Dietary Triggers of Pain and Inflammation Thwarting LDN Effectiveness

Low Dose Naltrexone
February 19-20, 2016
Orlando, Florida

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**

What Triggers the Systemic Symptoms Initiating the Autoimmune Syndrome?

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

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

Irritation/inflammation/dysbiosis (activating immune inflammatory response)

Increased intestinal permeability

Increased load on liver detoxification pathways (food antigens, endotoxin)
AND
Increased immune complexes in general circulation

Molecular Mimicry and tissue specific symptoms determined by genetics and antecedents

Development of autoimmune syndromes eventually diagnosed as an autoimmune disease

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SYSTEMIC INFLAMMATION INCREASES INTESTINAL PERMEABILITY DURING EXPERIMENTAL HUMAN ENDOTOXEMIA

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

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

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

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

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

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

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

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

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

MATERIALS AND METHODS

Subjects

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

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

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CASE STUDY #1

Conjunctival Tumor diagnosed as Kaposi's Sarcoma

Indian J Ophthalmol: 2010;58:433-434

Regression of conjunctival tumor during dietary treatment of celiac disease

Samuray Tuncer, Baris Yeniad, Gonul Peksayar

A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye. The medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention. Prior to her referral, endoscopic small intestinal biopsy had been carried out under

CD and the conjunctival tumor showed complete regression during gluten-free dietary treatment. The clinical fleshy appearance of the lesion with spider-like vascular extensions and subconjunctival hemorrhagic spots, possible association with an acquired immune system dysfunction due to CD, and spontaneous regression by a gluten-free diet led us to make a presumed diagnosis of conjunctival Kaposi sarcoma.

Key words: Celiac disease, conjunctiva, gluten-free diet, Kaposi sarcoma

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Her past medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention since 2 months. Her weight and height percentiles were subnormal compared to her age group. From 26 months of age, she had recurrent serous otitis media treated with systemic antibiotics. However, the primary etiology could not be determined by her pediatrician in the first 3 years of life.

Our initial visit showed that the visual acuities were 20/20 in both eyes. Slit-lamp examination of the right eye revealed

possible diagnosis of CD in another hospital. Therefore, her parents did not want their child to undergo general anesthesia for the second time for the excisional biopsy. We decided to follow the patient without any intervention until all systemic investigations were concluded.

The blood test for HIV antibody was negative. Serology showed high anti-gliadin and anti-endomysial immunoglobulin A antibody levels. Endoscopic intestinal biopsy demonstrated partial villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia consistent with CD. Genetic testing of the family members revealed high maternal autoantibody titers for CD.

After the diagnosis of CD, gluten-free diet was instituted. The conjunctival lesion gradually regressed [Fig. 1B] and

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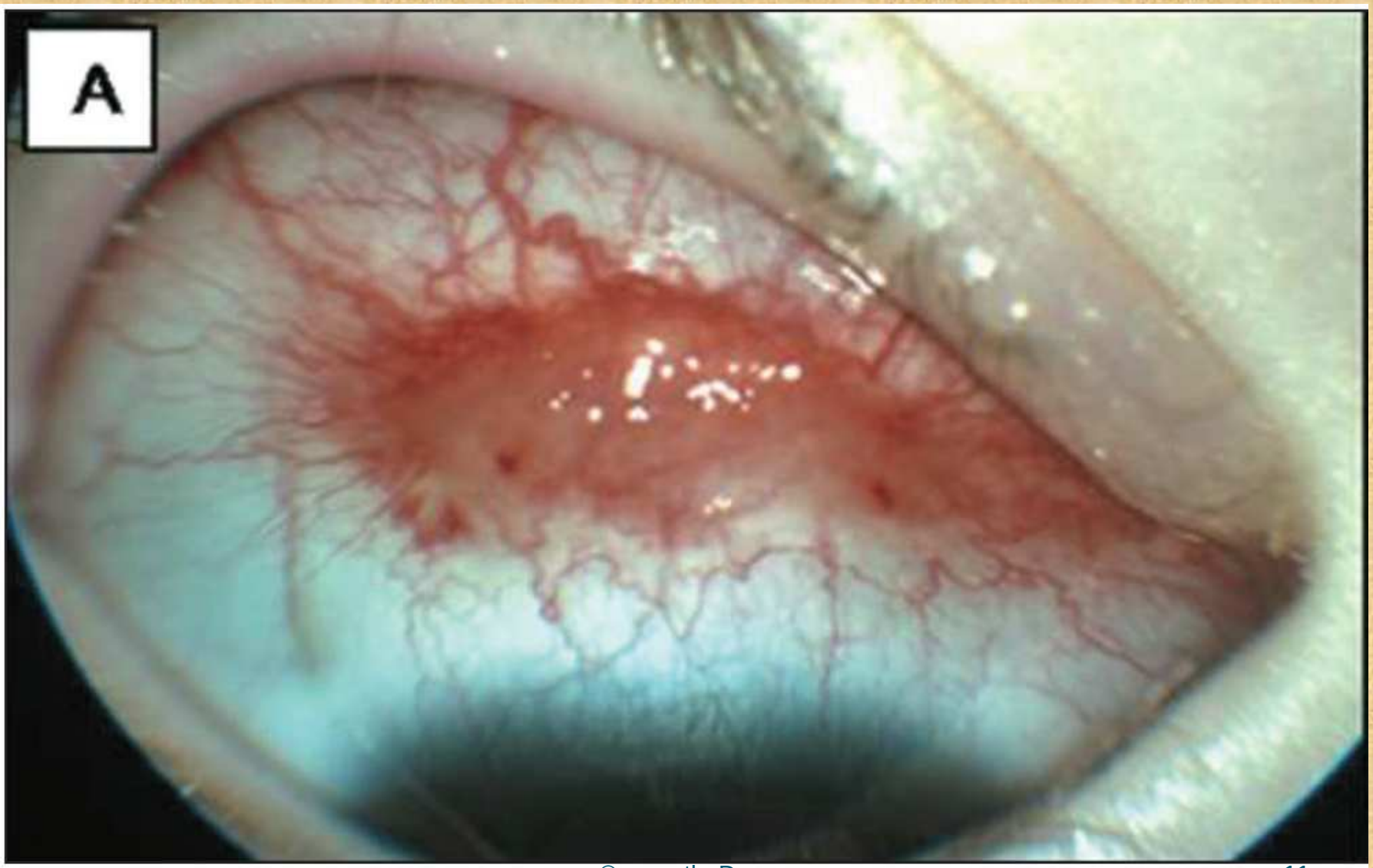

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The differential diagnoses of such a conjunctival lesion includes KS, subconjunctival hemorrhage, malignant melanoma, squamous cell carcinoma, pyogenic granuloma, cavernous hemangioma, lymphoma, caroticocavernous fistula, foreign body granuloma, and lymphangioma

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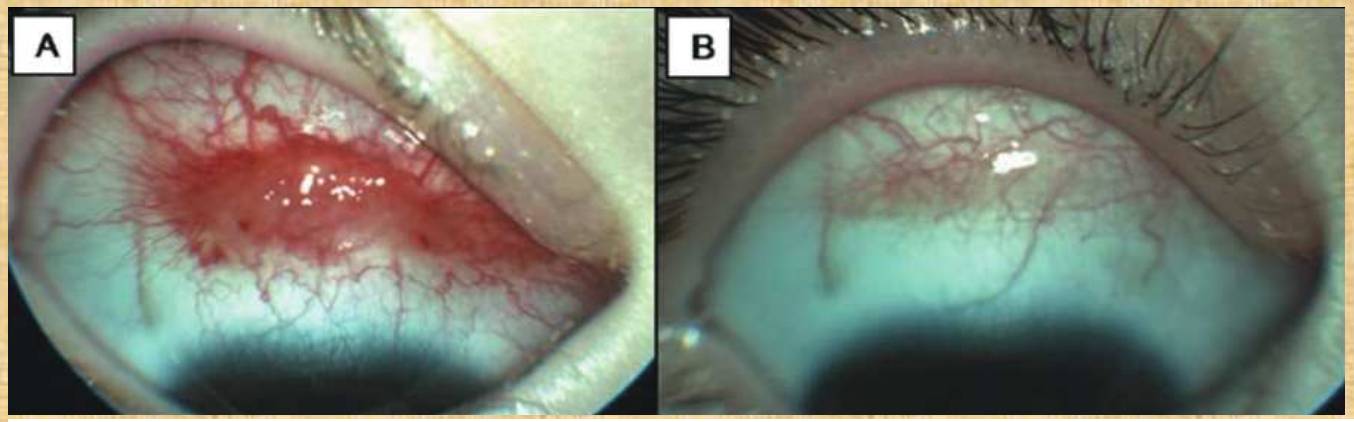

Figure 1: A 3-year-old girl, who had a 3-months history of hemorrhagic tear episodes, presented with a painless and reddish conjunctival lesion in the right eye. (A) Anterior segment photograph of the right eye showing reddish, fleshy, and highly vascular spider-like lesion on the superior bulbar conjunctiva. (B) After one week of follow-up with a gluten-free diet, spontaneous regression of the conjunctival lesion was noted. (C) After 2 months of follow-up, the conjunctival lesion disappeared completely

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Samuray Tuncer, Baris Yeniad, Gonul Peksayar

A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye. The medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention. Prior to her referral, endoscopic small intestinal biopsy had been carried out under general anesthesia with a possible diagnosis of CD in another hospital. Therefore, her parents did not want their child to undergo general anesthesia for the second time for the excisional biopsy. We decided to follow the patient until all systemic investigations were concluded. In evaluation, the case was diagnosed with CD and the conjunctival tumor showed complete regression during gluten-free dietary treatment. The clinical fleshy appearance of the lesion with spider-like vascular extensions and subconjunctival hemorrhagic spots, possible association with an acquired immune system dysfunction due to CD, and spontaneous regression by a gluten-free diet led us to make a presumed diagnosis of conjunctival Kaposi sarcoma.

Key words: Celiac disease, conjunctiva, gluten-free diet, Kaposi sarcoma

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DOI: 10.4103/0301-4738.67071

steroids, and hence, excisional biopsy was suggested. The patient was referred to our clinic to get a second opinion.

Her past medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention since 2 months. Her weight and height percentiles were subnormal compared to her age group. From 26 months of age, she had recurrent serous otitis media treated with systemic antibiotics. However, the primary etiology could not be determined by her pediatrician in the first 3 years of life.

Our initial visit showed that the visual acuities were 20/20 in both eyes. Slit-lamp examination of the right eye revealed

And disappeared completely after 2 months [Fig. 1C]

sarcoma (KS). Prior to her referral, endoscopic small intestinal biopsy had been carried out under general anesthesia with a possible diagnosis of CD in another hospital. Therefore, her parents did not want their child to undergo general anesthesia for the second time for the excisional biopsy. We decided to follow the patient without any intervention until all systemic investigations were concluded.

The blood test for HIV antibody was negative. Serology showed high anti-gliadin and anti-endomysial immunoglobulin A antibody levels. Endoscopic intestinal biopsy demonstrated partial villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia consistent with CD. Genetic testing of the family members revealed high maternal autoantibody titers for CD.

After the diagnosis of CD, gluten-free diet was instituted. The conjunctival lesion gradually regressed [Fig. 1B] and

Indian J Ophthalmol: 2010;58:433-434

1 week of GFD **2 months of GFD**

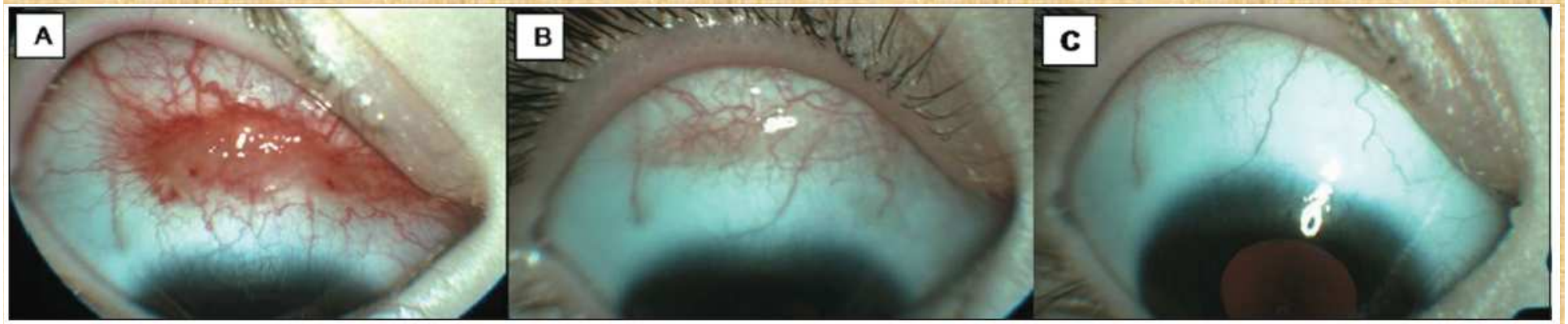

Figure 1: A 3-year-old girl, who had a 3-months history of hemorrhagic tear episodes, presented with a painless and reddish conjunctival lesion in the right eye. (A) Anterior segment photograph of the right eye showing reddish, fleshy, and highly vascular spider-like lesion on the superior bulbar conjunctiva. (B) After one week of follow-up with a gluten-free diet, spontaneous regression of the conjunctival lesion was noted. (C) After 2 months of follow-up, the conjunctival lesion disappeared completely

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She was completely asymptomatic and the conjunctival lesion did not recur after 9 months of follow-up.

