

# Fire in The Hole



**Intestinal Permeability: Precursor to Autoimmune Disease  
and a Comprehensive Approach to Healing the Gut**



**Presented at  
Silicon Valley Health Institute  
Palo Alto, Ca  
May 6, 2017**

*With Gratitude*

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- **Medical Advisory Board, Functional Medicine Coaching Academy**
- **Medical Advisory Board, Functional Medicine University**
- **Medical Advisory Board, Institute for Functional Nutrition**
- **Medical Advisory Board, Nutritional Therapy Association**
- **Medical Advisory Board-National Association  
of Nutritional Professionals**
- **Scientific Advisory Board-International and American  
Association of Clinical Nutritionists**



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## ORIGINAL ARTICLE



## Is autoimmunology a discipline of its own? A big data-based bibliometric and scientometric analyses

Abdulla Watad<sup>a,b,c</sup>, Nicola Luigi Bragazzi<sup>d</sup> , Mohammad Adawi<sup>e</sup>, Howard Amital<sup>a,b,c</sup>, Shaye Kivity<sup>b,c</sup>, Naim Mahroum<sup>a,b,c</sup>, Miri Blank<sup>b,c</sup> and Yehuda Shoenfeld<sup>b,c</sup>

<sup>a</sup>Department of Medicine 'B', Sheba Medical Center, Tel-Hashomer, Israel; <sup>b</sup>Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel; <sup>c</sup>Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; <sup>d</sup>School of Public Health Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy; <sup>e</sup>Padeh and Ziv Hospitals, Bar-Ilan Faculty of Medicine, Ramat Gan, Israel

**The panorama of medical specialties is highly dynamic, constantly under flux, thanks to new discoveries and advancements both in basic science and clinical practice.**

Bibliographic thesaurus. Journals specifically devoted to autoimmune disorders were six and covered approximately 4.15% of the entire scientific production. Compared with all the corpus (from 1946 on), these specialized journals have been established relatively few decades ago. Top countries were the United States, Japan, Germany, United Kingdom, Italy, China, France, Canada, Australia, and Israel. Trending topics are represented by the role of microRNAs (miRNAs) in the ethiopathogenesis of autoimmune disorders, contributions of genetics and of epigenetic modifications, role of vitamins, management during pregnancy and the impact of gender. New subsets of immune cells have been extensively investigated, with a focus on interleukin production and release and on Th17 cells. Autoimmunology is emerging as a new discipline within immunology, with its own bibliometric properties, an identified scientific community and specifically devoted journals.

autoimmunology; autoimmunity; autoantibodies; bibliometrics; Big Data; PubMed/MEDLINE; scientometrics



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analysis) were carried out using open-source software, namely, VOSviewer and SciCurve. A corpus of 169,519 articles containing the keyword "autoimmunity" was utilized, selecting PubMed/MEDLINE as bibliographic thesaurus. Journals specifically devoted to autoimmune disorders were six and covered approximately 4.15% of the entire scientific production. Compared with all the corpus (from 1946 on), these specialized journals have been established relatively few decades ago. Top countries were the United States, Japan, Germany, United Kingdom, Italy, China, France, Canada, Australia, and Israel. Trending topics are represented by the role of microRNAs (miRNAs) in the ethiopathogenesis of autoimmune disorders, contributions of genetics and of epigenetic modifications, role of vitamins, management during pregnancy and the impact of gender. New subsets of immune cells have been extensively investigated, with a focus on interleukin production and release and on Th17 cells. Autoimmunology is emerging as a new discipline within immunology, with its own bibliometric properties, an identified scientific community and specifically devoted journals.

**KEYWORDS**

Autoimmune disorders; autoimmunology; autoimmunity; autoantibodies; bibliometrics; Big Data; PubMed/MEDLINE; scientometrics

**Introduction**

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**The same holds for geriatrics: it was established in England in the fifties, thanks to the work of Marjory Warren (1897–1960) at the hospital in West Middlesex, but the board certification was initiated only in 1988.**

United States, Japan, Germany, United Kingdom, Italy, China, France, Canada, Australia, and Israel. Trending topics are represented by the role of microRNAs (miRNAs) in the ethiopathogenesis of autoimmune disorders, contributions of genetics and of epigenetic modifications, role of vitamins, management during pregnancy and the impact of gender. New subsets of immune cells have been extensively investigated, with a focus on interleukin production and release and on Th17 cells. Autoimmunology is emerging as a new discipline within immunology, with its own bibliometric properties, an identified scientific community and specifically devoted journals.

PubMed/MEDLINE;  
scientometrics



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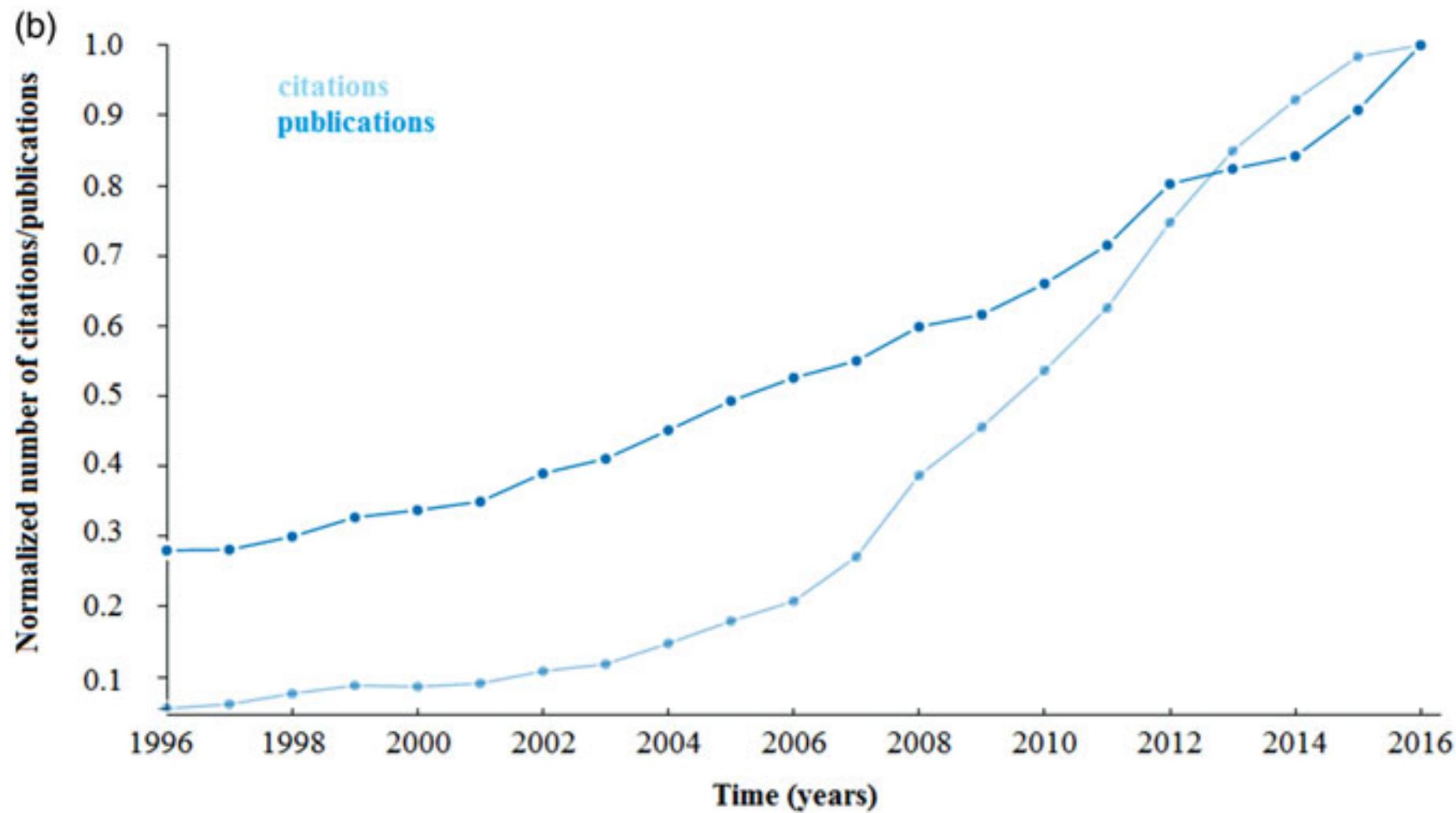
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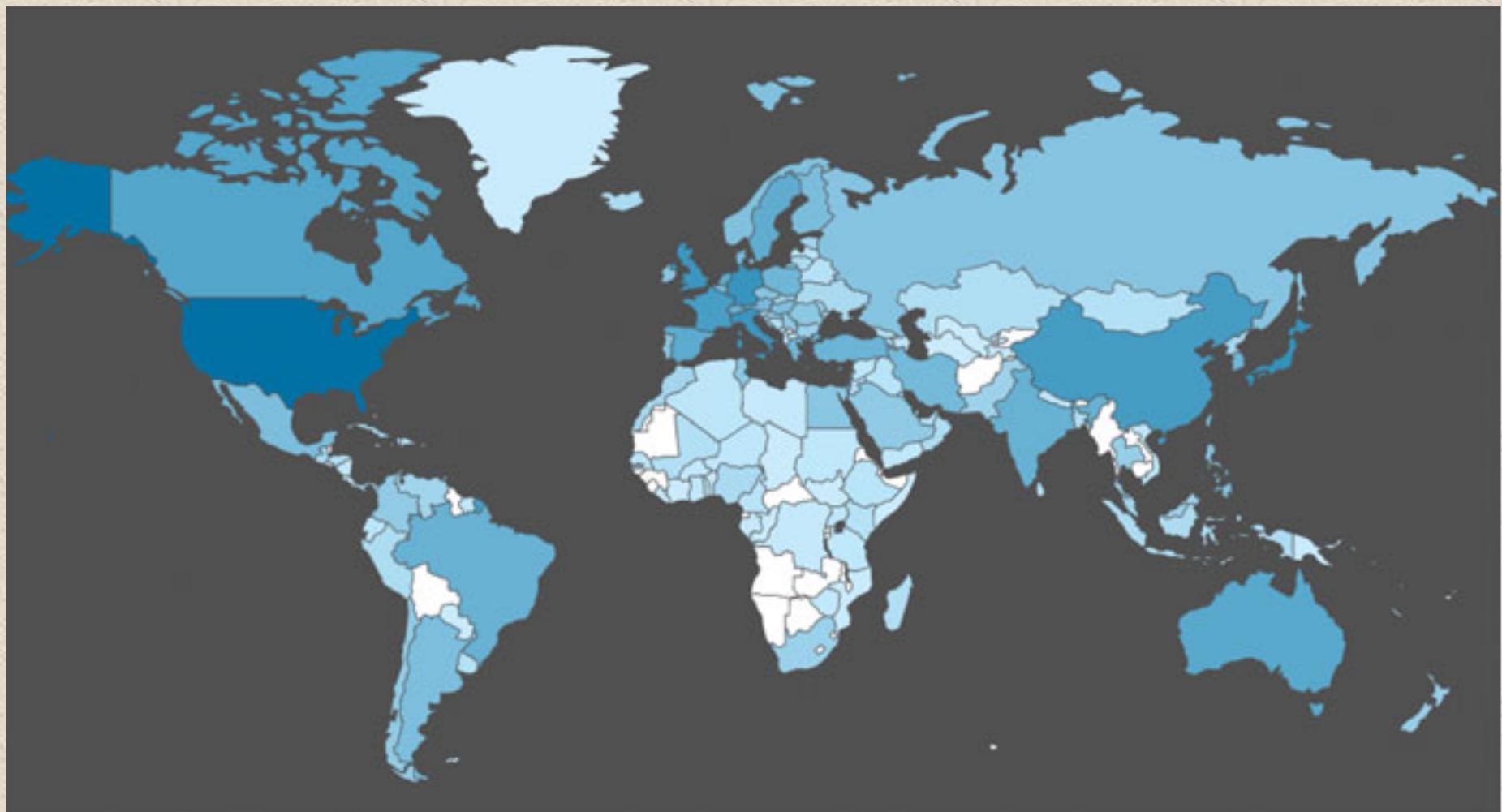
**Autoimmunology is a sub-category of immunology specifically dealing with autoimmune disorders, which impose a severe clinical and societal burden, comparable to the impact of cancer, cardiovascular disease and respiratory disease**

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(b) Pattern of the citations and scientific output concerning autoimmune disorders in the period 1996–2016 (normalized figures), showing an increasing trend throughout time.



**Figure 2.** Heat-map showing the leading countries in the production of scientific articles concerning autoimmune disorders. Color palette goes from light blue (countries with low number of articles and scientific production) to dark blue (countries with high number of articles and scientific output).

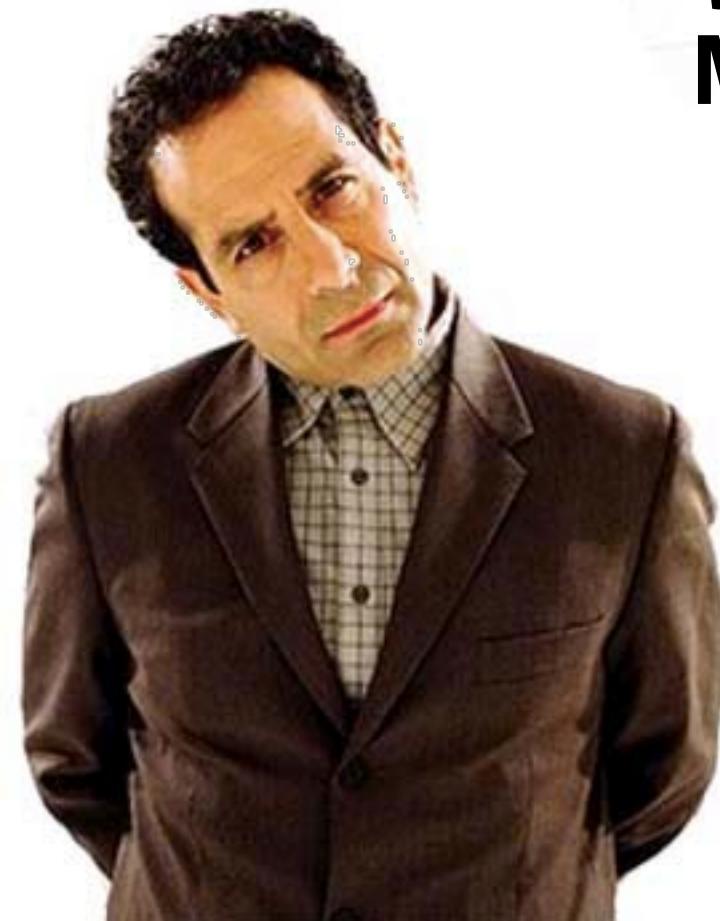
**How Many Know or Suspect you Currently have  
an Autoimmune Mechanism Occurring in Your  
Body (elevated antibodies to self protein)?**

# We're going to Talk About Where It Comes From, What's the Trigger?



# Premise #1

**If Autoimmune Disease is such a  
Growing Field, Why is There Such a  
Delay in Recognizing Its  
Manifestations?**



Detective Adrian Monk



## The answer is 17 years, what is the question: understanding time lags in translational research

J R Soc Med 2011 104: 510

Zoë Slote Morris<sup>1</sup> • Steven Wooding<sup>2</sup> • Jonathan Grant<sup>2</sup>

<sup>1</sup>Institute of Public Health, University of Cambridge, Cambridge CB2 0SR, UK

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Correspondence to: Jonathan Grant. Email: jgrant@rand.org

DECLARATIONS

Summary

**It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.**

RESEARCH

Programme in the Department of Health. The views expressed are not necessarily those of the Department

Ethical approval

Not applicable

Guarantor

JG

Contributorship

ZSM designed, conducted and analysed the literature review, and drafted and revised the paper;

JG initiated the project, drafted and revised the paper, and has led a number of studies cited that attempted to measure lags; SW revised the paper

face difficulties in knowing what they should or can do to reduce time lags.

