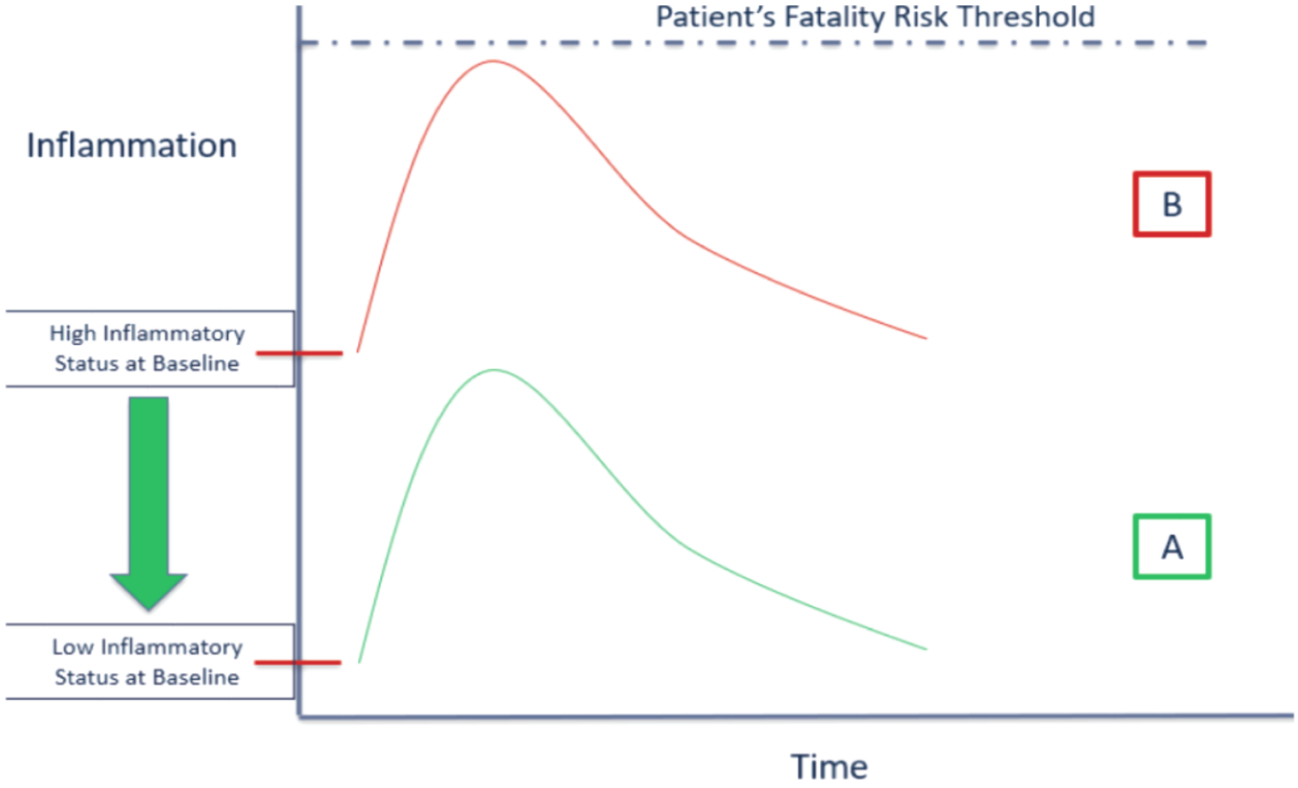
Critical to Decrease Inflammation Setpoint



Yanuck SF, Pizzorno J, Messier H, Fitzgerald KN. Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery. Focus on Covid-19. https://athmjournal.com/covid19/research/evidence-supporting-a-phased-immuno-physiological-approach-to-covid-19-from-prevention-through-recovery/. Published May 8, 2020. Accessed May 12, 2020.

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So How Does Chronic Inflammatory Disease Develop?



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Professor Alessio Fasano

- professor of pediatrics at HarvardMedical School
- professor of nutrition at Harvard T.H. Chan School of Public Health
- Chief of pediatric gastroenterology, Mass General Hospital
- Director, Mucosal Immunology Center, Harvard
- Director, Center for Celiac Research and Treatment
- Director, Mucosal Immunology and Biology Research Center;
- Associate Chief for Basic, Clinical and Translational Research
- 213 publications on pubmed.gov
- Identified zonulin as the protein activated in intestinal permeability





F1000Research F1000Research 2020, 9(F1000 Faculty Rev):69 Last updated: 31 JAN 2020

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REVIEW

All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases [version 1; peer review: 3 approved]

Alessio Fasano [1,2]

[1]Mucosal Immunology and Biology Research Center, Center for Celiac Research and Treatment and Division of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, Massachusetts, USA
[2]European Biomedical Research Institute of Salerno, Salerno, Italy

v1 **First published:** 31 Jan 2020, **9**(F1000 Faculty Rev):69 (https://doi.org/10.12688/f1000research.20510.1)
Latest published: 31 Jan 2020, **9**(F1000 Faculty Rev):69 (https://doi.org/10.12688/f1000research.20510.1)

Abstract

Improved hygiene leading to reduced exposure to microorganisms has been implicated as one possible cause for the recent "epidemic" of chronic inflammatory diseases (CIDs) in industrialized countries. That is the essence of the hygiene hypothesis that argues that rising incidence of CIDs may be, at least in part, the result of lifestyle and environmental changes that have made us too "clean" for our own good, so causing changes in our microbiota. Apart from genetic makeup and exposure to environmental triggers, inappropriate increase in intestinal permeability (which may be influenced by the composition of the gut microbiota), a "hyper-belligerent" immune system responsible for the tolerance–immune response balance, and the composition of gut microbiome and its epigenetic influence on the host genomic expression have been identified as three additional elements in causing CIDs. During the past decade, a growing number of publications have focused on human genetics, the gut microbiome, and proteomics, suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

Keywords

Chronic inflammatory diseases, Gut permeability, microbiome, zonulin

Open Peer Review

Reviewer Status ✔ ✔ ✔

	Invited Reviewers		
	1	**2**	**3**
version 1 31 Jan 2020	✔	✔	✔

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2 **Michael Maes**, Chulalongkorn University, Bangkok, Thailand
3 **Arul Jayaraman**, Texas A&M Health Science Center, Bryan, USA

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Page 1 of 12

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There is growing evidence that the elements of gut permeability, immune system response, and gut microbiome—together with genetic predisposition and exposure to environmental triggers— make the *"perfect storm"* for Chronic Inflammatory Disease development.

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the *"perfect storm"* for Chronic Inflammatory Disease development.

- Genetic Vulnerability
- Environmental triggers
- Altered Microbiome (Dysbiosis)
- Intestial Permeability
- Systemic Immune Response (Inflammation)

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If there is 1 concept, that becomes the paradigm you look through for all chronic disease, this is it.





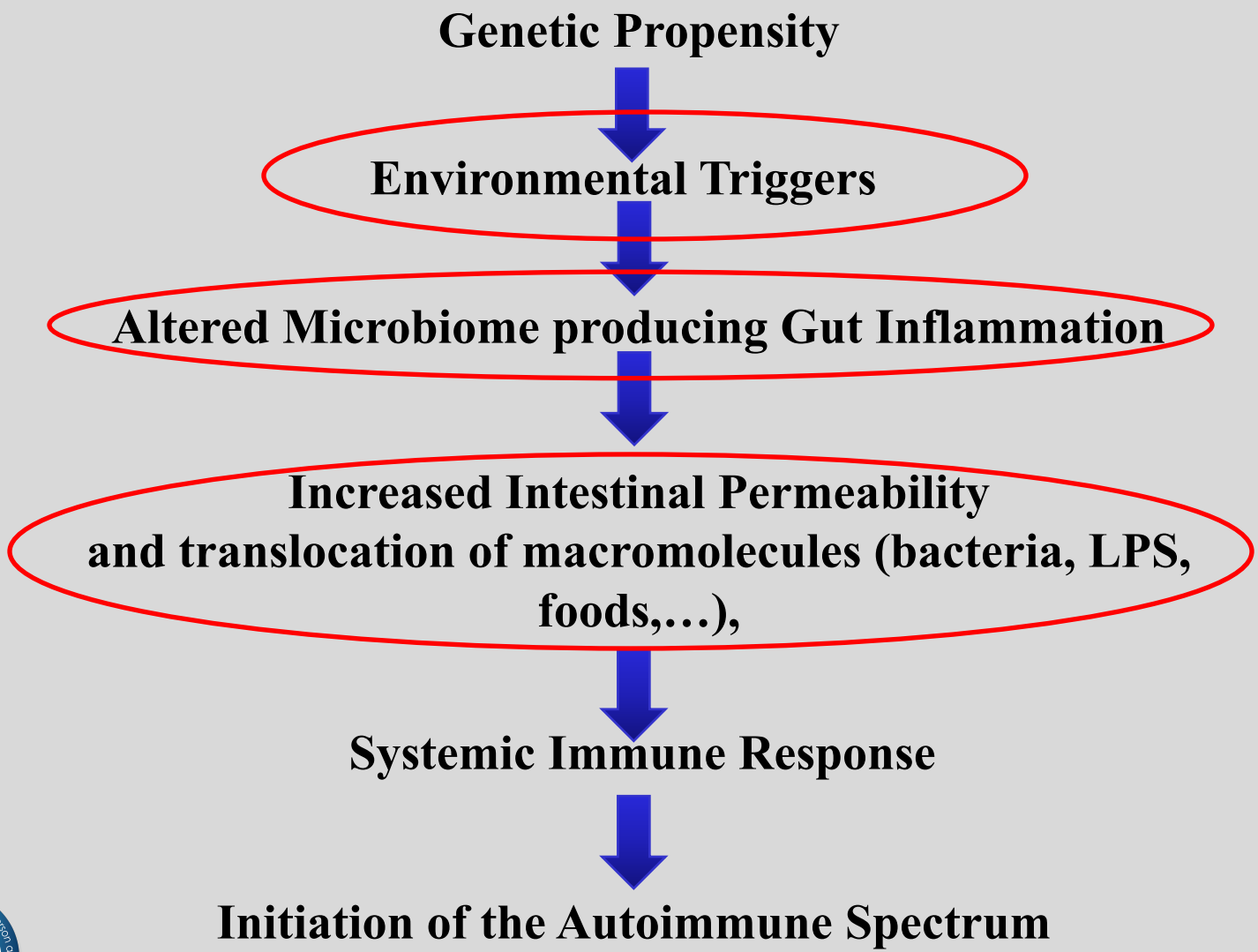
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The Autoimmune Tautology



Valitutti F, Fasano A, Breaking Down Barriers: How Understanding Celiac Disease Pathogenesis Informed the Development of Novel Treatments. Dig Dis Sci. 2019 Jul;64(7):1748-1758



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v1 **First published:** 31 Jan 2020, **9**(F1000 Faculty Rev):69 (https://doi.org/10.12688/f1000research.20510.1)

Open Peer Review

Among the several potential intestinal luminal stimuli that can stimulate zonulin release, small exposure to large amounts of bacteria (and its exhaust LPS) and gluten, have been identified as the two most powerful triggers

in causing CIDs. During the past decade, a growing number of publications have focused on human genetics, the gut microbiome, and proteomics, suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

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Reviewer Status ✓ ✓ ✓

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Any comments on the article can be found at the end of the article.