CD and the conjunctival tumor showed complete regression during gluten-free dietary treatment. The clinical fleshy appearance of the lesion with spider-like vascular extensions and subconjunctival hemorrhagic spots, possible association with an acquired immune system dysfunction due to CD, and spontaneous regression by a gluten-free diet led us to make a presumed diagnosis of conjunctival Kaposi sarcoma.

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A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye. The medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention. Prior to her referral, endoscopic small intestinal biopsy had been carried out under steroids, and hence, excisional biopsy was suggested. The patient was referred to our clinic to get a second opinion.

Her past medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention since 2 months. Her weight and height percentiles were subnormal compared to her age group. From 26 months of age, she had recurrent serous otitis media treated with systemic antibiotics. However, the primary etiology could not be determined by her pediatrician in the first 3 years of life.

Our initial visit showed that the visual acuities were 20/20 in both eyes. Slit-lamp examination of the right eye revealed

In conclusion, we present a very unusual conjunctival tumor in a patient with CD that showed complete regression by a gluten-free diet. Prompt regression of the conjunctival lesion during gluten-free diet suggests a possible relationship to CD and an autoimmune process.

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Can Foods Trigger Pathogenic Intestinal Permeability

Detective Adrian Monk

CLINICA

CLIN GASTRO AND HEP 2012;10:1096–1100

ADVANCES IN TRANSLATIONAL SCIENCE

Joseph H. Sellin, Section Editor

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

ALESSIO FASANO

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

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

Technological Primer

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

What Are the Findings

Regulation of Intestinal Permeability: The Zonulin Pathway

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

intestines exposed to enteric bacteria secreted zonulin.[2] This secretion was independent of the virulence of the microorganisms tested, occurred only on the luminal aspect of the bacteria-exposed small intestinal mucosa, and was followed by an increase in intestinal permeability coincident with the disengagement of the protein zonula occludens 1 from the tight junctional complex.[4] This zonulin-driven opening of the paracellular pathway may represent a defensive mechanism, which flushes out microorganisms so contributing to the innate immune response of the host against bacterial colonization of the small intestine.

Besides bacterial exposure, we have shown that gliadin, the main staple protein in wheat, also affects the intestinal barrier function by releasing zonulin by engaging the chemokine receptor CXCR3.[5] Our data demonstrate that in the intestinal epithelium, CXCR3 is expressed at the luminal level, is overexpressed in celiac disease (CD) patients, colocalizes with specific gliadin peptides, and that this interaction coincides with recruitment of the adapter protein, MyD88, to the receptor.[5]

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

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Digestive and Liver Disease 38 (2006) 732–736

Alimentary Tract

Intestinal permeability in patients with adverse reactions to food

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

[a] *Department of Internal Medicine, Immunology and Infectious Diseases (MIDIM), University of Bari Medical School, Policlinico, Piazza G. Cesare n° 11, 70124 Bari, Italy*

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

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

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

Keywords: Food allergy; Food hypersensitivity; Intestinal permeability

1. Introduction

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

* Corresponding author. Tel.: +39 080 5592789; fax: +39 080 5592789.
E-mail address: mt.ventura@allergy.uniba.it (M.T. Ventura).

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[b] *Department of Emergency and Organ Transplantation (DETO), Gastrointestinal section, University of Bari Medical School, Policlinico, Bari, Italy*

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

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

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

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

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Gastroenterology 2014;147:1012–1020

CLINICAL—ALIMENTARY TRACT

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

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

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

CLINICAL AT

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

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

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

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

CLINICAL AT

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

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

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

Keywords: Imaging; FODMAP; Food Allergy; Gluten.

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

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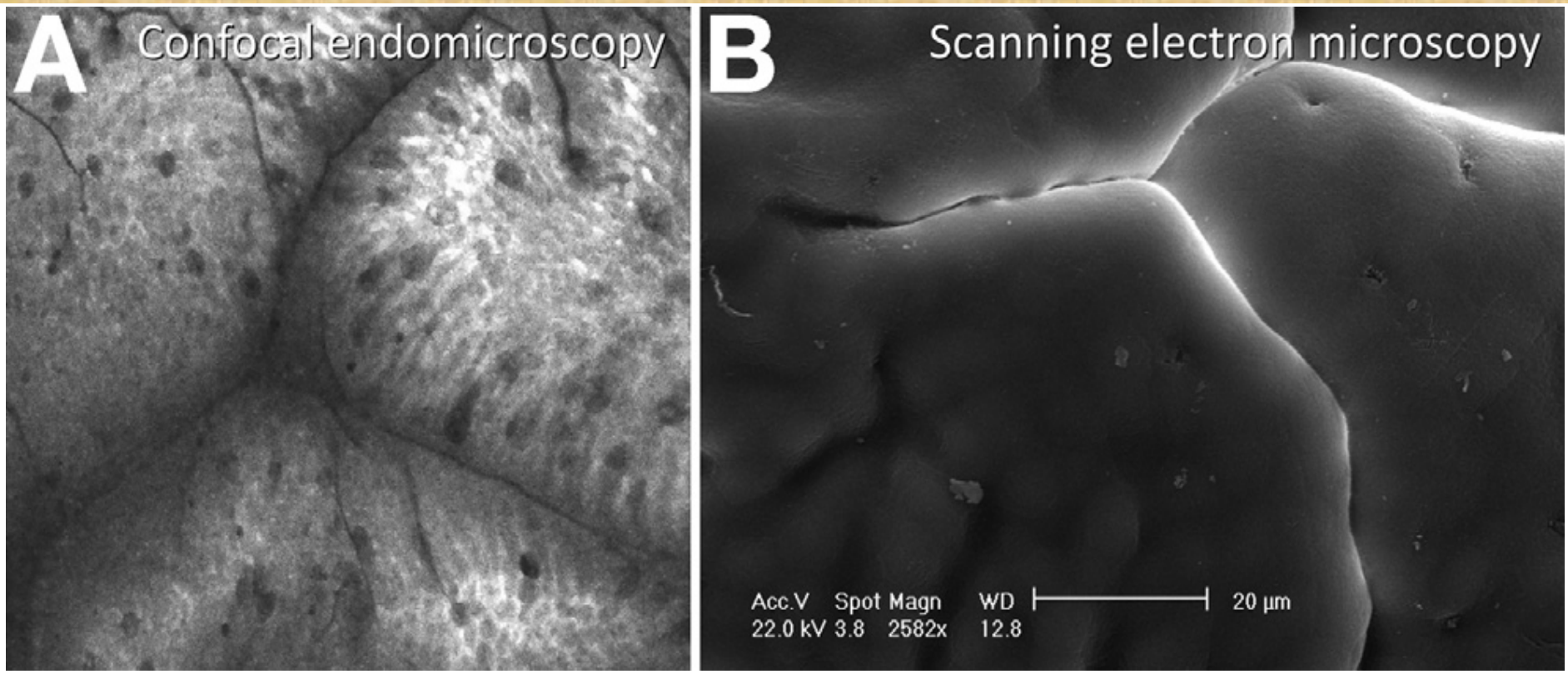

Figure 5. Intervillous space at baseline as visualized with endomicroscopy and scanning electron microscopy.

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

CLINICAL AT

Four commonly encountered major antigen mixtures and suspensions were applied;
•cow's milk mixed with 30% sterile water;
•wheat, 2 g;
•yeast, 1 g;
•soy, 2 g
18 mL sterile water/2 mL simethicone served as a control substance.

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

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

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

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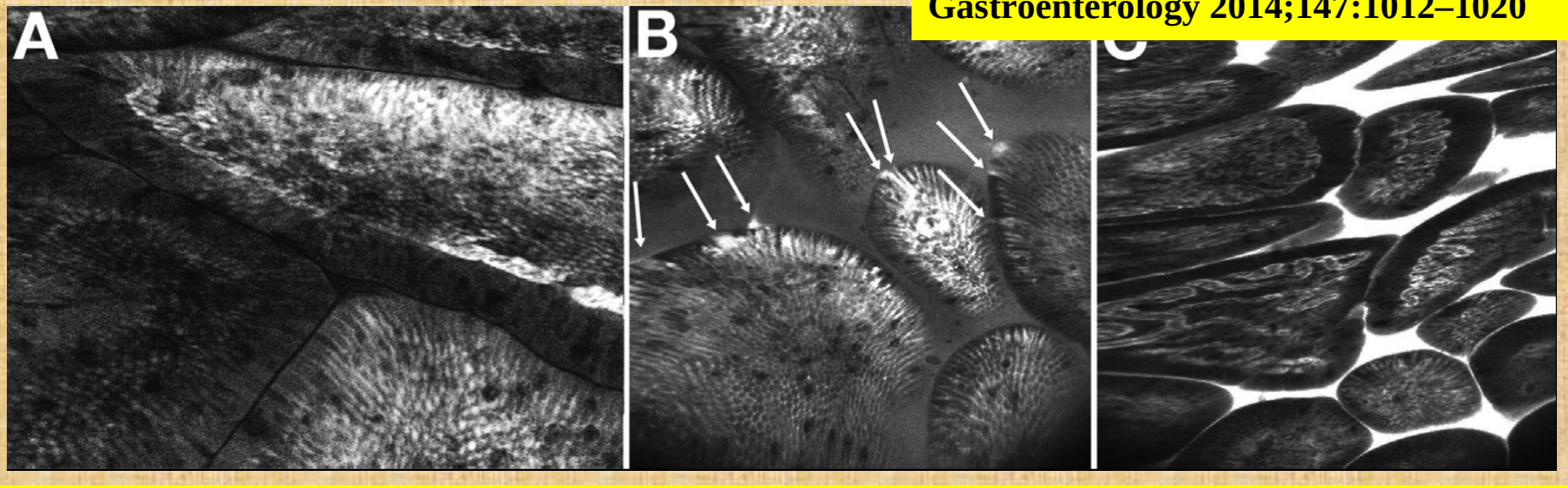
BACKGROUND & AIMS: We investigated suspected food intolerances in patients with irritable bowel syndrome (IBS) using confocal laser endomicroscopy (CLE) for real-time visualization of structural/functional changes in the intestinal mucosa after food challenge. Patients with functional changes after food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

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

Gastroenterology 2014;147:1012–1020



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

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

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

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

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REVIEW

See REVIEW page 213
See COMMENTARY page

Mucosal Immunology | VOLUME 3 NUMBER 3 | MAY 2010

Multiple facets of intestinal permeability and epithelial handling of dietary antigens

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

Increased intestinal permeability is an early biological change that often precedes the onset of autoimmune diseases. Such increased permeability could be due to environmental factors (such as infection, toxic molecules, allergenic foods) that possibly initiate the (autoimmune) disease.

