Put That Bread Down

The Conundrum of Gluten Sensitivity

Alpha-Plus
Stockholm/Malmo, Sweden
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www.theDr.com

Tom O'Bryan, DC holds Adjunct Faculty positions with:

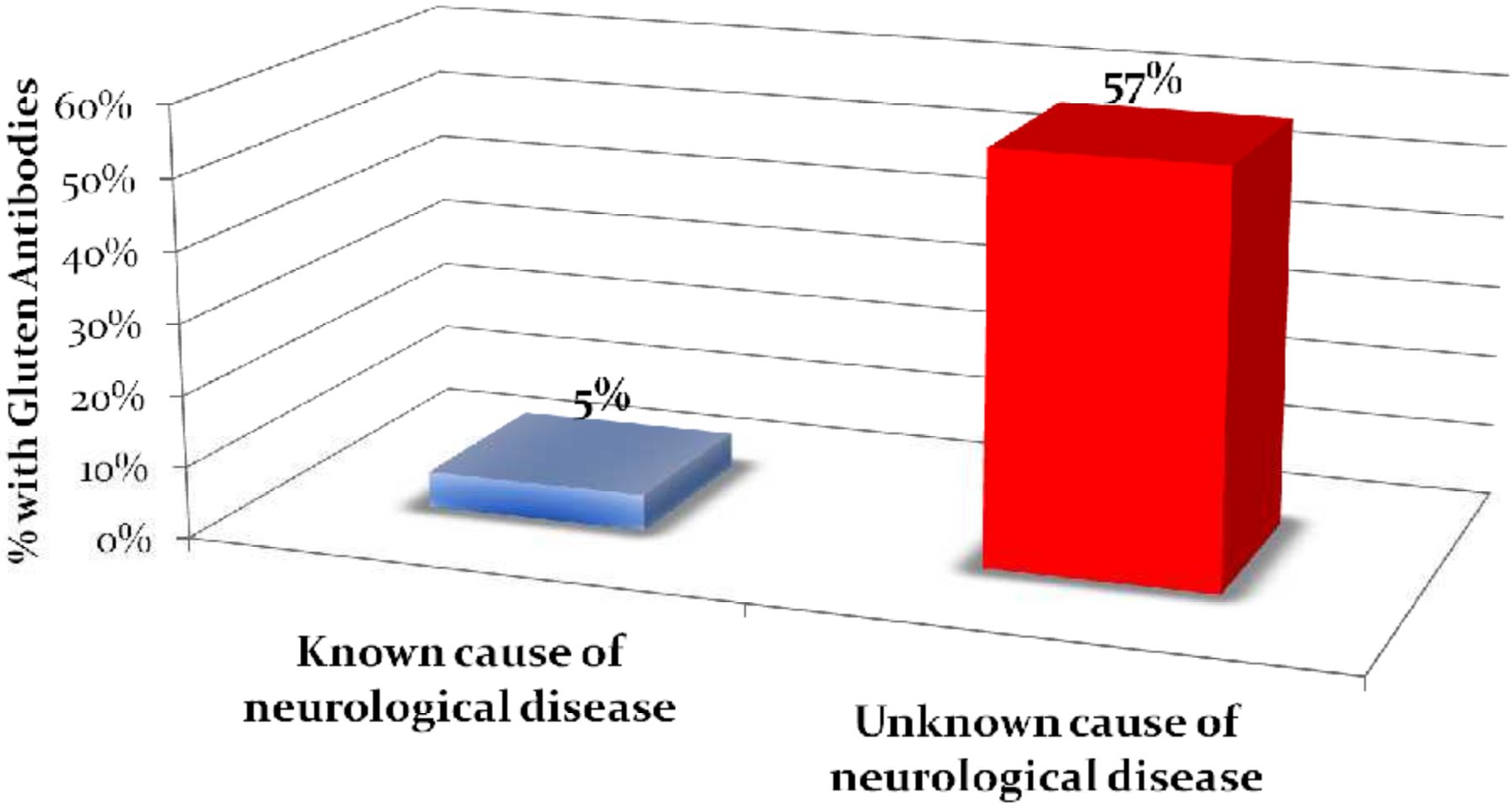
- **the National University of Life Sciences,**
- **the Institute for Functional Medicine,**
- **the Advisory Board of the National Association of Nutrition Professionals and**
- **the Scientific Committee of the International and American Association of Clinical Nutritionists.**

“You’ve been eating Gluten Free again, haven’t you”???

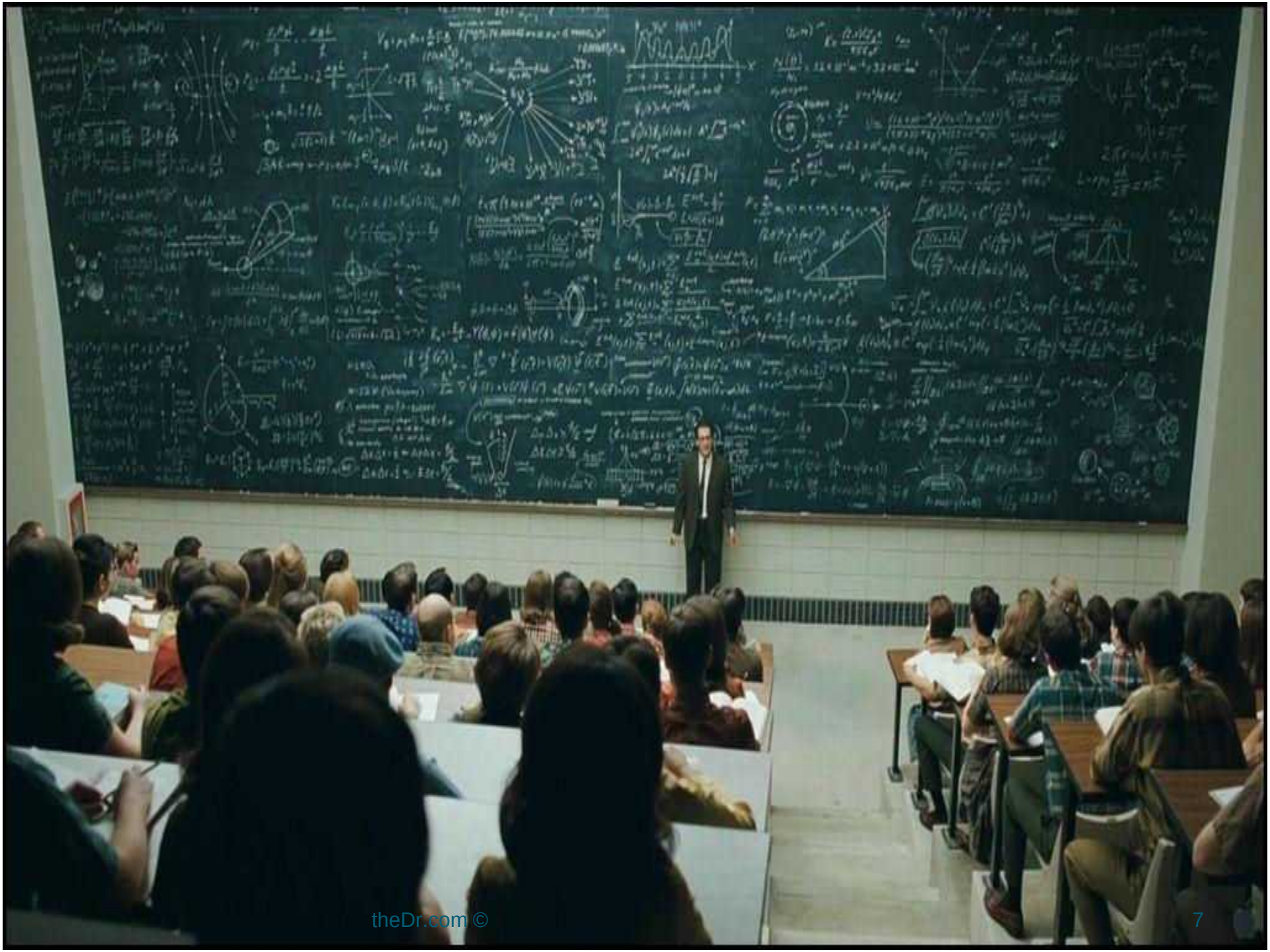
How many know or suspect they may have a Sensitivity to Gluten?

