/β-gliadins, γ-gliadins, ω-gliadins, high molecular weight glutenins, and low molecular weight glutenins [2]. Gluten sensitivity can be defined as a state of heightened immunologic reaction to gluten proteins, which may be accompanied by increased levels of antibodies against them. Heightened immune reactivity to gluten is recognized and understood best in the context of celiac disease, an autoimmune disorder primarily targeting the small intestine, and wheat allergy [3]. The humoral immune response in celiac disease also includes antibodies to deamidated sequences of gliadin and to the autoantigen transglutaminase 2 (TG2), which are highly specific and sensitive serologic markers of the condition [4]. Celiac disease is also closely linked with genes that code for human leukocyte antigens (HLA) DQ2 and DQ8 [5].

While the etiology and pathogenesis of autism are poorly understood, there is evidence that immune system abnormalities are associated with symptoms in a substantial number of affected individuals [6]. In addition, several studies have evaluated gastrointestinal (GI) symptoms and defects in GI barrier function in patients with autism [7–10]. A possible association between autism and celiac disease was first discussed over 40 years ago [11,12]. Although some studies have pointed to higher frequency

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PloS One 2011;6(12):e28032. Epub 2011 Dec 1

Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease

Christopher B. Forsyth[1]*, Kathleen M. Shannon[2], Jeffrey H. Kordower[3], Robin M. Voigt[1], Maliha Shaikh[1], Jean A. Jaglin[2], Jacob D. Estes[4], Hemraj B. Dodiya[3], Ali Keshavarzian[1]

1 Department of Internal Medicine, Section of Gastroenterology, Rush University Medical Center, Chicago, Illinois, United States of America, **2** Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, United States of America, **3** Center for Brain Repair, Rush Medical College, Chicago, Illinois, United States of America, **4** AIDS and Cancer Virus Program, SAIC-Frederick, Inc., National Cancer Institute-Frederick, Frederick, Maryland, United States of America

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging. The pathological hallmark of PD

Over the last decade there has been mounting evidence that supports a role for the GI tract and the enteric nervous system (ENS) in the pathogenesis of PD

negative bacteria and tissue oxidative stress. Our study may thus shed new light on PD pathogenesis as well as provide a new method for earlier diagnosis of PD and suggests potential therapeutic targets in PD subjects.

Trial Registration: Clinicaltrials.gov NCT01155492

Citation: Forsyth CB, Shannon KM, Kordower JH, Voigt RM, Shaikh M, et al. (2011) Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease. PLoS ONE 6(12): e28032. doi:10.1371/journal.pone.0028032

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Competing Interests: The authors have declared that no competing interests exist.

* E-mail: christopher_b_forsyth@rush.edu

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging, and is projected to affect nearly 10 million citizens of the world's most populous countries by 2030 [1,2]. The burden of disability from PD is considerable [3]. Unfortunately there is no optimal treatment for PD and this is at least partly because the majority of patients with PD will be diagnosed and receive treatment after the onset of neurological symptoms when substantial neuronal dysfunction and neuronal loss has already occurred. Thus, a more successful approach could be to diagnose and start treatment before neuronal degeneration results in the emergence of clinical signs of PD. In fact, although the etiology of PD is not known, the pathobiology of neuronal loss in PD is well characterized. It is now well established that the pathological hallmark of PD are neuronal inclusions termed Lewy bodies (LB) or Lewy neurites (LN) whose main component is aggregated and phosphorylated α-synuclein [4,5]. It is believed that these α-synuclein aggregates are the first steps resulting in neuronal loss that is responsible for neurological symptoms and signs of PD [5]. A better understanding of how α-synuclein aggregates form will be a key for advancing our understanding of the pathogenesis of PD that could lead to early diagnosis and treatment with potentially much better outcome.

While phosphorylated α-synuclein aggregates may be formed as a consequence of oxidative injury [4], the source of neuronal oxidative stress in PD is not known. It is believed that PD pathology is a consequence of interaction between genetic susceptibility and toxic environmental factors [6]. It is highly plausible that the gastrointestinal (GI) tract is a major site and source of oxidative stress in neuronal tissue based on the following: (1) The GI tract is the largest interface between neural tissue and the environment. (2) The GI tract has a large number of neuronal cells in the submucosal plexus and myentric plexus, large enough

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Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease

Christopher B. Forsyth[1]*, Kathleen M. Shannon[2], Jeffrey H. Kordower[3], Robin M. Voigt[1], Maliha Shaikh[1], Jean A. Jaglin[2], Jacob D. Estes[4], Hemraj B. Dodiya[3], Ali Keshavarzian[1]

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging. The pathological hallmark of PD

The GI system and the brain are directly linked anatomically with the dorsal motor nucleus of the vagus nerve, a brain region proposed to express Lewy pathology very early in the disease process.

Citation: Forsyth CB, Shannon KM, Kordower JH, Voigt RM, Shaikh M, et al. (2011) Increased Intestinal Permeability Correlates with Sigmoid Mucosa alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease. PLoS ONE 6(12): e28032. doi:10.1371/journal.pone.0028032

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Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging. The pathological hallmark of PD

Gut leakiness in patients with a genetic susceptibility to PD may be a pivotal early step promoting a pro-inflammatory/oxidative environment contributing to the initiation and/or progression of the PD process.

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Abstract

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Indeed, it has been suggested that the GI tract might be a portal of entry for a putative PD pathogen, triggering pathological changes in the submucosal/myenteric neurons, which then spread through the vagus nerve to the medulla oblongata

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From there, pathological changes may move rostrally, ultimately resulting in the clinically-defining motor symptoms of PD when there is extensive involvement in the middle portion of the disease at the level of the midbrain substantia nigra.

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An index of intestinal permeability, systemic exposure to intestinal bacterial products was determined by measuring plasma LPS binding protein (LBP). Lower levels of plasma LBP have been associated with increased exposure to gram negative bacteria.

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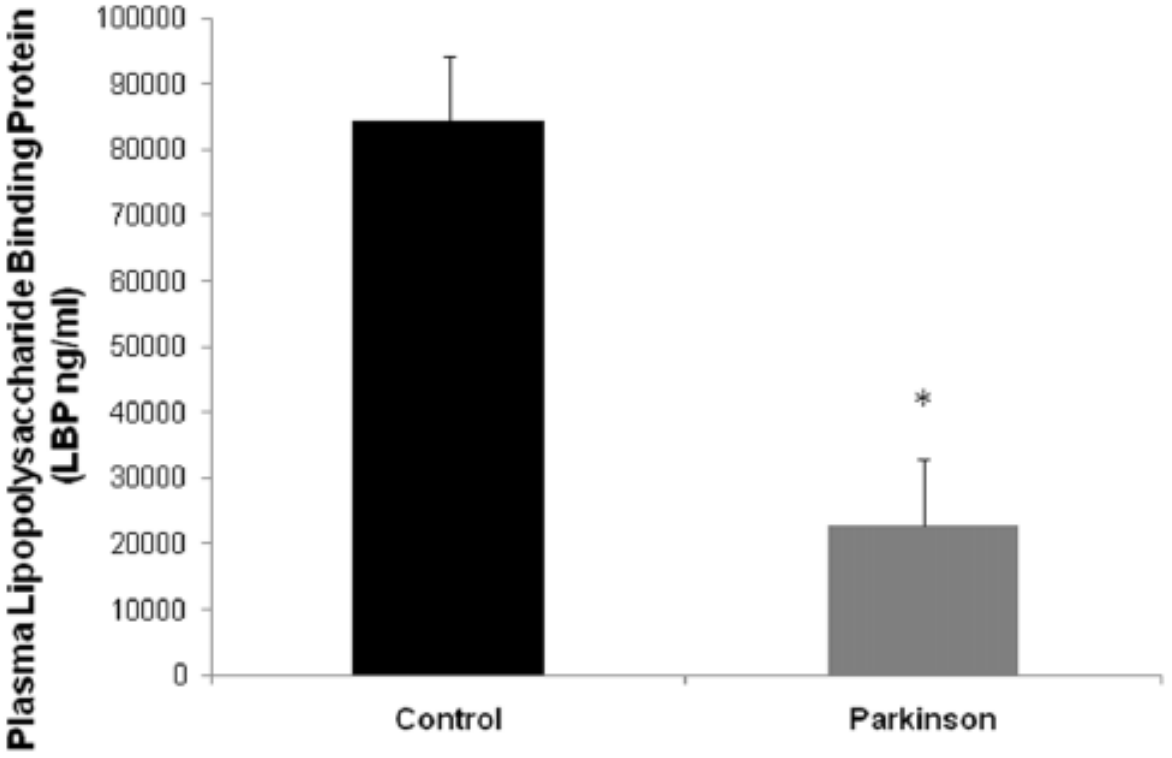