This effectively 'blindfolds' investment decisions and risks wasting effort.

The study concludes that understanding lags first requires agreeing models, definitions and measures, which can be applied in practice. A second task would be to develop a process by which to gather these data.

### Introduction

Timely realization of the benefits of expensive medical research is an international concern attracting considerable policy effort around 'translation'.<sup>1,2</sup> Policy interventions to improve translation respond to a vast empirical literature on the difficulties of getting research across research phases and into practice.<sup>3–11</sup>

Both literature and policy tend to assume that speedy translation of research into practice is a good thing. Delays are seen as a waste of scarce resources and a sacrifice of potential patient benefit.<sup>12</sup> Although some lag will be necessary to ensure the safety and efficacy of new interventions or advances, in essence we should aim to optimize lags. One recent study (of which JG and SW were co-authors) estimating the economic benefit of cardiovascular disease (CVD) research in the UK between 1975 and 2005, found an internal rate of return (IRR) of CVD research of 39%.<sup>13</sup> In other words, a £1.00 investment in public/charitable CVD research produced a stream of benefits

equivalent to earning £0.39 per year in perpetuity. Of this, 9% was attributable to the benefit from health improvements, which is the focus of this paper. (The remaining 30% arose from 'spillovers' benefiting the wider economy.) This level of benefit was calculated using an estimated lag of 17 years. Varying the lag time from 10 to 25 years produced rates of return of 13% and 6%, respectively, illustrating that shortening the lag between bench and bedside improves the overall benefit of cardiovascular research. What is notable is that all the above calculations depended upon an estimated time lag; estimated because, despite longstanding concerns about them,<sup>14</sup> time lags in health research are little understood.

**It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.**<sup>1,3,15</sup> Balas and Bohen,<sup>16</sup> Grant<sup>17</sup> and Wratschko<sup>18</sup> all estimated a time lag of 17 years measuring different points of the process. Such convergence around an 'average' time lag of 17 years hides complexities that are relevant to

# Why the Resistance?

JAMA, March 13, 2002, Vol. 287, No. 10

## From Clinical Trials to Clinical Practice Bridging the GAP

Michael W. Rich, MD

**E**VIDENCE-BASED MEDICINE. THE CONCEPT SEEMS SO simple. Take the best available information from clinical trials and observational studies and apply the results in clinical practice. What in medicine could be

more rational or straightforward? Yet, despite the promise of evidence-based medicine, many barriers stand in the way of its implementation. In this issue of THE JOURNAL, Mehta and colleagues<sup>6</sup> describe just such an approach to improving care for acute myocardial infarction (AMI)—the Guidelines Applied in Practice (GAP) initiative in Southeast Michigan. The GAP

**Take the best available information from clinical trials and observational studies and apply the results in clinical practice. What in medicine could be more rational or straightforward?**

program was developed in collaboration with the American College of Cardiology, the Center for Medicare and Medicaid Services (CMS), and the Michigan Peer Review Organization (MPRO). To facilitate adherence to established treatment guidelines for AMI, the GAP investigators worked closely with a consortium of 10 local hospitals that were se-

lected. The principal findings of the study<sup>6</sup> were that at participating hospitals, compliance with 9 of the 11 quality indicators improved following implementation of the GAP program, with absolute gains ranging from 4% to 12%, and with 4 of the improvements achieving statistical significance. However, favorable changes also occurred in several of the quality indicators at non-GAP hospitals, such that the only significant difference in change over time was in prescription of aspirin at hospital discharge, which improved to a greater extent at GAP hospitals than at non-GAP hospitals. Conversely, improvements in the use of  $\beta$ -blockers within 24 hours of admission and at discharge tended to be greater at non-GAP hospitals (16.6% vs 10.8% and 16.1% vs 5.6%, respectively), although these differences were not statistically significant. Notably, improvements were consistently greater when there was evidence for use of the GAP tools, and also tended to be greater among subgroups that typically exhibit greater disparities in guideline adherence, eg, racial minorities and elderly persons.

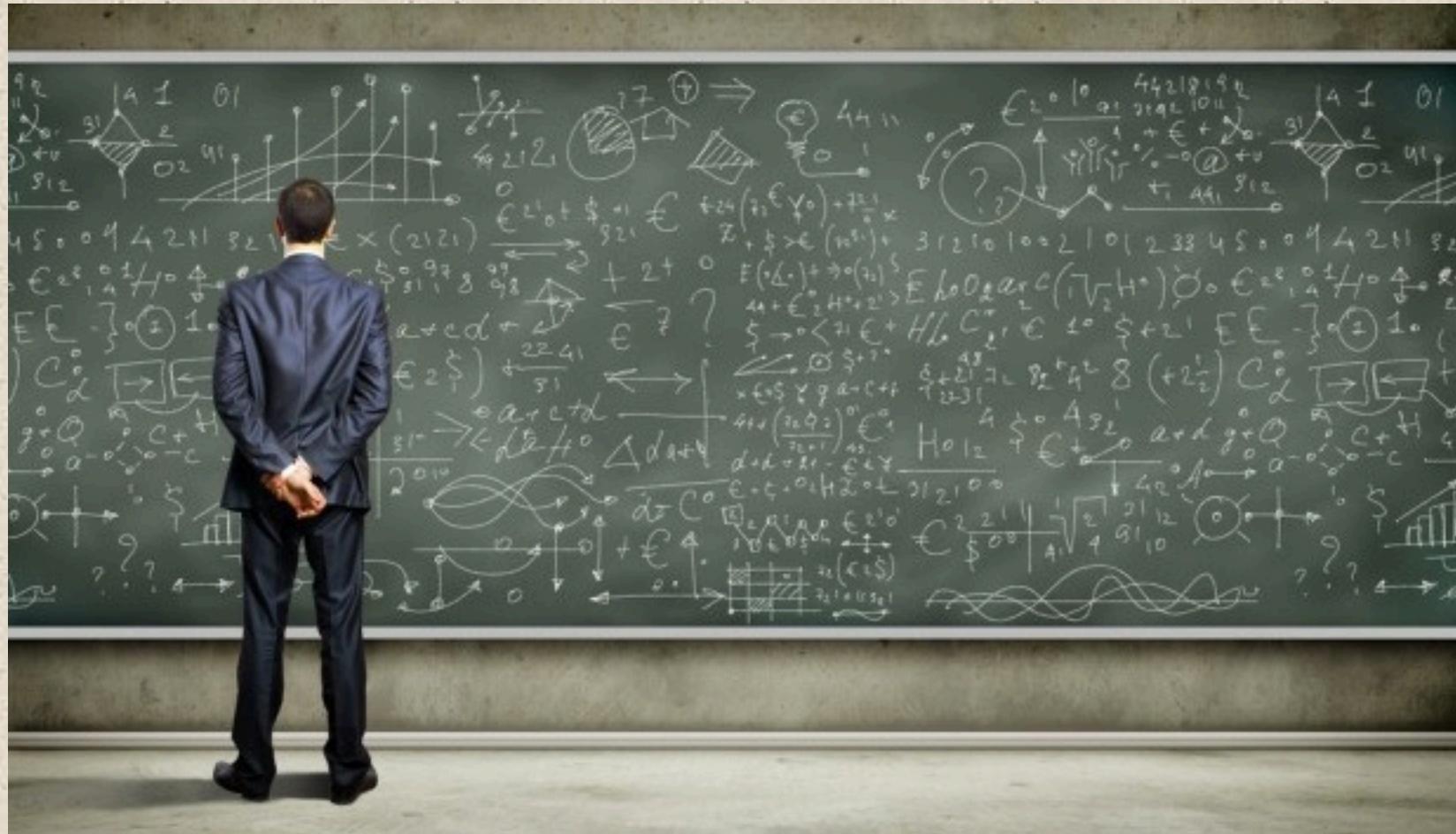
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See also p 1269.

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# Why the Resistance?





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

Nicolas Vuilleumier, Fabrizio Montecucco, Oliver Hartley

**In the United States, CVD prevalence in the general population is expected to reach 40%, with direct related costs set to reach 800 billion dollars per year in the next two decades.**

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

### Abstract

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

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

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

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





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

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

Supported by Swiss National Science Foundation Grants to Dr. Vuilleumier N No. 310030\_140736; and to Dr. Montecucco F No. 32003B\_134963/1; a grant from the Foundation "Gustave and Simone Prévot" to Dr. Montecucco F  
 Correspondence to: Dr. Nicolas Vuilleumier, MD, PD, Head of Laboratory Medicine Division, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland. [nicolas.vuilleumier@hcuge.ch](mailto:nicolas.vuilleumier@hcuge.ch)  
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porting the hypothesis that these autoantibodies may play a direct causal role in CVD, and furthermore that they could potentially represent a therapeutic target for CVD in the future.

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port every week, as well as time constraints and the overriding desire to avoid iatrogenic complications. Patient-related barriers include polypharmacy, time and financial constraints, and difficulties engaging in health-modifying behaviors such as smoking cessation, exercise participation, and dietary restriction. Health system-related barriers include the high number of uninsured and underinsured individuals, the lack of systematic approaches to the care of chronic illness,<sup>5</sup> and practical concerns about the high cost of health care, including the reality that few interventions actually reduce costs. The complexity of issues involved mandates a comprehensive and collaborative approach involving physicians and other health care professionals, patients and their families or other support systems, and the health care system itself, if the myriad barriers to implementing evidence-based care are to be overcome successfully.

In this issue of THE JOURNAL, Mehta and colleagues<sup>6</sup> describe just such an approach to improving care for acute myocardial infarction (AMI)—the Guidelines Applied in Practice (GAP) initiative in Southeast Michigan. The GAP

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Corresponding Author and Reprints: Michael W. Rich, MD, Cardiovascular Division, Washington University School of Medicine, 660 S Euclid Ave, Box 8086, St Louis, MO 63110 (e-mail: mrich@im.wustl.edu).

# How Many are Familiar with a Lipid Subfractionation and CV Risk Profile?

How Many Would Agree It is a Much More Sensitive Marker of CV Risk Than a Total Cholesterol and Chol/HDL Ratio?

How Many Use This Test in Their Practice?

How Many Have Had the Test Done on Themselves?



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## The answer is 17 years, what is the question: understanding time lags in translational research

J R Soc Med 2011 104: 510

Zoë Slote Morris<sup>1</sup> • Steven Wooding<sup>2</sup> • Jonathan Grant<sup>2</sup>

<sup>1</sup>Institute of Public Health, University of Cambridge, Cambridge CB2 0SR, UK

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DECLARATIONS

Summary

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RESEARCH

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Contributorship  
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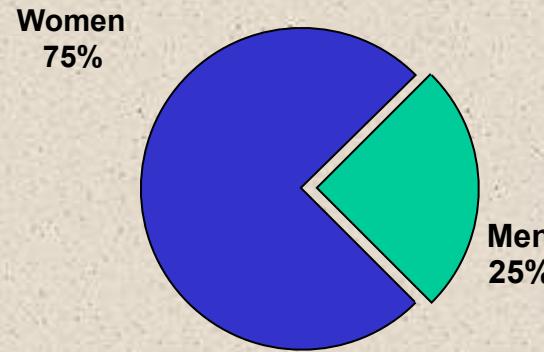
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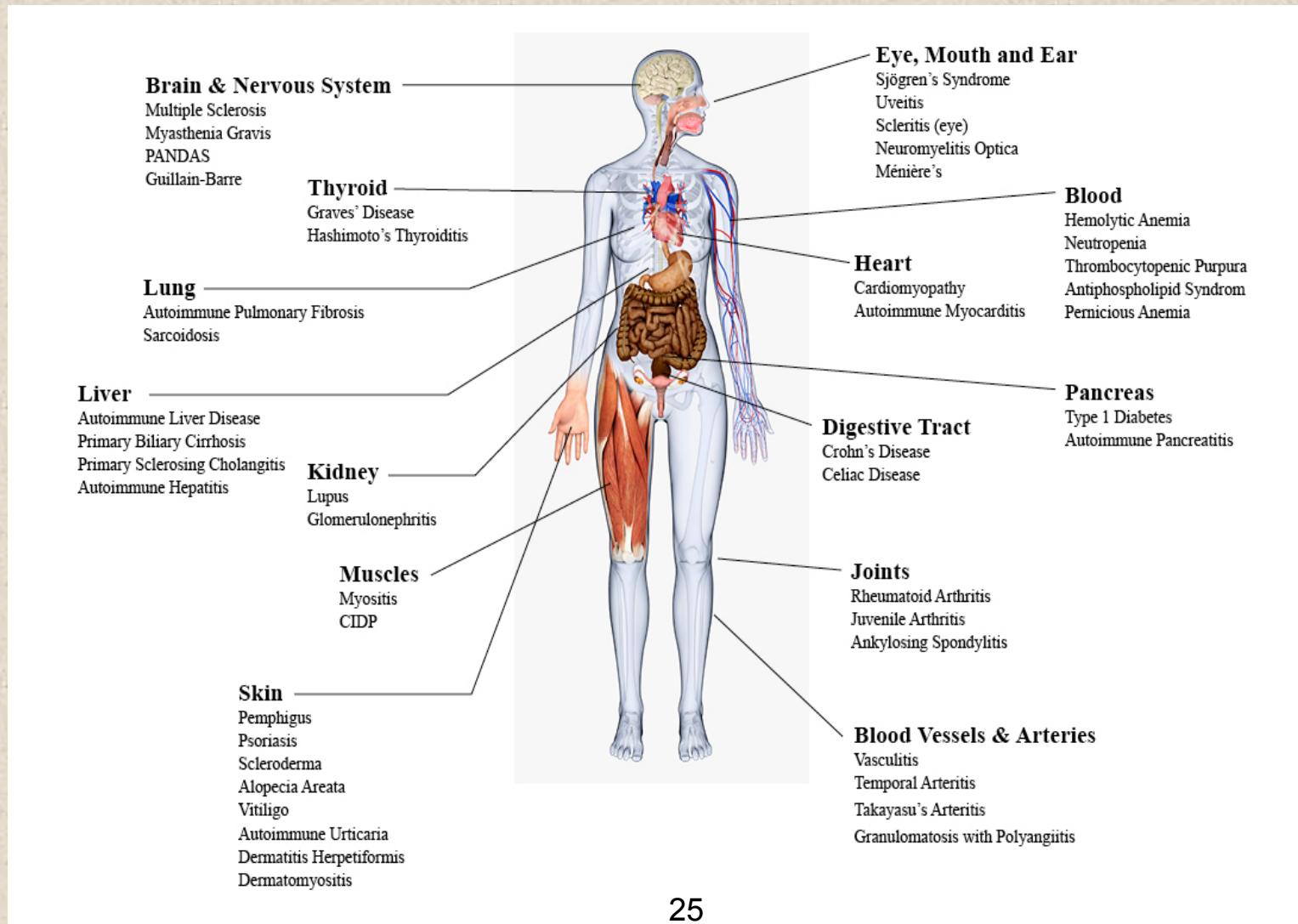
# Autoimmunity at a Glance