How Many Know or Suspect that if they have an inadvertent exposure to Gluten, it seems to affect their brain?

J Neurol Neurosurg Psychiatry 2002 72: 560-563



When the cause of a neurological disease is known, the percentage of those patients with elevated antibodies to gluten is 5%. When the cause of a neurological disease is unknown, the the percentage of those patients with elevated antibodies to gluten is 57%.



Name and Date of Medical Journal

Exact Quotes From the Authors

The Liver in Celiac Disease

Alberto Rubio-Tapia and Joseph A. Murray

Celiac disease is a common (1% prevalence) chronic immune-mediated disorder of the small intestine induced by dietary wheat, barley, and rye. Several hepatic disorders have been described in association with celiac disease. Isolat… histologic changes in a liver biopsy is the commo… A gluten-free diet normalizes liver enzymes and l… over, celiac disease can coexist with autoimmune liver disorders such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Celiac disease has increasingly been reported with a variety of other liver diseases. Thus, the hepatologist needs to consider celiac disease in the differential of abnormal liver blood tests and to be aware of the clinical implications of this frequent disease in patients with liver disorders. The possible mechanisms of liver injury and those common factors that explain the association of celiac disease with liver disorders are discussed. The aims of this article are (1) to review the spectrum and pathogenesis of liver injury related to celiac disease and (2) to provide direction to those caring for patients with chronic liver diseases regarding the detection and effective treatment of celiac disease. (HEPATOLOGY 2007;46:1650-1658.)

HEPATOLOGY, Vol. 46, No. 5, 2007

Liver blood test abnormalities may be the sole presentation of atypical CD.

with the removal of gluten from the diet.[1]

Although CD is defined by the small intestine injury and resulting malabsorption, more recently it has been recognized to be a multisystem disorder that may affect other organs, such as the nervous system, bones, skin, heart, and, likely, the liver.[2-4]

Abbreviations: AGA, anti-gliadin antibody; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, celiac disease; DEXA, dual energy X-ray absorptiometry; EmA, endomysial antibody; GFD, gluten-free diet; HFE, hemochromatosis susceptibility gene; HLA, human leukocyte antigen; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TSH, thyroid-stimulating hormone; tTG, tissue transglutaminase; tTGA, anti-tissue transglutaminase antibody.

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Potential conflict of interest: Dr. Murray is a consultant for Alvine. He received grants from Alba Inc.

detected by serologic screening of those subjects at risk, with villous atrophy in the intestine. Finally, an individual may have a latent predisposition to CD, which is defined by a positive serology in the absence of villous atrophy on the small intestine.[1,5]

CD itself may injure the liver but also may modify the clinical impact of chronic liver diseases when they coexist. The aims of this review are (1) to explore the spectrum and pathogenesis of liver abnormalities described in CD and (2) to summarize the association between CD and various chronic liver disorders to provide a basis for a rational diagnostic and therapeutic approach that those who care for patients with liver disease can incorporate into practice.

Material and Methods (Review Criteria)

PubMed was searched in June 2007 for full articles published in English-language journals from 1963 to June 2007 with the following keywords alone or in combination: "celiac disease," "sprue," "liver disorders," "liver involvement," "liver tests," "hepatitis," "cholangitis," and "cirrhosis." In this literature search, several points became obvious: (1) properly designed epidemiological studies are

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Increased liver enzymes have been reported in about 40% of adults and in 54% of children with a classical presentation of CD at the time of diagnosis

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A GFD leads to normalization of serum transaminases in 75% to 95% of patients with CD, usually within a year of good adherence to the diet.

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<u>All</u> the patients with nonspecific changes in the liver histology and a follow-up liver biopsy normalized the histological changes after adherence to a GFD.

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Even more, CD was found to be associated with an 8-fold increased risk of death from liver cirrhosis.

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REVIEW

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[1] • Steven Wooding[2] • Jonathan Grant[2]

[1]Institute of Public Health, University of Cambridge, Cambridge CB2 0SR, UK

[2]RAND Europe, Cambridge CB4 1YG, UK

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

DECLARATIONS

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

Summary

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.