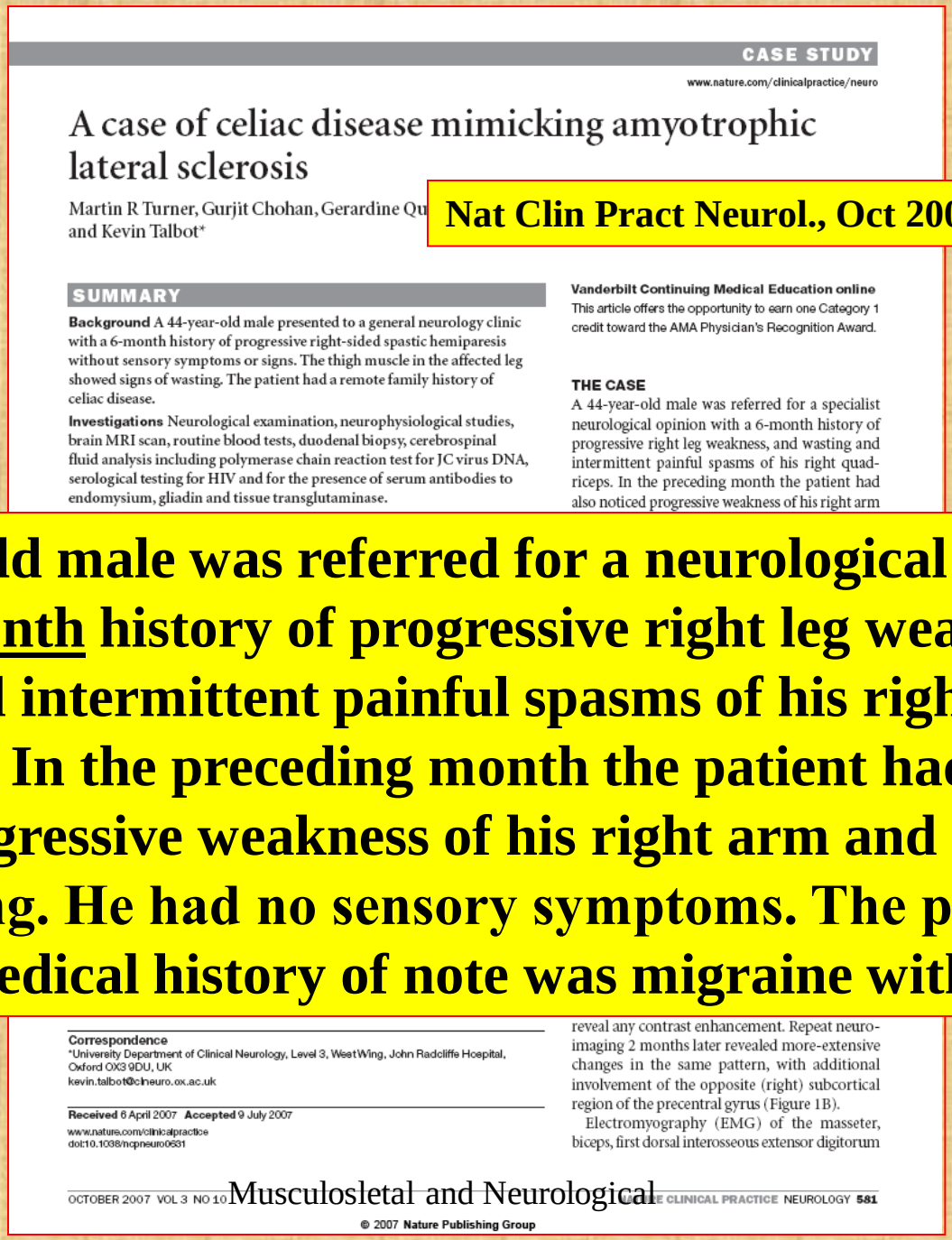
Figure 4. Plasma LBP is significantly lower in PD patients. Plasma levels of LPS binding protein (LBP), an indirect measure of systemic endotoxin exposure, were determined for PD subjects and healthy controls as described in Materials and Methods. Values for plasma LBP in PD subjects were significantly lower than in healthy controls. Data are presented as means (ng/ml) ± SE. *$p<0.05$.

CASE STUDY #1

A Fatal Diagnosis
Addressing the autoimmune component of ALS

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

101



CASE STUDY

www.nature.com/clinicalpractice/neuro

A case of celiac disease mimicking amyotrophic lateral sclerosis

Martin R Turner, Gurjit Chohan, Gerardine Qu
and Kevin Talbot*

Nat Clin Pract Neurol., Oct 2007 vol.3, no 10

SUMMARY

Background A 44-year-old male presented to a general neurology clinic with a 6-month history of progressive right-sided spastic hemiparesis without sensory symptoms or signs. The thigh muscle in the affected leg showed signs of wasting. The patient had a remote family history of celiac disease.

Investigations Neurological examination, neurophysiological studies, brain MRI scan, routine blood tests, duodenal biopsy, cerebrospinal fluid analysis including polymerase chain reaction test for JC virus DNA, serological testing for HIV and for the presence of serum antibodies to endomysium, gliadin and tissue transglutaminase.

Vanderbilt Continuing Medical Education online
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Correspondence
*University Department of Clinical Neurology, Level 3, West Wing, John Radcliffe Hospital, Oxford OX3 9DU, UK
kevin.talbot@clneuro.ox.ac.uk

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Electromyography (EMG) of the masseter, biceps, first dorsal interosseous extensor digitorum

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Examination revealed right-sided spastic hemiparesis with a pyramidal pattern of leg weakness associated with mild wasting of the right quadriceps. The patient had generalized bilateral hyperreflexia, sustained right ankle clonus and a right extensor plantar response. Results of cranial nerve, cerebellar and sensory examinations were normal.

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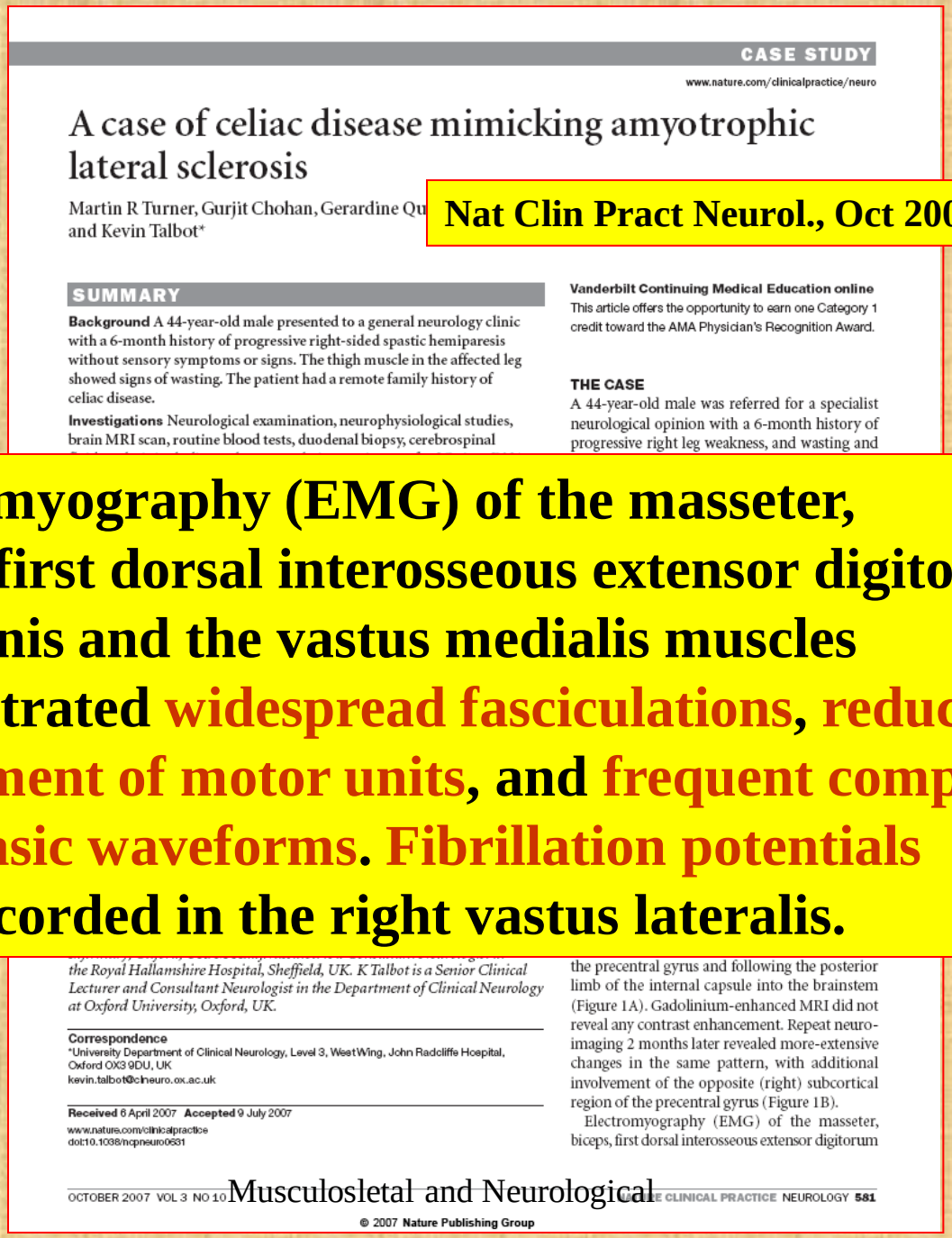

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the Royal Hallamshire Hospital, Sheffield, UK. K Talbot is a Senior Clinical Lecturer and Consultant Neurologist in the Department of Clinical Neurology at Oxford University, Oxford, UK.