American Autoimmune Related Disease Association

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



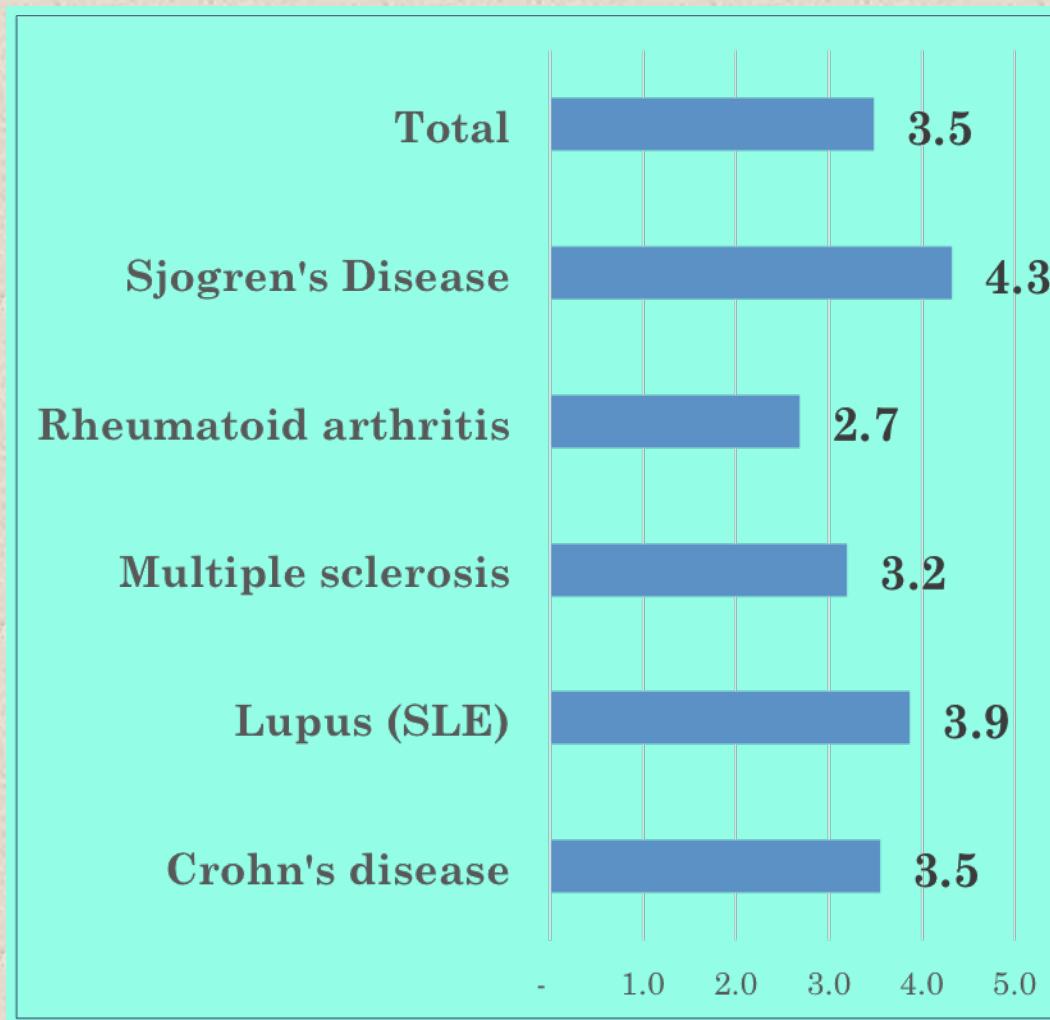
# Autoimmune disease can affect any part of the body



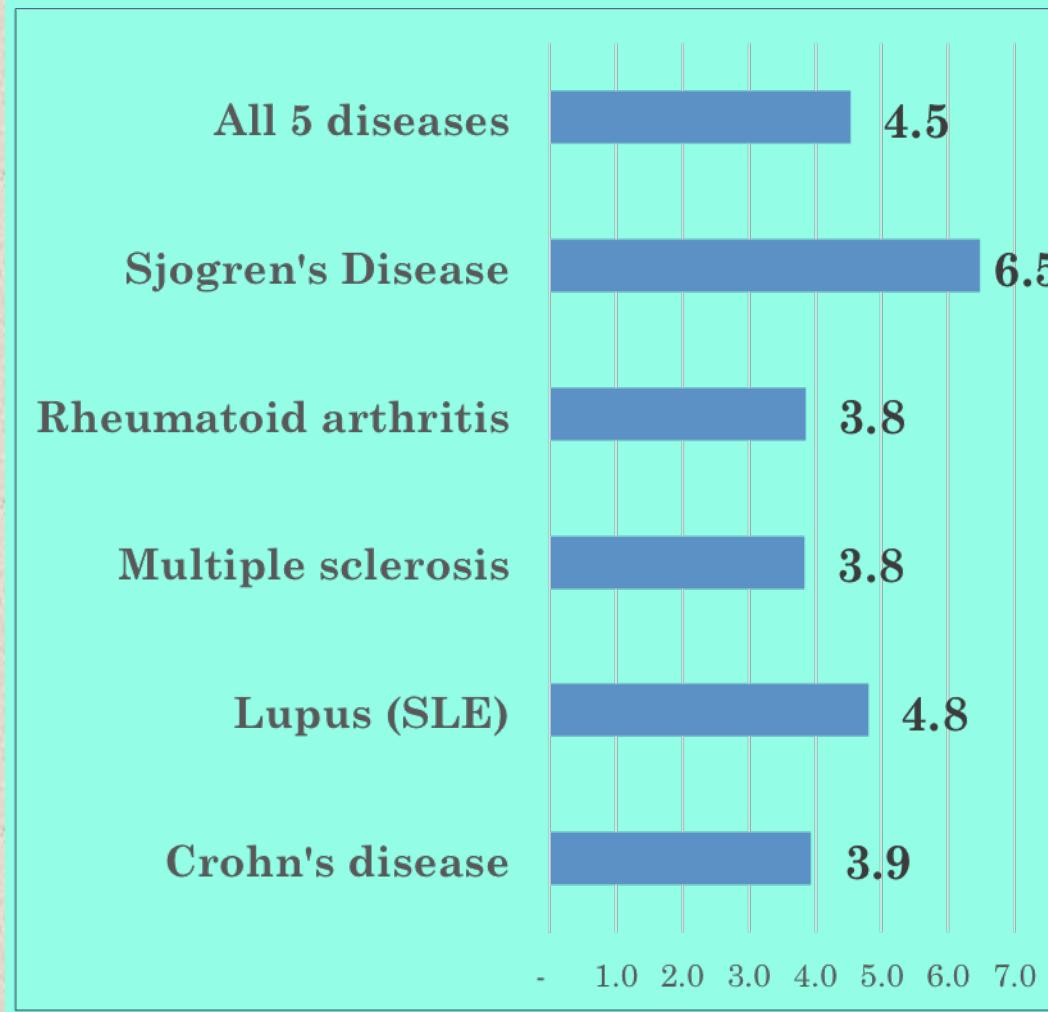
# AD Diagnosis Takes an Inordinate Amount of Time and Perseverance by the Patient

Survey Issues	1996	2001	2006	2013
Years to Diagnosis	5	4	4	4
No. Physicians Seen	6	4	4	5
Labeled Chronic Complainier	64%	45%	45%	51%

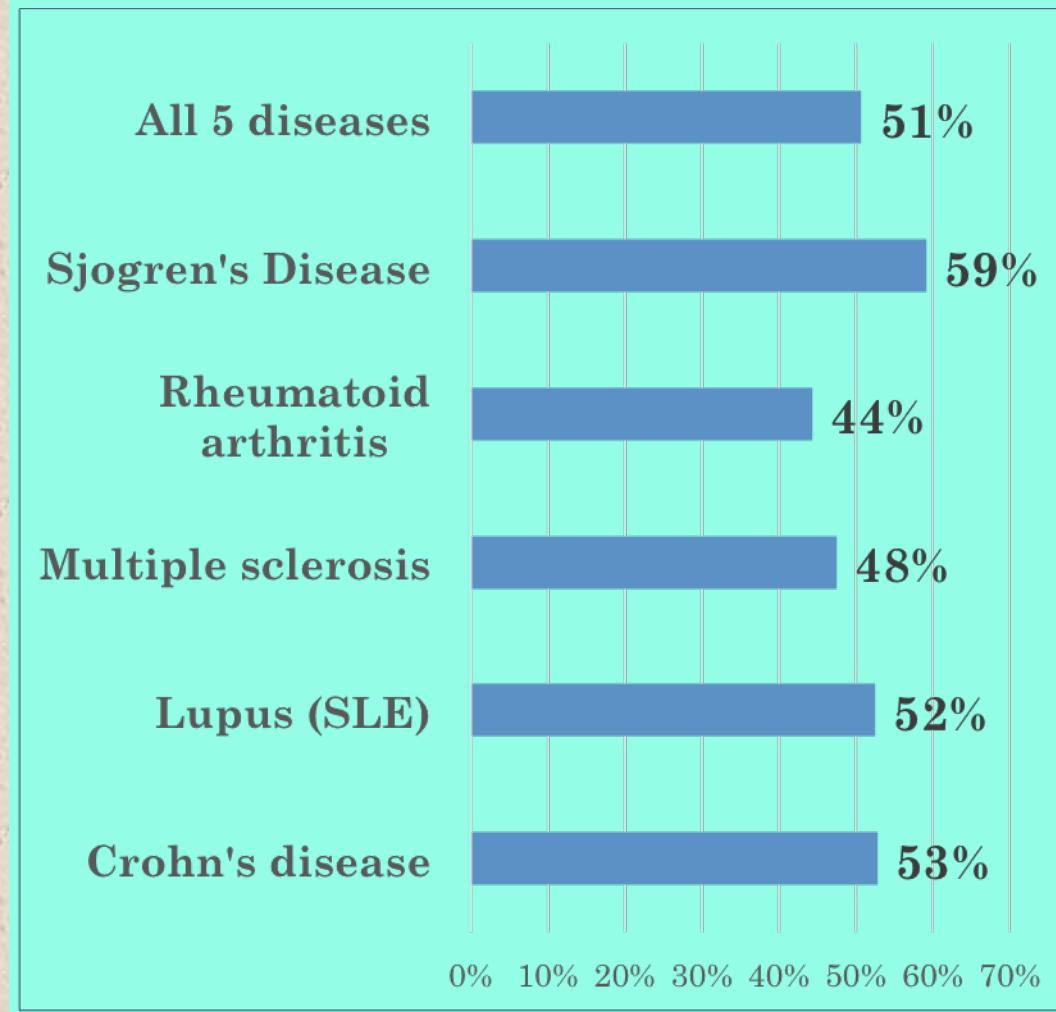
# Years to Diagnosis



# Number of Doctors Seen to get a Diagnosis



# Percent told their disease was imagined or they were overly concerned ...



# Why so Long and Difficult to Get a Correct Diagnosis?

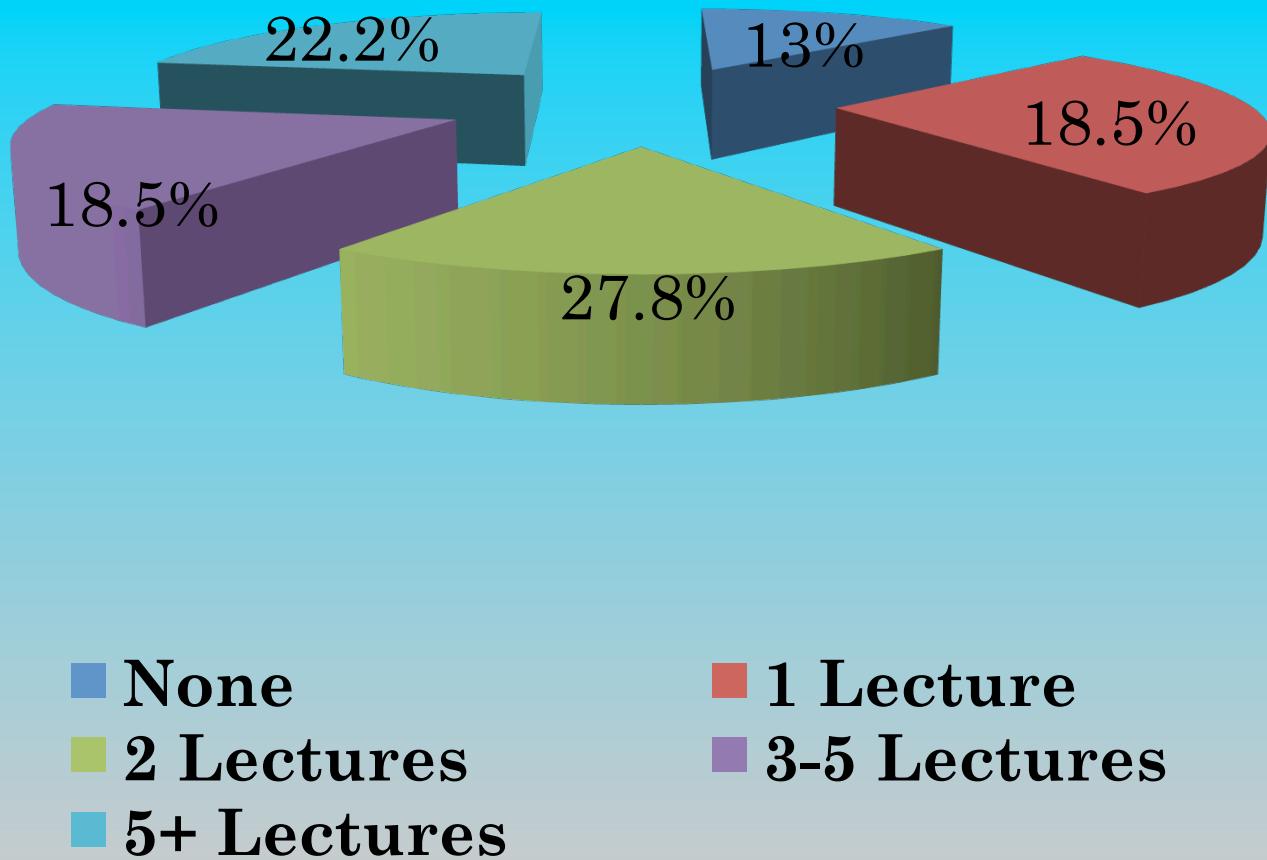
Physician Education was identified as a contributing factor.