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

Introduction

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

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.[12] 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%.[13] 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% arise 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,[14] 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.[1,3,15] Balas and Bohen,[16] Grant[17] and Wratschko[18] 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


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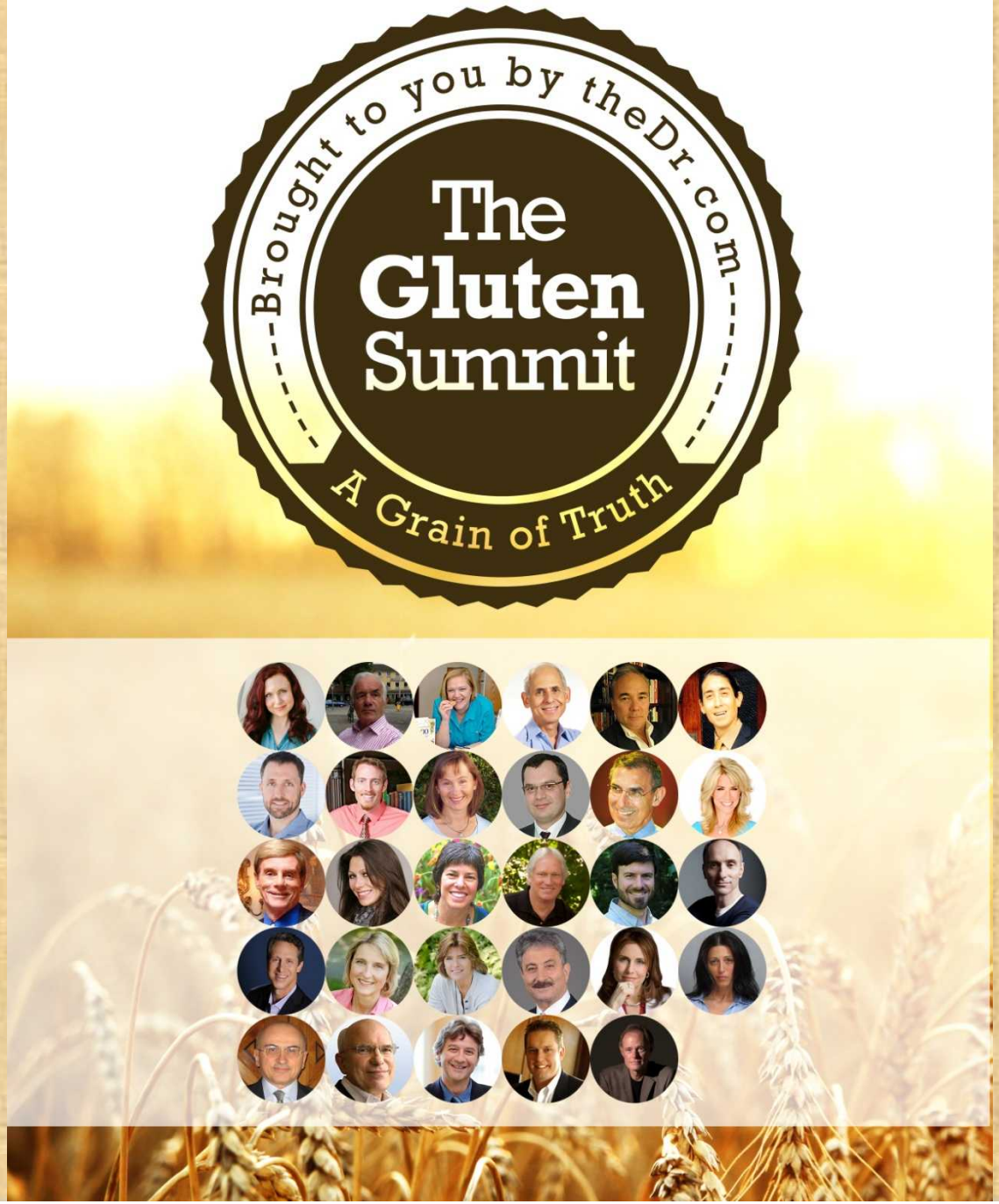
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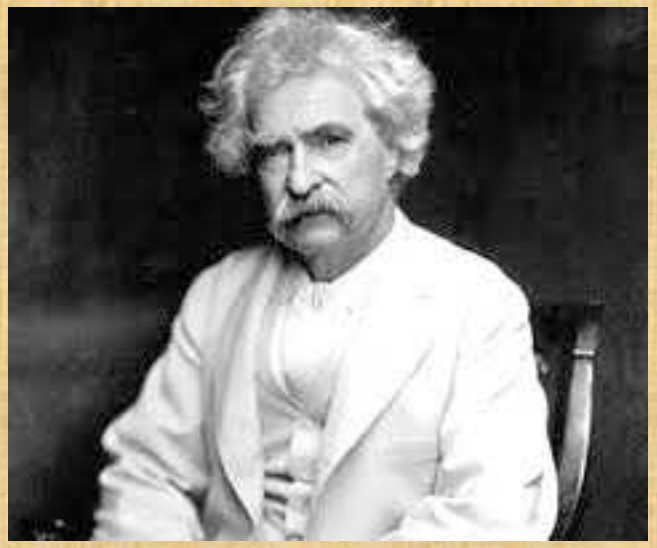
"It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so."

Mark Twain



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2011;364:818-28.

ORIGINAL ARTICLE

Long-Term Effects of Intensive Glucose Lowering on Cardiovascular Outcomes

The ACCORD Study Group*

As compared with standard therapy, the use of intensive therapy [glucose lowering] reduced 5-yr non-fatal MI's by 21%,

glycated hemoglobin level below 6.0%), or standard therapy (targeting a level of 7 to 7.9%). After termination of the intensive therapy, due to higher mortality in the intensive-therapy group, the target glycated hemoglobin level was 7 to 7.9% for all participants, who were followed until the planned end of the trial.

RESULTS

Before the intensive therapy was terminated, the intensive-therapy group did not differ significantly from the standard-therapy group in the rate of the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (P=0.13) but had more deaths from any cause (primarily cardiovascular) (hazard ratio, 1.21; 95% confidence interval [CI], 1.02 to 1.44) and fewer nonfatal myocardial infarctions (hazard ratio, 0.79; 95% CI, 0.65 to 0.95). These trends persisted during the entire follow-up period (hazard ratio for death, 1.19; 95% CI, 1.05 to 1.38; and hazard ratio for nonfatal myocardial infarction, 0.82; 95% CI, 0.70 to 0.96). After the intensive intervention was terminated, the median glycated hemoglobin level in the intensive-therapy group rose from 6.4% to 7.2%, and the use of glucose-lowering medications and rates of severe hypoglycemia and other adverse events were similar in the two groups.

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy for 3.7 years to target a glycated hemoglobin level below 6% reduced 5-year nonfatal myocardial infarctions but increased 5-year mortality. Such a strategy cannot be recommended for high-risk patients with advanced type 2 diabetes. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00000620.)