Gluten is misinterpreted by the zonulin pathway as a potential harmful component of a microorganism.

JAMA | Review

Celiac Disease and Nonceliac Gluten Sensitivity
A Review

Maureen M. Leonard, MD, MMSc; Anna Sapone, MD, PhD; Carlo Catassi, MD, MPH; Alessio Fasano, MD

IMPORTANCE The prevalence of gluten-related disorders is rising, and increasing numbers of individuals are empirically trying a gluten-free diet for a variety of signs and symptoms. This review aims to present current evidence regarding screening, diagnosis, and treatment for celiac disease and nonceliac gluten sensitivity.

OBSERVATIONS Celiac disease is a gluten-induced immune-mediated enteropathy characterized by a specific genetic genotype (*HLA-DQ2* and *HLA-DQ8* genes) and autoantibodies (antitissue transglutaminase and antiendomysial). Although the inflammatory process specifically targets the intestinal mucosa, patients may present with gastrointestinal signs or symptoms, extraintestinal signs or symptoms, or both, suggesting that celiac disease is a systemic disease. Nonceliac gluten sensitivity is diagnosed in individuals who do not have celiac disease or wheat allergy but who have intestinal symptoms, extraintestinal symptoms, or both, related to ingestion of gluten-containing grains, with symptomatic improvement on their withdrawal. The clinical variability and the lack of validated biomarkers for nonceliac gluten sensitivity make

Although both conditions are treated with a gluten-free diet, distinguishing between celiac disease and nonceliac gluten sensitivity is important for long-term therapy. Patients with celiac disease should be followed up closely for dietary adherence, nutritional deficiencies, and the development of possible comorbidities.

JAMA. 2017;318(7):647-656. doi:10.1001/jama.2017.9730

CME Quiz at jamanetwork.com/learning

Author Affiliations: Center for Celiac Research and Treatment, Division of Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Boston, Massachusetts (Leonard, Sapone, Catassi, Fasano); Celiac Research Program, Harvard

and Biology Research Center, Massachusetts General Hospital East, Bldg 114, 16th St (Mail Stop 114-3503), Charlestown, MA 02129-4404 (afasano@mgh.harvard.edu).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

an immediate and transient increase in gut permeability takes place in all individuals who ingest gluten.

Celiac disease is a chronic, small-intestinal immune-mediated enteropathy initiated by exposure to dietary gluten in genetically predisposed individuals and characterized by specific autoantibodies against tissue transglutaminase 2 (anti-tTG2), endomysium, and/or deamidated gliadin peptide.[1] Although up to 40% of the population carries the genotype *HLA-DQ2* or *HLA-DQ8*, which is required for the development of celiac disease, only 2% to 3% of *HLA-DQ2* or *HLA-DQ8* carriers subsequently develop celiac disease.[2] Celiac disease, once considered a relatively rare gastrointestinal condition affecting almost exclusively young white children, can develop at any age and can affect almost any race. Celiac disease was first described by Samuel Gee in 1887. Wheat was hypothesized as the possible offending agent by William Dicke in 1941.[3]

The epidemiology, clinical presentation, pathophysiology, and management of the disease have changed since its initial description. There is strong evidence that celiac disease is an autoimmune disease triggered by the ingestion of gluten present in wheat, barley, and rye in genetically predisposed individuals. The prevalence of celiac disease in the general population is 1%, with regional differences (**Table 1**).[4] Celiac disease can affect any human organ or tissue (Table 1 and **Table 2**).[6]

Nonceliac gluten sensitivity is a term used to describe individuals who have intestinal signs or symptoms, extraintestinal signs or symptoms, or both, related to ingestion of gluten-containing grains (Table 2), with improvement when these are removed from a patient's diet. The frequency of nonceliac gluten sensitivity is unknown owing to the lack of validated biomarkers, but it is thought to be more common than celiac disease. Wheat allergy, the third gluten-related disorder, which will not be addressed in this review, is defined as an adverse type-2 helper T-cell immunologic reaction to wheat proteins and typically presents soon after wheat

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So if you're resistant to the science, or just uncertain if this relates to you, what can you do?



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Wheat Zoomer

Final Report Date:	03-01-2017 15:19	**Specimen Collected:**	02-16-2017 10:00
Accession ID:	1702170113	**Specimen Received:**	02-17-2017 11:09

Last Name	First Name	Middle Name	Date of Birth	Gender	Physician ID

Celiac

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Total IgA (mg/dL)	137			89~404		≤88 ≥405	
Transglutaminase 2 IgG	0.57			≤1.01		≥1.02	
Transglutaminase 2 IgA	0.30			≤0.95		≥0.96	
DGP IgG	0.21			≤0.94	0.95~1.05	≥1.06	
DGP IgA	0.16			≤0.94	0.95~1.05	≥1.06	

Intestinal Permeability Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Zonulin (ng/mL)	29.7			≤45.3	45.4~55.3	≥55.4	
Anti-Zonulin IgG	0.58			≤0.94	0.95~1.05	≥1.06	
Anti-Zonulin IgA	0.48			≤0.94	0.95~1.05	≥1.06	
Anti-Actin IgG		0.97		≤0.94	0.95~1.05	≥1.06	
Anti-Actin IgA	0.49			≤0.94	0.95~1.05	≥1.06	
LPS IgG (U/ml)			134.9	≤125.9		≥126.0	
LPS IgM (U/ml)	8.1			≤38.3		≥38.4	

tTG/DGP Complex

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
tTG/DGP Fusion Peptide IgG	0.13			≤0.94	0.95~1.05	≥1.06	
tTG/DGP Fusion Peptide IgA	0.20			≤0.94	0.95~1.05	≥1.06	

Transglutaminase Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Transglutaminase 3 IgG	0.38			≤0.94	0.95~1.05	≥1.06	
Transglutaminase 3 IgA	0.24			≤0.94	0.95~1.05	≥1.06	
Transglutaminase 6 IgG	0.39			≤0.94	0.95~1.05	≥1.06	
Transglutaminase 6 IgA	0.19			≤0.94	0.95~1.05	≥1.06	

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Wheat Germ Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Wheat Germ Agglutinin IgG	0.56			≤0.94	0.95~1.05	≥1.06	
Wheat Germ Agglutinin IgA	0.35			≤0.94	0.95~1.05	≥1.06	

Gliadin Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Alpha Gliadin IgG	0.72			≤0.94	0.95~1.05	≥1.06	
Alpha Gliadin IgA	0.33			≤0.94	0.95~1.05	≥1.06	
Alpha-Beta Gliadin IgG	0.68			≤0.94	0.95~1.05	≥1.06	
Alpha-Beta Gliadin IgA	0.54			≤0.94	0.95~1.05	≥1.06	
Gamma Gliadin IgG	0.71			≤0.94	0.95~1.05	≥1.06	
Gamma Gliadin IgA	0.66			≤0.94	0.95~1.05	≥1.06	
Omega Gliadin IgG	0.72			≤0.94	0.95~1.05	≥1.06	
Omega Gliadin IgA	0.52			≤0.94	0.95~1.05	≥1.06	
Gluteomorphin IgG	0.66			≤0.94	0.95~1.05	≥1.06	
Gluteomorphin IgA	0.52			≤0.94	0.95~1.05	≥1.06	
Prodynorphin IgG	0.41			≤0.94	0.95~1.05	≥1.06	
Prodynorphin IgA	0.45			≤0.94	0.95~1.05	≥1.06	

Wheat Allergy Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Wheat Allergen IgE (kUA/L)			28.00	≤0.34	0.35~3.49	≥3.50	

Glutenin Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
HMW Glutenin IgG	0.37			≤0.94	0.95~1.05	≥1.06	
HMW Glutenin IgA	0.26			≤0.94	0.95~1.05	≥1.06	
LMW Glutenin IgG	0.61			≤0.94	0.95~1.05	≥1.06	
LMW Glutenin IgA	0.38			≤0.94	0.95~1.05	≥1.06	

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Non-Gluten Wheat Panel

Test name	In Control	Moderate	High Risk	In Control Range	Moderate Range	High Risk Range	Previous
Serpin IgG	0.58			≤0.94	0.95~1.05	≥1.06	
Serpin IgA	0.36			≤0.94	0.95~1.05	≥1.06	
Farinins IgG	0.54			≤0.94	0.95~1.05	≥1.06	
Farinins IgA	0.49			≤0.94	0.95~1.05	≥1.06	
Amylase/Protease Inhibitors IgG	0.71			≤0.94	0.95~1.05	≥1.06	
Amylase/Protease Inhibitors IgA	0.42			≤0.94	0.95~1.05	≥1.06	
Globulins IgG	0.65			≤0.94	0.95~1.05	≥1.06	
Globulins IgA	0.56			≤0.94	0.95~1.05	≥1.06	
Purinin IgG	0.64			≤0.94	0.95~1.05	≥1.06	
Purinin IgA	0.50			≤0.94	0.95~1.05	≥1.06	

Comments

Intestinal Permeability Panel

Potential Risk:

Antibodies to actin suggest leaky gut diagnosis.;

Increased levels of lipopolysaccharides antibodies indicate leaky gut condition.