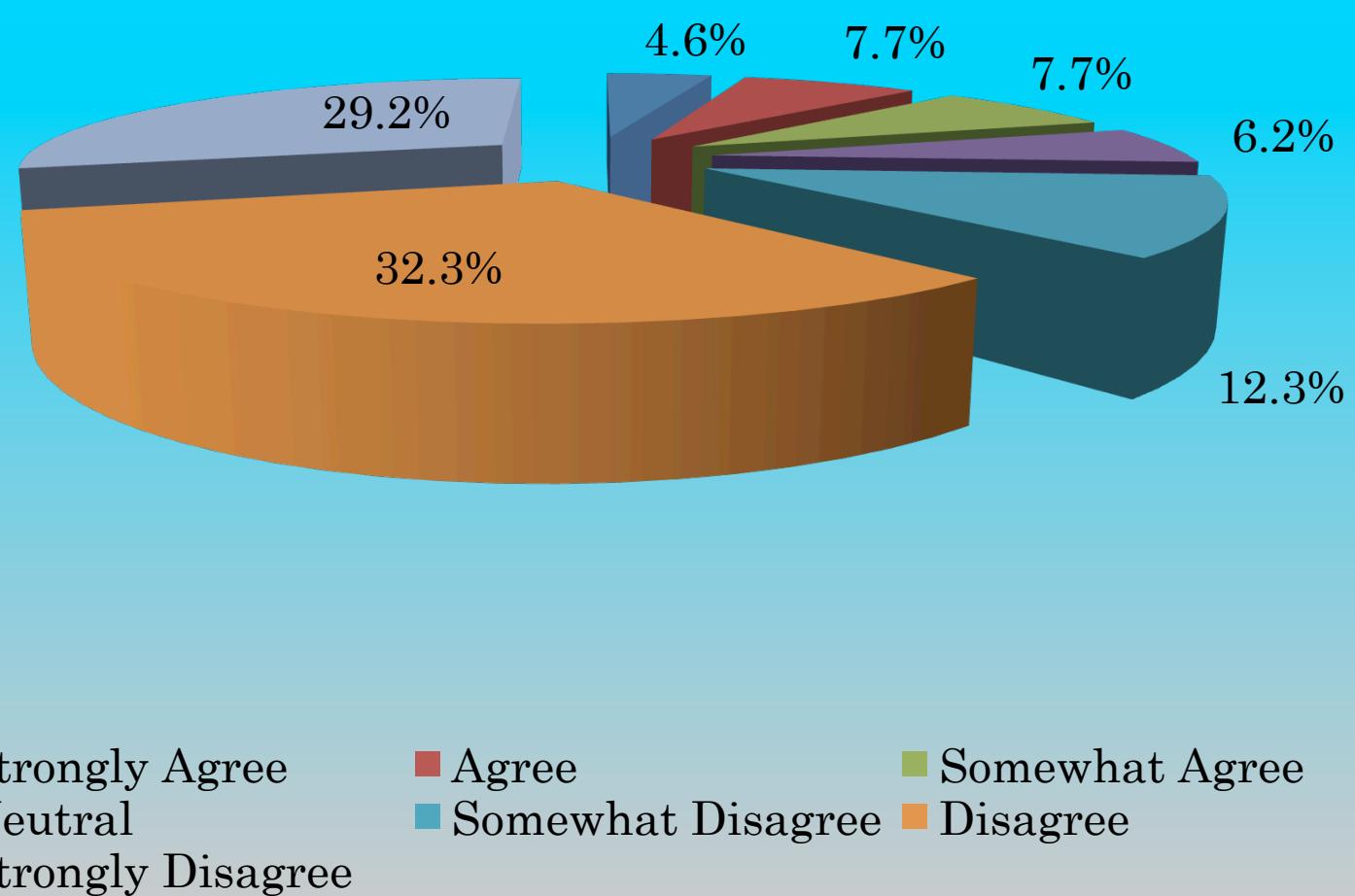
# AARDA Conducted a Survey of Physicians

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

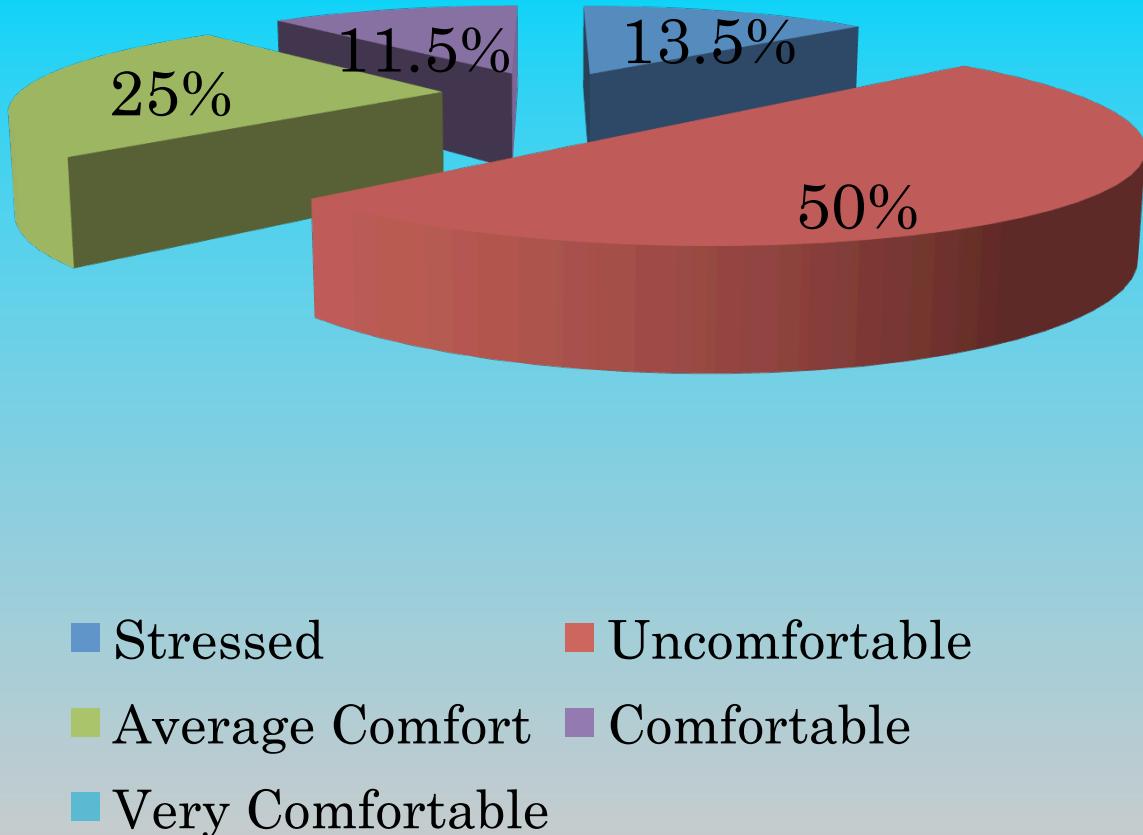
# IN MEDICAL SCHOOL, HOW MUCH TRAINING IN AUTOIMMUNE DISEASES DID YOU RECEIVE?



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



# What is your level of comfort in diagnosing autoimmune disease?





**It is unfair to expect our classically-trained Physicians to know of  
this platform and demand they change.**

# Premise #2

W

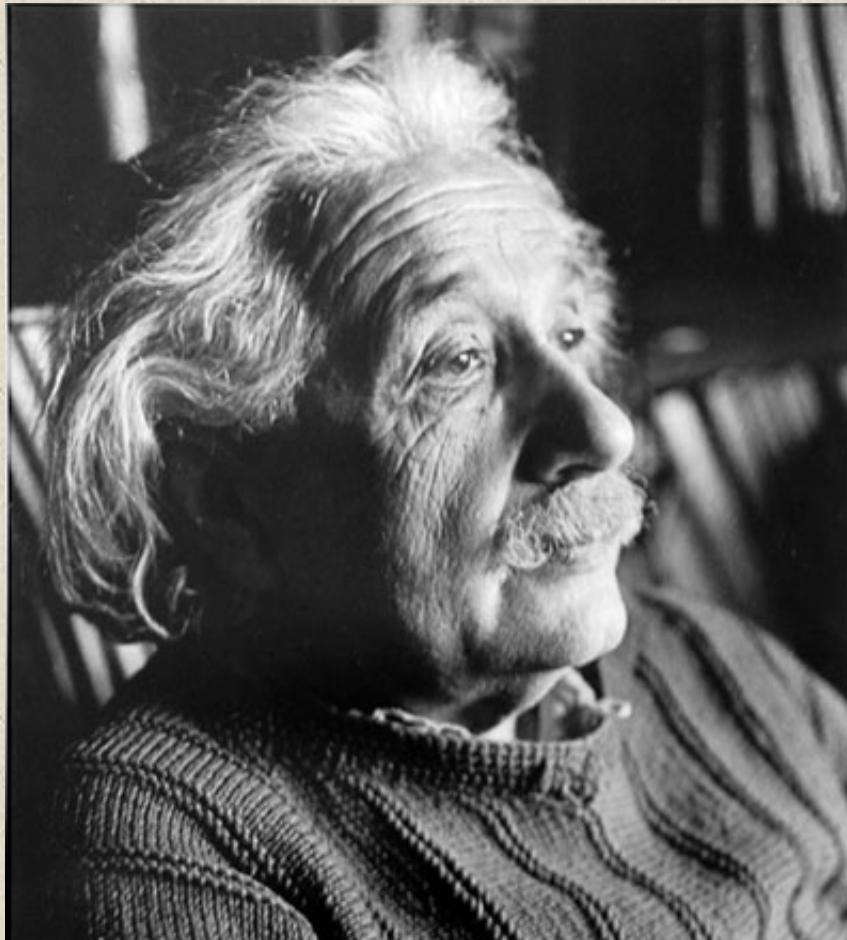
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Detective Adrian Monk

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*“The problems we have created today,  
can not be solved with the same level of thinking  
that created the problem”*





REPORT

INT  
2016

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Risk and resilience  
in a new era

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# 3748 species and 18296 populations

The Living Planet Index (LPI) is a measure of the state of global biological diversity based on population trends of vertebrate species from around the world. It does this in much the same way that a stock market index tracks the value of a set of shares or a retail price index tracks the cost of a basket of consumer goods.

# Report 2016

Risk and resilience  
in a new era

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**Of 14,152 populations of 3,706 species, there has been an average decline by 58% in abundance between 1970 and 2012.**

# Living Planet Report 2016

Risk and resilience  
in a new era

INT

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**Trends differ in the different systems, with**

- terrestrial systems declining by 38%,**
- marine systems declining by 36% and**
- freshwater being reduced by more than 75% of their abundance in 1970.**

# Report 2016

**Risk and resilience  
in a new era**

[www.LivingPlanetIndex.org](http://www.LivingPlanetIndex.org)

# Premise #3

## Where does Autoimmunity Initiate



Detective Adrian Monk

**REVIEW**

[www.nature.com/clinicalpractice/gasthep](http://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

**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 to nonself-antigens. When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur. This new paradigm subserves

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

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.<sup>1</sup>

**CLASSICAL THEORIES ON THE**

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

"autoimmunity", "tight junctions", "toll", "innate immunity", "occludin", "claudin", "claudins", and "intestinal AND disease AND permeability". Only full papers published in English were considered. Additional searches were performed using Retro Search and Google.

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[www.nature.com/clinicalpractice](http://www.nature.com/clinicalpractice)  
 doi:10.1038/ncpgasthep0259

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.<sup>3</sup> 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.<sup>3</sup>

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

**REVIEW**

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

**the use of probiotics.**

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

**REVIEW CRITERIA**

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

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specifically, epitopes) are postulated to resemble self-antigens.<sup>2</sup> 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.<sup>3</sup> 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.<sup>3</sup>

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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<sup>1</sup>, N Cerf-Bensussan<sup>1</sup> and M Heyman<sup>1</sup>

# Increased intestinal permeability is an early biological change that often precedes the onset of autoimmune diseases.

functional aspects of intestinal permeability with special emphasis on antigen handling in healthy and diseased states and consequences on local immune responses to food antigens.

#### INTRODUCTION

The intestinal epithelium forms a selective barrier, which favors fluxes of nutrients, regulates ion and water movements, and limits host contact with the massive intraluminal load of dietary antigens and microbes. However, this barrier is not fully impermeable to macromolecules; in the steady state, the transepithelial passage of small amounts of food-derived antigens and microorganisms participates in the induction of a homeostatic immune response dominated by immune tolerance to dietary antigens<sup>1,2</sup> and the local production of secretory immunoglobulin A (SIgA),<sup>3</sup> 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.<sup>4</sup> 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.

Herein, we will discuss the multiple pathways involved in the intestinal transport of luminal food antigens and analyze the contribution of the paracellular and transcellular pathways.

#### DIETARY ANTIGENS ARE AVAILABLE FOR INTESTINAL TRANSPORT

Although the majority of dietary proteins are totally degraded 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,<sup>5</sup> meaning that large immunogenic peptides or intact proteins are capable of reaching the small intestinal lumen.<sup>6</sup> For example,  $\beta$ -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<sup>7,8</sup> able to activate the lamina propria CD4<sup>+</sup> 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.<sup>9</sup> Despite this

<sup>1</sup>INSERM, U989, Interactions of the intestinal epithelium with the immune system, Université Paris Descartes, Paris, Cedex 15, France. Correspondence: M Heyman (martine.heymann@inserm.fr)

Received 15 December 2009; accepted 28 January 2010; published online 10 March 2010. doi:10.1038/mi.2010.5

See REVIEW page 213  
 See COMMENTARY page

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**Such increased permeability could be due to environmental factors (such as infection, toxic molecules, allergenic foods) that possibly initiate the (autoimmune) disease.**

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ORIGINAL ARTICLE

Development of Autoantibodies before the  
Clinical Onset of Systemic Lupus  
Erythematosus