Ph.D., University of North Carolina, Chapel Hill, David C. Goff, Jr., M.D., Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Jeffrey L. Probstfield, M.D., University of Washington, Seattle; William C. Cushman, M.D., Memphis Veterans Affairs Medical Center, Memphis; Henry N. Ginsberg, M.D., Columbia University College of Physicians and Surgeons, New York; Richard M. Grimm, Jr., M.S., Ph.D., University of Minnesota, Berman Center for Outcomes and Clinical Research, Minneapolis; Robert P. Byington, Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Yves L. Rosenberg, M.D., National Heart, Lung, and Blood Institute, Bethesda, MD; and W. Timothy Friedewald, M.D., for the ACCORD Study Group. Columbia University College of Physicians and Surgeons, New York) assume responsibility for the content of this article. Address reprint requests to Dr. Gerstein at McMaster University, Department of Medicine, HSC 3V38, 1200 Main St. W., Hamilton, ON L8N 3Z5, Canada, or at gerstein@mcmaster.ca.

*Members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND

Intensive glucose lowering has previously been shown to increase mortality among

but increased 5-year mortality by over 19%.

We randomly assigned participants with type 2 diabetes and cardiovascular disease or additional cardiovascular risk factors to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level of 7 to 7.9%). After termination of the intensive therapy, due to higher mortality in the intensive-therapy group, the target glycated hemoglobin level was 7 to 7.9% for all participants, who were followed until the planned end of the trial.

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The members of the writing group [illegible] M.D., Ph.D., Case Western Reserve University, Cleveland; John B. Buse, M.D., Ph.D., University of North Carolina, Chapel Hill; David C. Goff, Jr., M.D., Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Jeffrey L. Probstfield, M.D., University of Washington, Seattle; William C. Cushman, M.D., Memphis Veterans Affairs Medical Center, Memphis; Henry N. Ginsberg, M.D., Columbia University College of Physicians and Surgeons, New York; Pierre Biggar, M.D., Columbia University College of Physicians and Surgeons, New York; Richard [illegible], M.D., Ph.D., University of Minnesota, Berman Center for Outcomes and Clinical Research, Minneapolis; Robert P. Byington, Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Yves L. Rosenberg, M.D., National Heart, Lung, and Blood Institute, Bethesda, MD; and William [illegible], M.D., Albert Einstein College of Medicine, New York) assume responsibility for the content of this article. Address reprint requests to Dr. Gerstein at McMaster University, Department of Medicine, HSC 3V38, 1200 Main St. W., Hamilton, ON L8N 3Z5, Canada, or at gerstein@mcmaster.ca.

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participants, who were followed until the planned end of the trial.

RESULTS

Before the intensive therapy was terminated, the intensive-therapy group did not differ significantly from the standard-therapy group in the rate of the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (P=0.13) but had more deaths from any cause (primarily cardiovascular) (hazard ratio, 1.21; 95% confidence interval [CI], 1.02 to 1.44) and fewer nonfatal myocardial infarctions (hazard ratio, 0.79; 95% CI, 0.65 to 0.95). These trends persisted during the entire follow-up period (hazard ratio for death, 1.19; 95% CI, 1.05 to 1.38; and hazard ratio for nonfatal myocardial infarction, 0.82; 95% CI, 0.70 to 0.96). After the intensive intervention was terminated, the median glycated hemoglobin level in the intensive-therapy group rose from 6.4% to 7.2%, and the use of glucose-lowering medications and rates of severe hypoglycemia and other adverse events were similar in the two groups.

CONCLUSIONS

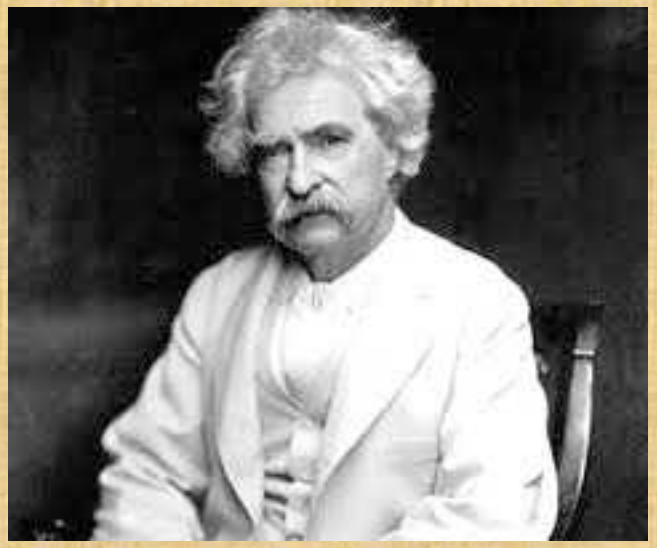
As compared with standard therapy, the use of intensive therapy for 3.7 years to target a glycated hemoglobin level below 6% reduced 5-year nonfatal myocardial infarctions but increased 5-year mortality. Such a strategy cannot be recommended for high-risk patients with advanced type 2 diabetes. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00000620.)

Members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2011;364:818-28.

"It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so."

Mark Twain



INTERNAL MEDICINE JOURNAL

Internal Medicine Journal **38** (2008) 790–799

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CLINICAL PERSPECTIVES

Coeliac disease: current approach and future prospects

R. P. Anderson

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Key words
coeliac disease, transglutaminase immunoglobulin A, deamidated gliadin peptide immunoglobulin G, immunotherapy.

Strict gluten-free diet is mandatory for CD

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Abstract

Public anxiety over gluten has fuelled widespread demand for gluten-free food, yet coeliac disease remains significantly underdiagnosed and some confusion [illegible] young, in people already following a gluten-reduced diet, and those using immunosuppressive medications. HLA DQA and DQB genotyping to show that alleles encoding HLA DQ2 and DQ8 are absent virtually excludes coeliac disease. Confirming histological remission reduces the risks of later complications, such as osteoporosis and cancer. Monitoring remission by serology is unreliable. Because gluten is an exogenous antigen and the small intestine is readily accessible, the immunopathogenesis of coeliac disease is better understood than other strongly major histocompatibility complex class II-associated diseases, such as type 1 diabetes mellitus. Therapeutic targets have been identified and drugs are under development to supplement or even replace gluten-free diet. With greater awareness and non-dietary therapeutics, diagnosis and treatment of coeliac disease will be increasingly prominent in medical practice.

Introduction

Approximately 1% of Australians and New Zealanders have coeliac disease.[1,2,3] Not surprisingly, subspecialists and primary care physicians regularly see patients with undiagnosed coeliac disease. This review stresses current challenges and provides some insights into the future of coeliac disease.