Related Information:

Actin is responsible for regulating paracellular flow across the intestinal epithelium. However, increased levels of actin suggest epithelial cell damage leading to increased intestinal permeability and decreased barrier function.;

High levels of lipopolysaccharides (LPS) antibodies are indicative of penetration of LPS into the bloodstream. LPS binds to cells lining the gut and increases synthesis of pro-inflammatory substances.

Potential Risk Mitigation Choices:

Consider subsequent testing of your gut bacteria profile to identify an optimum dosage of the right probiotic necessary to help fix your leaky gut. A combination therapy may be recommended using probiotics, L-glutamine, L-arginine and Omega3 supplementation.

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PLOS | ONE

PLoS One. 2015 Apr 17;10(4)

RESEARCH ARTICLE

Essential Amino Acids in the Gluten-Free Diet and Serum in Relation to Depression in Patients with Celiac Disease

57% Celiac patients had one or more (up to 4) current psychiatric diagnoses.

ry, Leiden University, Wageningen, The Netherlands, 4 Leyden Academy on Vitality and Ageing, Leiden, The Netherlands

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Citation: van Hees NJM, Giltay EJ, Tielemans SMAJ, Geleijnse JM, Puvill T, Janssen N, et al. (2015) Essential Amino Acids in the Gluten-Free Diet and Serum in Relation to Depression in Patients with Celiac Disease. PLoS ONE 10(4): e0122619. doi:10.1371/journal.pone.0122619

Academic Editor: Dmitri Boudko, Rosalind Franklin

Abstract

Introduction

Celiac disease (CD) is associated with an increased risk of major depressive disorder, possibly due to deficiencies in micronutrients in the gluten-free diet. We aimed to investigate whether essential amino acids (i.e., the precursors of serotonin, dopamine and other neurotransmitters) are depleted in the diet and serum of CD patients with major depressive disorder.

PLOS | ONE

PLoS One. 2015 Apr 17;10(4)

RESEARCH ARTICLE

Essential Amino Acids in the Gluten-Free Diet and Serum in Relation to Depression in Patients with Celiac Disease

22% had a current or partially remitted depressive disorder and 18% were suffering from an anxiety disorder.

Wageningen, The Netherlands, 4 Leyden Academy on Vitality and Ageing, Leiden, The Netherlands

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Digestive Diseases

Dig Dis 2008;26:140–148
DOI: 10.1159/000116772

Dig Dis 2008;26:140–148

Affective and Psychiatric Disorders in Celiac Disease

Giovanni Addolorato Lorenzo Leggio Cristina D'Angelo Antonio Mirijello
Anna Ferrulli Silvia Cardone Luisa Vonghia Ludovico Abenavoli
Veruscka Leso Antonio Nesci Salvatore Piano Esmeralda Capristo
Giovanni Gasbarrini

Social phobia is included among the anxiety disorders and is characterized by a marked fear of performance, an excessive fear of scrutiny, fear of acting in an embarrassing way and avoidance of situations that involve possible scrutiny by others.

toms may be useful since these disorders could be the expression of an organic disease rather than primary psychiatric illnesses.

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Introduction

Celiac disease (CD) is a chronic immune-mediated gluten-dependent enteropathy characterized by intestinal malabsorption and subtotal or total atrophy of intestinal villi which improves after gluten-free diet (GFD) [1]. CD can be diagnosed in early childhood with classical

anisms involved in these associations were analyzed.

Affective Disorders Associated with Celiac Disease

Anxiety and Depression

The presence of neurotic disorders, mostly depression, has been described in CD patients since the 1980s [6, 7]. From the 1980s to 1990s, depression in CD patients aroused the interest of some researchers [8, 9], but no data on anxiety disorders were published.

Using the State and Trait Anxiety Inventory and the Ipat Depression Scale Questionnaire, both anxiety and

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frontiers in Human Neuroscience

REVIEW
published: 29 March 2016
doi: 10.3389/fnhum.2016.00130

Bread and Other Edible Agents of Mental Disease

Paola Bressan and Peter Kramer*

Unfortunately, gluten resembles some brain-relevant substances too. Antibodies against gluten removed from human blood attack cerebellar proteins and components of the myelin sheath that insulates nerves

the gut more permeable and can thus encourage the migration of food particles to sites where they are not expected, prompting the immune system to attack both these particles and brain-relevant substances that resemble them, and (2) releases opioid-like compounds, capable of causing mental derangement if they make it to the brain. A grain-free diet, although difficult to maintain (especially for those that need it the most), could improve the mental health of many and be a complete cure for others.

Keywords: exorphins, food opioids, celiac disease, gluten sensitivity, gluten-free diet, microbiota, schizophrenia, autism

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Edited by:
Rajeev Krishnadas,
NHS Greater Glasgow and Clyde/University of Glasgow, UK

INTRODUCTION

"Give us this day our daily bread (. . .) but deliver us from evil"
—Matthew 6:11, 13

Nutritional Neuroscience, Volume 7 Number 3 (June 2004), pp. 151–161

Taylor & Francis
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Immune Response to Dietary Proteins, Gliadin and Cerebellar Peptides in Children with Autism

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Sera from 50 children with autism and 50 healthy controls were measured for simultaneous presence of IgG, IgM and IgA antibodies against gliadin and cerebellar peptides.

was 22%, whereas the binding of anti-myelin basic protein (MBP), anti-milk, anti-egg and anti-soy to gliadin was less than 10%.

Further examination of rabbit anti-gliadin (EQVPLVQQ) and anti-cerebellar (EDVPLLED) 8 amino acid (AA) peptides with human serum albumin (HSA) and an unrelated peptide showed no binding, but the reaction of these antibodies with both the cerebellar and gliadin peptides was greater than 60%. This cross-reaction was further confirmed by DOT-immunoblot and inhibition studies. We conclude that a subgroup of patients with autism produce antibodies against Purkinje cells and gliadin peptides, which may be responsible for some of the neurological symptoms in autism.

Keywords: Autism; Autoantibodies; Celiac disease; Gliadin and cerebellar peptides; Gluten ataxia

These dietary proteins and peptides, including casein, casomorphins, gluten and gluteomorphins, can stimulate T-cells, induce peptide-specific T-cell responses, and abnormal levels of cytokine production, which may result in inflammation, autoimmune reactions and disruption of neuroimmune communications (Jyonouchi *et al.*, 2001). Peptides from inadequate digestion of casein and gluten apparently are absorbed in excess by autistic children, as reflected by very high levels of urinary peptides (Reichelt *et al.*, 1990; Shattock *et al.*, 1991; Reichelt, 1994; Reichelt and Reichelt, 1997; Whiteley *et al.*, 1999; Horvath *et al.*, 1999; Nelson *et al.*, 2001; Reichelt and Knivsberg, 2003). Excessive peptides from undigested casein and gluten are suspected to exert significant toxicity. Indeed, parents and clinicians report improvement of autistic children

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ISSN 1028-415X print/ISSN 1476-8305 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10284150400004155

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(Received 3 May 2004; Revised 12 July 2004; In final form 27 July 2004)

The mechanisms behind autoimmune reaction to nervous system antigens in autism are not understood. We assessed the reactivity of sera from 50 autism patients and 50 healthy controls to specific peptides antigen-coated wells was measured. In comparison to anti-gliadin peptide binding to gliadin peptide at 100%, the reaction of anti-cerebellar peptide to gliadin peptide was 22%, whereas the binding of anti-myelin basic protein (MBP), anti-milk, anti-egg and anti-soy to gliadin was less than 10%.

Further examination of rabbit anti-gliadin (EQVPLVQQ) and anti-cerebellar (EDVPLLED) 8 amino acid (AA) peptides with human serum albumin (HSA) and an unrelated peptide showed no binding, but the reaction of these antibodies with both the cerebellar and gliadin peptides was greater than 60%. This cross-reaction was further confirmed by DOT-immunoblot and inhibition studies. We conclude that a subgroup of patients with autism produce antibodies against Purkinje cells and gliadin peptides, which may be responsible for some of the neurological symptoms in autism.

Keywords: Autism; Autoantibodies; Celiac disease; Gliadin and cerebellar peptides; Gluten ataxia

The reaction of anti-cerebellar peptide binding to gliadin peptide was 22%

INTRODUCTION

Autism is a complex developmental disorder with

components in the etiology of autism, and these peptides are available from a variety of food sources. These dietary proteins and peptides, including casein, casomorphins, gluten and gluteomorphins, can stimulate T-cells, induce peptide-specific T-cell responses, and abnormal levels of cytokine production, which may result in inflammation, autoimmune reactions and disruption of neuroimmune communications (Jyonouchi *et al.*, 2001). Peptides from inadequate digestion of casein and gluten apparently are absorbed in excess by autistic children, as reflected by very high levels of urinary peptides (Reichelt *et al.*, 1990; Shattock *et al.*, 1991; Reichelt, 1994; Reichelt and Reichelt, 1997; Whiteley *et al.*, 1999; Horvath *et al.*, 1999; Nelson *et al.*, 2001; Reichelt and Knivsberg, 2003). Excessive peptides from undigested casein and gluten are suspected to exert significant toxicity. Indeed, parents and clinicians report improvement of autistic children

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ISSN 1028-415X print/ISSN 1476-8305 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10284150400004155

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ISSN 1028-415X print/ISSN 1476-8305 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10284150400004155

EUROPEAN JOURNAL OF INFLAMMATION Vol. 6, no. 2, 0-0 (2008)

EDITORIAL

THE IMMUNOLOGY OF GLUTEN SENSITIVITY BEYOND THE INTESTINAL TRACT

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Received October 16, 2007 – Accepted January 18, 2008

Celiac disease and gluten-sensitive enteropathy are terms that have been used to refer to a disease process affecting the small bowel. However, evidence has been accumulated in literature demonstrating that gluten sensitivity or celiac disease can exist even in the absence of enteropathy, but affecting many organs. Based on overwhelming evidence, immunological pathogenesis has been demonstrated in the joint, the heart, thyroid, bone, and, in particular, the brain cerebellum and neuronal synapsin

The mechanism by which GAD antibody induces presynaptic impairment of cerebellar Purkinje cells through inhibition of GABA is shown in Fig. 1.

autoimmunity may enable clinicians to detect markers of autoimmune diseases. Early identification of gluten sensitive and celiac disease patients and implementation of a gluten-free diet may result in significant improvement and control of associated diseases.