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

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

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

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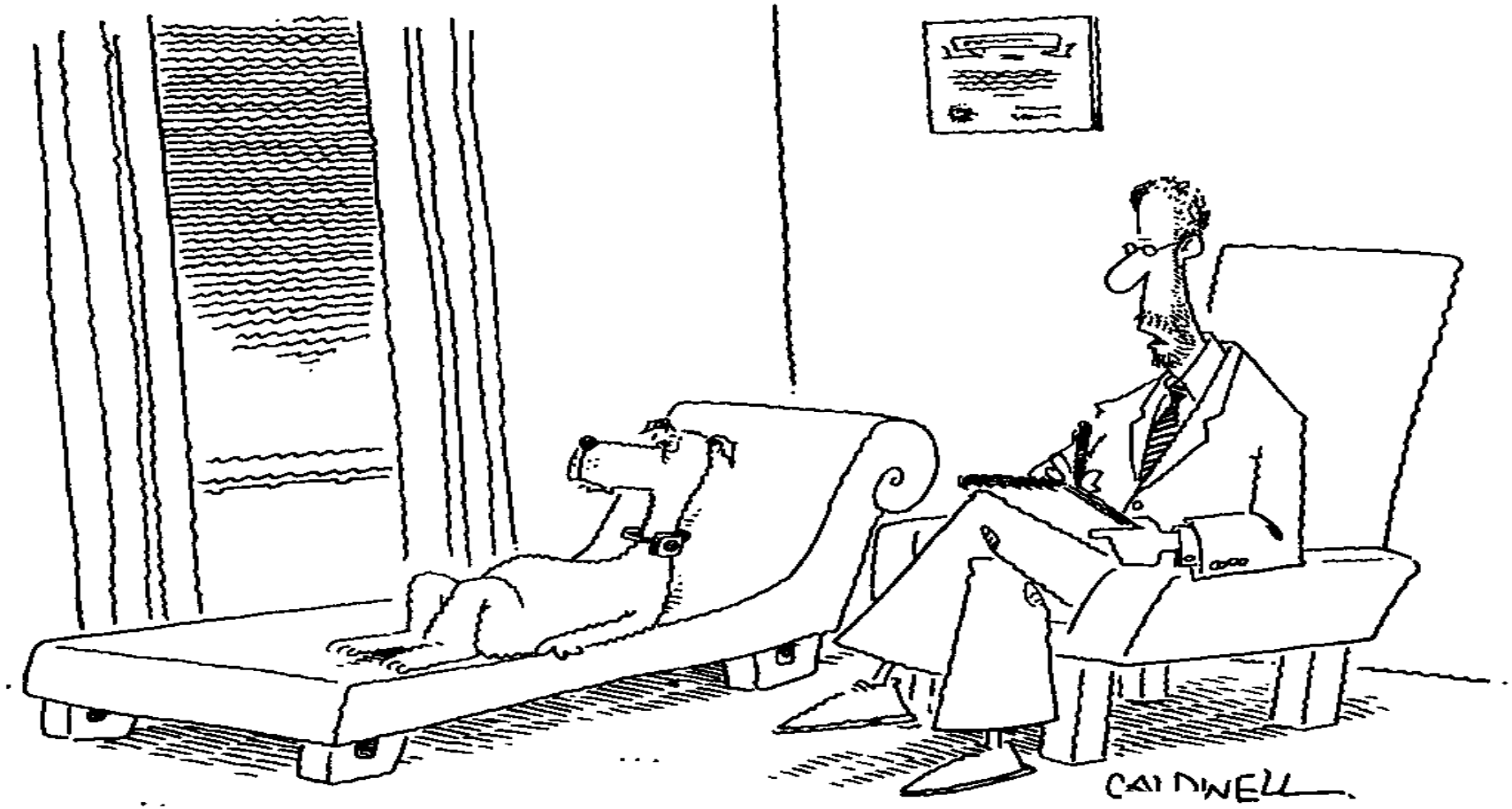
Is Gluten Sensitivity limited to Celiacs?

Detective Adrian Monk



“Please…tell me more about this imaginary fence.”

Nutrients 2015, 7, 1565-1576

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

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ISSN 2072-6643

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Article

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

We aimed to study response to gliadin exposure, in terms of barrier function and cytokine secretion, using intestinal biopsies obtained from four groups:

- **celiac patients with active disease (ACD),**
- **celiac patients in remission (RCD),**
- **non-celiac patients with gluten sensitivity (GS) and**
- **non-celiac controls (NC).**

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

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Article

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

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

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

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

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

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

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

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

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

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Taylor & Francis

Scand J of Gastro, 2006; 41: 408/419

ORIGINAL ARTICLE

Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines

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

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

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

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

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

Introduction

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

Correspondence: Alessio Fasano, MD, Mucosal Biology Research Center, University of Maryland School of Medicine, 20 Penn Street, HSF II Building, Room 345, Baltimore, Md. 21201, USA. Tel: +1 410 706 5501. Fax: +1 410 706 5508. E-mail: afasano@mbrc.umaryland.edu

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The Mechanism of LDN's anti-inflammatory effects

Detective Adrian Monk

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DOI 10.1007/s10067-014-2517-2

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REVIEW ARTICLE

The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain

Jarred Younger · Luke Parkitny · David McLain

Received: 16 January 2014 / Revised: 22 January 2014 / Accepted: 26 January 2014 / Published online: 15 February 2014

Abstract Low-dose naltrexone (LDN) has been demonstrat-

At the low dosage level, naltrexone exhibits paradoxical properties, including analgesia and anti-inflammatory actions, which have not been reported at larger dosages.

have been performed. We cover the typical usage of LDN in clinical trials, caveats to using the medication, and recommendations for future research and clinical work. LDN may represent one of the first *glial cell modulators* to be used for the management of chronic pain disorders.

Keywords Anti-inflammatory · Chronic pain · Fibromyalgia · Glial cell modulators · Low-dose naltrexone · Microglia

J. Younger
Stanford University, Stanford, CA, USA

L. Parkitny
Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, 1070 Arastradero Road, Suite 200, Palo Alto, CA 94304, USA

D. McLain
McLain Medical Associates, Birmingham, AL, USA

J. Younger (✉)
Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, 1070 Arastradero Road, Room 286, Palo Alto, CA 94304, USA
e-mail: jyounger@stanford.edu

Introduction

mechanism of action, and research use of LDN. We will be focusing this discussion on LDN as a monotherapy for chronic pain. The closely related concept of ultralow-dose naltrexone involves the use of microgram, nanogram, and picogram dosages of naltrexone co-administered with opioid analgesics [2]. The approach is used to both increase the efficacy of opioid analgesia therapy and reduce some adverse side effects. Ultralow-dose naltrexone has been covered extensively in previous reviews [3] and will not be discussed here.

Background

Naltrexone was synthesized in 1963 as an orally active competitive opioid receptor antagonist [4]. Naltrexone is structurally and functionally similar to the opioid antagonist naloxone, but it has greater oral bioavailability and a longer biologic half-life [5]. Naltrexone HCl was approved by FDA in 1984 for the treatment of opioid addiction. The typical daily dosage for opioid addiction is 50.0–100.0 mg daily, and 50.0-mg tablets are available commercially. A more complete review of the early history of naltrexone can be found elsewhere [6].

LDN refers to daily dosages of naltrexone that are approximately 1/10th of the typical opioid addiction treatment

LDN works by blocking the body's opioid/narcotic receptors for just a few hours rather than the all-day blockade caused by the standard 50 mg dosage. The opoid/narcotic receptors are the same receptors used by the body's endorphins. The body responds to this temporary blockade by greatly increasing its endorphin production, and those higher levels last all day—far after the blockade by LDN has ended. Endorphins are the major normalizer/upregulator of one's immune system.

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Abstract Low-dose naltrexone (LDN) has been demonstrat-

Naltrexone exerts its effects on humans via at least two distinct receptor mechanisms:

-the antagonist effect on mu-opioid and other opioid receptors,

-an antagonist effect on non-opioid receptors (Toll-like receptor 4 or TLR4) that are found on macrophages such as microglia.

Keywords Anti-inflammatory · Chronic pain · Fibromyalgia · Glial cell modulators · Low-dose naltrexone · Microglia

J. Younger
Stanford University, Stanford, CA, USA

L. Parkitny
Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, 1070 Arastradero Road, Suite 200, Palo Alto, CA 94304, USA

D. McLain
McLain Medical Associates, Birmingham, AL, USA

J. Younger (✉)
Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, 1070 Arastradero Road, Room 286, Palo Alto, CA 94304, USA
e-mail: jyounger@stanford.edu

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Ultralow-dose naltrexone has been covered extensively in previous reviews [3] and will not be discussed here.

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It is via the non-opioid antagonist path (TLR4) that LDN is thought to exert its anti-inflammatory effects.

on opioid receptors. As a daily oral therapy, LDN is inexpensive and well-tolerated. Despite initial promise of efficacy, the use of LDN for chronic disorders is still highly experimental. Published trials have low sample sizes, and few replications have been performed. We cover the typical usage of LDN in clinical trials, caveats to using the medication, and recommendations for future research and clinical work. LDN may represent one of the first *glial cell modulators* to be used for the management of chronic pain disorders.

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J. Younger
Stanford University, Stanford, CA, USA

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Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, 1070 Arastradero Road, Suite 200, Palo Alto, CA 94304, USA

D. McLain
McLain Medical Associates, Birmingham, AL, USA

J. Younger (✉)
Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, 1070 Arastradero Road, Room 286, Palo Alto, CA 94304, USA
e-mail: jyounger@stanford.edu

rationale for considering LDN as a primary example of a relatively new class of therapeutic agents called *glial cell modulators*. This review is intended for clinicians who are seeking additional information about the background, theory, mechanism of action, and research use of LDN. We will be focusing this discussion on LDN as a monotherapy for chronic pain. The closely related concept of ultralow-dose naltrexone involves the use of microgram, nanogram, and picogram dosages of naltrexone co-administered with opioid analgesics [2]. The approach is used to both increase the efficacy of opioid analgesia therapy and reduce some adverse side effects. Ultralow-dose naltrexone has been covered extensively in previous reviews [3] and will not be discussed here.

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LDN refers to daily dosages of naltrexone that are approximately 1/10th of the typical opioid addiction treatment

What is the irritant that TLR4 was designed to protect us from and that will inhibit the effectiveness of LDN?

Detective Adrian Monk

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

Toll-like Receptors as Sensors of Pathogens

MIKKO HALLMAN, MIKA RÄMET, AND R. ALAN EZEKOWITZ

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

Mammalian TLR4 is the signal-transducing receptor activated by the bacterial lipopolysaccharide. The activation of TLR4 leads to activation of the inflammatory cascade via NF-kB.

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

Abbreviations

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

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MIKKO HALLMAN, MIKA RÄMET, AND R. ALAN EZEKOWITZ

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

The TLRs that control the onset of an acute inflammatory response are critical antecedents for the development of adaptive acquired immunity. Genetic and developmental variation in the expression of microbial pattern recognition receptors may affect the individual's predisposition to infections in childhood and may contribute to susceptibility to severe neonatal inflammatory diseases, allergies, and autoimmune diseases.

other TLRs is likely to have similar consequences. TLR2 mediates the host response to Gram-positive bacteria and yeast. TLR1 and TLR6 may participate in the activation of macrophages by Gram-positive bacteria, whereas TLR9 appears to respond to a specific sequence of bacterial DNA. The TLRs that control the onset of an acute inflammatory response are critical antecedents for the development of adaptive acquired immunity. Genetic and

MBL, mannose-binding lectin
NF, nuclear transcription factor
SP, surfactant protein
TIR domain, Toll-IL-1 receptor domain (cytoplasmic part of TLR, IL-1 and IL-18)
TLR, Toll-like receptor
TNF, tumor necrosis factor alpha

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

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

Mak Adam Daulatzai*

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

The molecular basis for the inflammatory activity of endotoxin involves Toll-like receptor 4 (TLR4) that induces innate and adaptive immune responses to LPS. However, when pathogenic influx is excessive (via intestinal permeability), this induces immunopathology.

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

dysbiosis, gut inflammation, and chronic dyshomeostasis are of great clinical relevance. It is argued here that we need to be aware of NCGS and its chronic pathophysiological impact. Therapeutic measures including probiotics, vagus nerve stimulation, antioxidants, alpha 7 nicotinic receptor agonists, and corticotropin-releasing factor receptor 1 antagonist may ameliorate neuroinflammation and oxidative stress in NCGS; they may therefore, prevent cognitive dysfunction and vulnerability to Alzheimer's disease.

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

1. INTRODUCTION

colony-forming units per gram of predominantly anaerobes.

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

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

Mak Adam Daulatzai*

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

TLR4 acts as a co-receptor for LPS.

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

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1. INTRODUCTION

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9

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

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

Wheat amylase-trypsin inhibitors have been identified as the most likely triggers of NCWS. They are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa.