NEJM:2003;349:1526-1533

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

ABSTRACT

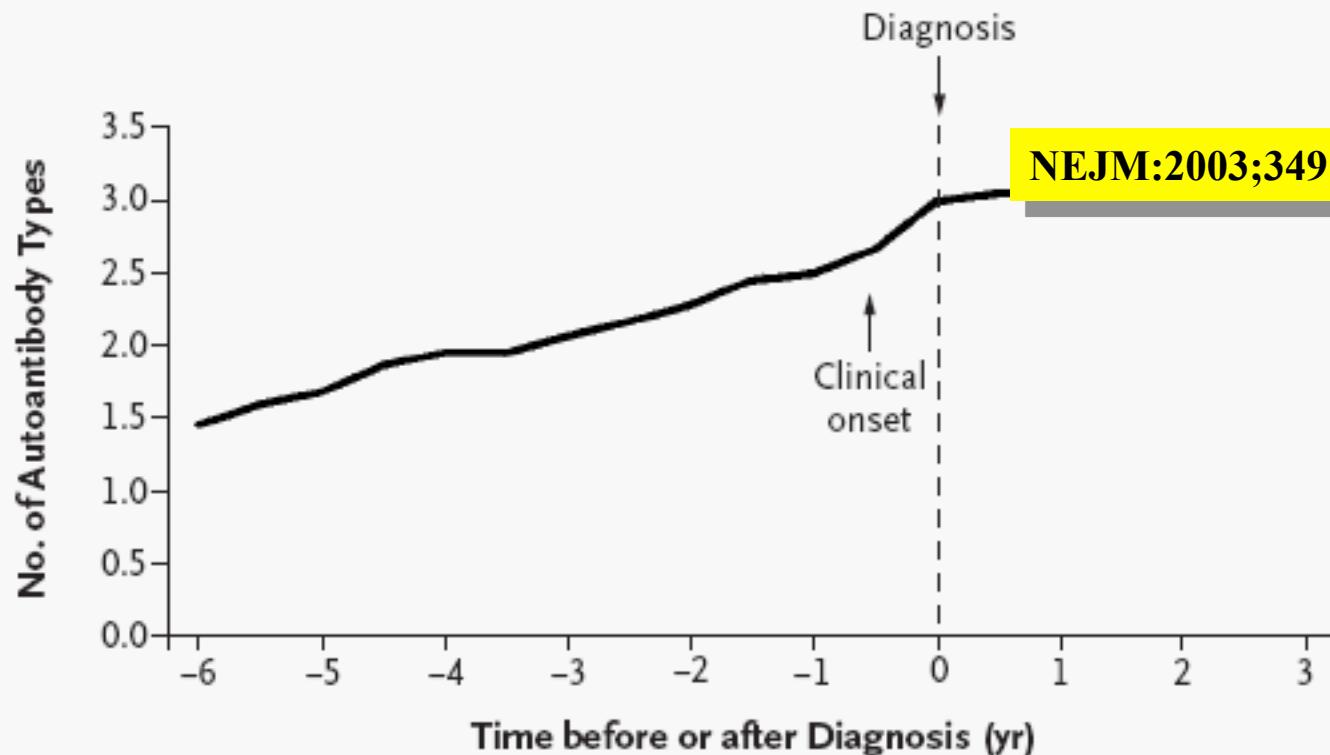
BACKGROUND

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

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

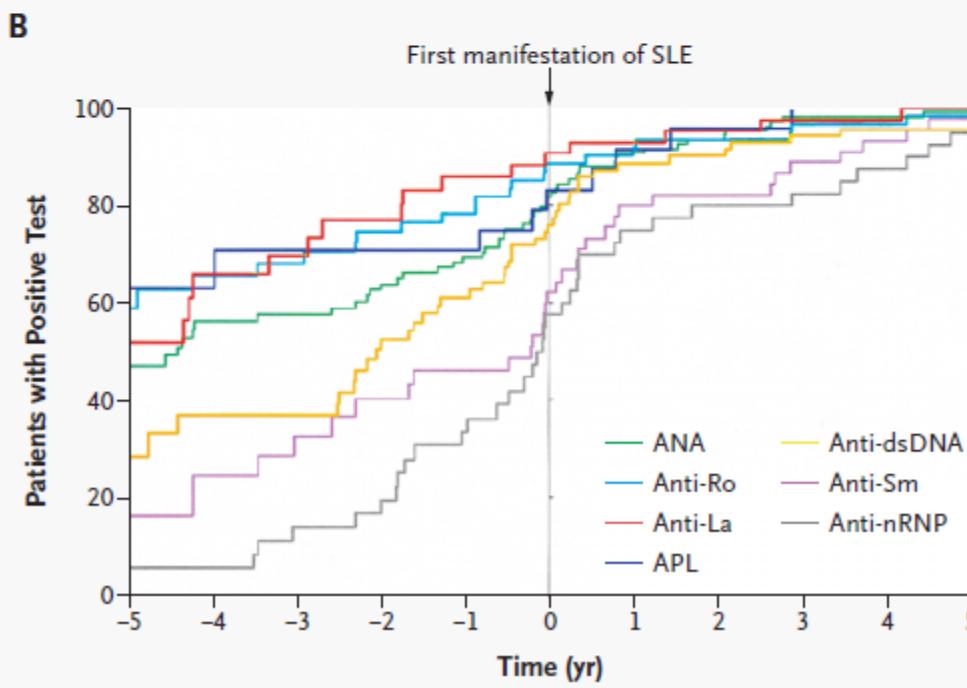
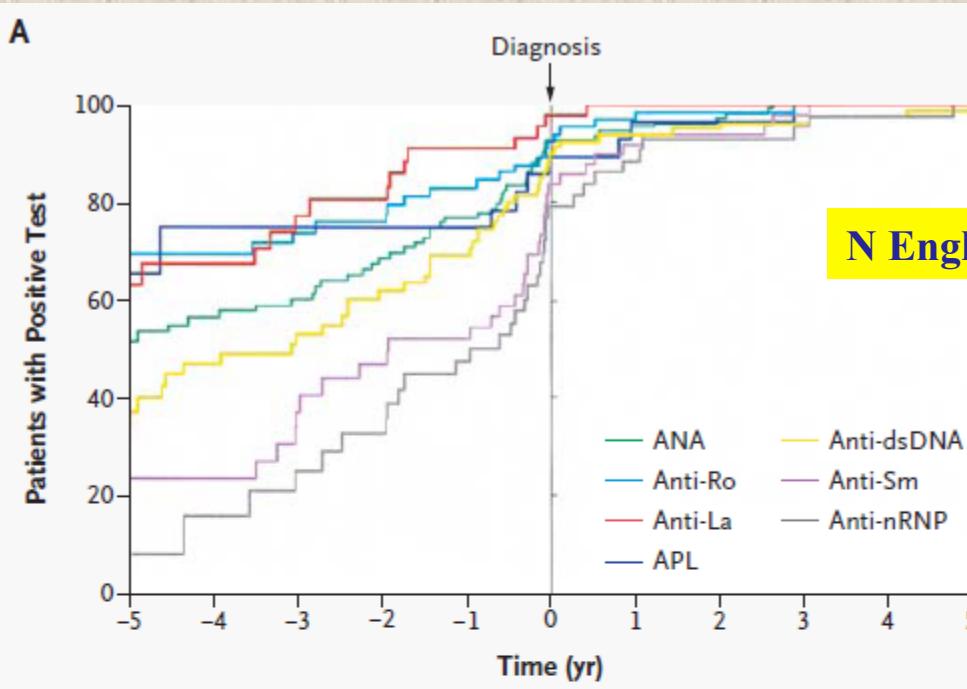
CONCLUSIONS

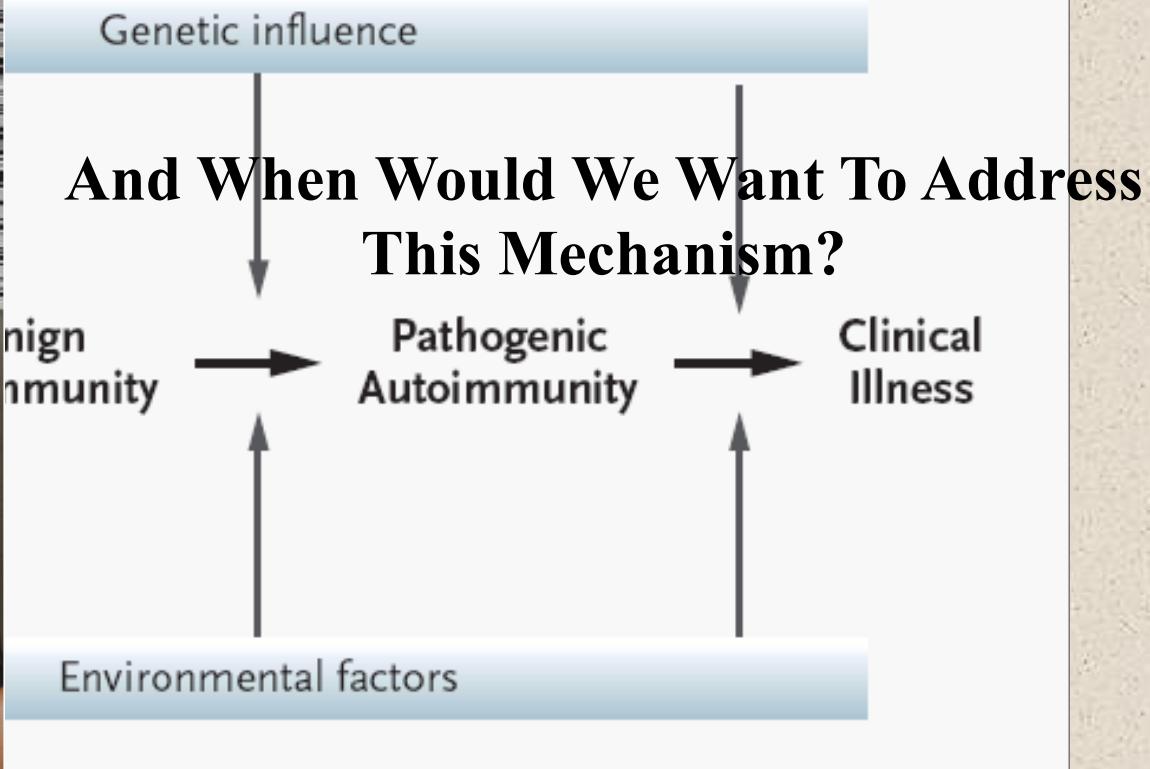
Autoantibodies are typically present many years before the diagnosis of SLE. Furthermore, the appearance of autoantibodies in patients with SLE tends to follow a predictable course, with a progressive accumulation of specific autoantibodies before the onset of SLE, while patients are still asymptomatic.



**Figure 2. Accumulation of Systemic Lupus Erythematosus Autoantibodies.**

The curve shows the average number of types of autoantibody in relation to the time of diagnosis of systemic lupus erythematosus. Seven autoantibodies were evaluated, which bind cellular constituents (antinuclear antibodies), Ro, La, double-stranded DNA, Sm, phospholipid, and nuclear ribonucleoprotein. The time of diagnosis and the median time of the first appearance of any clinical criterion useful for the classification of systemic lupus erythematosus (clinical onset) are indicated by arrows.





**Figure 3. Phases in the Development of Pathogenic Autoimmunity.**

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

## Premise #4

**What are the Offensive Things Passing  
Through a Permeable Intestine?**



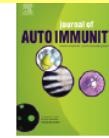
Detective Adrian Monk



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## Antigenic challenge in the etiology of autoimmune disease in women

Mary A.M. Rogers <sup>a,\*</sup>, Deborah A. Levine <sup>a</sup>, Neil Blumberg <sup>b</sup>, Gwenith G. Fisher <sup>c</sup>,  
Mohammed Kabeto <sup>a</sup>, Kenneth M. Langa <sup>a,c,d,e</sup>

<sup>a</sup>Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

<sup>b</sup>Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA

<sup>c</sup>Institute for Social Research, University of Michigan, Ann Arbor, MI, USA

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**The risk of autoimmune disease increased by 41% with a prior infection-related medical visit.  
The risk of autoimmune disease increased by 90% with a prior transfusion without infection.**

### 1. Introduction

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

Infectious agents have been hypothesized as triggers of autoimmune disease through molecular mimicry, alterations in self-antigens, immune cell activation or infection-mediated inflammation [4–6]. Conversely, some investigators have argued for the "hygiene hypothesis" which suggests that increases in autoimmune diseases over time are correlated with decreases in the incidence of

infection, particularly during childhood [7–9]. Unfortunately, there have been few population-based studies to substantiate or refute these hypotheses.

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

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

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

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## Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis

# Endocrine disrupting chemicals contribute substantially to certain forms of disease and disability.

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## Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis

There is substantial evidence recently summarized by the Endocrine Society, for effects of a host of EDCs, including bisphenol A (BPA), phthalates, pesticides, and persistent organic pollutants (POPs) on the developing ovary and reproductive tract.

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# Autoimmune host–microbiota interactions at barrier sites and beyond

**Environmental triggers of autoimmunity may thus enhance commensal-mediated inflammatory processes and thereby influence autoimmunity.**

influencing the pathogenesis of autoimmunity at both barrier sites and internal organs. Impinging on innate and adaptive immunity, commensals exert protective or detrimental effects on various autoimmune animal models. Human microbiome studies of autoimmunity remain largely descriptive, but suggest a role for dysbiosis in autoimmune disease. Humanized gnotobiotic approaches have advanced our understanding of immune–commensal interactions, but little is known about the mechanisms in autoimmunity. We propose that, similarly to infectious agents, the microbiota mediates autoimmunity via bystander activation, epitope spread, and, particularly under homeostatic conditions, via crossreactivity. This review presents an overview of the current literature concluding with outstanding questions in this field.

Host–microbe interactions: from Pasteur to present

influences the metabolism of drugs, neurological function, immune development and homeostasis, and various chronic diseases of modern societies [3]. Commensals exert profound effects on the development and function of the immune system and therefore likely influence immune-mediated diseases [4]. Indeed, gut bacteria prevent, exacerbate, or induce numerous autoimmune, allergic, or inflammatory diseases and malignancies in animal models [5–26]. A causal role for multifactorial autoimmune diseases in humans is still outstanding, but such a role has been demonstrated in murine models of multiple sclerosis (MS) [7–9], rheumatoid arthritis (RA) [11–13], and type 1 diabetes (T1D) [14–18], and is likely to extend to systemic

## Glossary

***Bacteroides fragilis*:** *B. fragilis* is a Gram-negative, human gut commensal with unique immunoregulatory functions. Strains containing polysaccharide A (PSA) induce gut T<sub>reg</sub> and splenic T<sub>H</sub>1 cell responses. Other strains contain

# Autoimmune host–microbiota interactions at barrier sites and beyond

**However, independently of environmental factors, the gut microbiota is emerging as a key player in the development of autoimmunity.**

**influencing the pathogenesis of autoimmunity at both barrier sites and internal organs. Impinging on innate and adaptive immunity, commensals exert protective or detrimental effects on various autoimmune animal models. Human microbiome studies of autoimmunity remain largely descriptive, but suggest a role for dysbiosis in autoimmune disease. Humanized gnotobiotic approaches have advanced our understanding of immune–commensal interactions, but little is known about the mechanisms in autoimmunity. We propose that, similarly to infectious agents, the microbiota mediates autoimmunity via bystander activation, epitope spread, and, particularly under homeostatic conditions, via crossreactivity. This review presents an overview of the current literature concluding with outstanding questions in this field.**

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## Glossary

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CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

**Helicobacter pylori (H. pylori) infection is present in around 50% of the world's population and has been associated with a variety of immune-mediated extra-digestive disorders including autoimmune thyroiditis, idiopathic thrombocytopenic purpura, and psoriasis.**

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Campuzano-Maya G. Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association? *World J Gastroenterol* 2011; 17(26): 3165-3170 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i26/3165.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i26.3165>

### Abstract

Alopecia areata is a disease of the hair follicles with

## Epidemiology of *Helicobacter pylori* infection among the healthy population in Iran and countries of the Eastern Mediterranean Region: A systematic review of prevalence and risk factors

**It has been estimated that more than 50% of the population aged 5 years is infected and this rate may exceed 90% during adulthood.**

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Kingdom of Saudi Arabia, 4 studies from Egypt, 2 from the United Arab Emirates, and one study from Libya, Oman, Tunisia, and Lebanon, respectively. The overall prevalence of *H. pylori* infection in Iran, irrespective of time and age group, ranged from 30.6% to 82%. The overall prevalence of *H. pylori* infection, irrespective of time and age group, in other EMRO countries ranged from 22% to 87.6%.

**CONCLUSION:** The prevalence of *H. pylori* in EMRO countries is still high in the healthy asymptomatic population. Strategies to improve sanitary facilities, educational status, and socioeconomic status should be

# Case Study #1

## Alopecia Areata Secondary to Molecular Mimicry



## CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

### A 43-year-old man presented with an 8-mo history of patchy hair loss in the scalp and beard (Figure 1A-C).

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Author contributions: Campuzano-Maya G wrote this paper.

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lecular mimicry; Eradication treatment

**Peer reviewers:** Eivind J Paulssen, MD, PhD, Department of Gastroenterology, University Hospital of North Norway, PO Box 83, Tromsø, N-9038, Norway; Zeinab Nabil Ahmed, Professor of Microbiology, Microbiology and Immunology Department, Faculty of Medicine (for girls), Al-Azhar University, Nasr City, 1047, Cairo, Egypt

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#### Abstract

Alopecia areata is a disease of the hair follicles with



**Figure 1 Photographic sequence of lesions before and after *Helicobacter pylori* eradication. A-C: Alopecia areata of the scalp (A and B) and beard (C) at baseline visit (week 0)**

CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

**He had consulted a dermatologist who prescribed 0.25% desoximetasone and 5% minoxidil, according to the guidelines for the management of alopecia, and had psychiatric support with escitalopram 5 mg/d, without any response other than progression of the condition.**

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CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

The patient had a history of dyspepsia, therefore, he underwent analysis to determine *H. pylori* status.