Gluten sensitivity, celiac disease (CD) and gluten-sensitive enteropathy are terms that have been used synonymously to refer to a disease process affecting the small bowel and characterized by gastrointestinal symptoms and malabsorption. However, since 1966 scientific evidence has been accumulated demonstrating that gluten sensitivity can exist even in the absence of enteropathy. For example, patients with dermatitis herpetiformis and presentation of blistering skin do not have any gastrointestinal symptoms but have elevated gliadin antibody in the blood which improves on a gluten-free diet (1). Additionally, associations of CD with the involvement of other organs such as the central and peripheral nervous systems also go as far back as 1966 (2). However, until recently, this phenomenon of immune reaction against neural tissue, in particular the cerebellum, was attributed to vitamin deficiencies. During the past five years, based on overwhelming evidence of immune pathogenesis involving organs other than gut and skin, many scientists have begun to re-evaluate

Key words: celiac disease, gluten sensitivity, enteropathy, synapsin, autoimmune disease

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1721-727 (2008)
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Eur J Inflammation 6(2):49-57, 2008

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EDITORIAL

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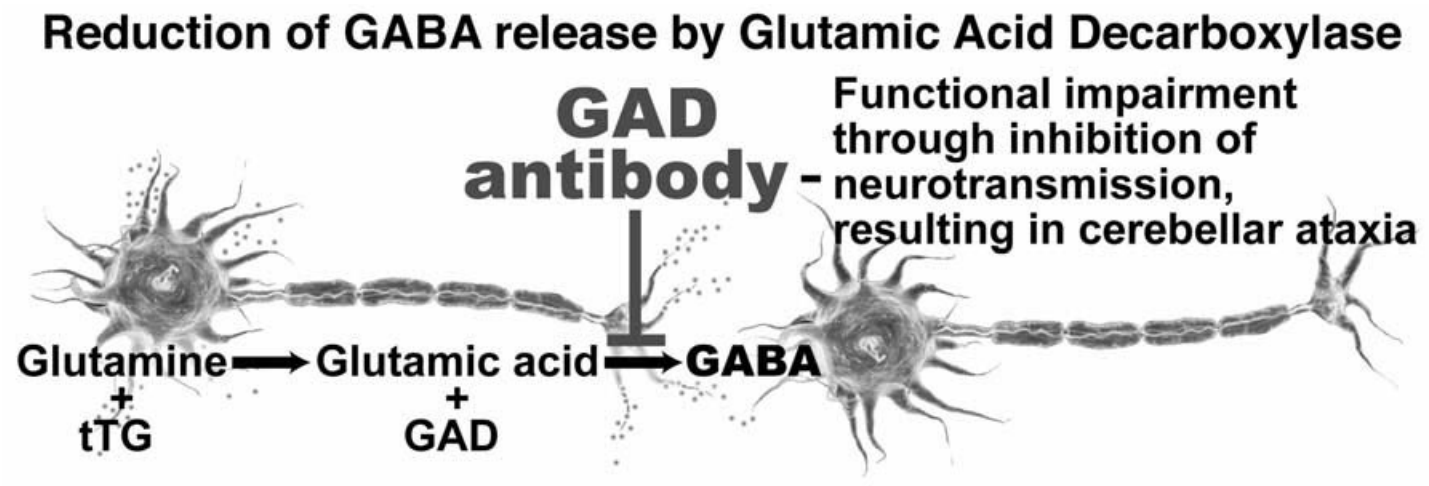


Fig. 1. *Presynaptic impairment of cerebellar Purkinje cells by an antibody to glutamic acid decarboxylase (GAD).*

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Eur J Inflammation 6(2):49-57, 2008

frontiers in Human Neuroscience

Front Hum Neurosci. 2016 Mar 29;10:130

published: 29 March 2016
doi: 10.3389/fnhum.2016.00130

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Bread and Other Edible Agents of Mental Disease

*Paola Bressan * and Peter Kramer*

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These antibodies also attack an enzyme involved in the production of GABA—our prime inhibitory neurotransmitter, whose dysregulation is implicated in both anxiety and depression.

sites where they are not expected, prompting the immune system to attack both these particles and brain-relevant substances that resemble them, and (2) releases opioid-like compounds, capable of causing mental derangement if they make it to the brain. A grain-free diet, although difficult to maintain (especially for those that need it the most), could improve the mental health of many and be a complete cure for others.

Keywords: exorphins, food opioids, celiac disease, gluten sensitivity, gluten-free diet, microbiota, schizophrenia, autism

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Edited by:
Rajeev Krishnadas, NHS Greater Glasgow and Clyde/University of Glasgow, UK

INTRODUCTION

"Give us this day our daily bread (. . .) but deliver us from evil"
—Matthew 6:11, 13

CASE STUDY #1

A 14 year old girl misdiagnosed with psychosis

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Nutrients 2015, 7, 5532-5539

Nutrients **2015**, *7*, 5532-5539; doi:10.3390/nu7075235

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ISSN 2072-6643

www.mdpi.com/journal/nutrients

Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

A 14-year-old girl came to our outpatient clinic for psychotic symptoms that were apparently associated with gluten consumption.

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Nutrients 2015, 7, 5532-5539

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ISSN 2072-6643

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

In May 2012, after a febrile episode, she became increasingly irritable and reported daily headache and concentration difficulties. One month after, her symptoms worsened presenting with severe headache, sleep problems, and behavior alterations, with several unmotivated crying spells and apathy.

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Nutrients 2015, 7, 5532-5539

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

Her school performance deteriorated, as reported by her teachers. The mother noted severe halitosis, never suffered before. The patient was referred to a local neuropsychiatric outpatient clinic, where a conversion somatic disorder was diagnosed and a benzodiazepine treatment (*i.e.*, bromazepam) was started.

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ISSN 2072-6643

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

In June 2012, during the final school examinations, psychiatric symptoms, occurring sporadically in the previous two months, worsened. Indeed, she began to have complex hallucinations. The types of these hallucinations varied and were reported as indistinguishable from reality (she saw people coming off the television to follow and scare her).

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ISSN 2072-6643

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Case Report

Gluten Psychosis: Confirmation of a New Clinical Entity

She also presented weight loss (about 5% of her weight) and gastrointestinal symptoms such as abdominal distension and severe constipation. She was admitted to a psychiatric ward.

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Case Report

A computed tomography scan of the brain and a blood pressure holter were also performed and resulted normal. Electroencephalogram (EEG) showed mild nonspecific abnormalities and slow-wave activity. Due to the abnormal autoimmune parameters and the recurrence of psychotic symptoms, autoimmune encephalitis was suspected, and steroid treatment was initiated.

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Nutrients **2015**, *7*, 5532-5539; doi:10.3390/nu7075235

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ISSN 2072-6643

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Case Report

In September 2012, shortly after eating pasta, she presented crying spells, relevant confusion, ataxia, severe anxiety and paranoid delirium. Then she was again referred to the psychiatric unit. A relapse of autoimmune encephalitis was suspected and treatment with endovenous steroid and immunoglobulins was started. During the following months, several hospitalizations were done, for recurrence of psychotic symptoms.

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ISSN 2072-6643

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Case Report

Cerebral and spinal cord magnetic resonance imaging, lumbar puncture, and fundus oculi examination did not show any pathological signs. Several EEG were performed confirming bilateral slow activity. The laboratory tests showed only mild microcytic anemia with reduced levels of ferritin and a slight increase in fecal calprotectin values.
All markers for CD were negative.

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Case Report

In September 2013, she presented with severe abdominal pain, associated with asthenia, slowed speech, depression, distorted and paranoid thinking and suicidal ideation up to a state of pre-coma. The clinical suspicion was moving towards a fluctuating psychotic disorder. Treatment with a second-generation anti-psychotic (*i.e.*, olanzapine) was started, but psychotic symptoms persisted.

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ISSN 2072-6643

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Case Report

November 2013, due to gastro-intestinal symptoms and further weight loss (about 15% of her weight in the last year), a nutritionist was consulted, and a gluten-free diet (GFD) was recommended for symptomatic treatment of the intestinal complaints; unexpectedly, within a week of gluten-free diet, the symptoms (both gastro-intestinal and psychiatric) dramatically improved, and the GFD was continued for four months.

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Case Report

Until a few years ago, the spectrum of gluten-related disorders included only CD and wheat allergy, therefore our patient would be turned back home as a "psychotic patient" and receive lifelong treatment with anti-psychotic drugs. Recent data, however, suggested the existence of another form of gluten intolerance, known as NCGS

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Case Report

Due to parental choice, the girl did not continue assuming gluten and she started a gluten-free diet with a complete regression of all symptoms within a week. Her mother finally recalled that she was returned a "normal girl". Nine months after definitely starting the GFD, she is still symptoms-free.

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Case Report

It has been hypothesized that some neuro-psychiatric symptoms related to gluten may be the consequence of the excessive absorption of peptides with opioid activity that formed from incomplete breakdown of gluten. Increased intestinal permeability, also referred to as "leaky gut syndrome", may allow these peptides to cross the intestinal membrane, enter the bloodstream, and cross the blood brain barrier, affecting the endogenous opiate system and neurotransmission within the nervous system.

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Annals of Gastroenterology (2015) **28,** 203-209

The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems

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Abstract

The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. Recent advances in research have described the importance of gut microbiota in influencing these interactions. This interaction between microbiota and GBA appears to be bidirectional, namely through signaling from gut-microbiota to brain and from brain to gut-microbiota by means of neural, endocrine, immune, and humoral links. In this review we summarize the available evidence supporting the existence of these interactions, as well as the possible pathophysiological mechanisms involved. Most of the data have been acquired using technical strategies consisting in germ-free animal models, probiotics, antibiotics, and infection studies. In clinical practice, evidence of microbiota-GBA interactions comes from the association of dysbiosis with central nervous disorders (i.e. autism, anxiety-depressive behaviors) and functional gastrointestinal disorders. In particular, irritable bowel syndrome can be considered an example of the disruption of these complex relationships, and a better understanding of these alterations might provide new targeted therapies

Studies conduced on germ-free animals have also demonstrated that microbiota influences stress reactivity and anxiety-like behavior, and regulates the set point for HPA activity.

have multiple effects on affect, motivation, and higher cognitive functions. The complexity of these interactions is enclosed in the denomination of "gut-brain axis" (GBA) [1]. Its role is to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling. The mechanisms underlying GBA communications involve neuro-immuno-endocrine mediators.