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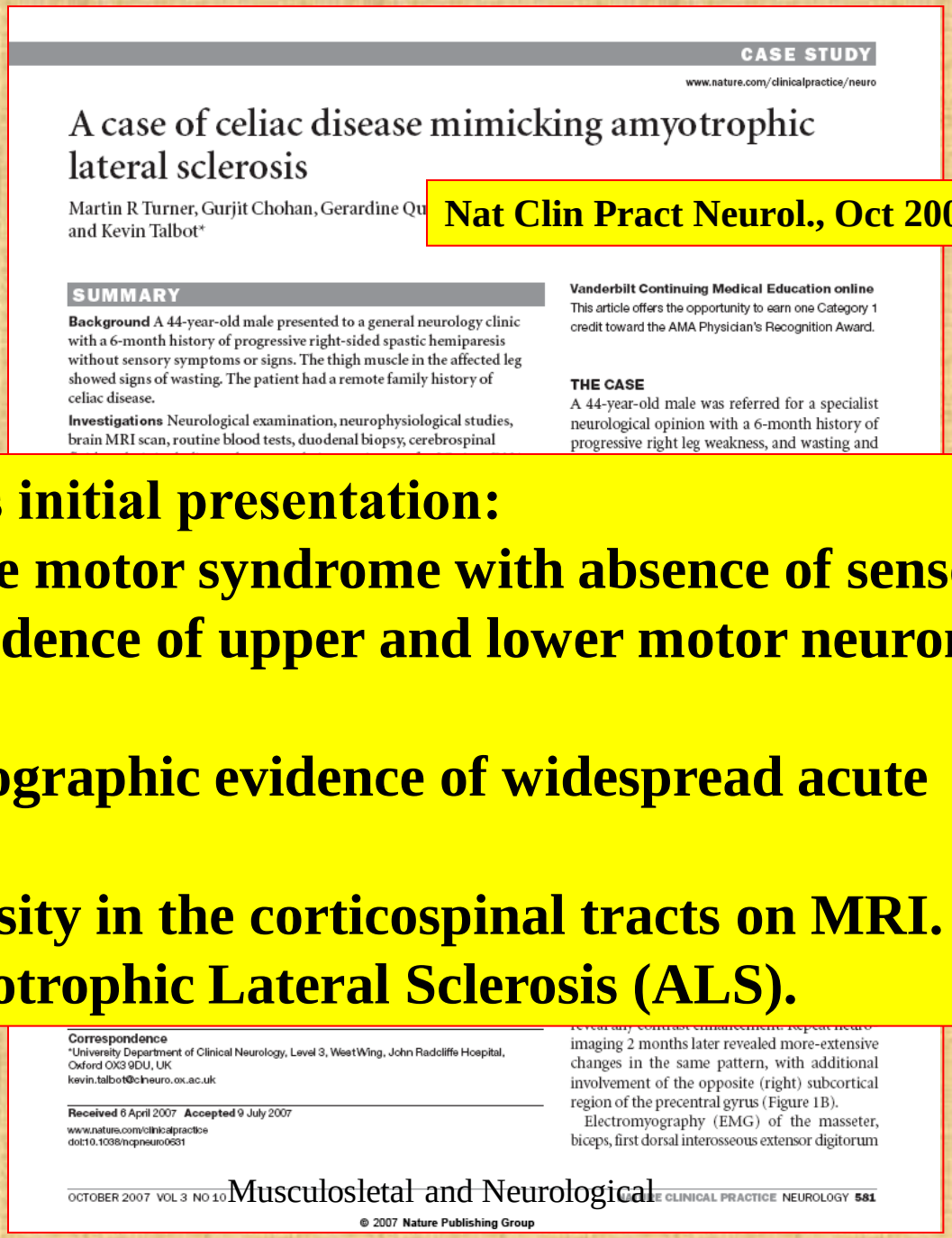

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The patient's initial presentation:

✓ progressive motor syndrome with absence of sensory signs

✓ clinical evidence of upper and lower motor neuron degeneration

✓ electromyographic evidence of widespread acute denervation

✓hyperintensity in the corticospinal tracts on MRI.

A dx of Amyotrophic Lateral Sclerosis (ALS).

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His family hx revealed that a maternal aunt had CD, a sister had Crohn's disease, and his maternal grandmother had MS.

flexion, 4+/5 in hip extension, 4/5 in knee flexion and 4–/5 in ankle dorsiflexion) associated with mild wasting of the right quadriceps. The patient had generalized bilateral hyperreflexia, sustained right ankle clonus and a right extensor plantar response. Results of cranial nerve, cerebellar and sensory examinations were normal.

T_2 and fluid-attenuated inversion recovery brain MRI sequences revealed a region of hyperintensity along the course of the left corticospinal tract, arising from the subcortical white matter of the precentral gyrus and following the posterior limb of the internal capsule into the brainstem (Figure 1A). Gadolinium-enhanced MRI did not reveal any contrast enhancement. Repeat neuroimaging 2 months later revealed more-extensive changes in the same pattern, with additional involvement of the opposite (right) subcortical region of the precentral gyrus (Figure 1B).

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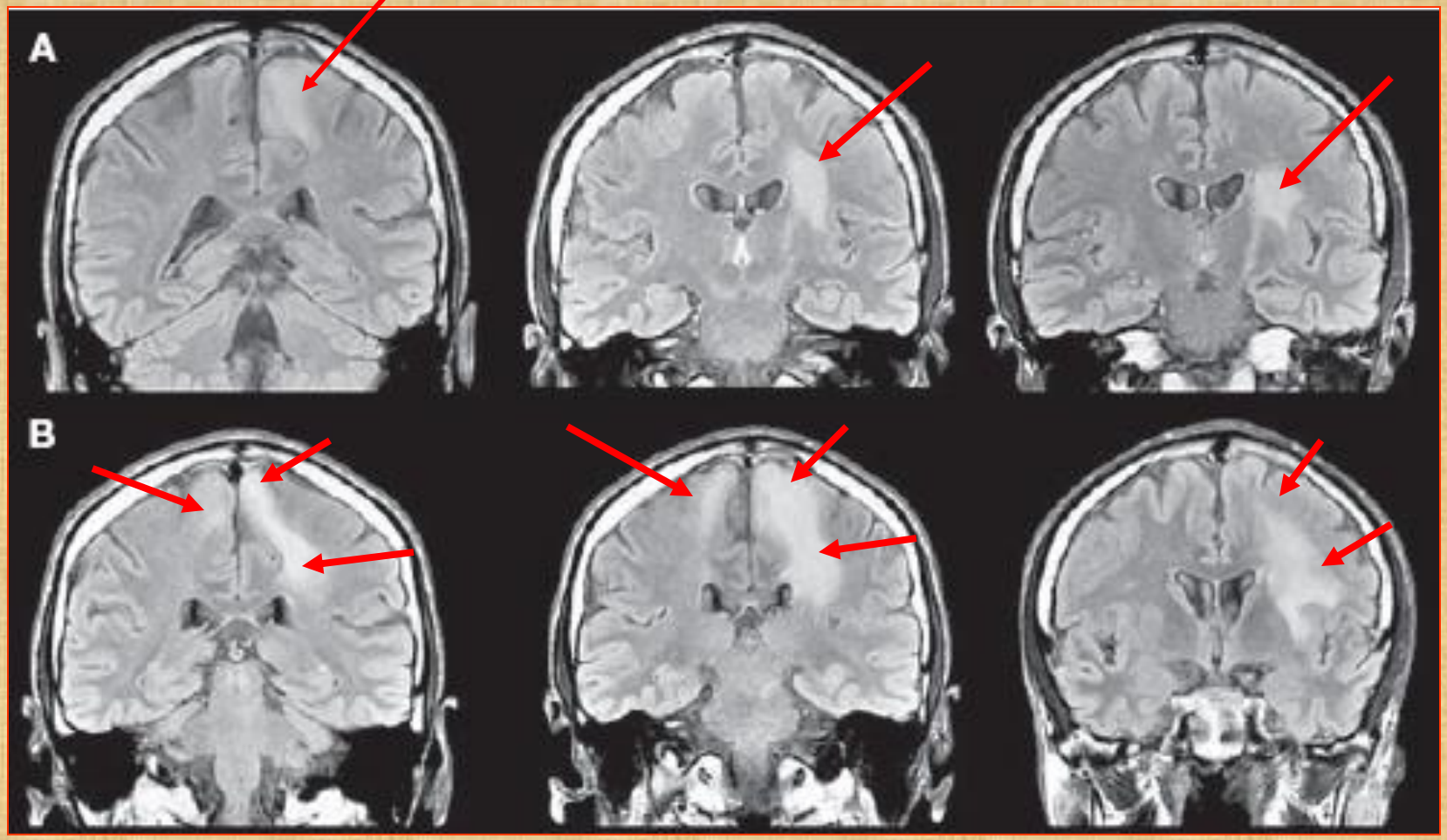

A is initial presentation, B is 2 months later

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Routine blood tests revealed:
- **a mild microcytic anemia**
- **↓ levels of serum iron**
- **↓ serum ferritin**
- **↓ serum folate**

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Screening for celiac disease was prompted by the discovery of microcytic anemia with low serum iron and folate levels.