Extraintestinal
Gliadin
Intestine
Macrophage
Monocyte
Rye

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

Thus the more LPS or wheat peptides that pass through a permeable intestine, the stronger the inflammatory response and the more difficult for LDN to exert its anti-inflammatory benefits via TLR4

Detective Adrian Monk

REVIEW
www.nature.com/clinicalpractice/gasthep

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

Alessio Fasano* and Terez Shea-Donohue

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

SUMMARY

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

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

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

REVIEW CRITERIA

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

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

Correspondence
*Mucosal Biology Research Center, University of Maryland School of Medicine, 20 Penn Street, HSF II Building, Room S345, Baltimore, MD 21201, USA
afasano@mbrc.umaryland.edu

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doi:10.1038/ncpgasthep0259

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

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

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


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How do we Arrest Pathogenic Intestinal Permeability

Detective Adrian Monk


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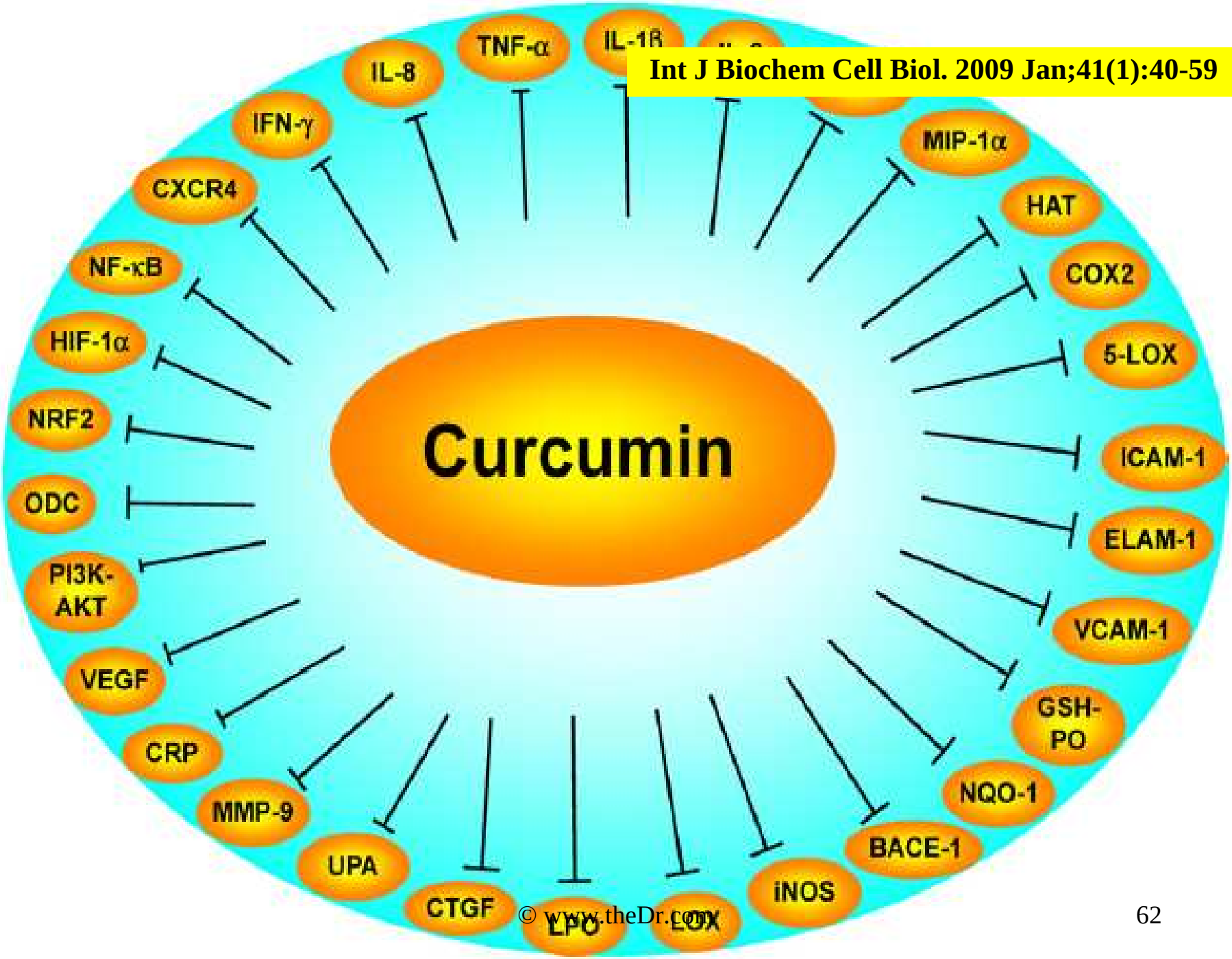
In Healing the Gut, Consider a Pleiotropic Approach

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



Int J Biochem Cell Biol. 2009 Jan;41(1):40-59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a powerful combination of five nutritional formulas in convenient daily dose packets. Each packet offers daily support for the maintenance of a healthy immune system, eicosanoid balance and gastrointestinal issues caused by gluten sensitivity. This formula promotes healthy tissue in the skin, joints, digestive system and nearly every other organ system in the body, and it has been specifically designed to exclude wheat and gluten.
gluten free
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A powerful combination of five nutritional formulas.
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Daily Dose Packets

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

PERSPECTIVES IN RENAL MEDICINE

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

ADEERA LEVIN and YAN CHUN LI

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

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

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

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

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

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

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

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

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

CARDIOVASCULAR DISEASE IS ASSOCIATED WITH CKD

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

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

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D-Hormone and the Immune System

MARGHERITA T. CANTORNA and BRETT D. MAHON

ABSTRACT. D-hormone [1,25(OH)$_2$ D$_3$] is an important immune system regulator that has been shown to inhibit development of autoimmune diseases including experimental inflammatory bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes. Paradoxically, Th2 cytokines (experimental asthma) and immunity to infectious organisms were not affected by D-hormone treatment. The effectiveness of D-hormone treatment of autoimmunity is due in part to the development and function of Th1 cells and the induction of other Th cells including Th2 cells. We report results of microarray analysis of colons from D-hormone treated mice with experimental IBD. Two hundred thirty-nine genes were inhibited and 298 genes were upregulated in the colon by D-hormone treatment of mice with IBD. Of interest was the D-hormone mediated inhibition of 3 tumor necrosis factor-α (TNF-α, lipopolysaccharide-induced TNF-α factor, and TNF receptor) related genes in the colon. It is likely that the effectiveness of D-hormone treatment of experimental autoimmunity is due in part to the inhibition of the TNF family of genes. D-hormone is a selective regulator of the immune system, and the outcome of D-hormone treatment depends on the nature (infectious disease, asthma, autoimmune disease, etc.) of the immune response. (J Rheumatol 2005;32 Suppl 76:11-20)

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

J Rheumatol 2005;32 Suppl 76:11-20

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

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

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

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

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

Address reprint requests to Dr. M.T. Cantorna, Department of Nutritional Sciences, 126 S. Henderson Bldg., University Park, PA 16802. E-mail: mxc69@psu.edu

VITAMIN D AND AUTOIMMUNITY

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

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

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

MINIREVIEW

Exp Biol Med 229:1136–1142, 2004

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

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

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

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

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

Introduction

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

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

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

[1] To who correspondence should be addressed at Department of Nutritional Sciences, 126 S. Henderson Building, Pennsylvania State University, University Park, PA 16802. E-mail: mxc69@psu.edu

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MINIREVIEW

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

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

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Introduction

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

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

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Endocrinology

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

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

ROBERT GNIADECKI, BARBARA GAJKOWSKA, AND MICHAEL HANSEN

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

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

1,25-DIHYDROXYVITAMIN D $1,25-(OH)_2D_3$ PLAYS an important role in regulation of growth of epithelial cells. The effects of $1,25-(OH)_2D_3$ have been particularly well investigated in keratinocytes. $1,25-(OH)_2D_3$ at concentrations 10^{-8}-10^{-6} M has been reproducibly shown to inhibit proliferation and induce differentiation of murine and human keratinocytes in culture (1–4). Inhibition of cell growth is also manifested *in vivo*, where $1,25-(OH)_2D_3$ and its synthetic analogs inhibit excessive proliferation of keratinocytes in psoriasis (5). Recent evidence suggests that $1,25-(OH)_2D_3$ may also be useful in the treatment of skin, breast, and colon cancer (6–9).

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

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

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Address all correspondence and requests for reprints to: Robert Gniadecki, M.D., Ph.D., Department of Dermatology D92, University of Copenhagen, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark.

Materials and Methods

Chemicals

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

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Endocrinology

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

tional proteins (E-cadherin, P-cadherin, α-catenin, and vinculin) to the cell-cell borders. The presence of α-catenin and vinculin at cell-cell bor- and neoplastic diseases. (*Endocrinology* **138:** 2241–2248, 1997)

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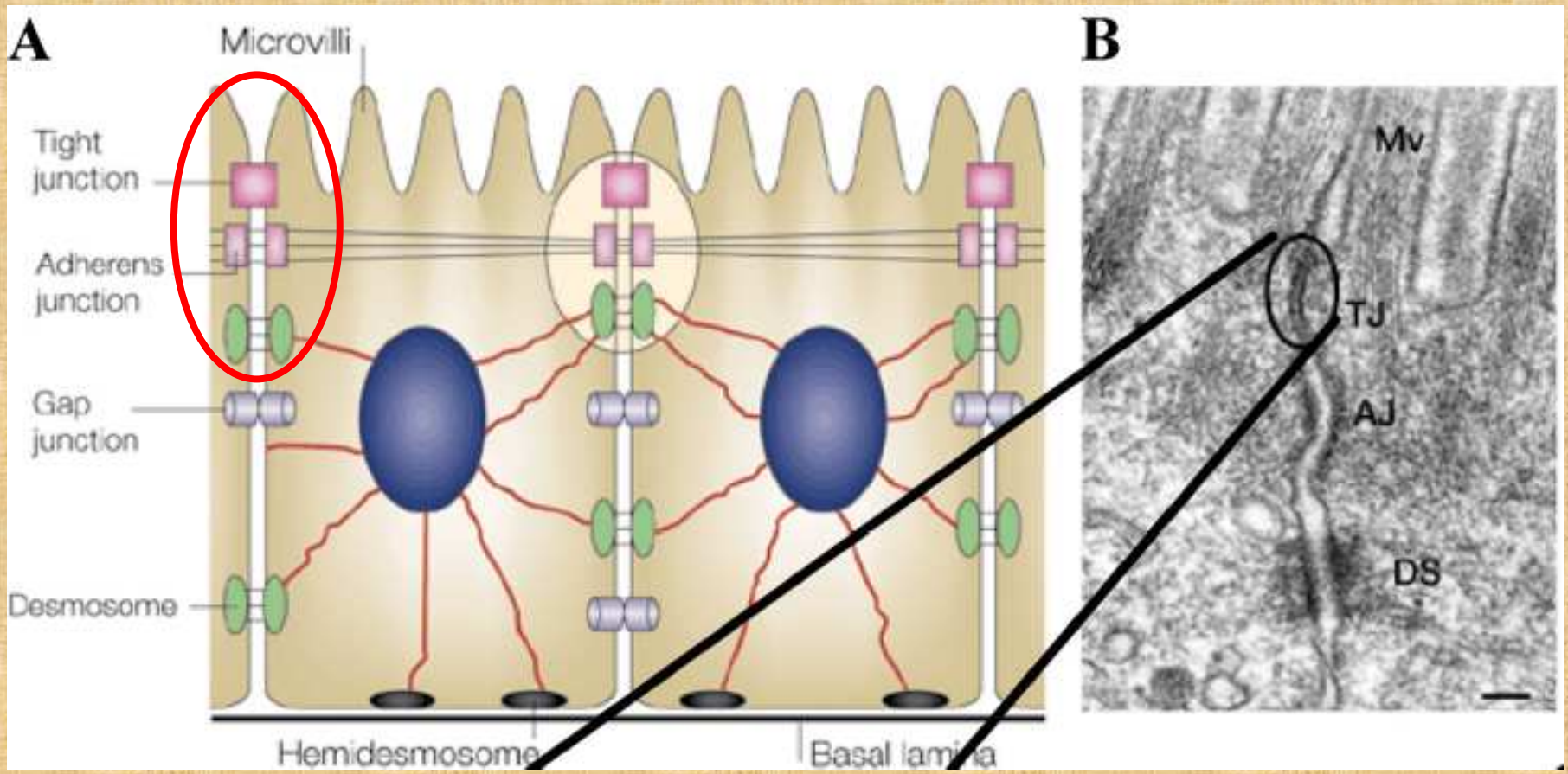

Am J Physiol Gastrointest Liver Physiol 294: G000–G000, 2008.
First published October 25, 2007; doi:10.1152/ajpgi.00398.2007.

Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier

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

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

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

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

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

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tight junction; inflammatory bowel disease; dextran sulfate sodium

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

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

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

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VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of tight junction complexes and the healing capacity of the colonic epithelium.