- Urea breath test (6.95; negative < 1), and
- *H. pylori* IgG antibodies (52.4; negative < 9) were positive.

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CASE REPORT

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The patient was prescribed first line *H. pylori* eradication with proton pump inhibitor (omeprazole) 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily for 14 d, according to recommendations from the Maastricht III Consensus Report, and was followed photographically every 2 wk.

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## CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

**He was instructed not to take or apply any medications for alopecia areata. *H. pylori* eradication was confirmed 6 wk after treatment with a negative result (on retest) (0.81, negative < 1).**

**Author contributions:** Campuzano-Maya G wrote this paper.

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**Figure 1 Photographic sequence of lesions before and after *Helicobacter pylori* eradication. A-C: Alopecia areata of the scalp (A and B) and beard (C) at baseline visit (week 0)**

A



B



C



D



E



F



**Figure 1 D-F: Evidence of hair regrowth at week 4**

**G**



**H**



**I**

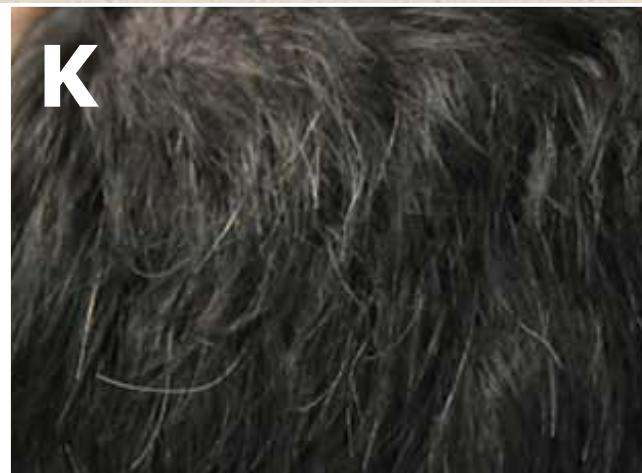


**Figure 1 G-I: Hair re- growth at week 8.**

J



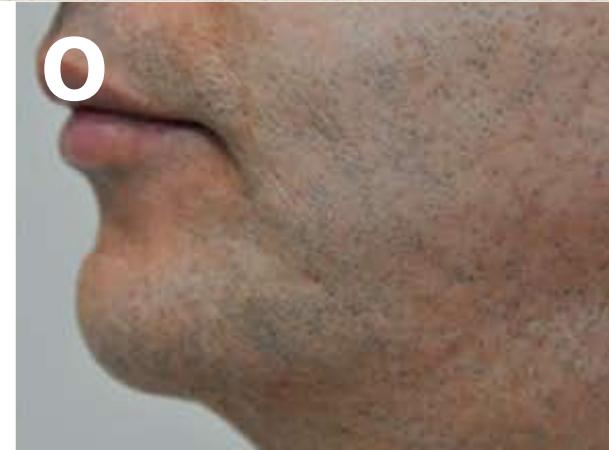
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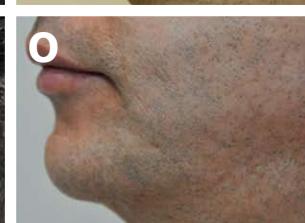
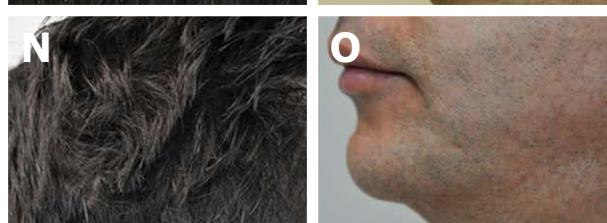
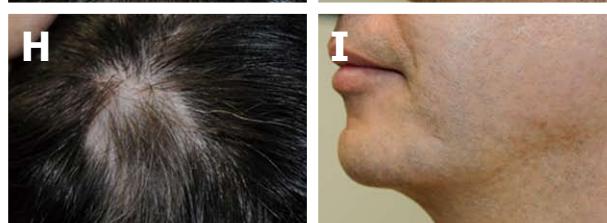
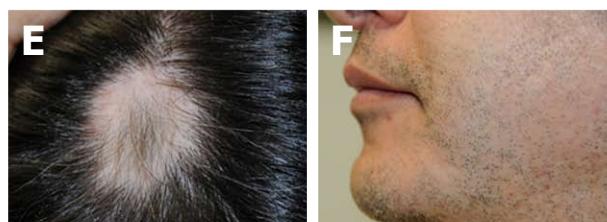
L



**Figure 1 J-L: Hair regrowth at week 16**



**Figure 1 M-O: Hair regrowth at week 44**



**Figure 1 Photographic sequence of lesions before and after *Helicobacter pylori* eradication.** A-C: Alopecia areata of the scalp (A and B) and beard (C) at baseline visit (week 0) before *Helicobacter pylori* (*H. pylori*) eradication. Positive  $^{13}\text{C}$ -UBT ( $6.95 \delta^{13}\text{CO}_2$ ); D-F: Evidence of hair regrowth at week 4; G-I: Hair regrowth at week 8. Negative  $^{13}\text{C}$ -UBT ( $0.81 \delta^{13}\text{CO}_2$ ); J-L: Hair regrowth at week 16;

CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

***H. pylori* infection has been associated with numerous immune and non-immune disorders including dermatological conditions, such as chronic urticaria, rosacea, psoriasis, Schönlein-Henoch purpura, Behçet's disease, prurigo nodularis, chronic cutaneous pruritus, progressive systemic sclerosis, Sjögren's syndrome, and Sweet's syndrome; many of them improving or going into remission after eradication of *H. pylori* infection.**

2011, 17(26): 3165-3170 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i26/3165.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i26.3165>

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CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

**antibodies developed against *H. pylori* cross-react with autoantigens to cause tissue damage, as has been reported in atrophic gastritis, chronic gastritis, chronic idiopathic thrombocytopenic purpura, Hashimoto's thyroiditis, ....**

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...atherosclerosis, arterial hypertension, unstable angina pectoris, ischemic heart disease, Alzheimer's disease, systemic sclerosis, central serous chorioretinopathy, iron deficiency, autoimmune pancreatitis, and chronic urticaria.

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Alopecia areata is a disease of the hair follicles with

CASE REPORT

## Cure of alopecia areata after eradication of *Helicobacter pylori*: A new association?

Alopecia areata has been associated with other autoimmune disorders including thyroid disease, psoriasis, and celiac disease; conditions that have also been associated with *H. pylori* infection.

**Author contributions:** Campuzano-Maya G wrote this paper.

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### Abstract

Alopecia areata is a disease of the hair follicles with

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<sup>1</sup>, N Cerf-Bensussan<sup>1</sup> and M Heyman<sup>1</sup>

The intestinal epithelium, the largest interface between the host and environment, regulates fluxes of ions and nutrients and limits host contact with the massive load of luminal antigens. Local protective and tolerogenic immune responses toward luminal content depend on antigen sampling by the gut epithelial layer. Whether, and how exaggerated, the

**Increased intestinal permeability is an early biological change that often precedes the onset of autoimmune diseases.**

### INTRODUCTION

The intestinal epithelium forms a selective barrier, which favors fluxes of nutrients, regulates ion and water movements, and limits host contact with the massive intraluminal load of dietary antigens and microbes. However, this barrier is not fully impermeable to macromolecules; in the steady state, the transepithelial passage of small amounts of food-derived antigens and microorganisms participates in the induction of a homeostatic immune response dominated by immune tolerance to dietary antigens<sup>1,2</sup> and the local production of secretory immunoglobulin A (SIgA),<sup>3</sup> 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.<sup>4</sup> 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.

Herein, we will discuss the multiple pathways involved in the intestinal transport of luminal food antigens and analyze the contribution of the paracellular and transcellular pathways.

### DIETARY ANTIGENS ARE AVAILABLE FOR INTESTINAL TRANSPORT

Although the majority of dietary proteins are totally degraded 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,<sup>5</sup> meaning that large immunogenic peptides or intact proteins are capable of reaching the small intestinal lumen.<sup>6</sup> 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<sup>7,8</sup> able to activate the lamina propria CD4<sup>+</sup> 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.<sup>9</sup> Despite this

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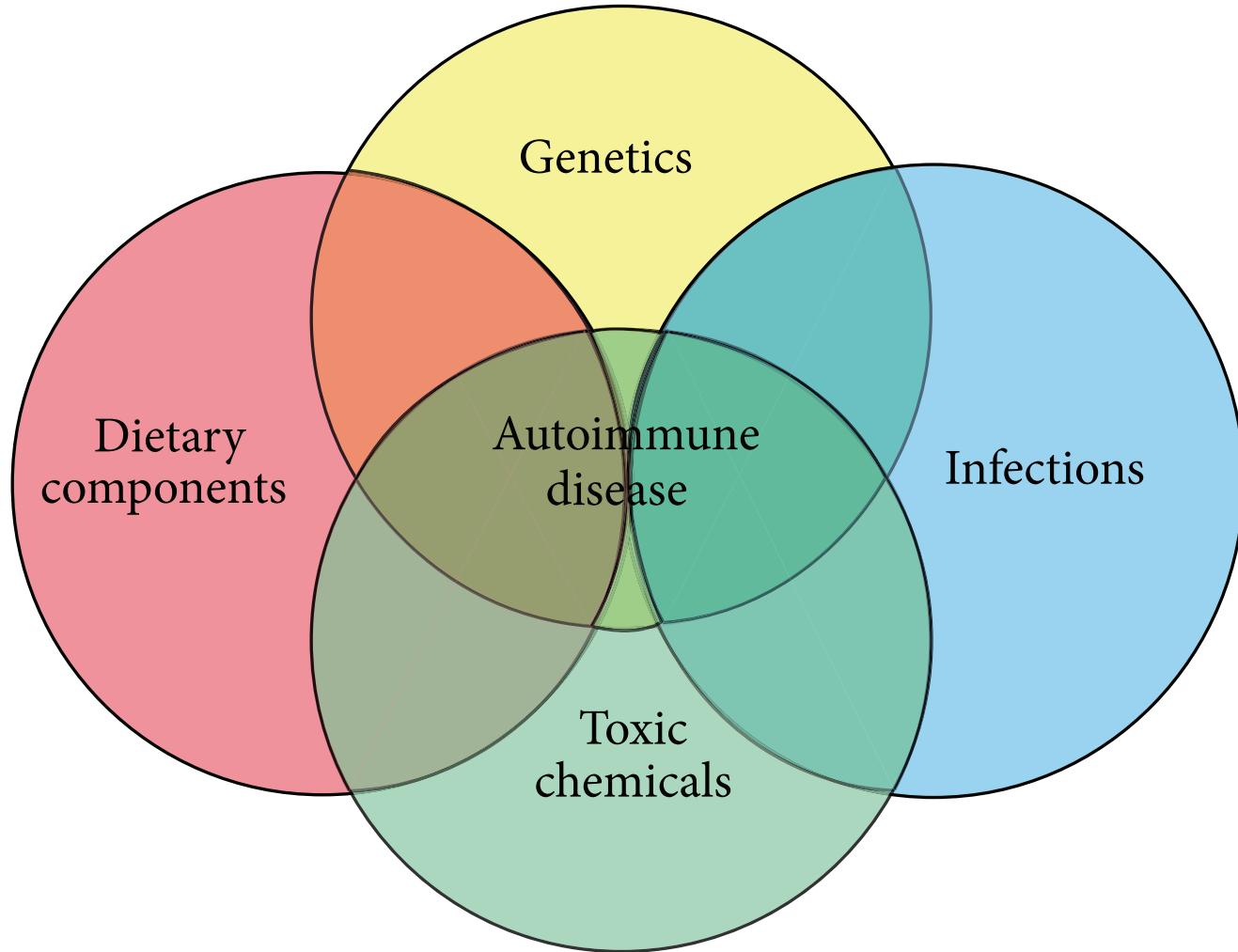
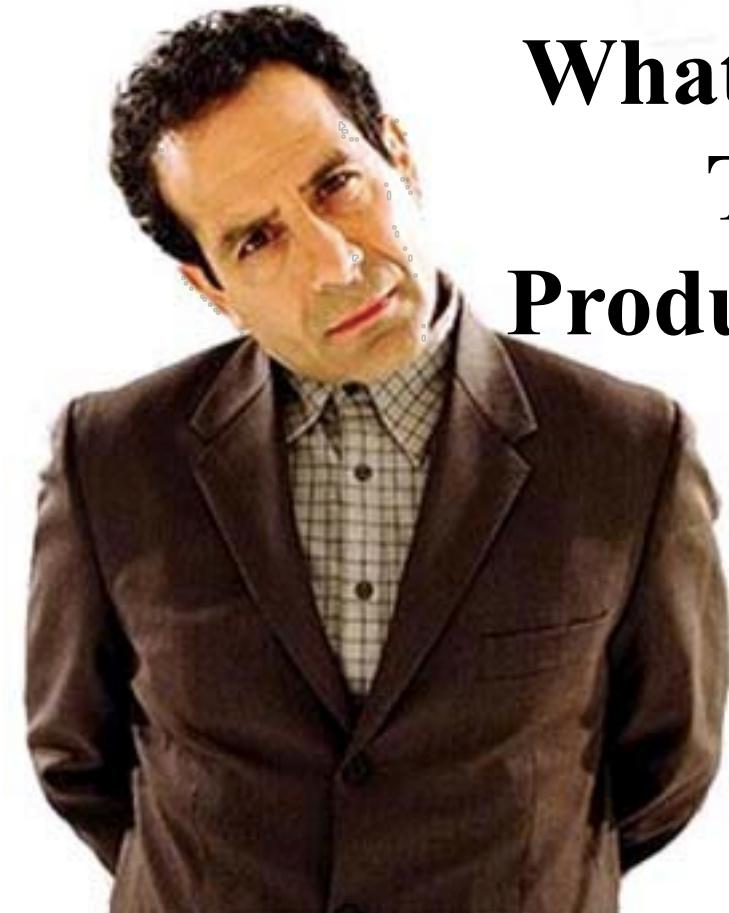


FIGURE 1: Factors that contribute to autoimmune disease.

## Premise #5

What is the One Identifiable and  
Treatable Trigger in the  
Production of Antibodies To Self?



Detective Adrian Monk  
© www.theDr.com

**REVIEW**

[www.nature.com/clinicalpractice/gasthep](http://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

**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 to nonself-antigens. When the finely tuned trafficking of macromolecules

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

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.<sup>1</sup>

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

the use of probiotics.

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

**REVIEW CRITERIA**

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

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

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[www.nature.com/clinicalpractice](http://www.nature.com/clinicalpractice)  
doi:10.1038/ncpgasthep0259

(specifically, epitopes) are postulated to resemble self-antigens.<sup>2</sup> 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.<sup>3</sup> 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.<sup>3</sup>

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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**REVIEW**

[www.nature.com/clinicalpractice/gasthep](http://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

**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 to nonself-antigens. When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur. This neuroepidemiologic evidence

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

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.<sup>1</sup>

**CLASSICAL THEORIES ON THE**

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

"autoimmunity", "tight junctions", "toll", "innate immunity", "occludin", "claudin", "claudins", and "intestinal AND disease AND permeability". Only full papers published in English were considered. Additional searches were performed using Retro Search and Google.