Coeliac disease is not an exclusively Irish or Celtic condition. Approximately 1 of 30 people living in Europe, North America, Australia and New Zealand consuming gluten and carrying genes encoding human leucocyte antigen (HLA) DQ2 (20% of Caucasians, North Africans, South and West Asians) or HLA DQ8 (10% of all Europeans and Asians) has coeliac disease.[4,5]

The epidemiology of coeliac disease has been a moving target because of the rapid improvements in diagnostics.[4] For example, in England in 1950, coeliac disease was estimated to affect 1 in 8000 people, but by the 1960s this was revised to 1 in 500 based on tests of malabsorption and per-oral capsule biopsy.[4] In the last 10 years, prevalence data based on serological screening verified by small bowel histology has typically shown 1 in 70–100 Europeans to be affected.[6] With some important exceptions such as the Swedish epidemic in the early 1990s,[7] the stated prevalence of coeliac disease has increased with each successive study from the same geographical region. The change has been attributable to improved technology and medical awareness rather than true

Funding: WEHI-Melbourne Health Ian Mackay Fellowship, NHMRC, Nexpep Pty Ltd.
Potential conflicts of interest: The author is inventor of patents relating to diagnostics, therapeutics and non-toxic gluten based on knowledge of peptides recognized by T cells in coeliac disease. The author is also involved in the commercialization of these patents as Director, Chief Scientist and Chief Medical Officer and is substantial shareholder in Nexpep Pty Ltd and Nexgrain Pty Ltd.

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Long-Term Mortality in People With Celiac Disease Diagnosed in Childhood Compared With Adulthood: A Population-Based Cohort Study

Masoud Solaymani-Dodaran, M.D., Ph.D., M.P.H., Joe West, M.B., Ph.D., M.R.C.P., and Richard F.A. Logan, M.B., M.Sc., F.R.C.P.
University of Nottingham, Division of Epidemiology and Public Health, Medical School, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom

INTRODUCTION: To explore whether the excess mortality in celiac disease is related directly to the disease and

Children diagnosed with celiac disease had a threefold increased risk of long-term mortality. (with or without a GFD)

mortality was modest. The increased mortality in children from external causes may reflect behavioral change associated with coping with a chronic disease and its treatment.

(Am J Gastroenterol 2007;102:864–870)

INTRODUCTION

Various studies have found that celiac disease still confers about a 1.3- to 2-fold increase in all-cause mortality compared with the general population (1–6). It is unclear how much this increase is related to celiac disease itself and how much the increase might be only indirectly related via various associated conditions. In addition, there has been speculation that the duration of gluten exposure prior to diagnosis has long-term adverse effects and therefore contributes to mortality (6). If the mortality increase is directly the result of celiac disease and/or the duration of preceding gluten exposure, then celiac disease diagnosed in childhood might be expected to be associated with a lesser increase of mortality than adult diagnosed disease (3, 4).

Previous studies have been unable to precisely estimate the mortality in children with celiac disease mainly because of lack of long-term follow-up (5–8). In adults most of the excess mortality in celiac disease has previously been reported as resulting from malignant disease (6). As children with celiac disease are mostly diagnosed around the age of 1–3 yr they have little long-term gluten exposure, assuming they are compliant with a gluten-free diet. It is plausible then that children may be protected in some way from the excess malignant risk that is apparent in adults.

To examine whether there are differences in the long-term mortality experience of people diagnosed with celiac disease as children and as adults we have analyzed further data from the Lothian celiac disease cohort. As this study has good quality follow-up we have been able to examine cause-specific mortality over many years following diagnosis compared with the general population.

METHODS

Participants

Our study cohort was originally set up in 1979 through an attempt to identify all cases of celiac disease diagnosed in the Lothian region of Scotland. Details of the recruitment process have been published previously (2, 9). In brief, the following sources were used to identify celiac cases: the records of gastrointestinal units of all the hospitals in the region including the Edinburgh Royal Infirmary, Western General Hospital, and Royal Hospital for Sick children up to December 1981; The Scottish Hospital Inpatient Statistics for the years 1961–1977; all the existing regional histopathology records in the

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This excess mortality in children was primarily because of an increased risk of death from suicide, violence, cancer, cerebrovascular disease and accidents

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Alimentary Tract

Increased suicide risk in coeliac disease—A Swedish nationwide cohort study☆

Jonas F. Ludvigsson[a,b,*], Carl Sellgren[c], Bo Runeson[d], Niklas Långström[c,e], Paul Lichtenstein[c]

[a] Department of Paediatrics, Örebro University Hospital, Sweden
[b] Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital and Karolinska Institutet, Sweden
[c] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden
[d] Department of Clinical Neuroscience, Karolinska Institutet, Sweden

CD diagnosed in childhood was associated with a 40% increase in suicide risk (this includes both on or off a GFD)

tion controls (HR = 1.55; 95%CI = 1.15–2.10; based on 54 completed suicides). Whilst suicide was also more common amongst individuals with inflammation (HR = 1.96; 95%CI = 1.39–2.77), no such increase was seen amongst individuals with a normal mucosa but positive coeliac disease serology (HR = 1.06; 95%CI = 0.37–3.02).

Conclusions: We found a moderately increased risk of suicide amongst patients with coeliac disease. This merits increased attention amongst physicians treating these patients.

1. Introduction

Coeliac disease (CD) is an immune-mediated disorder triggered by exposure to gluten. CD occurs in some 1/100 individuals, and is associated with a number of other somatic disorders including endocrine disease [1], sepsis [2] and osteoporosis [3]; but there are also several studies suggesting a positive association between CD and depression [4–10]. The mechanism behind the association between CD and depression may include conditions of the central nervous system [11], somatic comorbidity [1–3], poor quality of life [12], and economic restraints caused by health care and adherence to a gluten-free diet [13] – or a combination of these. Some data also indicate that the association with depression does not abate with a gluten-free diet [4,7]. Since CD has been associated with psychiatric disorders, it is possible that patients with CD are at increased risk for suicide.

In a recent paper, we found a 39% increased risk of overall death in CD [14]; most individuals died from cardiovascular disorder, malignancy and respiratory disease. However, other causes of death were also more common in individuals with CD (Hazard ratio, HR = 1.65; 95%CI = 1.51–1.81)[14].

We know of no large-scale studies on CD and suicide. An earlier Swedish study indicated an increased risk of death from external causes in CD [15], but that study was restricted to inpatients, and did not specifically examine the risk of suicide. A British study suggested an increased risk of death from accidents, suicides and violence in *children*, but not in adults, with CD [16].