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tight junction; inflammatory bowel disease; dextran sulfate sodium

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1,25(OH)2D3 markedly enhanced tight junctions by increasing junction protein expression (at the kissing joints) and preserved the structural integrity of tight junctions (tight junction strands)

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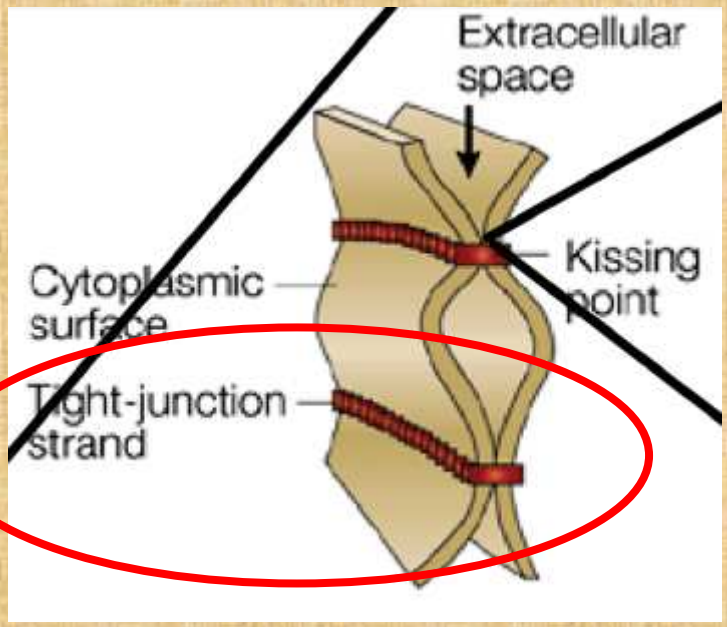

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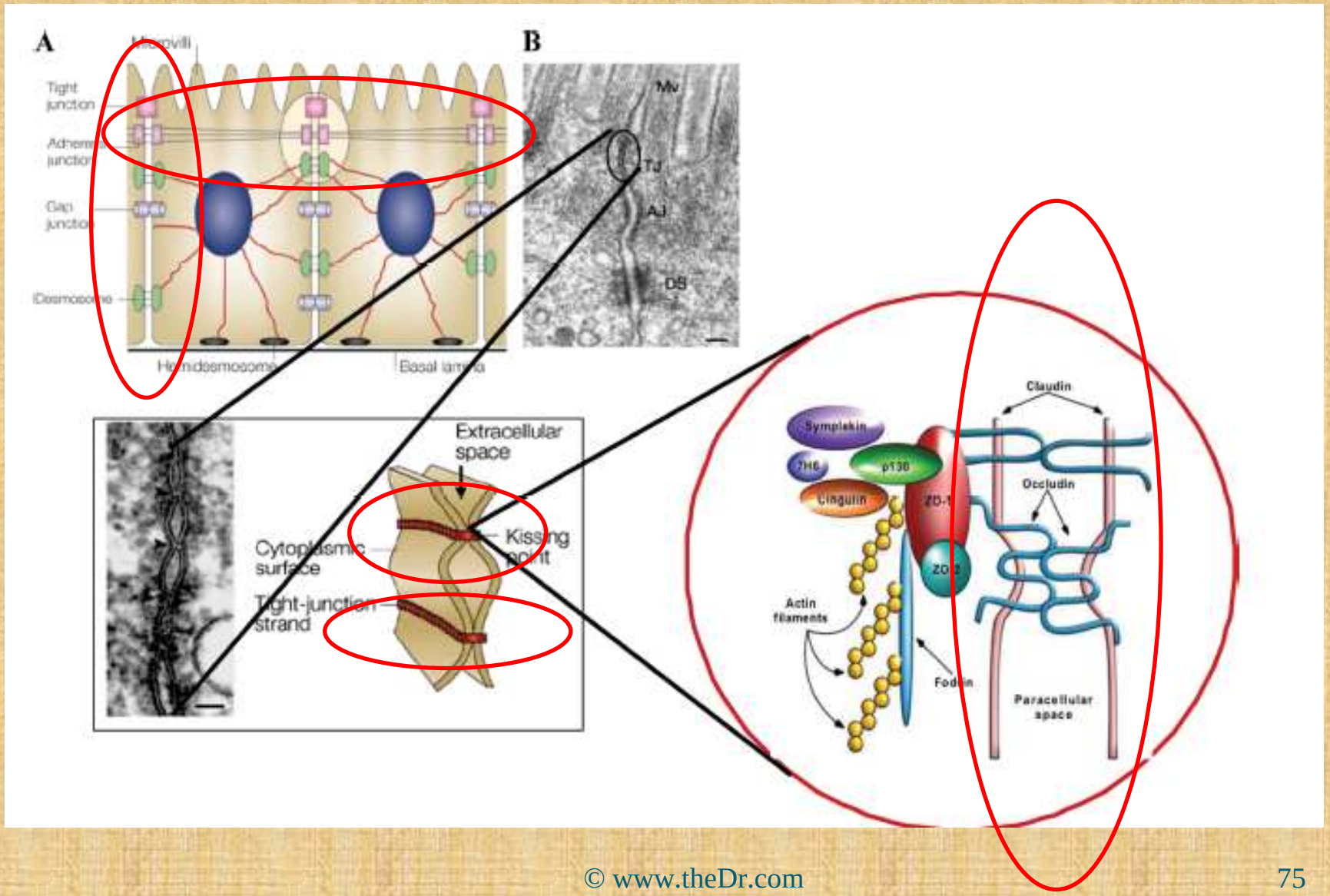

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EPA (eicosapentaenoic acid)	318-360 mg
DHA (docosahexaenoic acid)	204-240 mg
Curcumin (C3 Complex™, 95% pure curcuminoids)	250 mg
L-Lysine (as L-lysine HCl)	200 mg
Boswellia Extract (standardized to 65% boswellic acid)	200 mg
L-Glutamine	623 mg
L-Threonine	80 mg
Bromelain (2400 GDU/g)	63 mg
Bilberry Extract (standardized to 25% anthocyanosides)	50 mg
Ashwagandha Root Extract (Withania somnifera)	43 mg
Rosemary Leaf Extract	40 mg
Rutin	33 mg
Quercetin	33 mg
Hesperidin	33 mg
Ginger Extract (4:1; Zingiber officinale root)	17 mg
L-Citrulline	17 m
N-Acetyl Cysteine (NAC)	17 m
Broccoli Seed Extract	600
Providing:	
Sulforaphane Glucosinolate†	60 m

REVIEW ARTICLE

Effect of Intestinal Microbial Ecology on the Developing Brain

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

JAMA Pediatr. 2013;167(4):374-379

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

The intestine is the largest and most complex immune organ of the body. Between 70% and 80% of the body's immune cells are in the gut-associated lymphoid tissue, and they can sense changes in the microbiota through specific gastrointestinal cells and receptors.

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

The use of newly developed nonculture-based technologies is providing new insights into the temporal colonization patterns in infants born at term[5,6] or preterm.[7-9] The combination of emerging microbial genomic technologies with metabolic and immunologic analyses is revealing impor-

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

ROLES OF THE MICROBIOTA

Metabolic Role

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

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

INNOVISION COMMUNICATIONS

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

CME
CONTINUING MEDICAL EDUCATION

BALANCE OF FLORA, GALT, AND MUCOSAL INTEGRITY

Patrick Hanaway, MD

The critical functions of the commensal flora are:

- **Metabolic processes:**
- **fermentation,**
- **vitamin synthesis,**
- **energy production;**
- **Trophic stimulation:**
- **epithelial cell differentiation,**
- **immunomodulation;**
- **Pathogen protection:**
- **competing for nutrients, space, adherence;**
- **producing bacteriocidins.**

APMIS ACTA PATHOLOGICA, MICROBIOLOGICA ET IMMUNOLOGICA SCANDINAVICA

APMIS 121: 403–421

DOI

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

REVIEW ARTICLE

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

MILOSLAV KVERKA and HELENA TLASKALOVA-HOGENOVA

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

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

There are three main mechanisms, how probiotics contribute to human health, and any single probiotic bacterium could possess more than one of them:

Probiotics shape the ecosystem,

- **by competition for limited resources and adhesion sites,**
- **by decreasing the local pH via the production of organic acids, and**
- **by production of specific antibacterial substances**

increase. The role of genetics is probably over-

Received 25 July 2012. Accepted 13 September 2012

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

Probiotics
(treatment time – indefinitely)

- ***Lactobacillus*** **(various species): 10–100 billion live organisms daily or higher**
- ***Saccharomyces boulardii*****: 500 mg–3 g daily**
- ***Bifidobacterium*** **(various species): 10–100 billion live organisms daily**
- ***Probiotic mixtures:*** **10 billion-3.6 trillion live organisms daily**

Prebiotics
(treatment time – indefinitely)

- **FOS: 500–5,000 mg QD-TID**
- **Inulin: 500–5,000 mg QD-TID**
- **Fiber (high soluble)**
- **Larch (arabinogalactans): 500–5,000 mg QD-TID**

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

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

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

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

EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation and thus reducing elaboration of proinflammatory mediators.

INTRODUCTION

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

ing errors[3], hospital injuries, and what is described as "substandard care."[4] A recent article in the *New England Journal of Medicine*[5] concluded that deficits in allopathic medical care pose "serious threats to the health of the American public." A 1997 review published by the American Academy of Family Physicians[6] stated, "Recent estimates suggest that each year more than 1 million patients are injured while in the hospital and approximately 180,000 die because of these injuries. Furthermore, drug-related morbidity and mortality are common and are estimated to cost more than $136 billion a year." New research also shows that several popular "antidepressant" drugs actually increase the risk for suicide in children[7] and adults[8,9], and, similarly, "antipsychotic" drugs may worsen clinical outcomes in a large percentage of patients with mental illness.[10] Chiropractic diet therapy—not drugs—is the most effective treatment for chronic hypertension.[11, 12] Many anti-inflammatory drugs for the treatment of joint

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

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

FATTY ACID SUPPLEMENTATION: UNDERSTANDING IS THE KEY TO MASTERY

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

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Invited Review

A Review of Complementary and Alternative Approaches to Immunomodulation

John O. Clarke, MD; and Gerard E. Mullin, MD
Division of Gastroenterology, The Johns Hopkins Hospital, Baltimore, Maryland

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

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

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

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

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

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

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

Polyphenols

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

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

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

Treatment Protocols
(personal recommendations-EPA/DHA)

Therapeutic dosages:

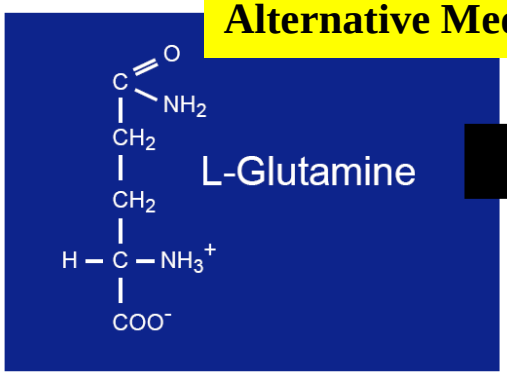
30-75 lbs = at least 1 g/d (Total Omega 3's)

76-125 lbs = at least 2g/d (Total Omega 3's)

> 125 lbs = 3+ g/d (Total Omega 3's)

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

Alternative Medicine Review Volume 6, Number 4 2001



Monograph

L-Glutamine

Introduction

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

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

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

Biochemistry

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

Clinical Indications

Gastrointestinal Disease

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

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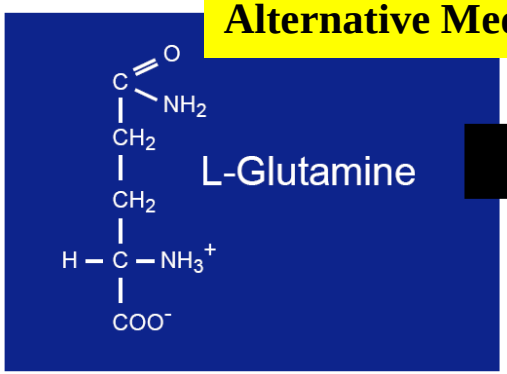

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A clinical study of ulcerative colitis patients