(Medical Research Council Grade 4–/5 in hip flexion, 4+/5 in hip extension, 4/5 in knee flexion and 4–/5 in ankle dorsiflexion) associated with mild wasting of the right quadriceps. The patient had generalized bilateral hyperreflexia, sustained right ankle clonus and a right extensor plantar response. Results of cranial nerve, cerebellar and sensory examinations were normal.

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Blood tests revealed:

- **elevated antiendomysial antibody**
- **duodenal biopsy demonstrated villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes (Marsh 3A), consistent with gluten-sensitive enteropathy (Celiac Disease)**

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The patient was started on a gluten-free diet approximately 7 months after the onset of his initial neurological symptoms. No drugs, including riluzole or other agents with neuroprotective potential were given.

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9 months after initiation of treatment, the patient's right arm function, had returned to normal. Improvement in the patient's right leg function was noted, wasting was still present and there was some residual spasticity. He was now able to walk unaided, however, and his handwriting and ability to fasten buttons had returned to normal.

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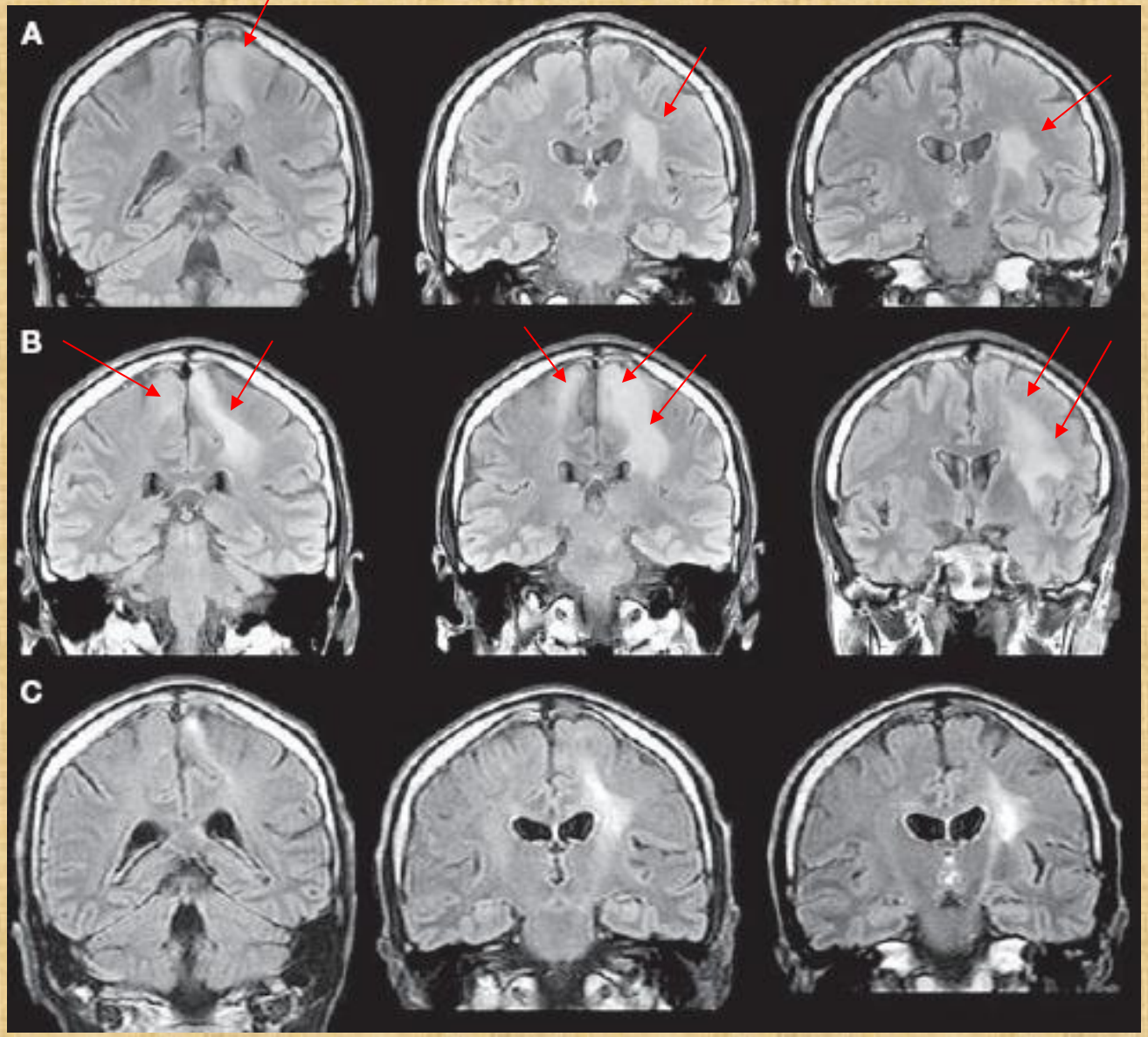
initial

2 months later

9 months after GFD



"Because ALS is a progressive and untreatable disease while CD is easily treatable, considering the latter as a cause of neurologic disorders in patients with ALS-like symptoms may be indicated".

Am J Neuroradiol. 2010 May;31(5):880-1

Brain White-Matter Lesions in Celiac Disease: A Prospective Study of 75 Diet-Treated Patients

Matthias Kieslich, MD*; Germán Errázuri
Walter Moeller-Hartmann, MD‡; Friedhelm Za

Pediatrics Vol.108 No.2, August 2001

ABSTRACT. *Objective.* **Celiac disease (CD), or gluten sensitivity, is considered to be a state of heightened immunologic responsiveness to ingested gluten proteins in genetically predisposed individuals. The gastrointestinal manifestation suggests a severe enteropathy of the small intestine with malabsorption, steatorrhea, and weight loss because of a deranged mucosal immune response. Neurologic complications occur, especially epilepsy, possibly associated with occipital calcifications or folate deficiency and cerebellar ataxia. There have been reports of brain white-matter lesions as an extraintestinal manifestation in Crohn disease and ulcerative colitis but not in CD.**

Gluten sensitivity should be considered as a state of heightened immunologic responsiveness to ingested gluten proteins in genetically predisposed individuals. The brain seems to be particularly vulnerable.

Conclusions. **Focal white-matter lesions in the brain may represent an extraintestinal manifestation of CD. They may be ischemic in origin as a result of a vasculitis or caused by inflammatory demyelination. They seem to be more typical of pediatric CD than cerebral calcifications. Their prognostic value is unclear and needs to be elucidated in additional studies. CD should be suggested as a differential diagnosis in children with unclear white-matter lesions even without intestinal symptoms.** *Pediatrics* **2001;108(2). URL: http://www.pediatrics.org/cgi/content/full/108/2/e21;** *celiac disease, neurologic complications, brain white-matter lesions, child.*

ABBREVIATIONS. CD, celiac disease; EEG, electroencephalography; CT, computed tomography; MRI, magnetic resonance imaging; AU, arbitrary units.

From the *Departments of Pediatrics and ‡Neuroradiology, Johann Wolfgang Goethe University, Frankfurt/Main, Germany.
Received for publication Dec 20, 2000; accepted Apr 9, 2001.
Reprint requests to (M.K.) Department of Pediatrics, Johann Wolfgang Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt/Main, Germany.
E-mail: mkieslich@zki.uni-frankfurt.de

Celiac disease (CD), or gluten sensitivity, is considered to be a state of heightened immunologic responsiveness to ingested gluten proteins in genetically predisposed individuals. The gastrointestinal manifestation implies a severe enteropathy of the small intestine with malabsorption, steatorrhea, and weight loss associated with characteristic lesions of the small bowel mucosa, which

of neurologic involvement of CD in a mainly pediatric cohort.