This bidirectional communication network includes the central nervous system (CNS), both brain and spinal cord,

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Conflict of Interest: None

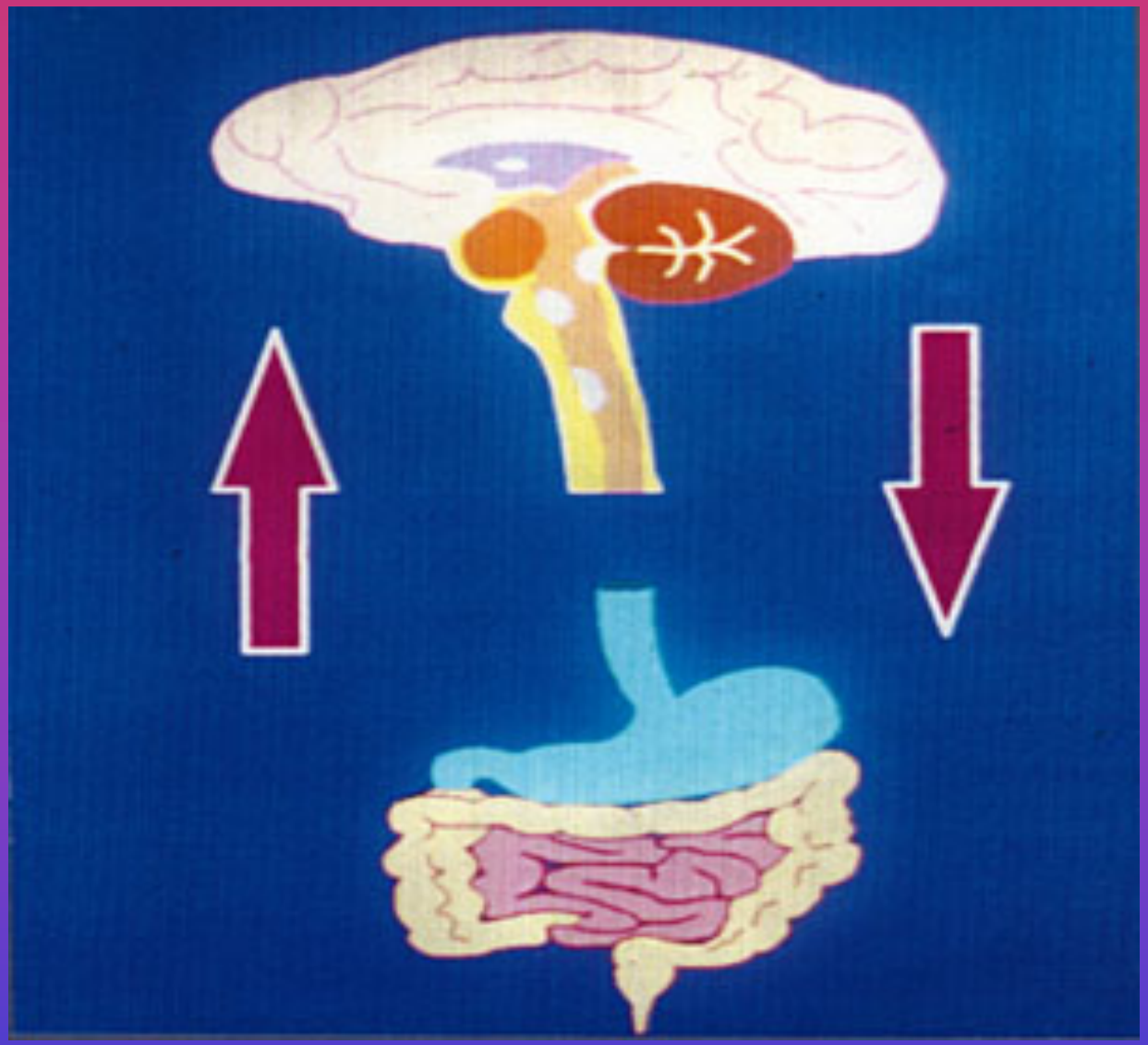
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Received 5 September 2014; accepted 7 December 2014

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pathways to CNS, and efferent signals from CNS to the intestinal wall. The HPA axis is considered the core stress efferent axis that coordinates the adaptive responses of the organism to stressors of any kind [2]. It is a part of the limbic system, a crucial zone of the brain predominantly involved in memory and emotional responses. Environmental stress, as well as elevated systemic pro-inflammatory cytokines, activate this system that, through secretion of the corticotropin-releasing factor (CRF) from the hypothalamus, stimulates adrenocorticotropic hormone (ACTH) secretion from pituitary gland that, in turn, leads to cortisol release from the adrenal glands. Cortisol is a major stress hormone that affects many human organs, including the brain. Thus, both neural and hormonal lines of communication combine to allow brain to influence the activities of intestinal functional effector cells, such as immune cells, epithelial cells, enteric neurons, smooth muscle cells, interstitial cells of Cajal and enterochromaffin cells. These same cells, on the other hand, are under the influence of the gut microbiota [3] whose contributing role in brain-gut reciprocal communications has recently been assessed. The concept of a microbiome GBA is now emerging.

The enteric microbiota is distributed in the human gastrointestinal tract and, although each person's microbiota profile is distinct, relative abundance and distribution along the



Gut Pathogens

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Short report

A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome

A Venket Rao[1], Alison C Bested[2,3], Tracey M Beaulne[3], Martin A Katzman[4,5], Christina Iorio[5], John M Berardi[6] and Alan C Logan*[3]

Address: [1]Department of Nutritional Sciences, University of Toronto, 50 College Street, Toronto, Ontario M5S 3E2, Canada, [2]Environmental Health Clinic, Women's College Hospital, 76 Grenville Street, Toronto, Ontario M5S 1B2, Canada, [3]Integrative Care Centre of Toronto, 3600 Ellesmere Road, Unit 4, Toronto, Ontario M1C 4Y8, Canada, [4]Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario M5T 1R8, Canada, [5]START Clinic for Mood and Anxiety Disorders, 790 Bay Street, Toronto, Ontario M5G 1N8, Canada and [6]Precision Nutrition, 1665 Gregory Road, St Catharines, Ontario L2R6P9, Canada

Email: A Venket Rao - v.rao@utoronto.ca; Alison C Bested - acbes@rogers.com; Tracey M Beaulne - dr-beaulne@rogers.com;

In recent years the interface between neuropsychiatry and gastroenterology has converged into a new discipline referred to as enteric neuroscience.

Abstract

Chronic fatigue syndrome (CFS) is complex illness of unknown etiology. Among the broad range of symptoms, many patients report disturbances in the emotional realm, the most frequent of which is anxiety. Research shows that patients with CFS and other so-called functional somatic disorders have alterations in the intestinal microbial flora. Emerging studies have suggested that pathogenic and non-pathogenic gut bacteria might influence mood-related symptoms and even behavior in animals and humans. In this pilot study, 39 CFS patients were randomized to receive either 24 billion colony forming units of *Lactobacillus casei* strain Shirota (LcS) or a placebo daily for two months. Patients provided stool samples and completed the Beck Depression and Beck Anxiety Inventories before and after the intervention. We found a significant rise in both *Lactobacillus* and *Bifidobacteria* in those taking the LcS, and there was also a significant decrease in anxiety symptoms among those taking the probiotic vs controls ($p = 0.01$). These results lend further support to the presence of a gut-brain interface, one that may be mediated by microbes that reside or pass through the intestinal tract.

Background

Chronic Fatigue Syndrome (CFS) is a medically unexplained illness, characterized by persistent and relapsing fatigue [1,2]. This severe pathological fatigue is worsened by periods of physical and mental exertion. Along with the ongoing fatigue, it has also been noted that 97% of CFS patients report neuropsychological disturbances. This can manifest as cognitive dysfunction, sleep disturbances, headaches, and a variety of symptoms in the emotional realm. Of these emotion-related symptoms, anxiety and depression are the most prevalent, with approximately half or patients meeting the criteria for an anxiety disorder or major depressive disorder. Over 40% of patients report symptoms that are often part of anxiety and depressive disorders, including dizziness, lightheadedness, heart palpitations, sleep disturbances, appetite changes and shortness of breath [3].

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Even minute doses of microbes within the gastrointestinal tract, levels that do not trigger an immune response, are capable of influencing neurotransmission in the paraventricular hypothalamus, the central nucleus of the amygdala, and the bed nucleus of the stria terminalis.