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

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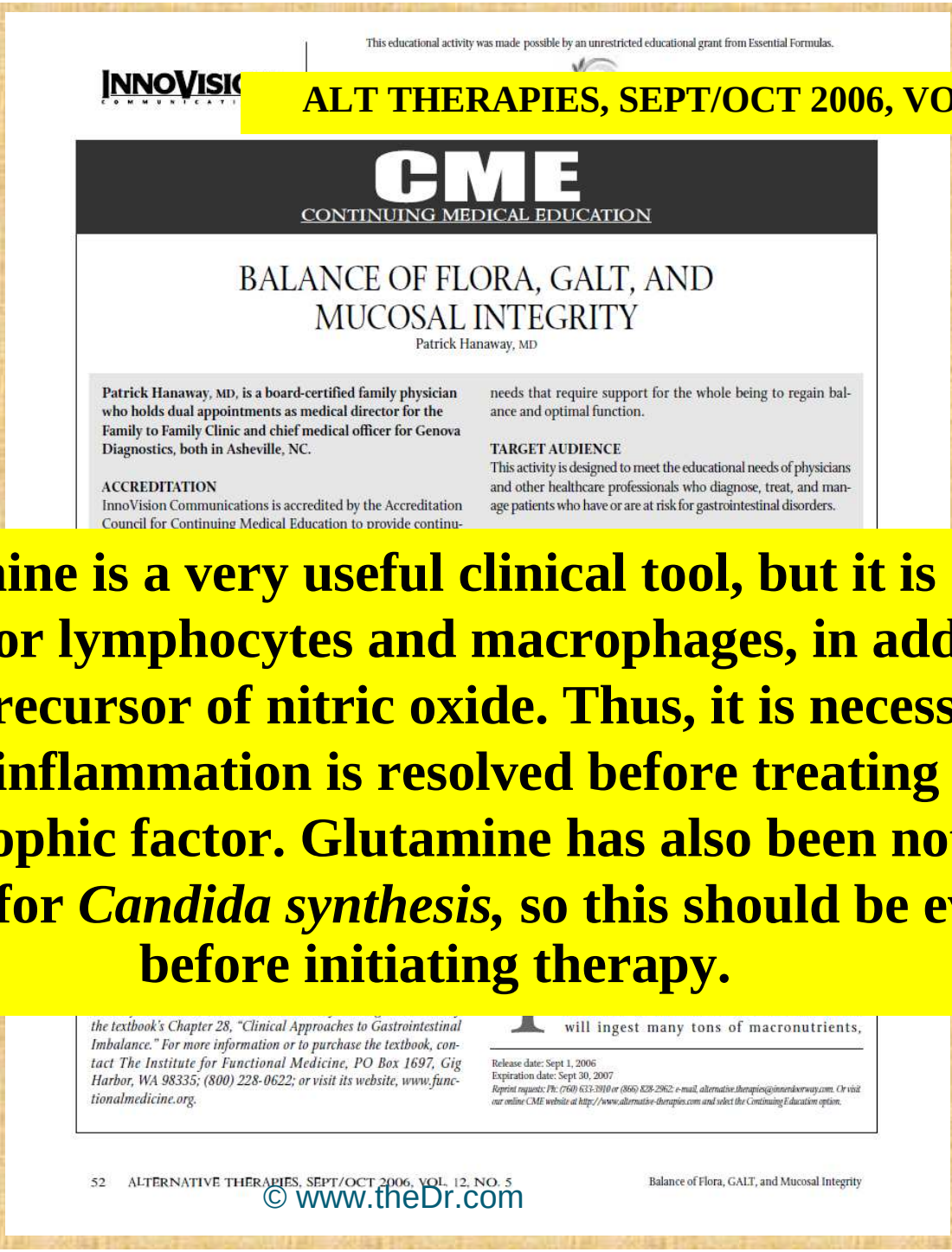

This educational activity was made possible by an unrestricted educational grant from Essential Formulas.

INNOVISION COMMUNICATIONS

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

CME
CONTINUING MEDICAL EDUCATION

BALANCE OF FLORA, GALT, AND MUCOSAL INTEGRITY

Patrick Hanaway, MD

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

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

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

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

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

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

will ingest many tons of macronutrients,

Release date: Sept 1, 2006
Expiration date: Sept 30, 2007
Reprint requests: Ph: (760) 633-3910 or (866) 828-2962; e-mail, alternative.therapies@innervisionway.com. Or visit our online CME website at http://www.alternative-therapies.com and select the Continuing Education option.

52 ALTERNATIVE THERAPIES, SEPT/OCT 2006, VOL. 12, NO. 5 Balance of Flora, GALT, and Mucosal Integrity

Treatment Protocols
(personal recommendations-Glutamine)

Therapeutic dosages:

Dosages vary greatly depending on the clinical situation

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

0148-6071/06/3001-0045$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 30, No. 1
Printed in U.S.A.

Review

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

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

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

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

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

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

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

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

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

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

Curcumin (CU): A Promising Tool

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

Received for publication November 12, 2004.
Accepted for publication August 4, 2005.
Correspondence: Stig Bengmark, MD, PhD, FRACS (hon), FRCPS (hon), 185 Barrier Point Road, Royal Docks, London, E16 2SE, United Kingdom. Electronic mail may be sent to s.bengmark@ucl.ac.uk.

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

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

polyphenols have been identified, 4 in particular have a preponderance of evidence in the role of immune modulation and will be addressed in this review: resveratrol, epigallocatechin, curcumin, and boswellia. The findings of polyphenols to prevent and treat animal models of IBD are summarized in Table 1.[3–22]

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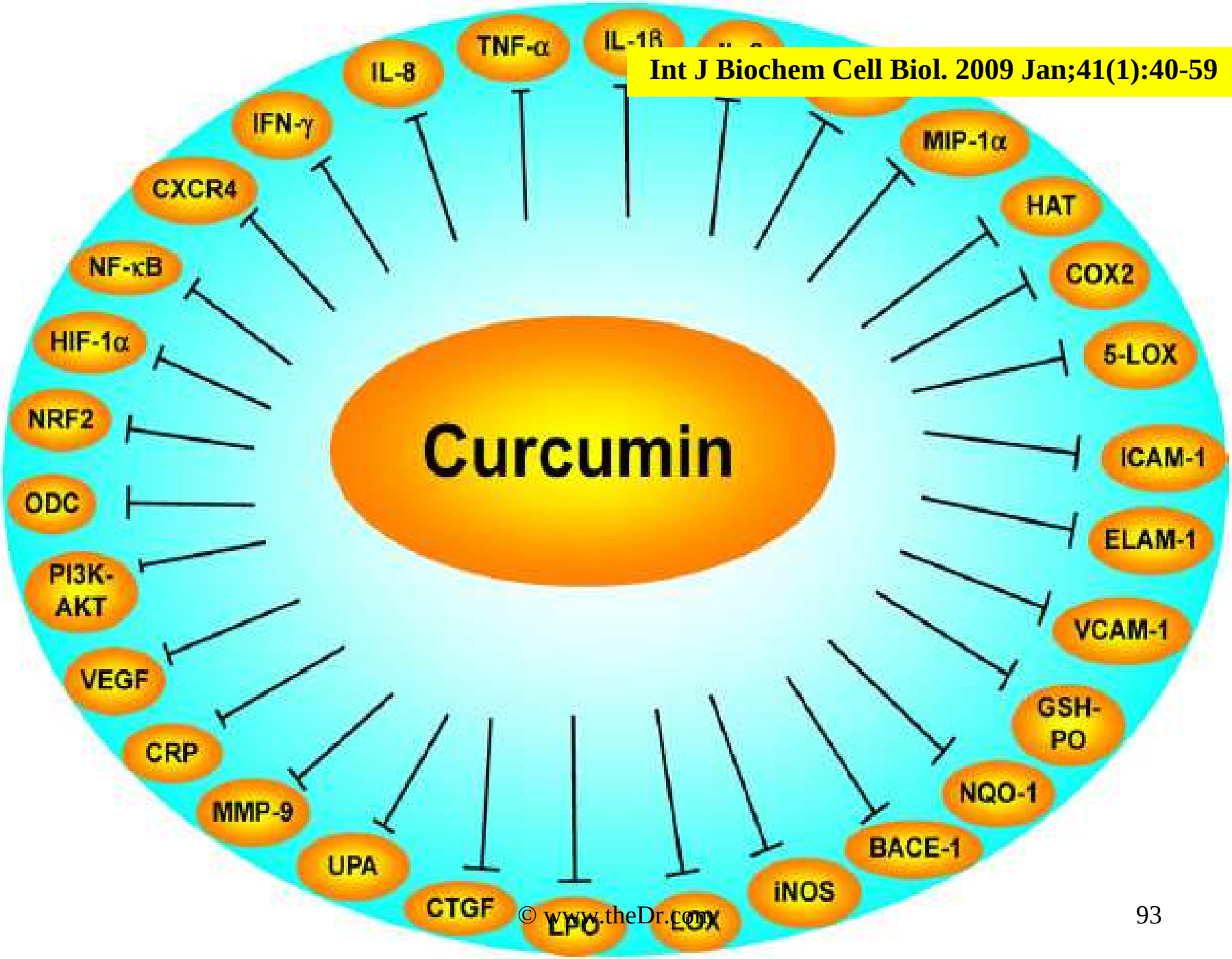


Int J Biochem Cell Biol. 2009 Jan;41(1):40-59

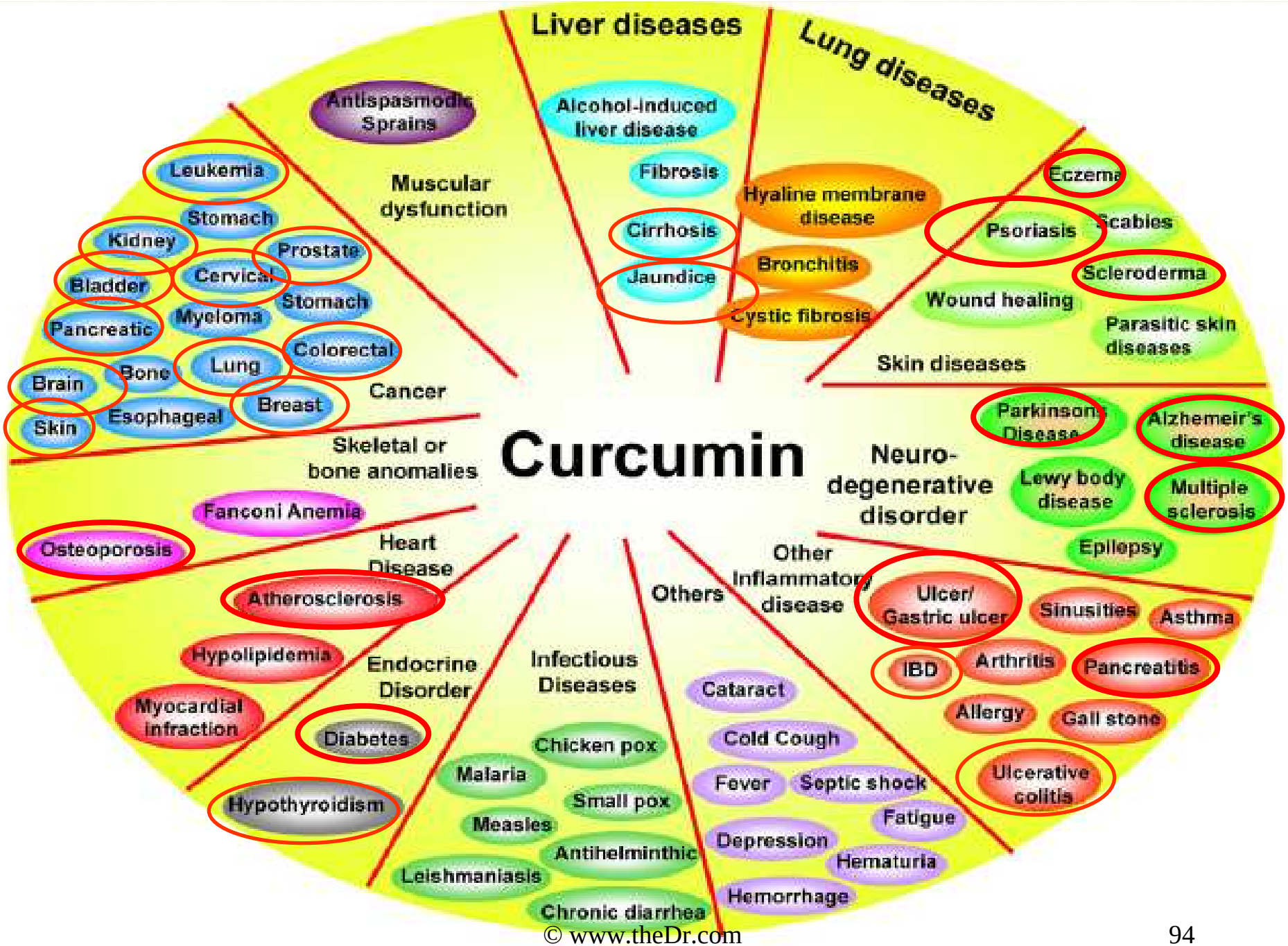
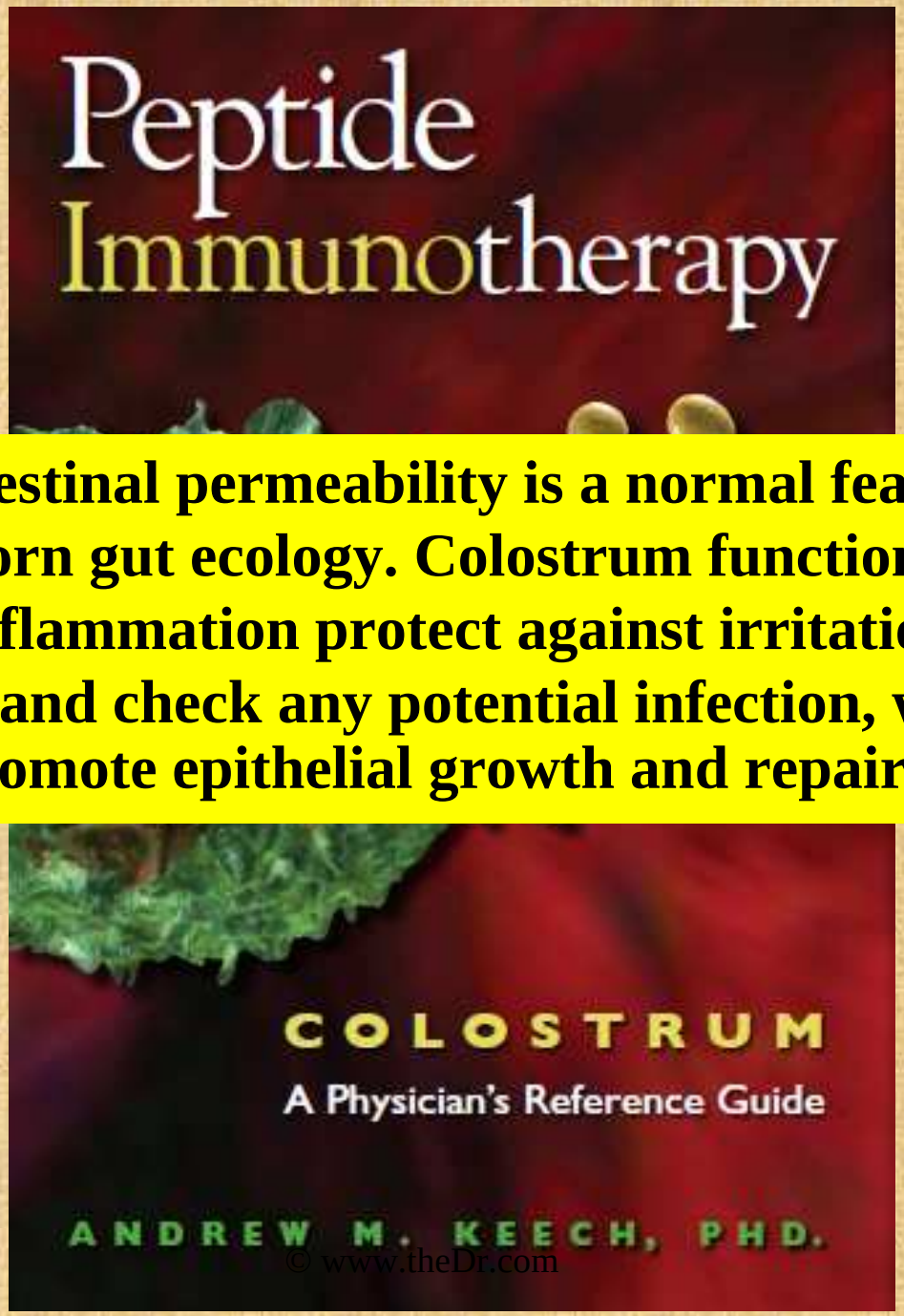