METHODS

Seventy-five diet-treated patients who attended the pediatric outpatient clinic of Frankfurt University between 1997 and 1999 were enrolled in this prospective study. The age range was 2.8 to 24.2 years with a median of 10.7 years and a mean of 11.6 years (standard deviation: 5.13). Informed consent was obtained from the patients or their parents. For all patients, the diagnosis was based on biopsies of the small intestine combined with gluten exposition. Fifty-two female patients (69%) and 23 male patients (31%) underwent clinical neurologic examination, laboratory investigation, electroencephalography (EEG), computed tomography (CT), and magnetic resonance imaging (MRI). Medical history concerning concomitant diseases and perinatal problems was evaluated. The quality of dietary compliance was analyzed by a questionnaire, confirmed by the presence of gliadin antibodies (IgA) and classified into 3 groups: 1) good: no dietary mistakes, 2) moderate: 1 or 2 dietary mistakes per week, or 3) poor: more than 2 dietary mistakes per week. IgA were measured in arbitrary units (AU) by the gluten-IgA-enzyme immunometric assay (Pharmacia, Erlagen, Germany). The gluten exposure time was defined as age at diagnosis minus the age at the beginning of gluten-containing nutrition plus the time of diagnostic gluten exposition. EEG re-


Inside the cells of autoimmune targeted tissue, is a roaring fire

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

“Differentiating Gluten Related Disorders”

Both written by Dr. Thomas O’Bryan DC, CCN,

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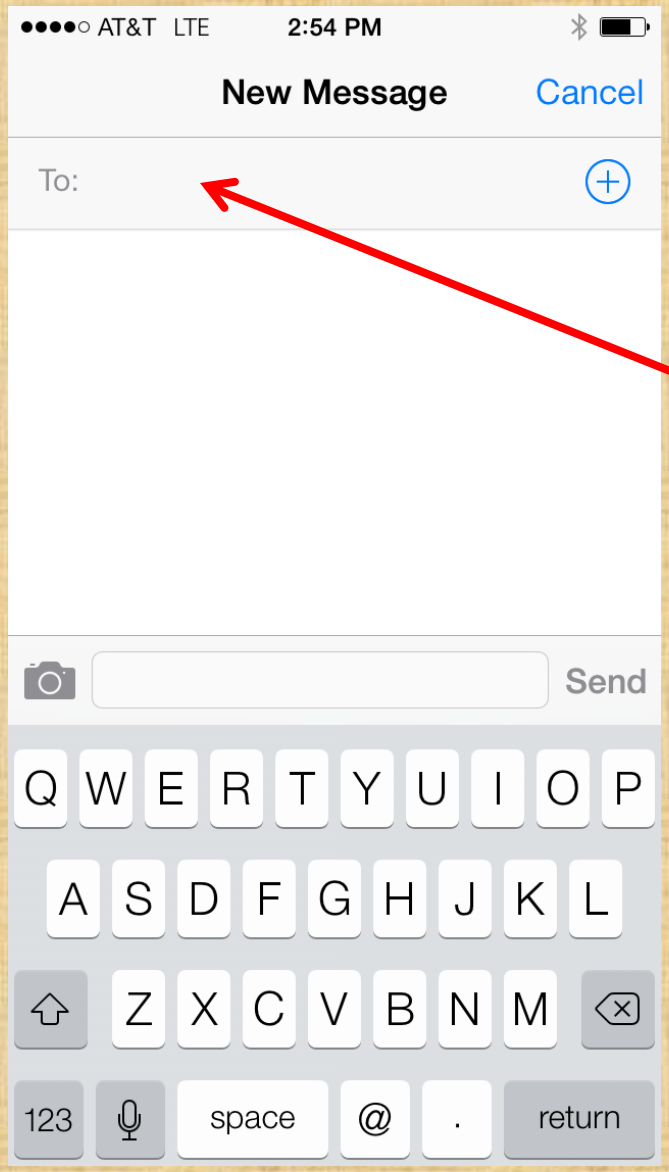
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Gluten

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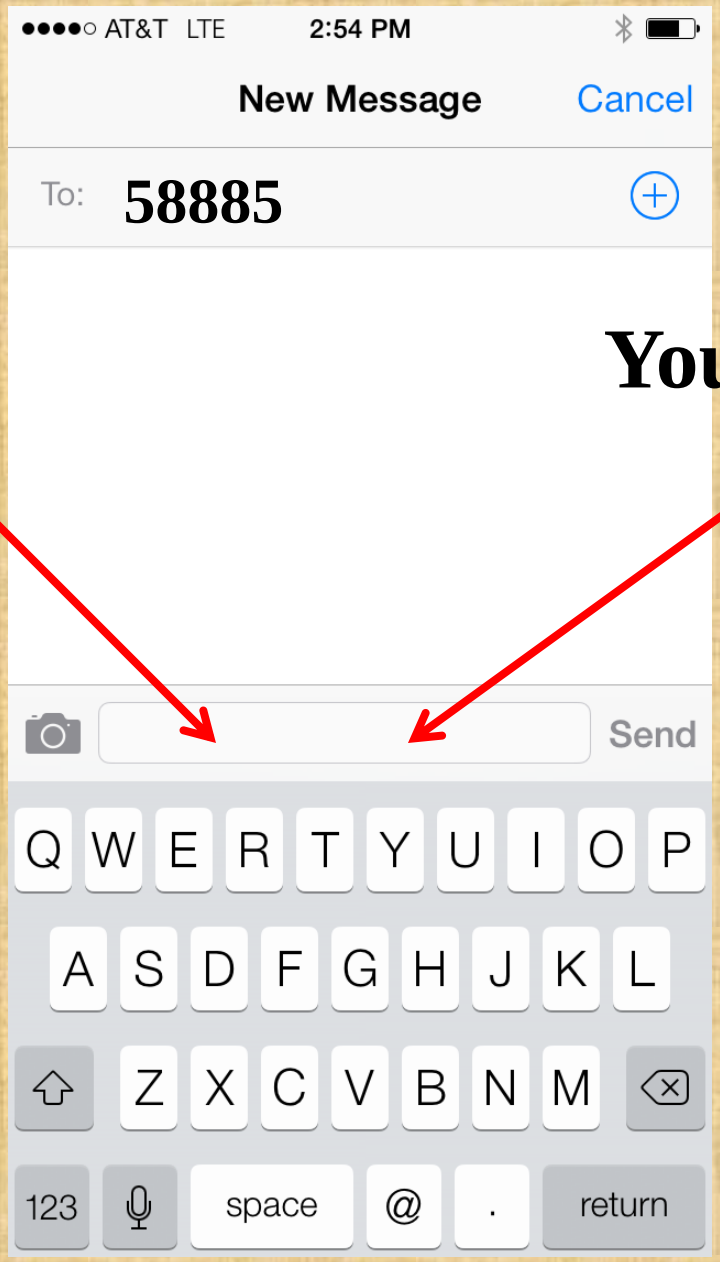
Email Address



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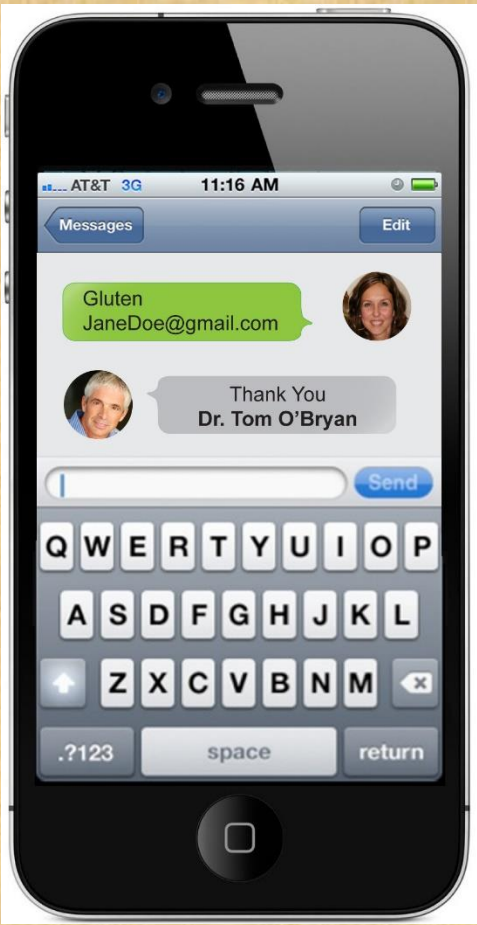
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We will send you all 49 references I used to create the presentation you are hearing today.

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


7 Premises To Look At

Premise #1

Incompletely digested peptides of wheat (exorphins) modulate opiod receptor activity

Detective Adrian Monk

Premise #2

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

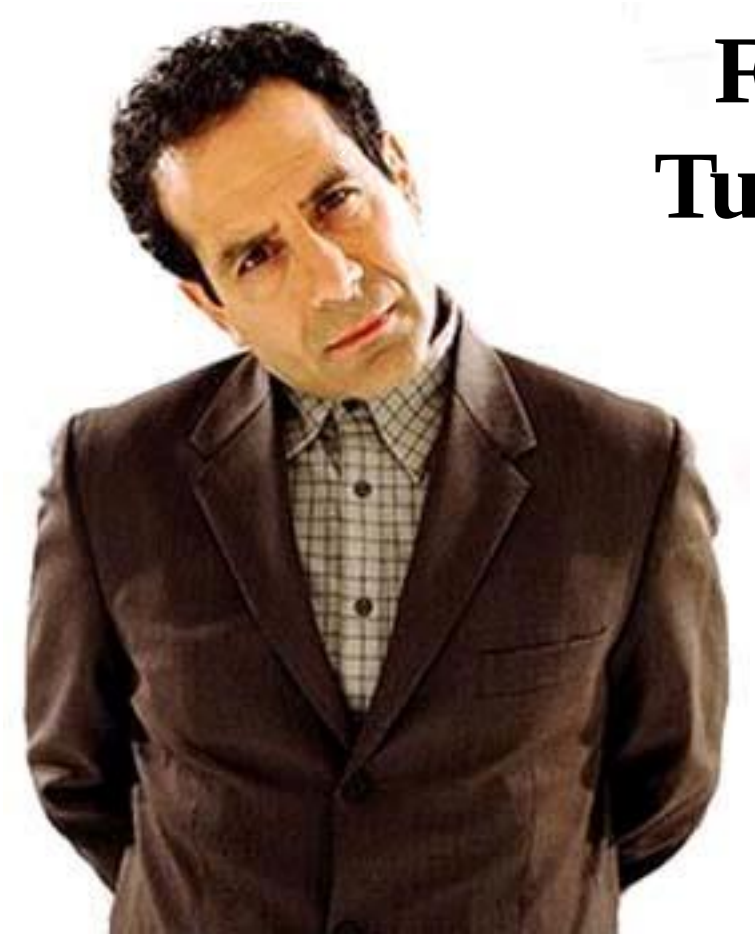
While many individual autoimmune diseases are rare, collectively they are thought to affect approximately 8 percent of the United States population – 24 million persons.