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All three of these regions are involved in the processing of emotions related to anxiety and mood

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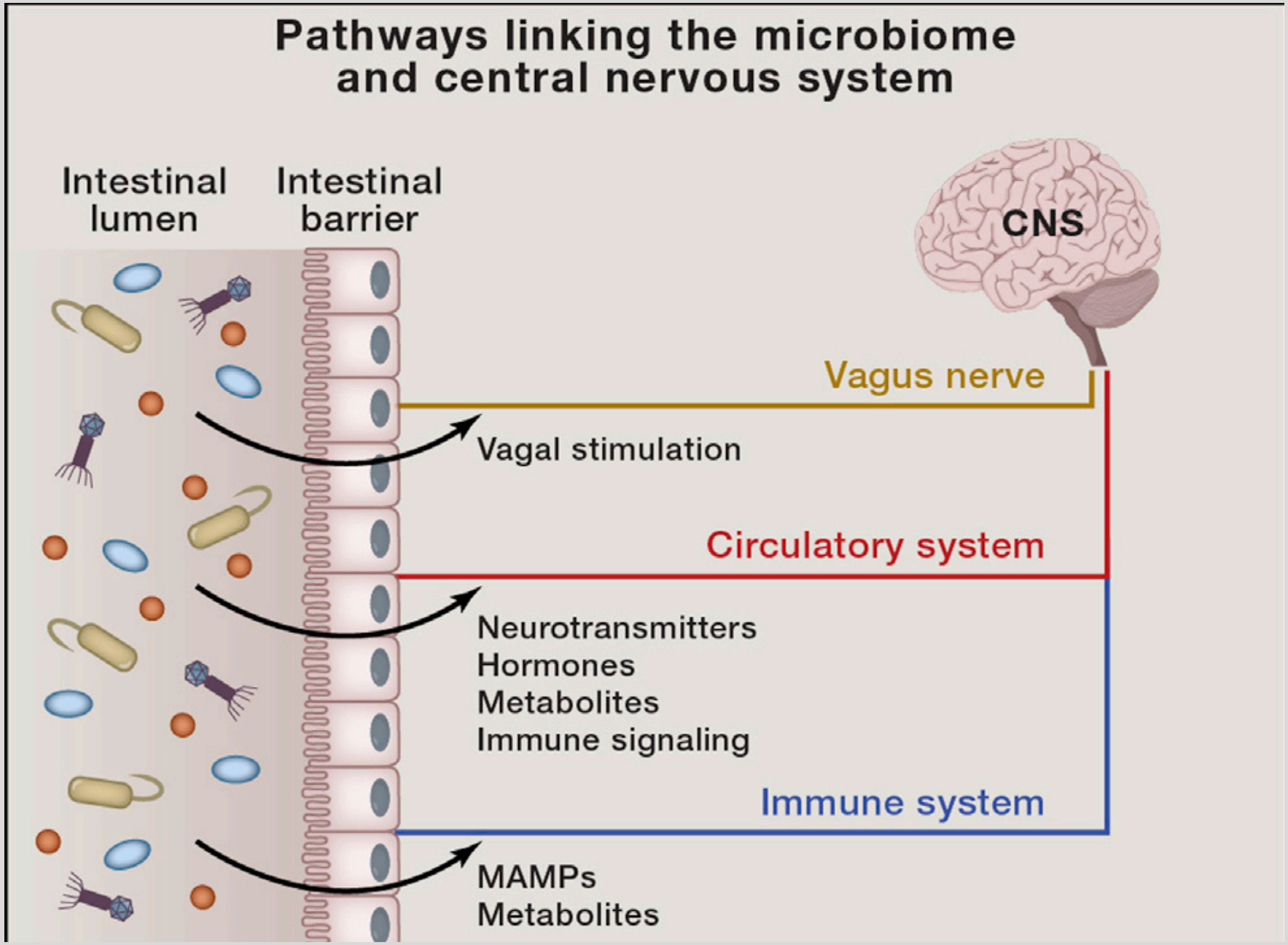
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Pathways linking the microbiome and central nervous system
Intestinal lumen
Intestinal barrier
CNS
Vagus nerve
Vagal stimulation
Circulatory system
Neurotransmitters
Hormones
Metabolites
Immune signaling
Immune system
MAMPs
Metabolites

CHAPTER 10

Infection, Autoimmunity, and Vitamin D

Amy D. Proal[*,1], Paul J. Albert[†], Trevor G. Marshall[*]
[*]Autoimmunity Research Foundation, Thousand Oaks, California, USA
[†]Weill Cornell Medical College, New York, USA
[1]Corresponding Author: amy.proal@gmail.com

1 INTRODUCTION

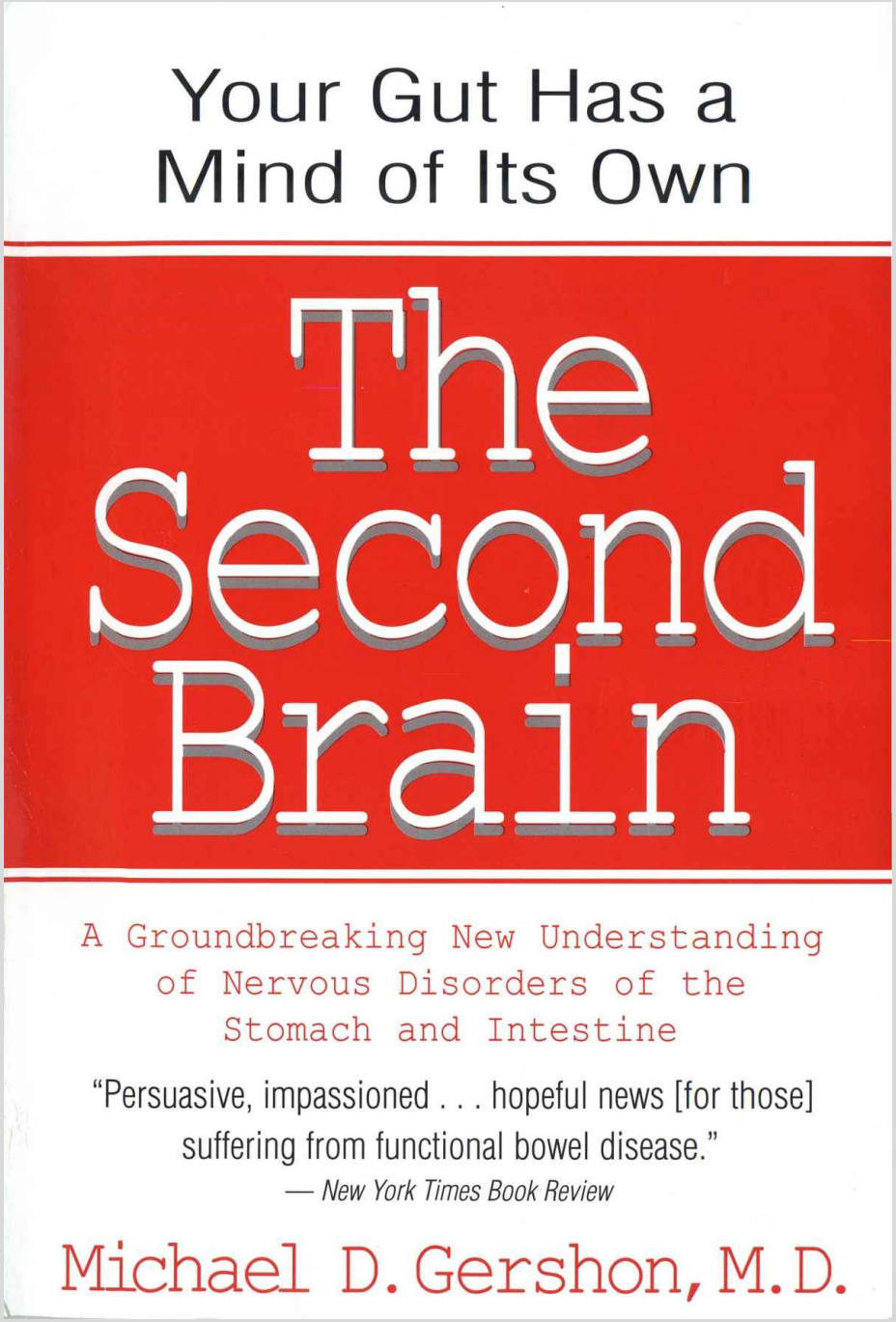
Proteins and metabolites generated by the microbiome permeate the body. Of the small molecules found in healthy human blood, 36% are created by the human gut microbiome.

viruses, and fungi now known to persist in nearly every body site, called the human microbiome. This discovery has uncovered thousands of new microbial species capable of contributing to autoimmune and inflammatory disease processes. In lieu of a single pathogen causing a single disease, many of these microbes instead seem to generate dysfunction by continually interacting with other species in a shared intra-phagocytic environment. Yet to persist inside host immune cells, the microbiome must necessarily degrade the host's innate immune defences. In doing so, the pathogens also dysregulate other aspects of human metabolism by directly altering the expression of human genes. This chapter describes how the cumulative effect of these changes to the human metabolome and interactome may lead to the catastrophic failure of human metabolism so often observed in chronic idiopathic disease.

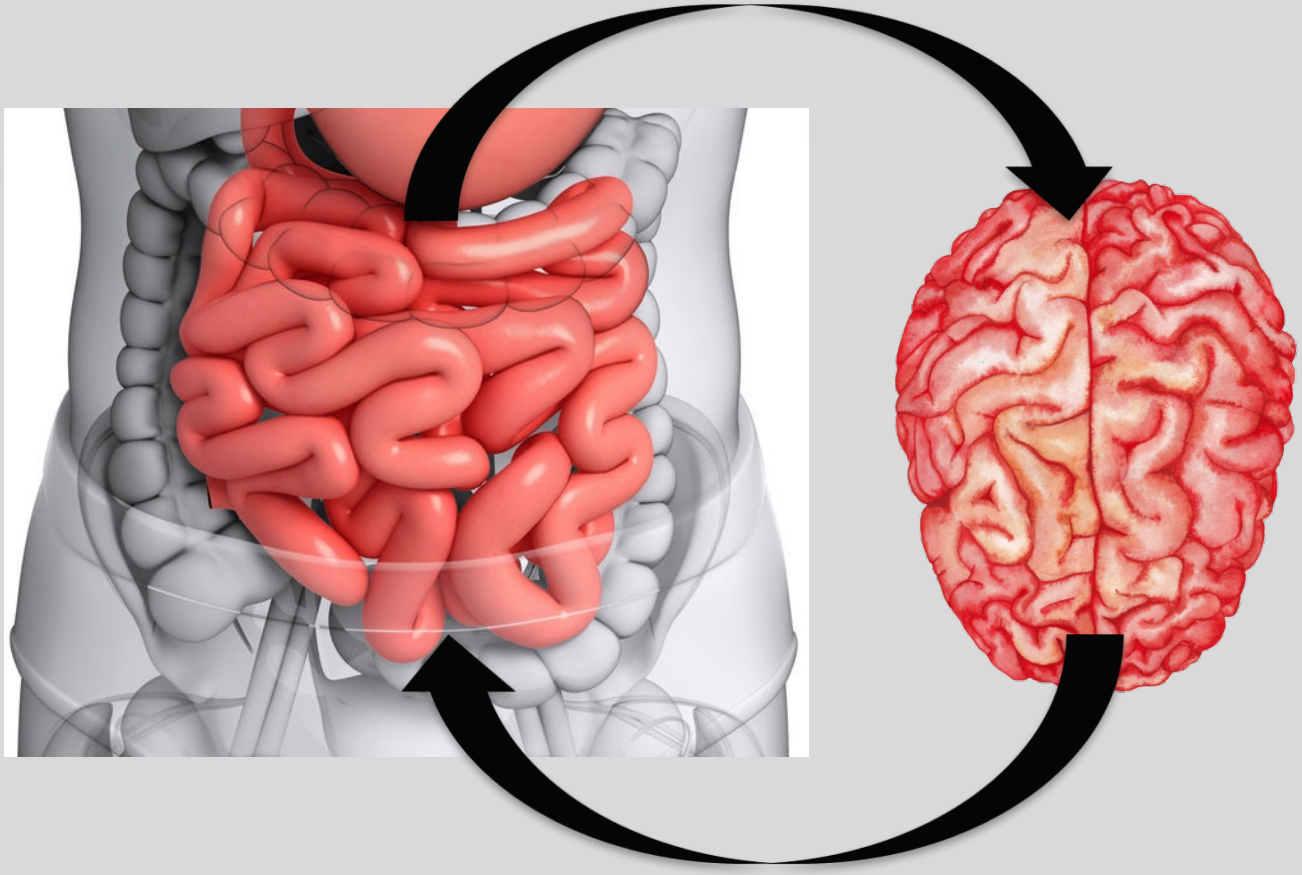
Infection and Autoimmunity
http://dx.doi.org/10.1016/B978-0-444-63269-2.00007-6
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INFECTION AND AUTOIMMUNITY, 2ND EDITION, 2015, YEHUDA SHOENFELD, EDITOR