Fig. 2. Effect of curcumin on various proinflammatory diseases.

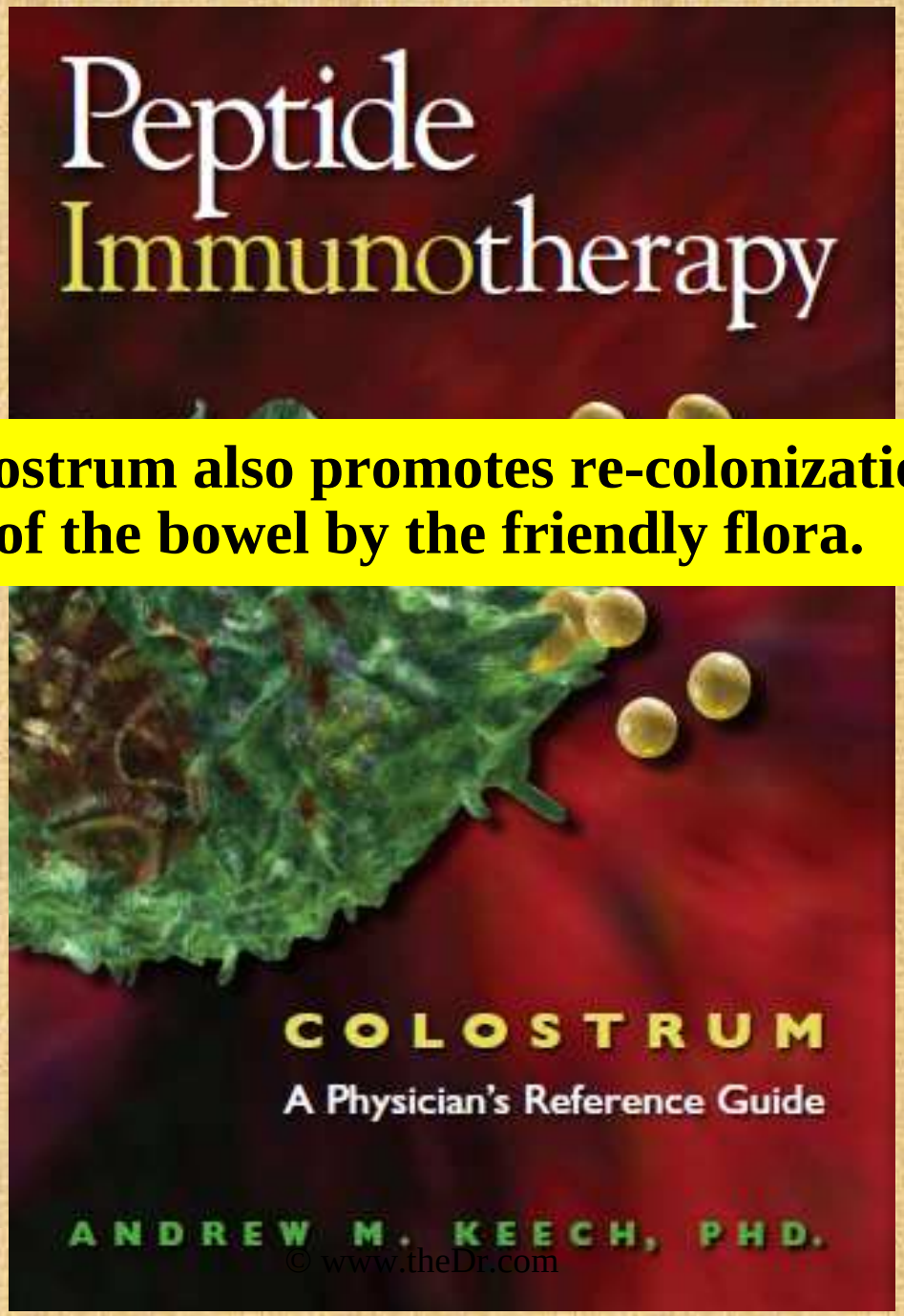
Treatment Protocols
(personal recommendations-Curcumin)

Therapeutic dosages:

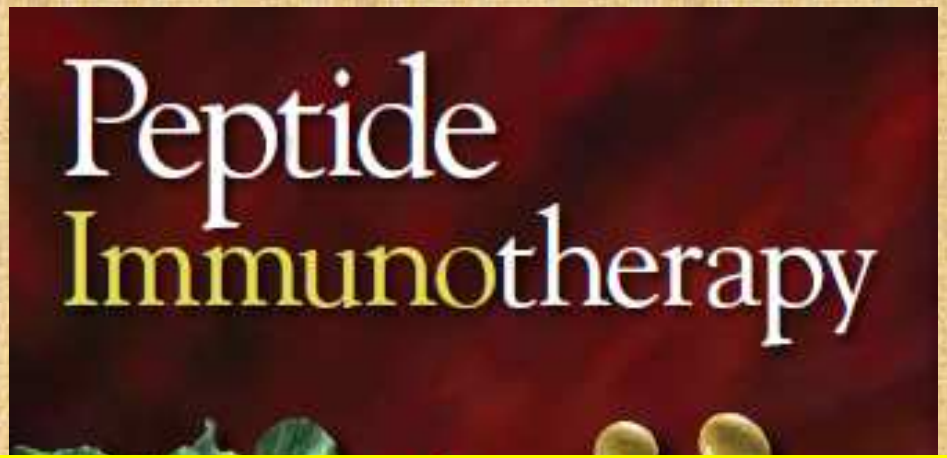
<u>Turmeric</u> (*Curcuma longa*) standardized to curcuminoids 200-1000 mg TID



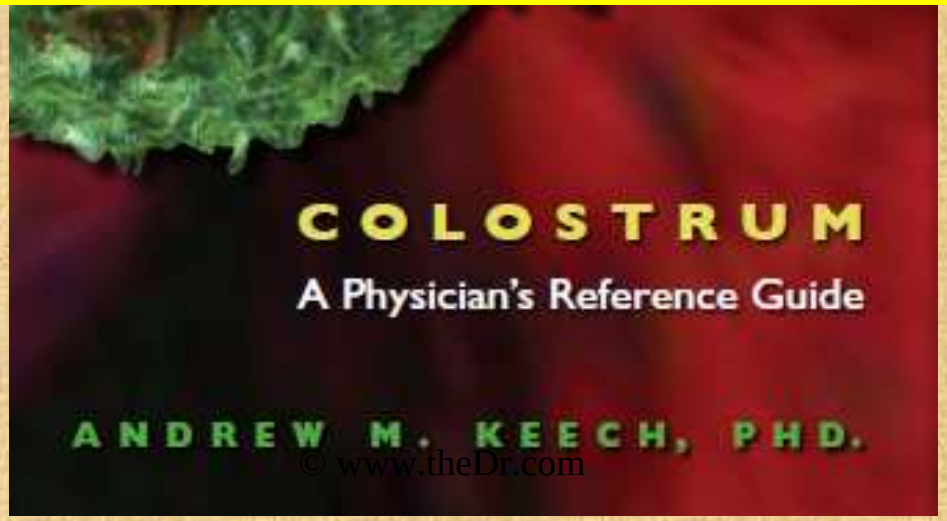
High intestinal permeability is a normal feature of newborn gut ecology. Colostrum functions to reduce inflammation protect against irritation from toxins and check any potential infection, while promote epithelial growth and repair.

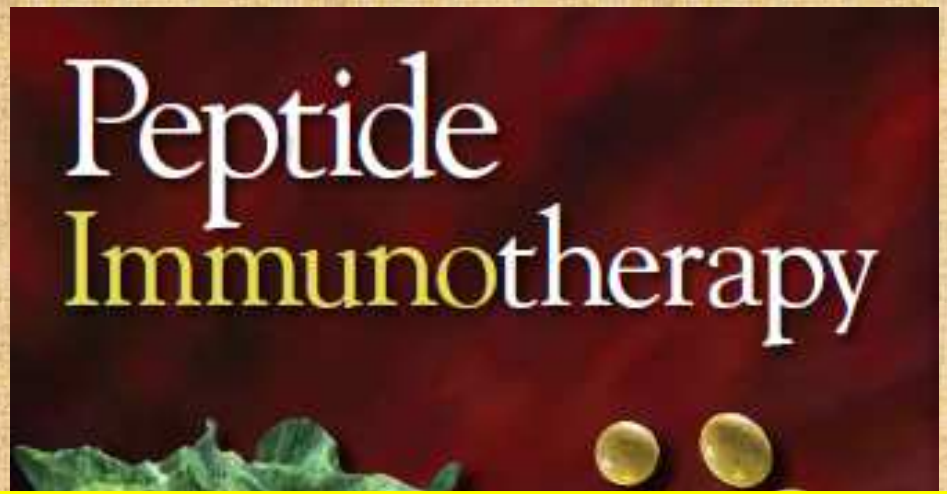


Colostrum also promotes re-colonization of the bowel by the friendly flora.