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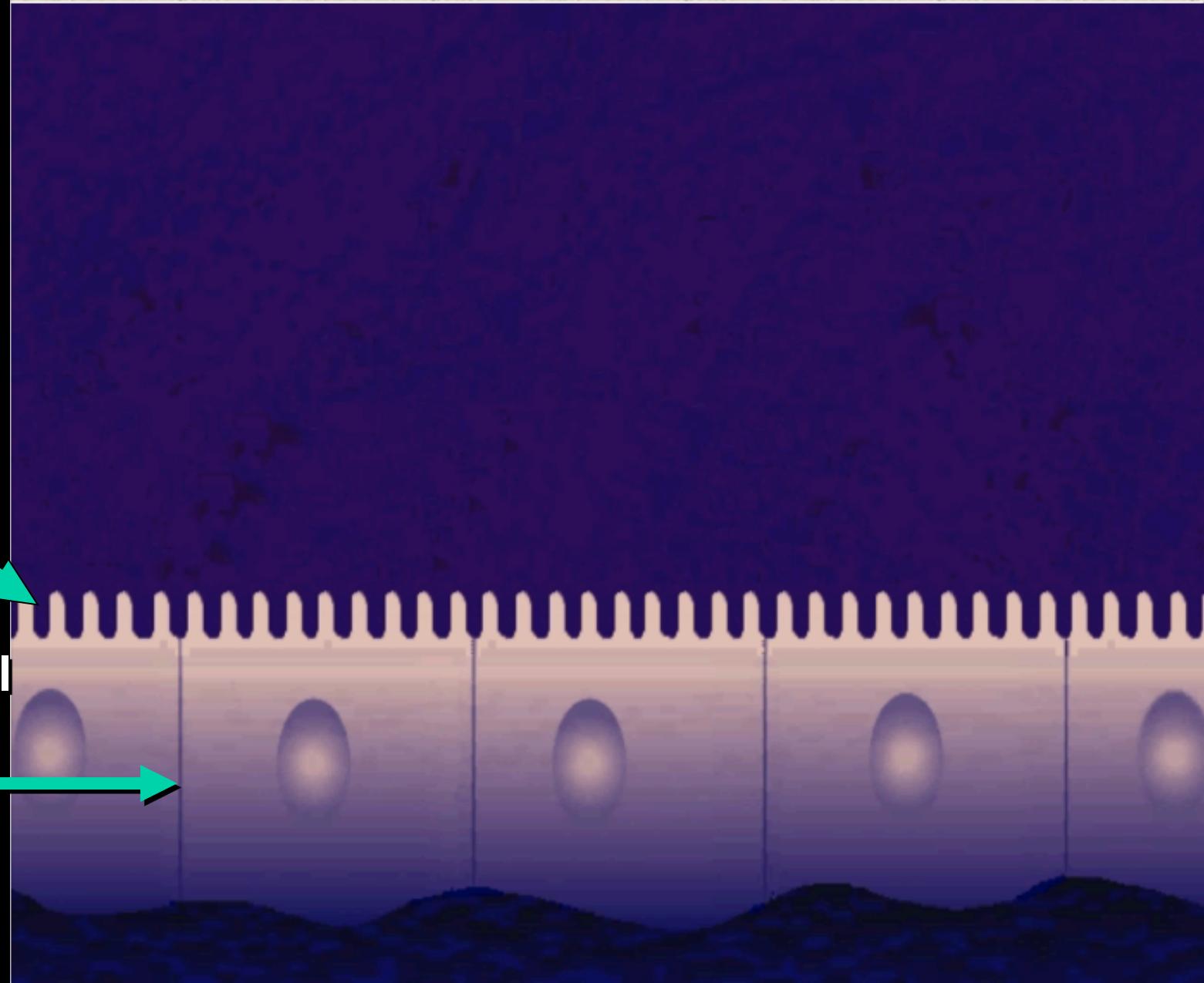
It becomes independent of continuous exposure to the environmental trigger, and is therefore self-perpetuating and irreversible. Epitope-specific cross-reactivity between microbial antigens and self-antigens has been shown in some animal models to initiate autoimmunity.<sup>3</sup> Conversely, in most 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.<sup>3</sup>

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

# Healthy Gut

Healthy  
Villi/Good  
Absorption

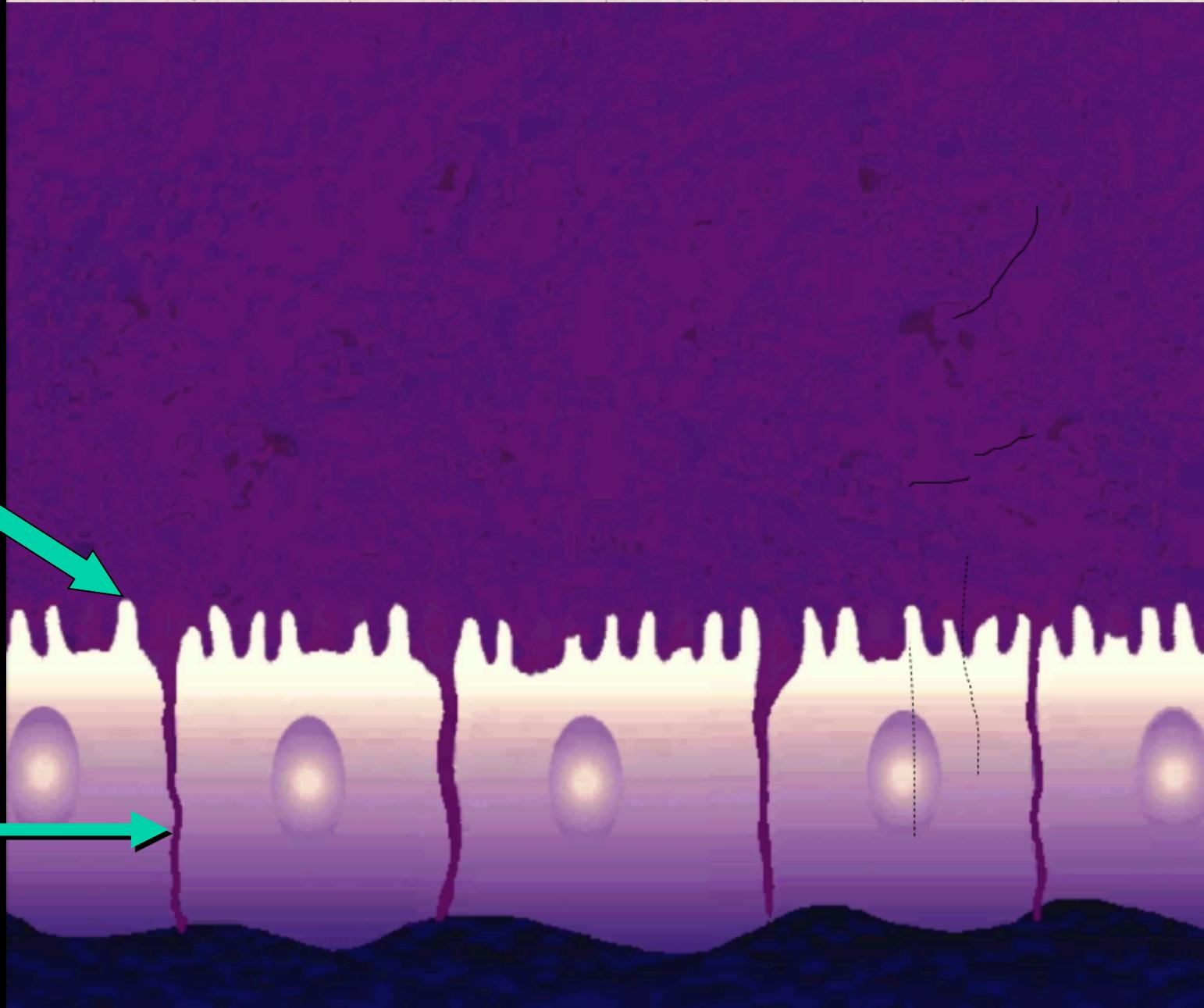
Healthy Cell  
Junctions



# Pathogenic Intestinal Permeability

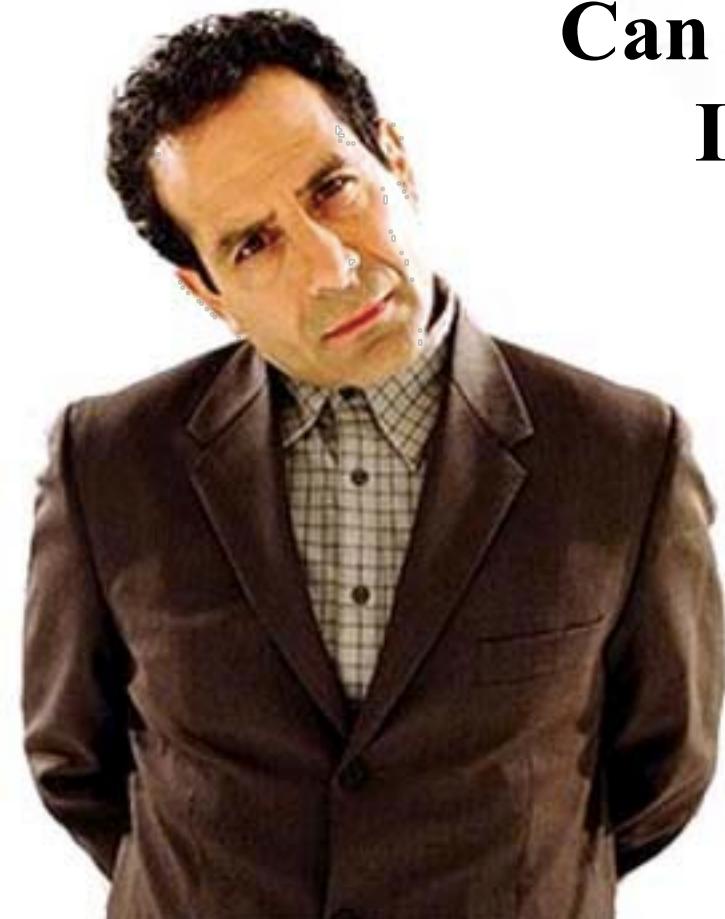
Damaged  
Villi/ Poor  
Absorption

Damaged  
Cell  
junctions



# Premise #6

## Can Foods Trigger Pathogenic Intestinal Permeability



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

# **Conclusions: Increased intestinal permeability after gliadin exposure occurs in all individuals.**

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<sup>4</sup> Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; E-Mail: aguerrero@jhmi.edu

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45 of the 56 are the full articles and are free. HAPPY READING**





*Scientific References from,*

## **Fire in The Hole**

**Intestinal Permeability: The Development of Autoimmune Disease  
and a Comprehensive Approach to Healing the Gut**

by DR. THOMAS O'BRYAN, DC, CCN, DACBN



**BETRAYAL**

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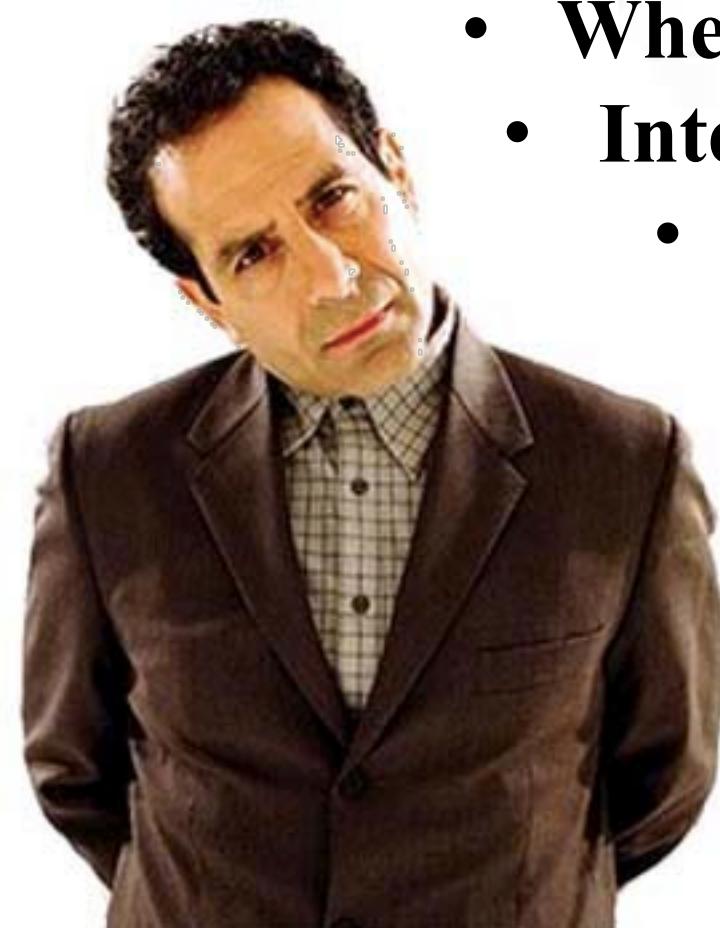
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23

# Premise #7

## Breakthroughs in Identifying:

- Wheat Related Disorders
  - Intestinal Permeability
    - Autoimmunity



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BRIEF COMMUNICATION

Open Access



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## Very low prevalence of IgE mediated wheat allergy and high levels of cross-sensitisation between grass and wheat in a UK birth cohort

# Wheat is composed of four classes of proteins; albumins, globulins, gliadins and glutenins, which together are known as prolamins or gluten.

Flour with/without sensitization to grass pollen is a clinical problem.

**Aim:** We set out to determine the prevalence of wheat allergy in a birth cohort (10/11 year olds) and investigate the usefulness of performing skin prick tests (SPT), specific IgE tests and component resolved diagnostics to wheat pollen and flour.

**Methods:** The Food Allergy and Intolerance Research (FAIR) birth cohort included babies born on the Isle of Wight (UK) between September 2001–August 2002 ( $n = 969$ ). Children were followed up at 1, 2, 3 and 10/11 years. 588 children had SPTs to wheat pollen and grass during the 10 year follow-up. 294 children underwent further SPT to wheat flour and 246 had specific IgE testing to wheat and grass.

**Results:** Eight children underwent oral food challenges (OFC). We diagnosed 0.48 % (4/827; 95 % CI 0–1 %) children with wheat allergy based on OFC. 16.3 % (96/588) were sensitized to grass pollen, 13.4 % (79/588) to wheat pollen; 78 % (75/96) sensitized to both. Only one child was sensitized to wheat flour and wheat pollen, but not grass pollen. For specific IgE, 15.0 % (37/246) and 36.2 % (89/246) were sensitized to wheat and grass pollen, with 40.5 % (36/89) sensitized to both. Of the 37 children sensitized to wheat, 3 (8.1 %) were sensitized to omega 5 gliadin, 1 (2.7 %) to wheat lipid transfer protein and 1 to wheat gliadin.

**Conclusion:** Clinicians should be aware of the high level of cross-sensitization when performing tests to wheat and grass pollen i.e. sensitisation to wheat specific IgE and wheat pollen SPT should be assessed in the presence of grass pollen SPT and/or specific IgE.