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Your Gut Has a Mind of Its Own
The Second Brain
A Groundbreaking New Understanding of Nervous Disorders of the Stomach and Intestine
"Persuasive, impassioned . . . hopeful news [for those] suffering from functional bowel disease."
— New York Times Book Review
Michael D. Gershon, M.D.

Gut-Brain Axis



Normal levels of brain antibodies

Elevated levels of brain antibodies



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the *"perfect storm"* for Chronic Inflammatory Disease development.

- Genetic Vulnerability
- Environmental triggers
- Altered Microbiome (Dysbiosis)
- Intestial Permeability
- Systemic Immune Response (Inflammation)

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You ever wake up in the morning and look at yourself in the mirror and think,
“well that can’t be right.”



BioMed Research International Vol 2014, Article ID 736385

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BioMed Research International
Volume 2014, Article ID 736385, 8 pages
http://dx.doi.org/10.1155/2014/736385

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Review Article

Neurotoxicants Are in the Air: Convergence of Human, Animal, and *In Vitro* Studies on the Effects of Air Pollution on the Brain

Lucio G. Costa,[1,2] Toby B. Cole,[1,3] Jacki Coburn,[1] Yu-Chi Chang,[1] Khoi Dao,[1] and Pamela Roque[1]

[1] *Department of Environmental and Occupational Health Sciences, University of Washington, 4225 Roosevelt, Suite No. 100, Seattle, WA 98105, USA*
[2] *Department of Neuroscience, University of Parma, Via Volturno 39, 43100 Parma, Italy*
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Received 6 November 2013; Revised 23 December 2013; Accepted 24 December 2013; Published 12 January 2014

While considering potential sources of compounds that may contribute to the etiology of neurodevelopmental and neurodegenerative diseases, diet has often been considered as a primary vehicle of exposure.

1. Introduction

Air pollution is a mixture comprised of several components, including ambient particulate matter (PM), gases, organic compounds, and metals. The association between air pollution and morbidity and mortality caused by respiratory and cardiovascular diseases is well established [1–3]. Among air pollution components, PM is believed to be the most widespread threat and has been heavily implicated in disease [2, 4, 5]. PM is broadly characterized by aerodynamic diameter (e.g., PM_{10} and $PM_{2.5}$, equivalent to <10 μm and 2.5 μm in diameter, respectively; [2]). Ultrafine particulate matter (UFPM; <100 nm) is of much concern, as these particles can more easily enter the circulation and distribute to various organs, including the brain [6, 7]. Of most relevance is also the fact that UFPM can gain access to the brain directly through the nasal olfactory mucosa, reaching first the olfactory bulb [7–11]. *In vitro* studies have shown that PM is cytotoxic and that toxicity is size-dependent, with the smaller UFPM being better able to enter the cells and exert toxic effects [12–15].

The populations of many countries (e.g., China, India, Middle East, and Central America) are commonly exposed for extended periods to relatively high levels (>100 $\mu g/m^3$) of PM [2], and such concentrations can be easily reached near trafficked roads and significantly exceeded in certain occupational settings [16]. Oxidative stress and inflammation are the two cardinal processes by which air pollution is believed to exert its peripheral toxicity [2, 17, 18]. PM has been shown to affect lung, cardiovascular, and nervous system functions by mechanisms that involve oxidative stress [19, 20], and oxidative damage has been shown to be a primary mechanism of PM toxicity [4, 19, 21]. For example, alterations in expression of some oxidative stress-related genes

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Indeed, many known neurotoxicants and developmental neurotoxicants are food contaminants. Yet, the air we breathe is a logical potential source of chemicals which may exert neurotoxicity, though attention has been limited for several decades only to effects on the respiratory system and more recently on the cardiovascular system.

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Elevated air pollution is associated with decreased cognitive function in children, adults, and the elderly

by air pollution are oxidative stress and neuroinflammation, which are seen in both humans and animals and are confirmed by *in vitro* studies. Among factors which can affect neurotoxic outcomes, age is considered the most relevant. Human and animal studies suggest that air pollution (and DE) may cause developmental neurotoxicity and may contribute to the etiology of neurodevelopmental disorders, including autistic spectrum disorders. In addition, air pollution exposure has been associated with increased expression of markers of neurodegenerative disease pathologies.

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In Clinical Practice,60-65% of all cognitive decline Alzheimer patients are identified as '*Inhalation Alzheimer's'* patients



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Two studies found that residential proximity to freeways and gestational and early life exposure to traffic-related air pollution were associated with autism (OR = 1.86).

mostly ascribed to diesel exhaust (DE). Human epidemiological studies and controlled animal studies have shown that exposure to air pollution may lead to neurotoxicity. In addition to a variety of behavioral abnormalities, two prominent effects caused by air pollution are oxidative stress and neuroinflammation, which are seen in both humans and animals and are confirmed by *in vitro* studies. Among factors which can affect neurotoxic outcomes, age is considered the most relevant. Human and animal studies suggest that air pollution (and DE) may cause developmental neurotoxicity and may contribute to the etiology of neurodevelopmental disorders, including autistic spectrum disorders. In addition, air pollution exposure has been associated with increased expression of markers of neurodegenerative disease pathologies.

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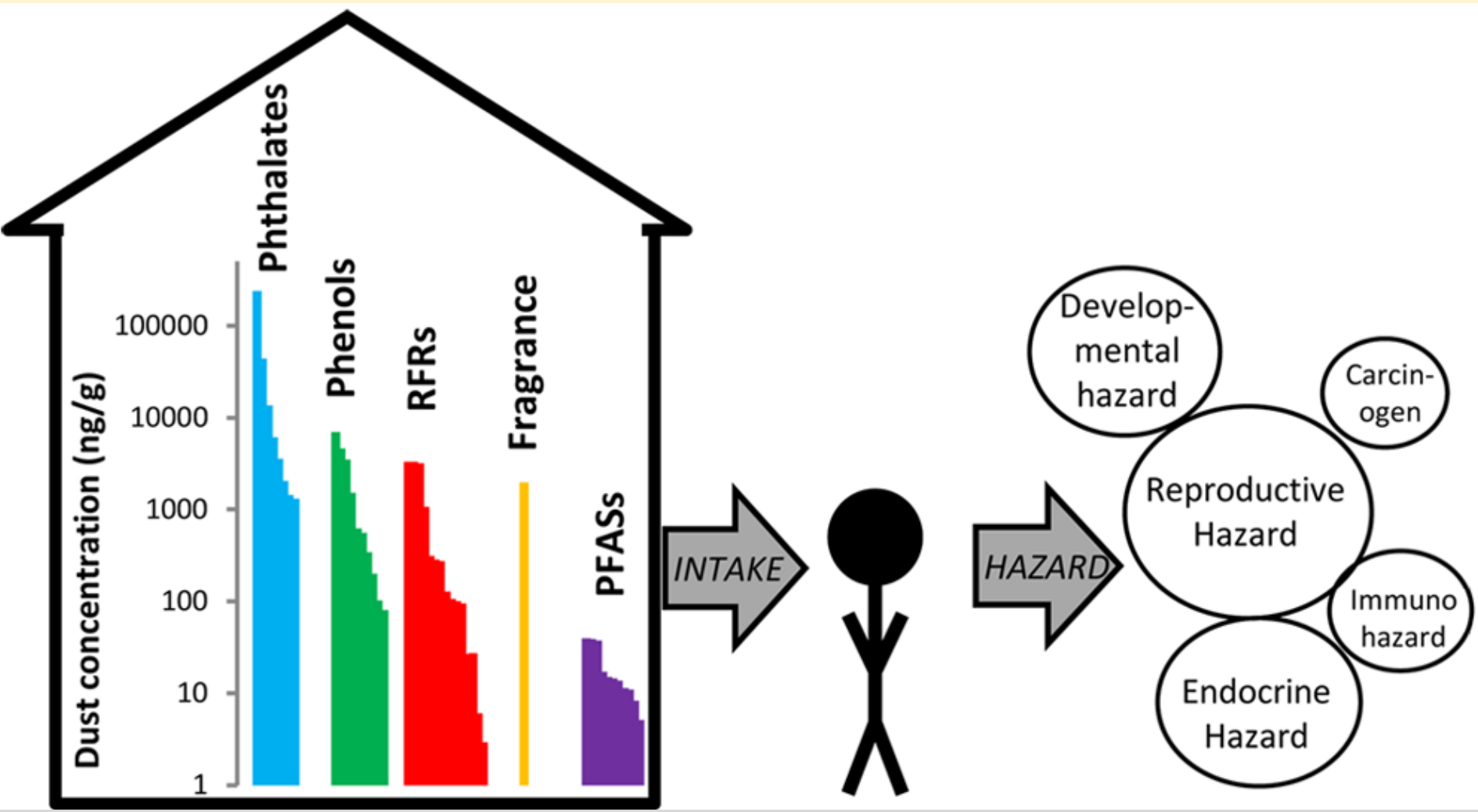
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Environ. Sci. Technol. 2016, 50, 10661−10672