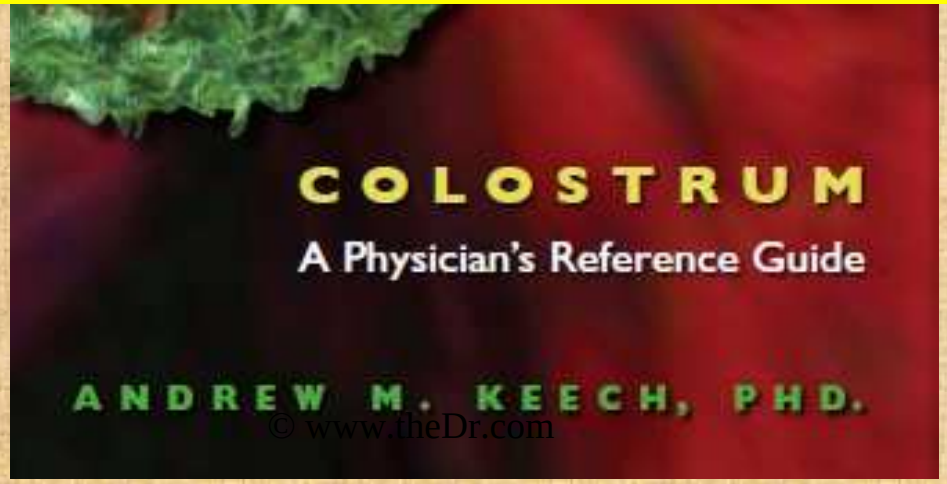


Colostrum is the best remedy known for all-around gut health. Colostrum restores leaky gut to normal permeability levels. It contains growth factors and hormones to help repair damage to the intestinal lining, and restore gut integrity.





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



Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry, Published: March 6, 2013

Chapter 4

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

Elizabeth M. Sajdel-Sulkowska and
Romuald Zabielski

Additional information is available at the end of the chapter

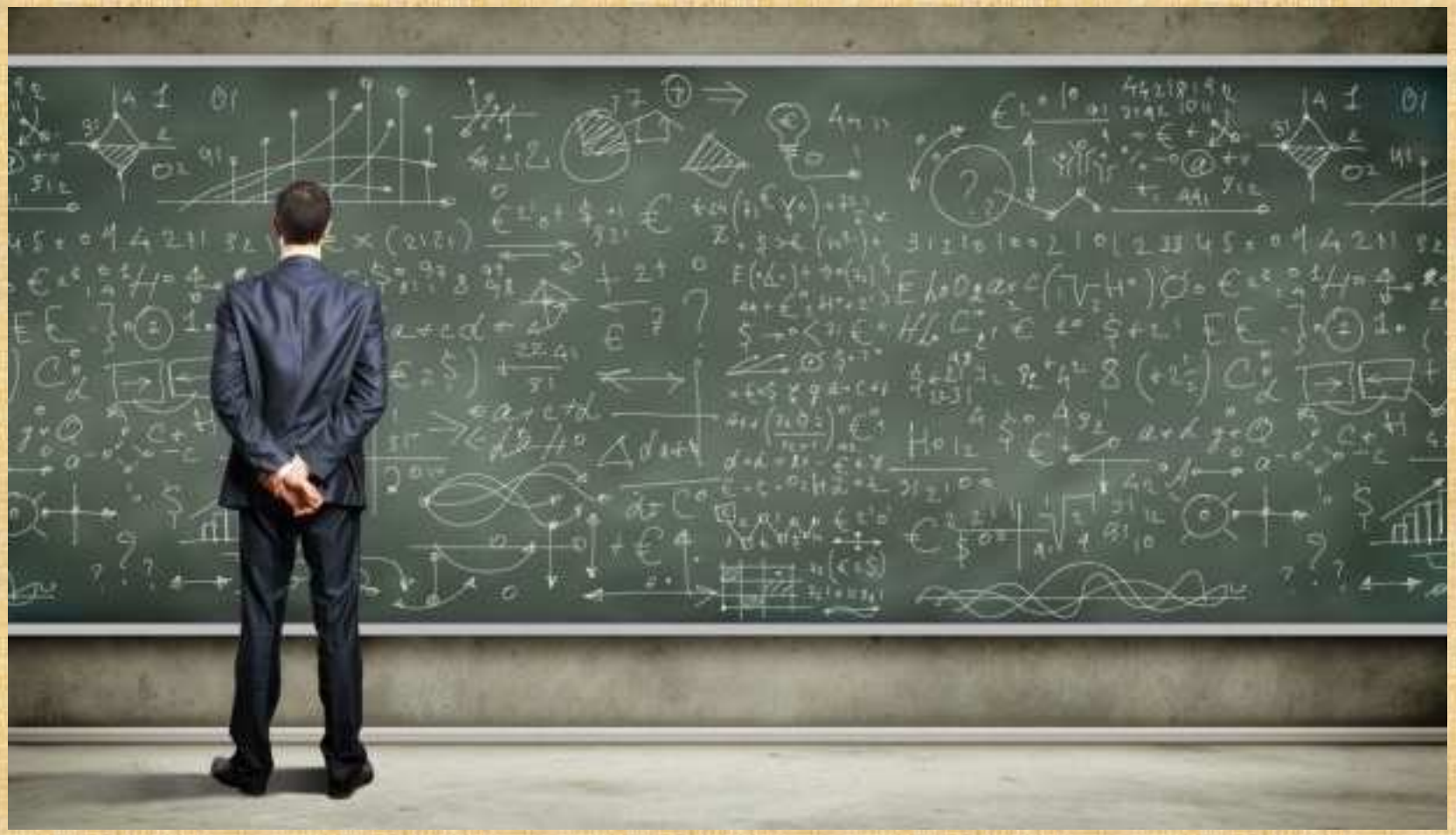
The two key developmental time-points in the regulation of the GIT both occur postnatally, the first few days after birth when all gut digestive functions are launched by first colostrum ingestion and the second at weaning when the digestive system has to modify its function following a switch from mother's milk to solid food. The first time-point is particularly relevant for all mammalian species since it is associated with a complex of dynamic changes in the GIT structure and function leading to a temporary drop in the gut permeability barrier.

Gut on FIRE!
Body on Fire

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

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

All 27 studies are available to you for free at www.theDr.com
15 of the 27 are the full articles



Where may the Systemic Symptoms come from with Autoimmune Syndromes?

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

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

Irritation/inflammation (activated immune system)

Increased intestinal permeability

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

AND

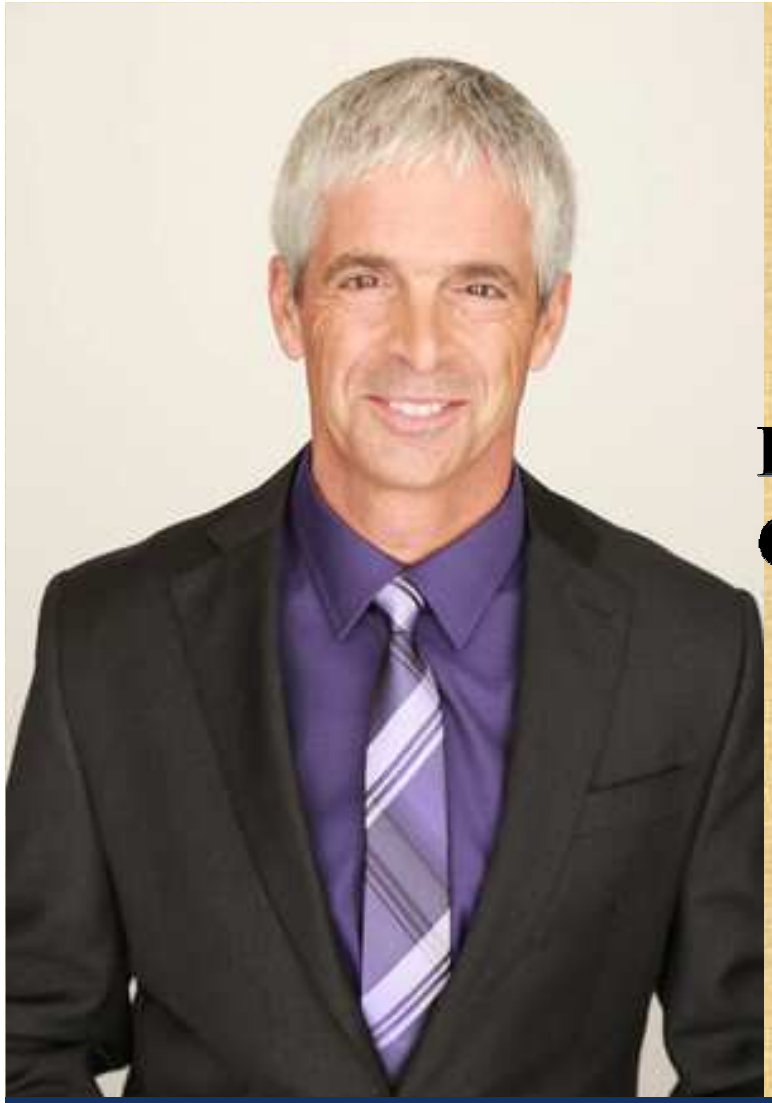
Increased immune complexes in general circulation

Tissue specific symptoms determined by genetics and antecedents

Development of autoimmune syndromes

You can enhance the effectiveness of LDN Therapy by reducing the noxious stimulation of TLR4 from LPS and Gluten peptides.

ess the Intestinal Permeability



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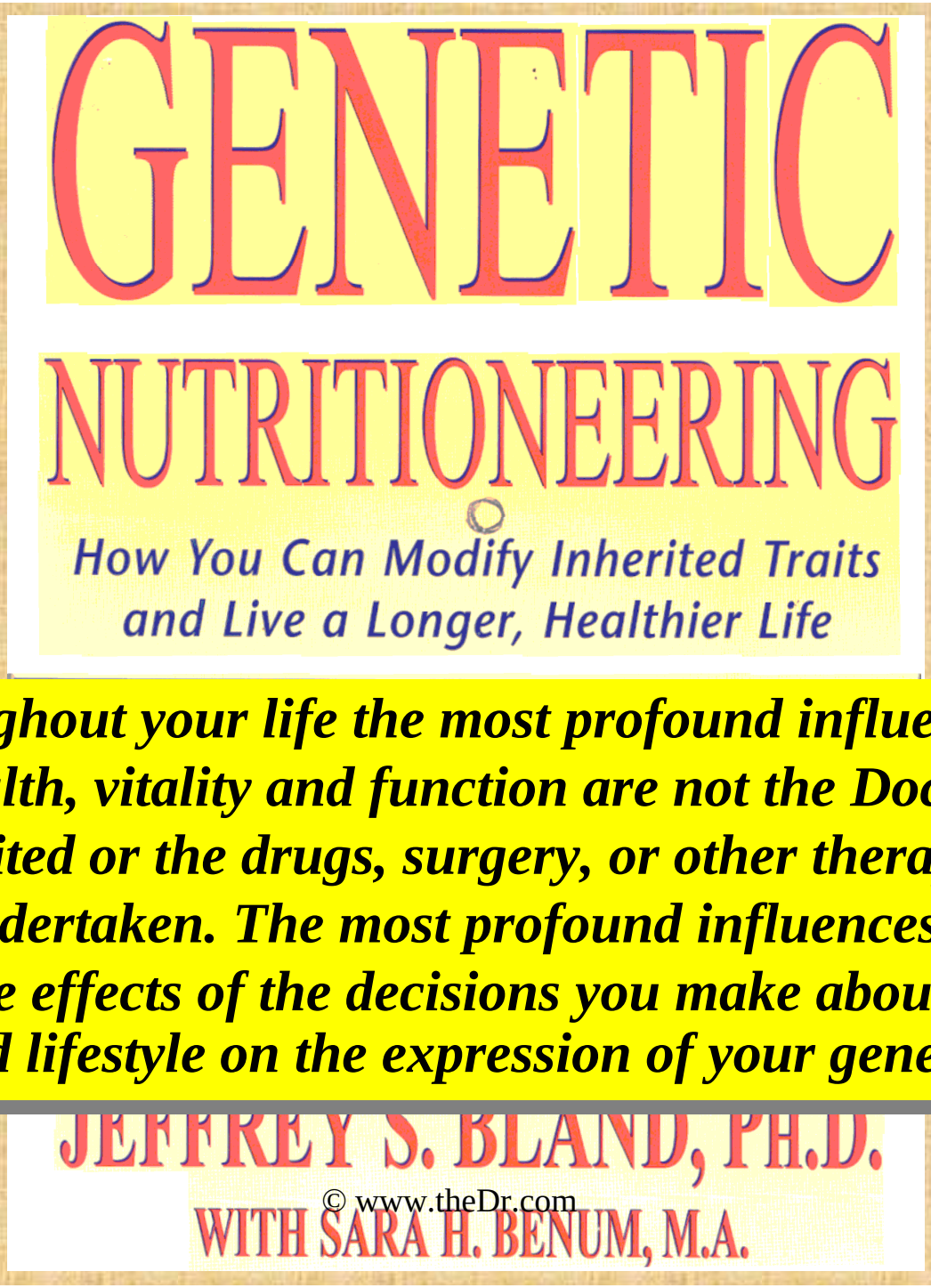
Make Sure to Tell those Important to You How Much You Love them



"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