Since the association between CD and suicide remains uncertain, we conducted a retrospective cohort study to compare the risk of suicide amongst 29,000 individuals in Sweden with biopsy-verified CD (with villous atrophy, VA) during 1969–2007 with that amongst general population controls. For comparative reasons, we also estimated the risk of suicide in individuals with small intestinal inflammation but without VA, and those with normal mucosa but positive CD serology.

☆ *Disclaimer*: None of the funders had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. *Guarantor*: JFL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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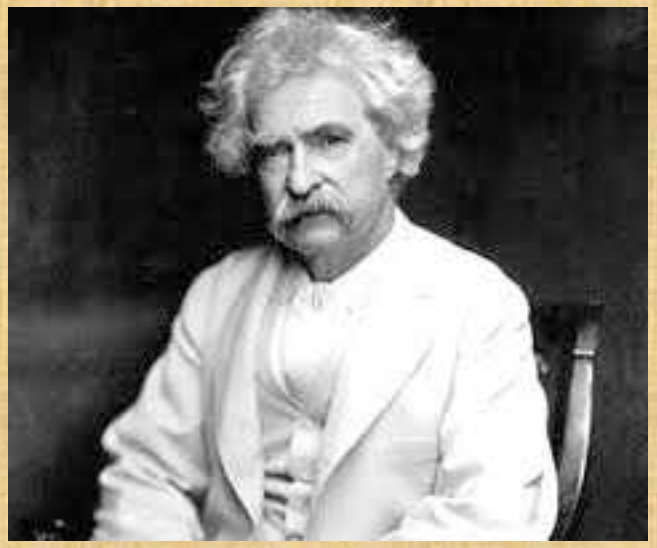

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University of Nottingham, Division of Epidemiology and Public Health, Medical School, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom

INTRODUCTION: To explore whether the excess mortality in celiac disease is related directly to the disease and duration of gluten exposure before diagnosis we have examined the long-term mortality experience

WHY???

suicide, and violence (seven deaths, SMR 3.22, 95% CI 1.29–6.63), cancer (five deaths, SMR 3.72, 95% CI 1.21–8.67), and cerebrovascular disease (two deaths, SMR 10.03, 95% CI 1.21–36.00).

CONCLUSIONS: Children diagnosed with celiac disease had a threefold increased risk of long-term mortality. This is in marked contrast to the experience of adult celiac disease where the long-term increase of mortality was modest. The increased mortality in children from external causes may reflect behavioral change associated with coping with a chronic disease and its treatment.

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CLINICAL PERSPECTIVES

Coeliac disease: current approach and future prospects

R. P. Anderson

Autoimmunity and Transplantation Division, Walter and Eliza Hall Institute and Department of Gastroenterology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia

Key words
coeliac disease, transglutaminase immunoglobulin A, deamidated gliadin peptide, immunoglobulin G, immunotherapy.

Abstract

Public anxiety over gluten has fuelled widespread demand for gluten-free food, yet coeliac disease remains significantly underdiagnosed and some confusion

Strict gluten-free diet is mandatory for CD, but it frequently does not lead to normalization of (the damage to the intestines).

such as type 1 diabetes mellitus. Therapeutic targets have been identified and drugs are under development to supplement or even replace gluten-free diet. With greater awareness and non-dietary therapeutics, diagnosis and treatment of coeliac disease will be increasingly prominent in medical practice.

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Aliment Pharmacol Ther 2005; 21: 421–429 doi: 10.1111/j.1365-2036.2005.02345.x

Grown-up coeliac children: the effects of only a few years on a gluten-free diet in childhood

C. CIACCI, P. IOVINO, D. AMORUSO, M. SINISCALCHI, R. TORTORA, A. DI GILIO, M. FUSCO & G. MAZZACCA

Gastrointestinal Unit, Federico II University of Napoli, N...

Accepted for publication 29 November 2004

Aliment Pharmacol Ther 2005; 21: 421–429.

SUMMARY

Aim: To evaluate clinical and psychological status of adults with childhood diagnosis of coeliac disease who were re-exposed to gluten after only a few years and now on a gluten-containing diet, compared with adults never on gluten-free diet when compared with the transient gluten-free diet and gluten-free diet groups. Histology revealed villous subatrophy in all patients of never on gluten-free diet group, in 39 of 110 patients of gluten-free diet and in 84 of 85 of transient gluten-free diet groups. Herpetiform dermatitis was found in

Prevalence of autoimmune disorders was increased in effects of gluten sensitivity.

After at least 2 years on a GFD

- **Intestinal damage was completely corrected in only 43.6%,**
- **Intestinal damage was modest in 32.6%, and**
- **Intestinal damage was severe in 23.8%**

INTRODUCTION

Coeliac disease is a condition in which, in genetically predisposed people, there is a reaction to gluten, a protein in some cereal grains.[1, 2] This reaction causes the formation of autoantibodies and the destruction of the villi in the small intestine, resulting in malabsorption of nutrients. Lifelong gluten withdrawal from diet is now considered as the sole main therapy.

Once thought to be a childhood disease that would be outgrown, diagnosis of coeliac disease was mainly made on a clinical and histological basis.[3, 4] In Europe, after a variable period of being on a gluten-free diet (GFD), children were re-exposed to gluten.[5] In the case of absence of clinical signs, patients were often left on a gluten-containing diet. Recent evidence indicates that it