Premise #3

Genes Control Function

Detective Adrian Monk

Premise #4

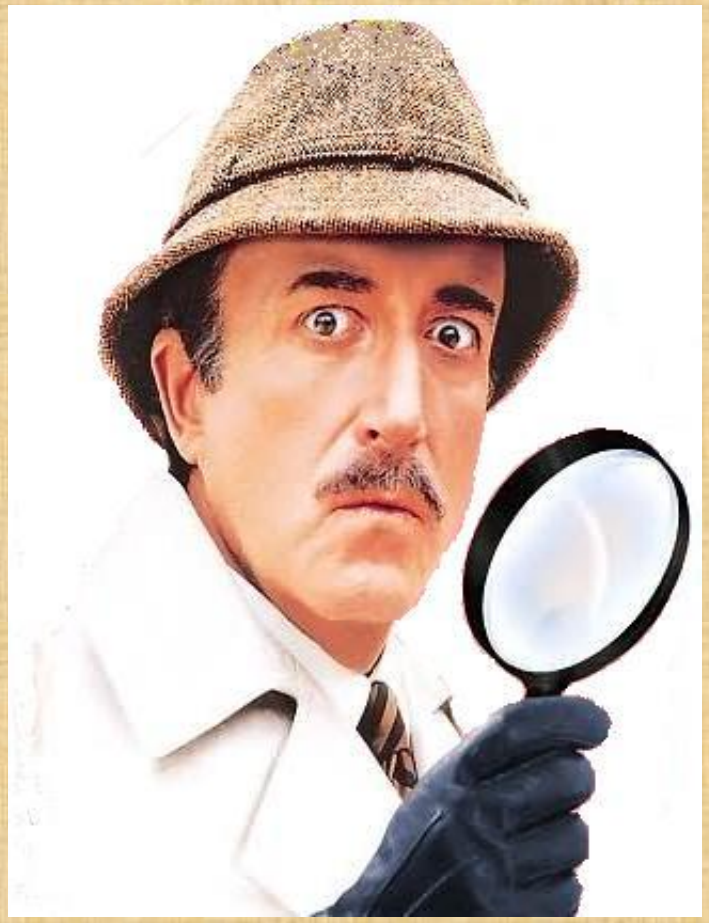


Food Turns On and Turns OFF Our Genes

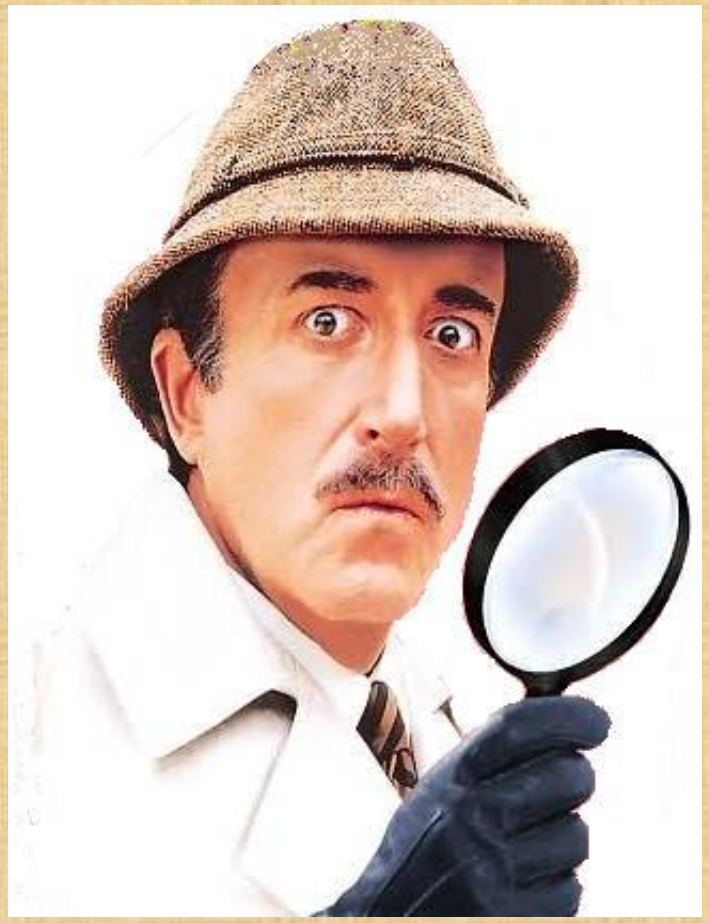
Detective Adrian Monk

Premise #5

Where Does the Persisting Inflammation Come From?



Premise #5
What is the Impact of Intestinal Permeability?