**Keywords:** Wheat allergy, Cross-reactions, Cross-sensitization, Hay fever, Food allergy

## CLINICAL RESEARCH

## GASTROENTEROLOGY 2002;122:1729–1737

## The Gluten Response in Children With Celiac Disease Is Directed Toward Multiple Gliadin and Glutenin Peptides

WILLEMIJN VADER,\* YVONNE KOY,\* PETER VAN VEELEN,\* ARNOUD DE RU,\* DIANA HARRIS,\*  
WILLEMIEN BENCKHUIJSSEN,\* SALVADOR PEÑA,§ LUISA MEARIN,† JAN WOUTER DRIJFHOUT,\*  
and FRITS KONING\*

Departments of \*Immunohematology and Blood Transfusion and †Paediatrics, Leiden University Medical Centre, Leiden, The Netherlands;  
and the §Free University, Amsterdam, The Netherlands

# The identification of the toxic gluten peptides provides new opportunities to screen

*which GLU peptide(s) are involved early in disease.*

**Methods:** We have characterized the GLU-specific T-cell response in HLA-DQ2 positive children with recent onset CD. **Results:** We found that 50% of these patients do not respond to the  $\alpha$ -GLIA peptide but to a diverse set of GLIA and glutenin (GLT) peptides, including 6 novel epitopes. Moreover, individual patients respond to distinct (combinations of) GLU peptides. T-cell cross-reactivity toward homologous GLIA and GLT peptides was observed, which might play a role in the initial spreading of the GLU-specific T-cell response. Although all pediatric patients displayed deamidation-dependent responses, deamidation-independent responses were found in the majority of patients as well. Finally, T-cell responses to 3 of these novel GLU peptides were found in adult CD patients. **Conclusions:** The diversity of the GLU-specific T-cell response is far greater than was previously appreciated. Both adult and young CD patients can respond to a diverse repertoire of GLU peptides. The observation that T-cell responses to 3 of the novel peptides are independent of deamidation indicates that T-cell responses can be initiated toward native GLU peptides. The possibility that deamidation drives the GLU response toward immunodominant T-cell stimulatory peptides after disease initiation is discussed.

Celiac disease (CD) is the most common food-sensitive enteropathy in humans, caused by a permanent intolerance for the dietary gluten (GLU) and is considered to be a T cell-mediated disease.<sup>1–3</sup> The large majority of patients express the HLA-DQ2 [DQ( $\alpha 1^*$ 0501,  $\beta 1^*$ 02)] and/or -DQ8 [DQ( $\alpha 1^*$ 03,  $\beta 1^*$ 0302)] mole-

has been solved by the finding that the enzyme tissue transglutaminase (tTG), the target of the endomysium-specific antibodies in CD patients,<sup>10</sup> can modify GLU peptides by conversion of glutamine residues into glutamic acid (termed deamidation<sup>11</sup>), which introduces the negative charges favored for binding. Recent work has led to the identification of 5 GLU peptides that are recognized by small intestinal T cells from CD patients and has revealed that the T-cell response to these peptides is usually enhanced or even dependent on deamidination.<sup>12–18</sup> Importantly, this work has also indicated that the response to GLU appears to focus on only a limited number of GLU peptides. All HLA-DQ8 patients examined were found to respond to a unique GLIA peptide<sup>16</sup> and 2 independent studies showed that all HLA-DQ2 patients respond to a particular  $\alpha$ -GLIA peptide.<sup>12,13</sup> Obviously, such a limited response would greatly facilitate tolerance induction protocols as an alternative treatment for CD or the development of safer food products. However, these studies have been carried out with adult patients<sup>12,13,15,16,18</sup> and the observed immunodominance may thus reflect an advanced stage in the development of the GLU-specific T-cell response and may not be indicative for the initiation of the disease. In

*Abbreviations used in this paper: CD, celiac disease; GLIA, gliadin; GLT, glutenin; GLU, gluten; TCC, T-cell clone; tTG, tissue transglutaminase.*

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0016-5085/02/\$35.00  
doi:10.1053/gast.2002.33606

## RESEARCH ARTICLE

# Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays

Rok Seon Choung<sup>1</sup>, Eric V. Marietta<sup>1</sup>, Carol T. Van Dyke<sup>1</sup>, Tricia L. Brantner<sup>1</sup>, John Rajasekaran<sup>2</sup>, Pankaj J. Pasricha<sup>3</sup>, Tianhao Wang<sup>2</sup>, Kang Bei<sup>2</sup>, Karthik Krishna<sup>2</sup>, Hari K. Krishnamurthy<sup>2</sup>, Melissa R. Snyder<sup>4</sup>, Vasanth Jayaraman<sup>2†</sup>, Joseph A. Murray<sup>1‡\*</sup>

1 Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, United States of America,



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**Recent advances in semiconductor methods and the generation of high-throughput peptide microarrays using a combination of lithography and biochemistry for peptide synthesis have opened the door to a new era in the identification of novel biomarkers of disease.**

## OPEN ACCESS

**Citation:** Choung RS, Marietta EV, Van Dyke CT, Brantner TL, Rajasekaran J, Pasricha PJ, et al. (2016) Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays. PLoS ONE 11(1): e0147777. doi:10.1371/journal.pone.0147777

**Editor:** Massimo Pietropaolo, Baylor College of Medicine, UNITED STATES

Most antibodies recognize conformational or discontinuous epitopes that have a specific 3-dimensional shape; however, determination of discontinuous B-cell epitopes is a major challenge in bioscience. Moreover, the current methods for identifying peptide epitopes often involve laborious, high-cost peptide screening programs. Here, we present a novel microarray method for identifying discontinuous B-cell epitopes in celiac disease (CD) by using a silicon-based peptide array and computational methods.

## RESEARCH ARTICLE

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1 Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, United States of America,



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We identified 2 distinct discontinuous gliadin sequence sets that, when combined, significantly improved the sensitivity (IgG, 97%; IgA, 99%) and specificity (IgG, 98%; IgA, 100%) ( $P < .001$ ) for the diagnosis of CD.

## OPEN ACCESS

**Citation:** Choung RS, Marietta EV, Van Dyke CT, Brantner TL, Rajasekaran J, Pasricha PJ, et al. (2016) Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays. PLoS ONE 11(1): e0147777. doi:10.1371/journal.pone.0147777

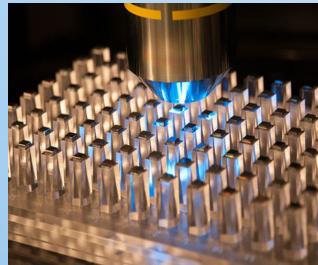
**Editor:** Massimo Pietropaolo, Baylor College of Medicine, UNITED STATES

## Background

Most antibodies recognize conformational or discontinuous epitopes that have a specific 3-dimensional shape; however, determination of discontinuous B-cell epitopes is a major challenge in bioscience. Moreover, the current methods for identifying peptide epitopes often involve laborious, high-cost peptide screening programs. Here, we present a novel microarray method for identifying discontinuous B-cell epitopes in celiac disease (CD) by using a silicon-based peptide array and computational methods.

# THE ADVANTAGE

## WHEAT ZOOMER



	Vibrant Wheat Zoomer	Cyrex Labs	Genova Diagnostics
Alpha Gliadin	✓		✓
Deamidated Gliadin Peptide	✓		✓
Native and Deamidated 33mer	✓	✓	
Alpha Gliadin			
Alpha Gliadin 17mer	✓	✓	
Gamma Gliadin 15mer	✓	✓	
Native and Deamidated 26mer	✓		
Gamma Gliadin			
Omega Gliadin 17mer	✓	✓	
Glutenin 21mer	✓	✓	
Gluteomorphin	✓	✓	
Prodynorphin	✓	✓	
Transglutaminase 2	✓	✓	✓
Transglutaminase 3	✓	✓	
Transglutaminase 6	✓	✓	
Wheat Germ Agglutinin	✓	✓	
Alpha-Beta Gliadin	✓		
Gamma Gliadin	✓		
Omega Gliadin	✓		
Zonulin/Occludin	✓	✓	
LMW Glutenin family	✓		
HMW Glutenin Family	✓		
Serpins	✓		
Farinins	✓		
Amylase/Protease Inhibitors	✓		
Globulins	✓		
Peroxiredoxin	✓		
Somatostatin	✓		
Multiple gluten fusion peptides	✓		
Actomyosin	✓	✓	
Lipopolysaccharides			✓
Tri A 37 Wheat Allergen	✓		

Final Report Date: 03-01-2017 15:19  
 Accession ID: 1702170113

Specimen Collected: 02-16-2017 10:00  
 Specimen Received: 02-17-2017 11:09

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

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

Last Name	First Name	Middle Name	Date of Birth	Gender	Physician ID
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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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Specimen Collected: 02-16-2017 10:00  
 Specimen Received: 02-17-2017 11:09

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

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
	<b>Potential Risk:</b> Antibodies to actin suggest leaky gut diagnosis.; Increased levels of lipopolysaccharides antibodies indicate leaky gut condition.
	<b>Related Information:</b> 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.
	<b>Potential Risk Mitigation Choices:</b> 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.

# Premise #8

## How do we Arrest Pathogenic Intestinal Permeability



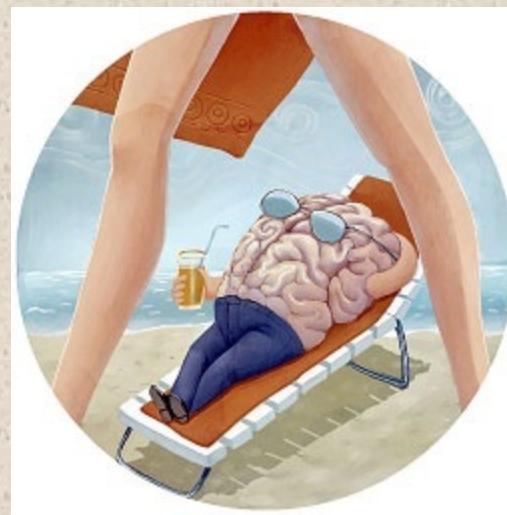
Detective Adrian Monk  
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# In Healing the Gut, Consider a Pleiotropic Approach

we stand a greater chance of success by considering *pleiotropic* approaches 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 by their very nature impacting on several systems of the body.



# A Pleiotropic Approach to Addressing Pathogenic Intestinal Permeability

Consider 3 categories to your Therapeutic Protocol:

- Avoid inflammatory triggers



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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**

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## **Conclusions: Increased intestinal permeability after gliadin exposure occurs in all individuals.**

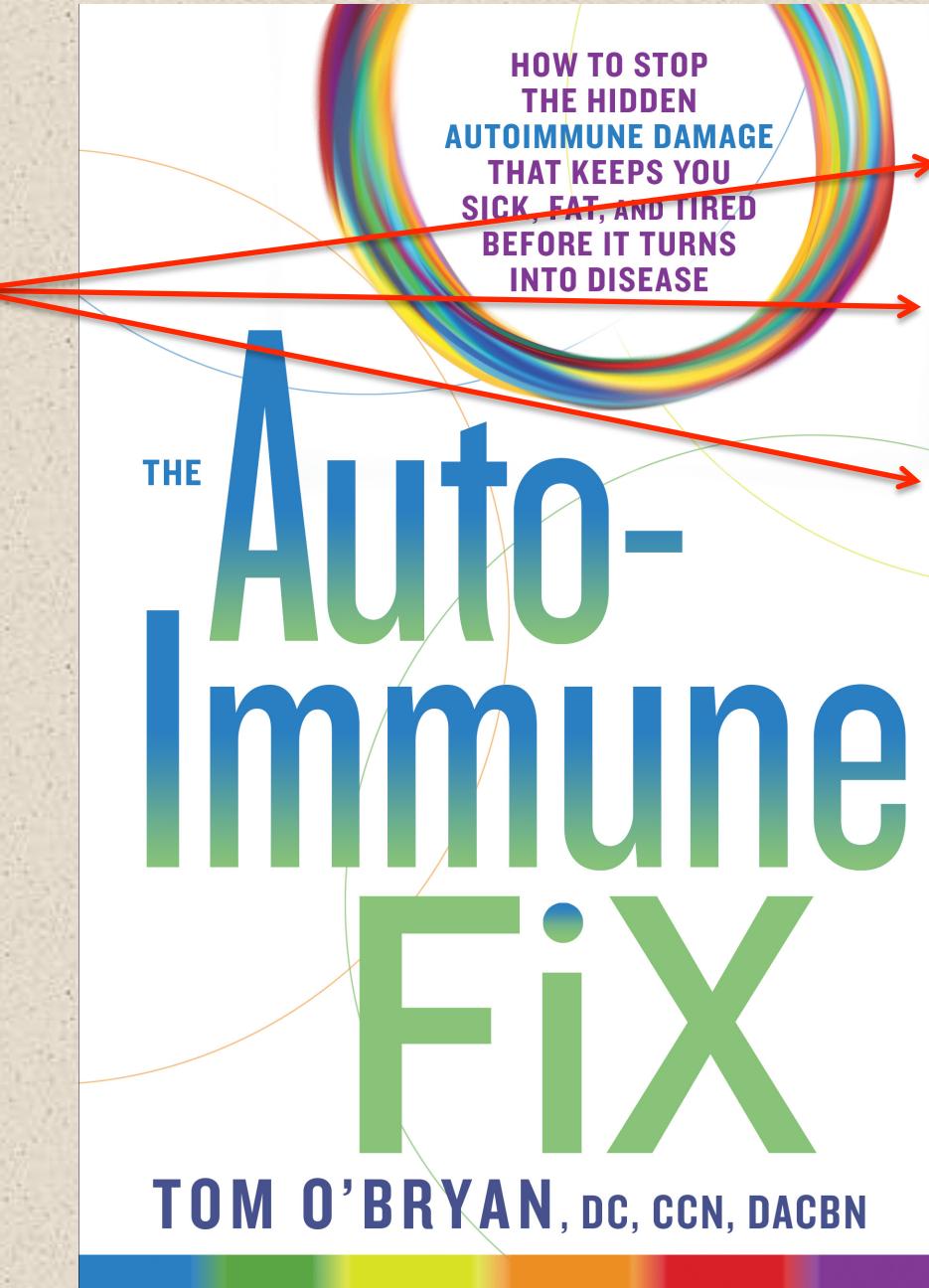
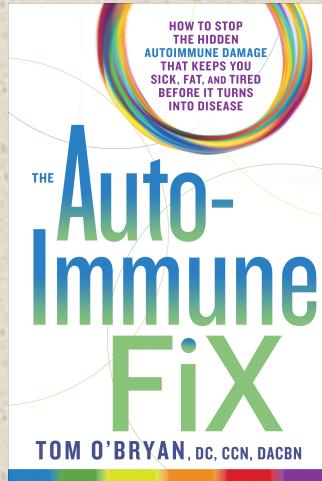
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REVIEW

Open Access

## Intestinal permeability – a new target for disease prevention and therapy

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### Abstract

Data are accumulating that emphasize the important role of the intestinal barrier and intestinal permeability for health and disease. However, these terms are poorly defined, their assessment is a matter of debate, and their clinical significance is not clearly established. In the present review, current knowledge on mucosal barrier and its role in disease prevention and therapy is summarized. First, the relevant terms 'intestinal barrier' and 'intestinal permeability' are defined. Secondly, the key element of the intestinal barrier affecting permeability are described.

**The effect of diet on intestinal permeability is dependent on individual factors such as the host's genetic susceptibility, and also on the intestinal microbiota.**

means vary enormously and probably assess different functional components of the barrier. The barrier assessments are further hindered by the natural variability of this functional entity depending on species and genes as well as on diet and other environmental factors. In the final part, we discuss selected diseases associated with increased intestinal permeability such as critically illness, inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and – more recently recognized – obesity and metabolic diseases. All these diseases are characterized by inflammation that might be triggered by the translocation of luminal components into the host. In summary, intestinal permeability, which is a feature of intestinal barrier function, is increasingly recognized as being of relevance for health and disease, and therefore, this topic warrants more attention.

**Keywords:** Intestinal barrier, Intestinal permeability, Obesity, Inflammatory bowel disease, Irritable bowel syndrome, Prebiotics, Probiotics, Gut health