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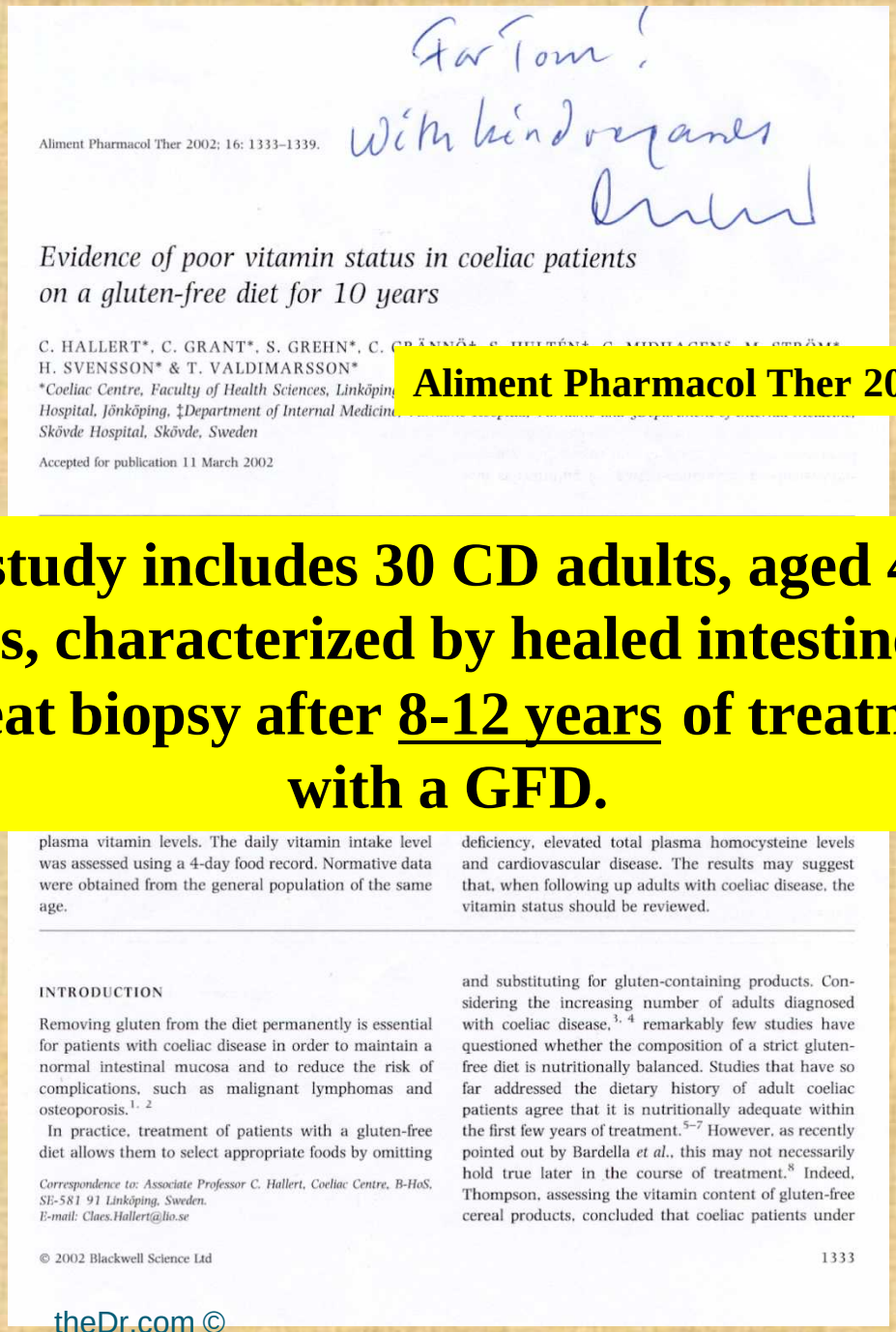

For Tom!
With kind regards

Aliment Pharmacol Ther 2002; 16: 1333–1339.

Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years

C. HALLERT*, C. GRANT*, S. GREHN*, C. GRÄNNÖ†, S. HULTÉN†, G. MIDHAGEN‡, M. STRÖM§, H. SVENSSON* & T. VALDIMARSSON*
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Accepted for publication 11 March 2002

Aliment Pharmacol Ther 2002; 16: 1333-1339

The study includes 30 CD adults, aged 45-64 years, characterized by healed intestines at repeat biopsy after 8-12 years of treatment with a GFD.

plasma vitamin levels. The daily vitamin intake level was assessed using a 4-day food record. Normative data were obtained from the general population of the same age.

deficiency, elevated total plasma homocysteine levels and cardiovascular disease. The results may suggest that, when following up adults with coeliac disease, the vitamin status should be reviewed.

INTRODUCTION

Removing gluten from the diet permanently is essential for patients with coeliac disease in order to maintain a normal intestinal mucosa and to reduce the risk of complications, such as malignant lymphomas and osteoporosis.[1, 2]

In practice, treatment of patients with a gluten-free diet allows them to select appropriate foods by omitting and substituting for gluten-containing products. Considering the increasing number of adults diagnosed with coeliac disease,[3, 4] remarkably few studies have questioned whether the composition of a strict gluten-free diet is nutritionally balanced. Studies that have so far addressed the dietary history of adult coeliac patients agree that it is nutritionally adequate within the first few years of treatment.[5–7] However, as recently pointed out by Bardella *et al.*, this may not necessarily hold true later in the course of treatment.[8] Indeed, Thompson, assessing the vitamin content of gluten-free cereal products, concluded that coeliac patients under

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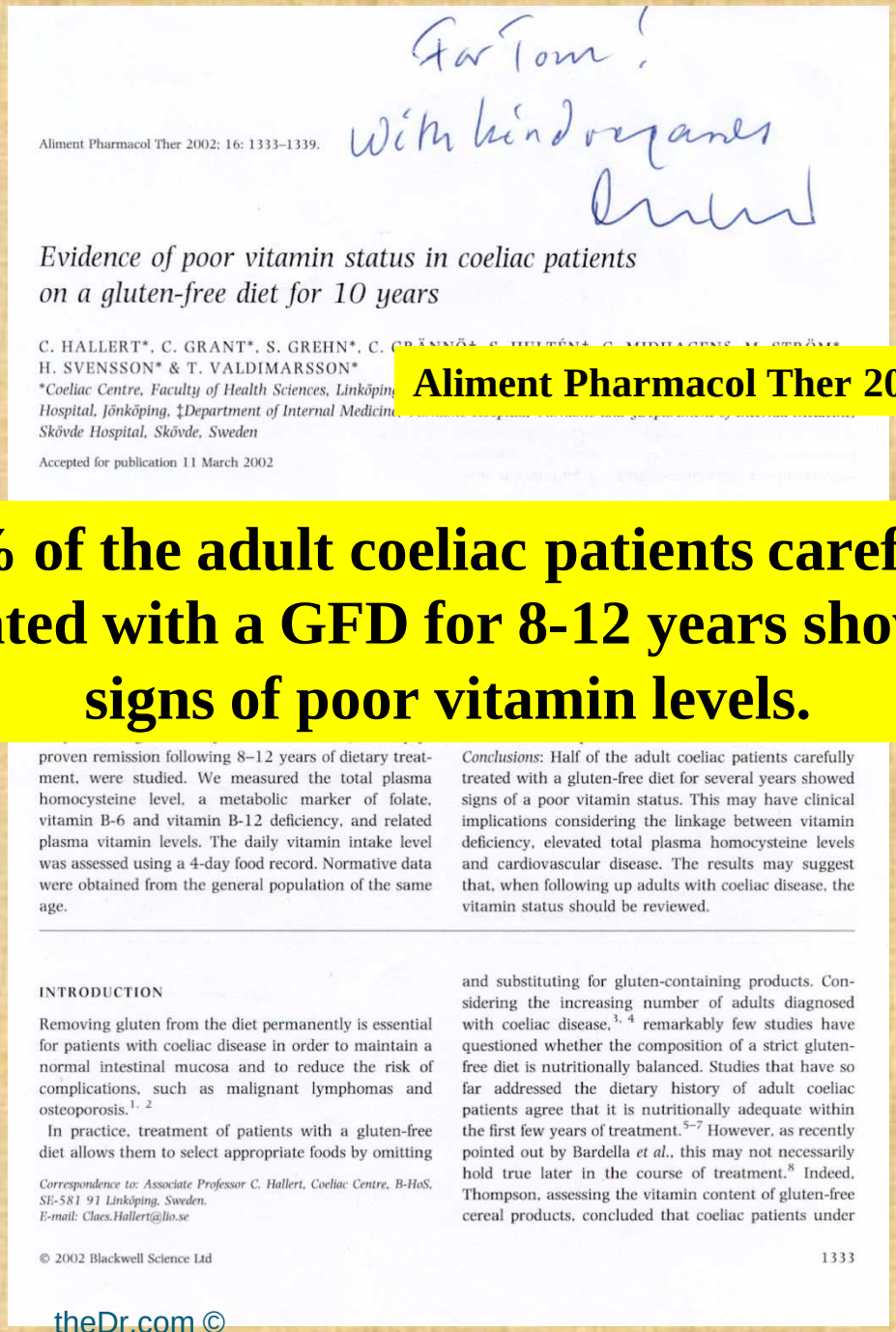