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Environmental Science & Technology

Article

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Consumer Product Chemicals in Indoor Dust: A Quantitative Meta-analysis of U.S. Studies

Susanna D. Mitro,[†] Robin E. Dodson,[‡] Veena Singla,[§] Gary Adamkiewicz,[∥] Angelo F. Elmi,[†]

The indoor environment is a haven for chemicals associated with reproductive and developmental toxicity, endocrine disruption, cancer and other health effects. Additionally, the existing dust literature has allowed us to identify the chemicals and chemical classes found at the highest levels indoors (phthalates and phenols), with the highest estimated intakes (phthalates and replacement flame retardants (RFRs), and associated with the most hazard traits (phthalates and PFASs).

retardants, and polyfluorinated alkyl substances (PFASs) are widely detected in the U.S. general population, including vulnerable populations such as pregnant women and children.[4−8]

Exposure to one or more of these chemical classes has been associated with adverse health effects including reproductive toxicity, endocrine disruption, cognitive and behavioral impairment in children, cancer, asthma, immune dysfunction, and chronic disease.[7−9]

Many emerging and current use consumer product chemicals of concern are semivolatile organic compounds (SVOCs), which

characterized.[21,22] The chemical properties, sources, exposure pathways and major health effects associated with each chemical class are reviewed in the following sources: phthalates,[16,23−26] flame retardants,[25,27,28] environmental phenols,[25,26,29,30] synthetic fragrances,[29,31,32] and PFASs.[25,33,34]

Received: April 22, 2016
Revised: July 29, 2016
Accepted: August 5, 2016
Published: September 14, 2016

ACS Publications © 2016 American Chemical Society

DOI: 10.1021/acs.est.6b02023
Environ. Sci. Technol. 2016, 50, 10661−10672

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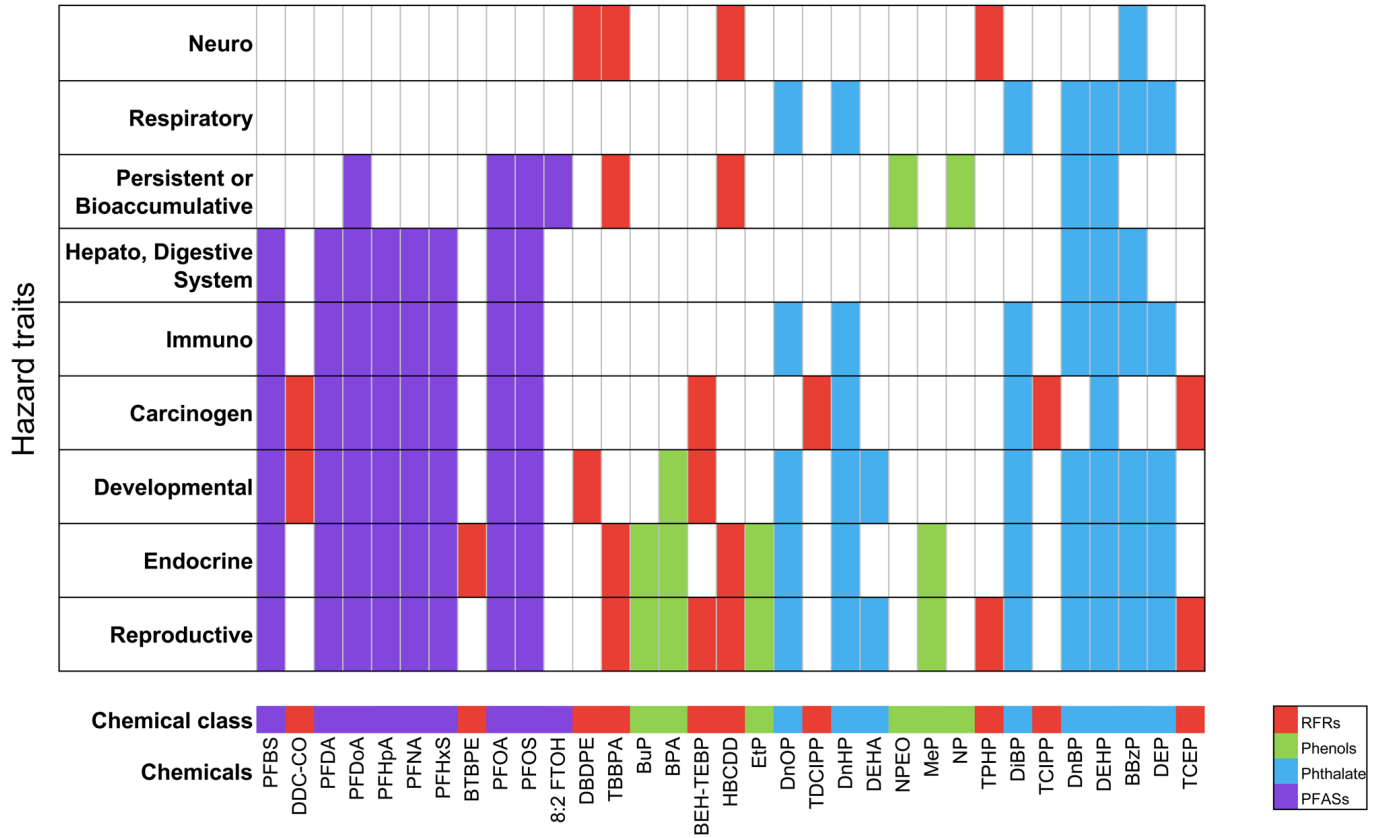


Figure 4. Each row on the chart represents potential chemical hazard traits, and each column represents a chemical. Chemicals are listed in order of estimated adult daily residential intake (lowest intake on the left-hand side). For hazard traits associated with a mixture rather than individual chemicals (HBCDD, DDC−CO, NPEO) the intakes of the chemicals composing the mixture were added to generate the mixture's position in the intake ranking. The hazard traits associated with each chemical, according to the SCP CC list are represented by filled cells; hazard traits not associated with the chemical are left blank. Chemicals not included in the intake assessment and those not listed in SCP CC list are not shown in the chart.

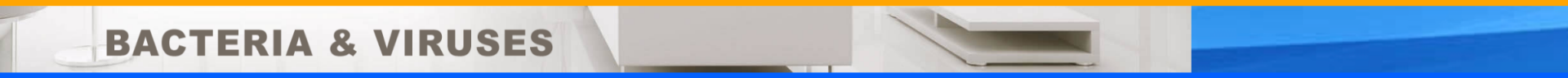


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THE CONTAMINANTS IN OUR HOME AIR



Indoor air pollution is caused by a combination of particles like pollen, dust, Bacteria & Viruses, pet dander, mold spores and smoke combined with ozone, invisible gases and volatile organic compounds which are emitted by building materials, furniture, carpeting, paint, cleaning and personal care products.

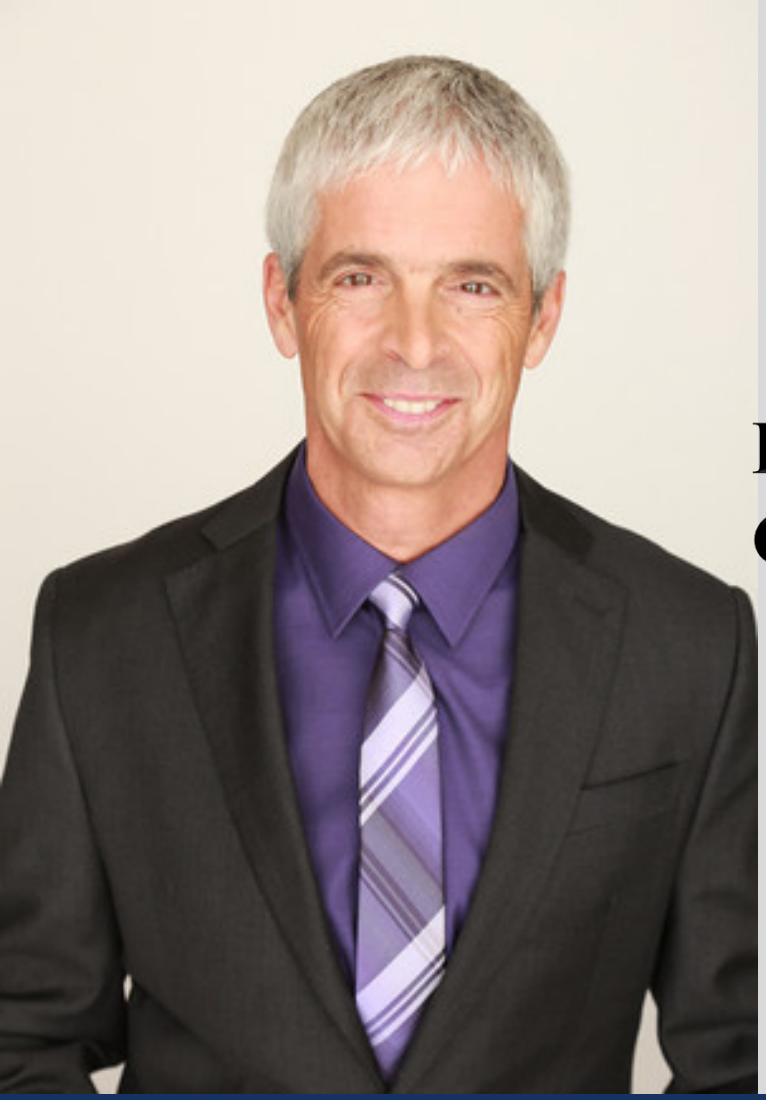


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- Genetic Vulnerability
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