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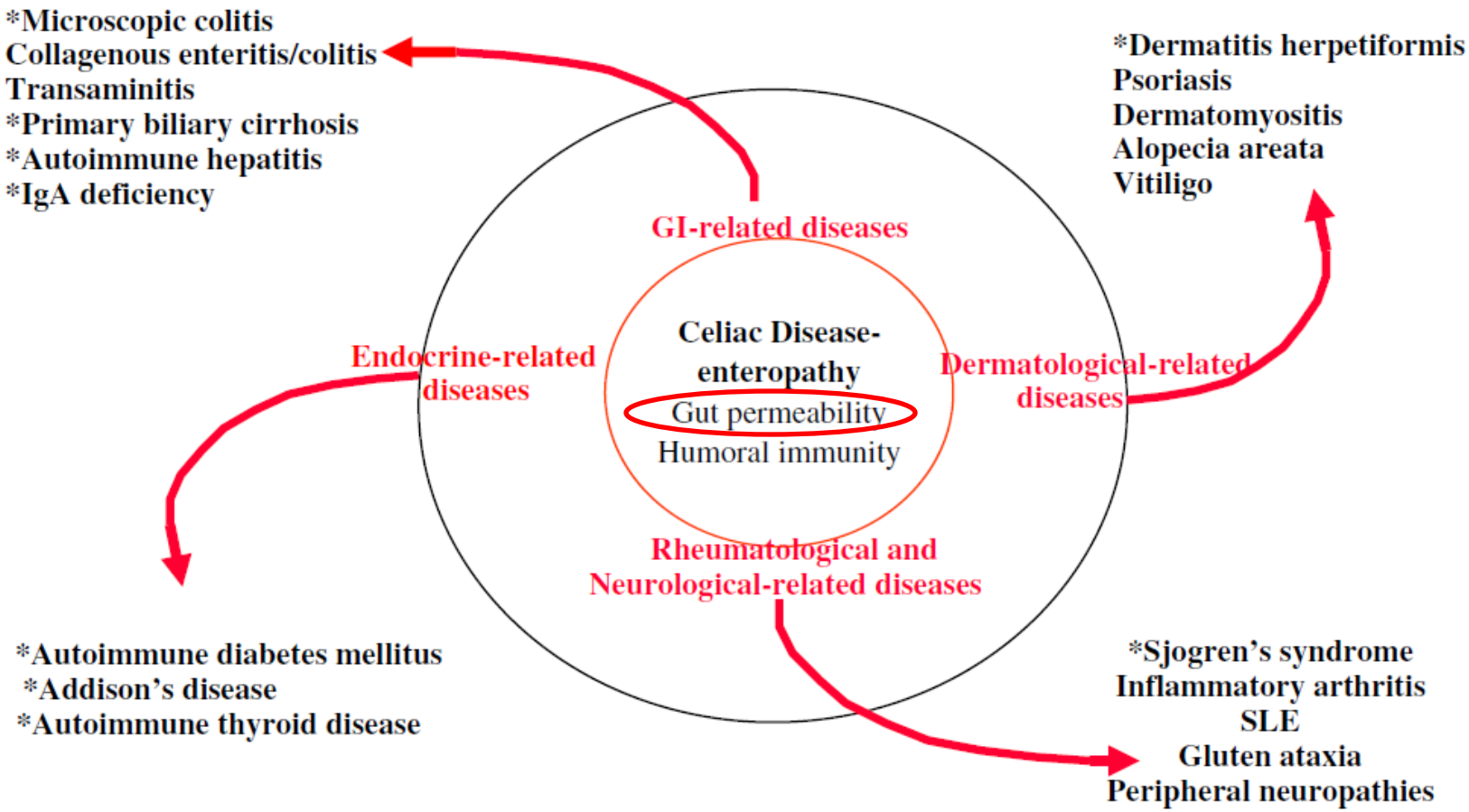
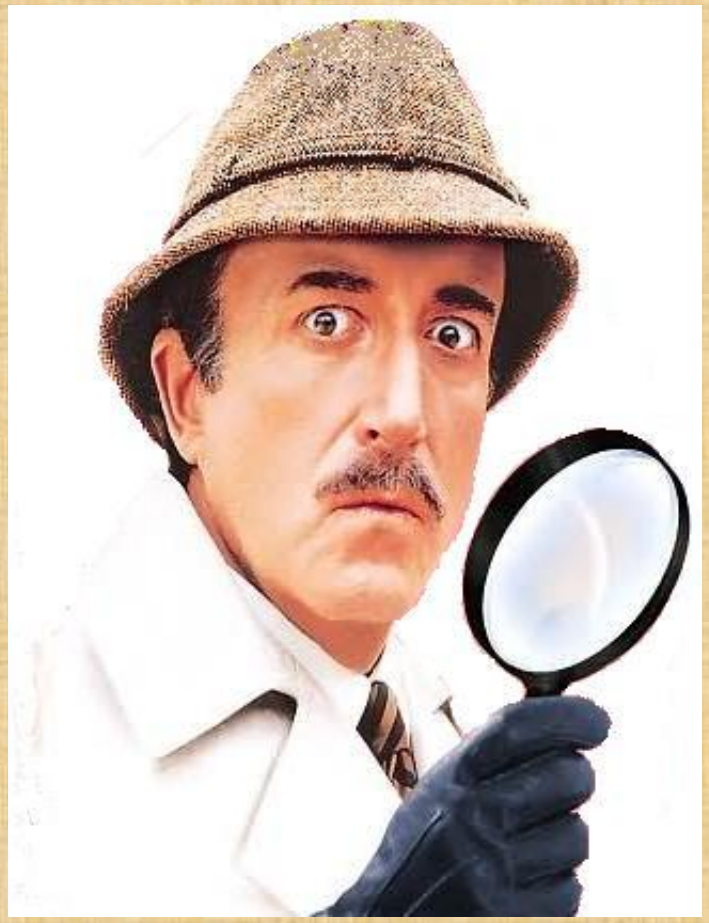
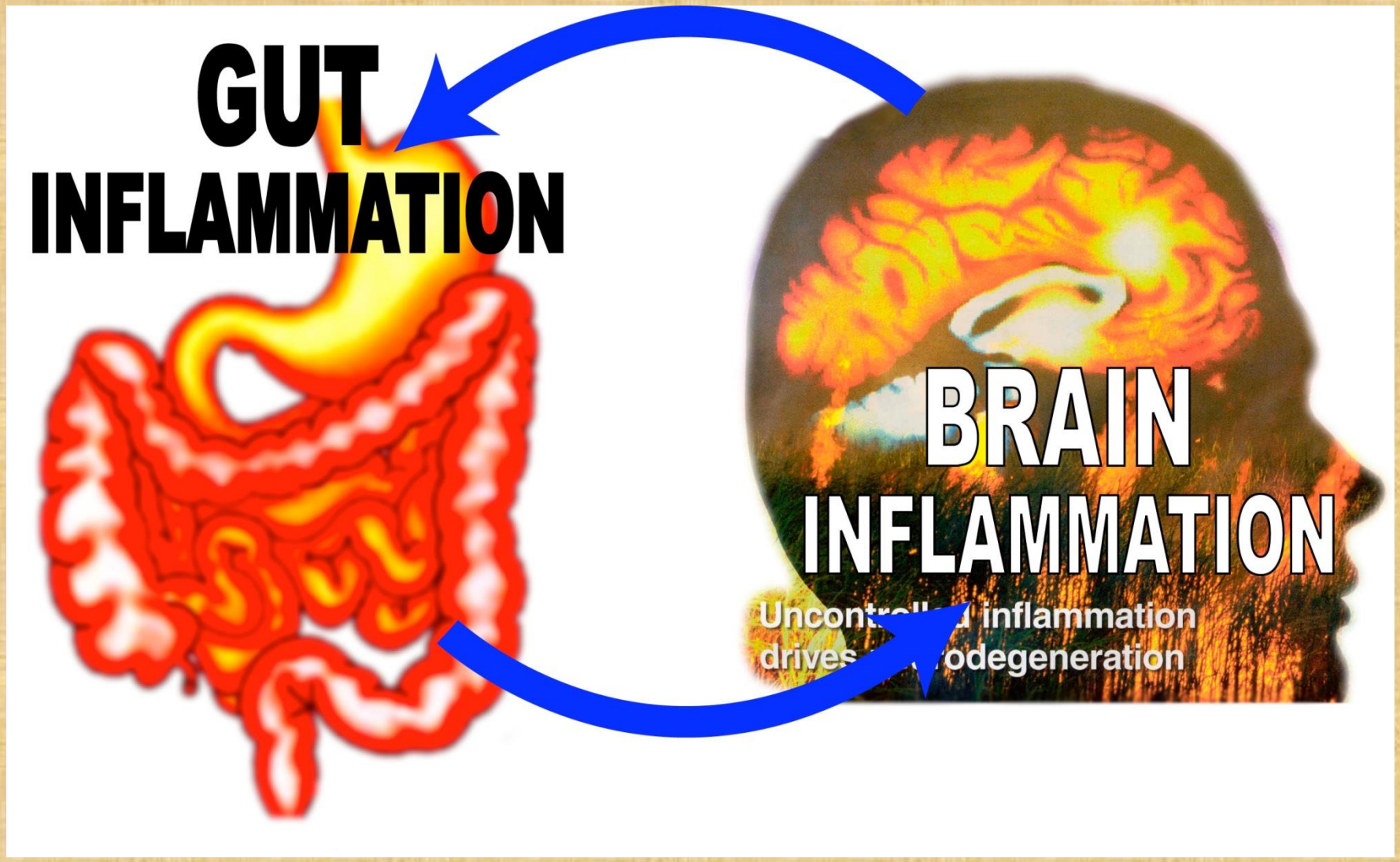


Fig. 1. Autoimmune and inflammatory diseases in relation to celiac disease. *Strongest associations.

Premise #7

How Might The Impact of Intestinal Permeability Present?





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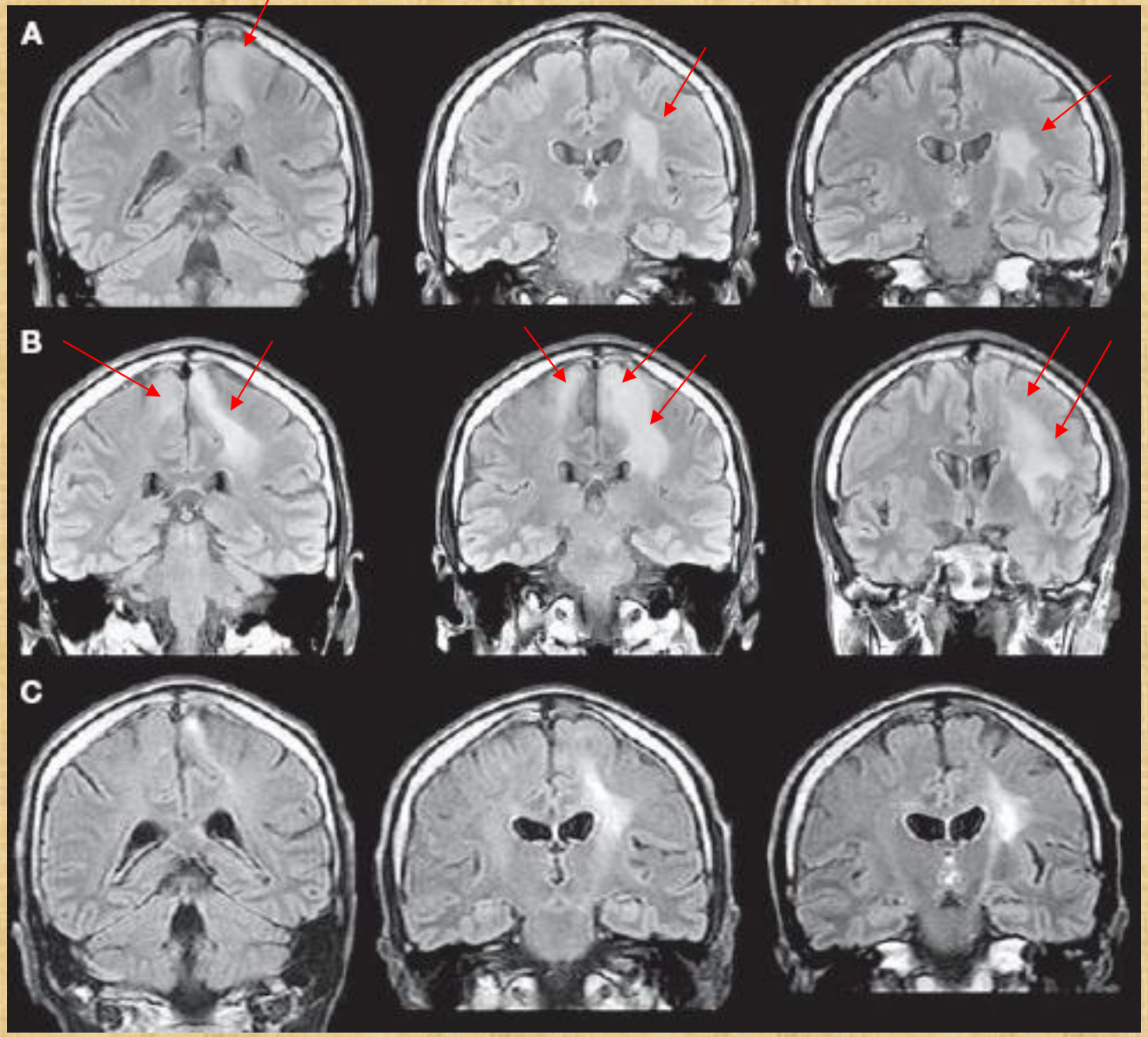
initial

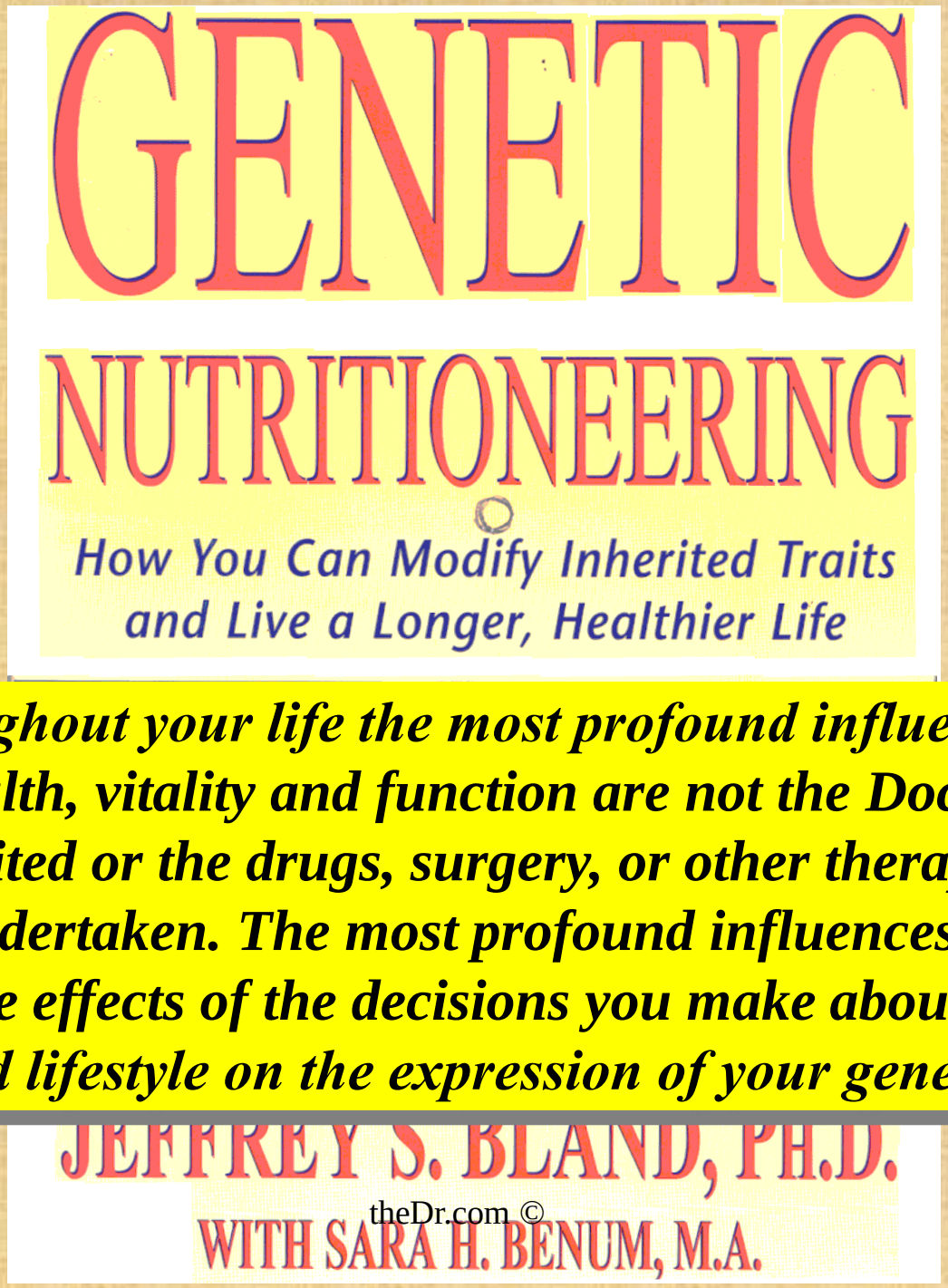
2 months later

9 months after GFD

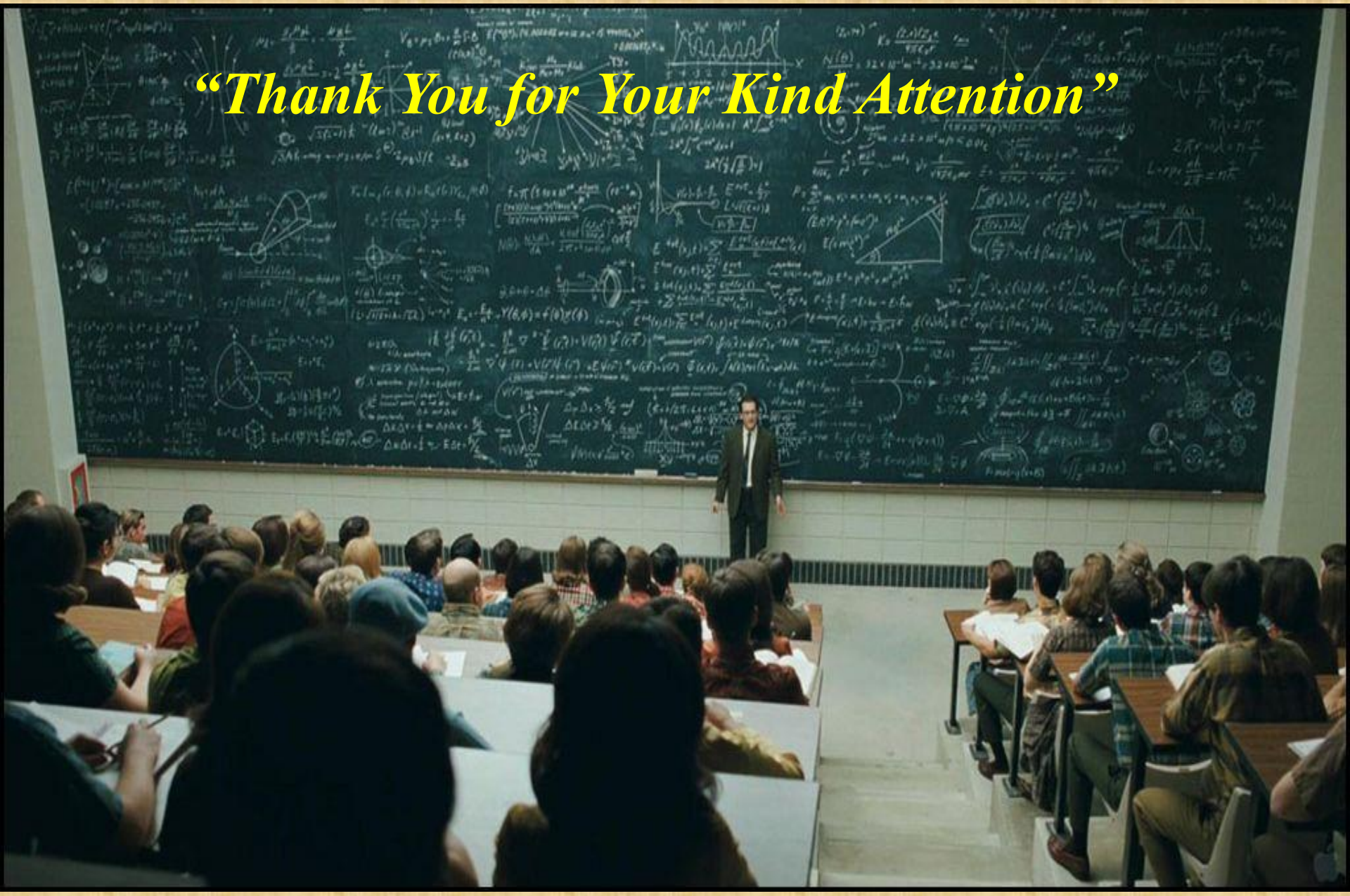


Take Care of Yourself

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