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50% of the adult coeliac patients carefully treated with a GFD for 8-12 years showed signs of poor vitamin levels.

proven remission following 8–12 years of dietary treatment, were studied. We measured the total plasma homocysteine level, a metabolic marker of folate, vitamin B-6 and vitamin B-12 deficiency, and related plasma vitamin levels. The daily vitamin intake level was assessed using a 4-day food record. Normative data were obtained from the general population of the same age.

Conclusions: Half of the adult coeliac patients carefully treated with a gluten-free diet for several years showed signs of a poor vitamin status. This may have clinical implications considering the linkage between vitamin deficiency, elevated total plasma homocysteine levels and cardiovascular disease. The results may suggest that, when following up adults with coeliac disease, the vitamin status should be reviewed.

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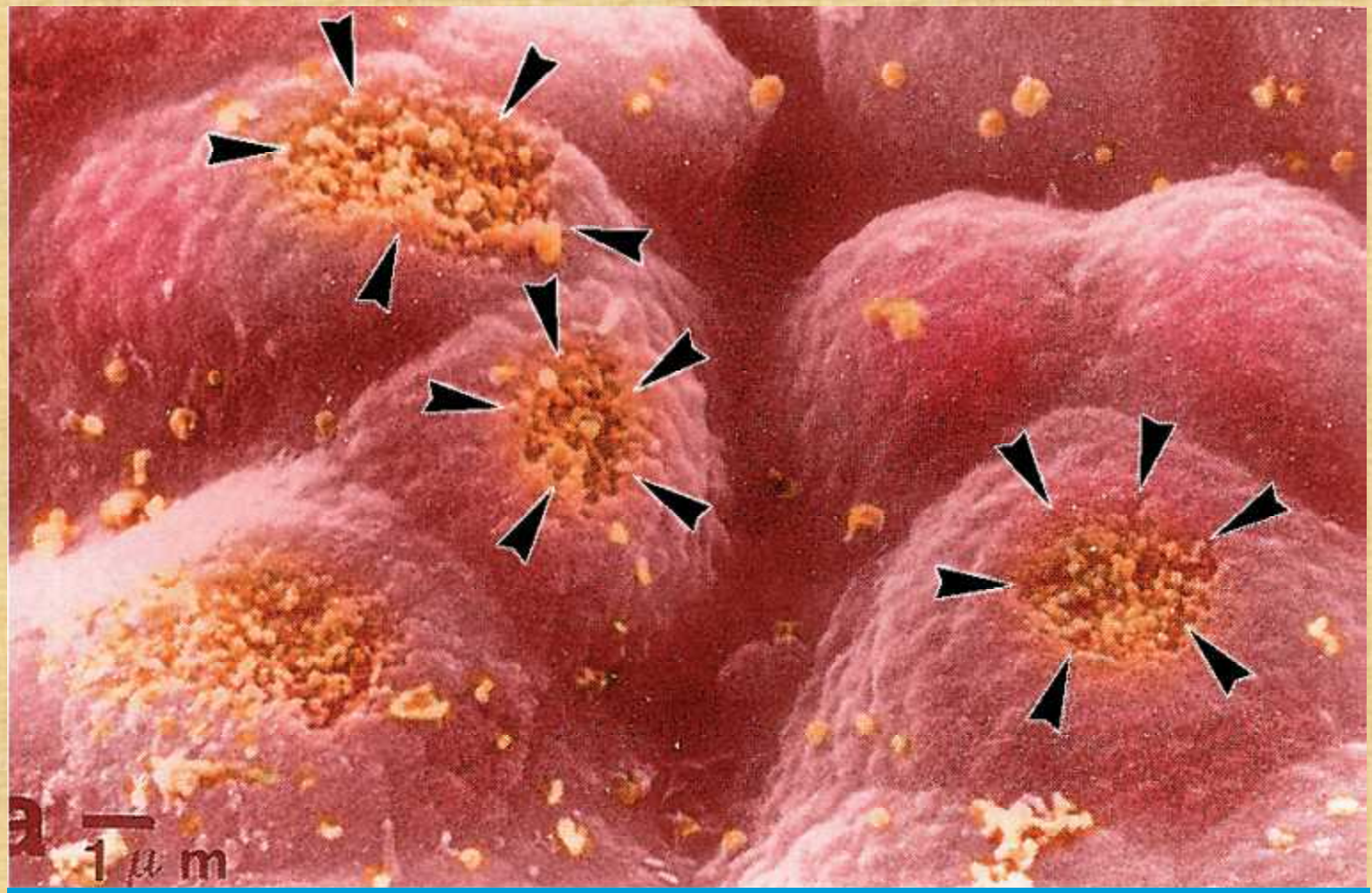
We Must Heal the Damage That Has Accrued from Gluten Sensitivity



Explaining Intestinal Permeability

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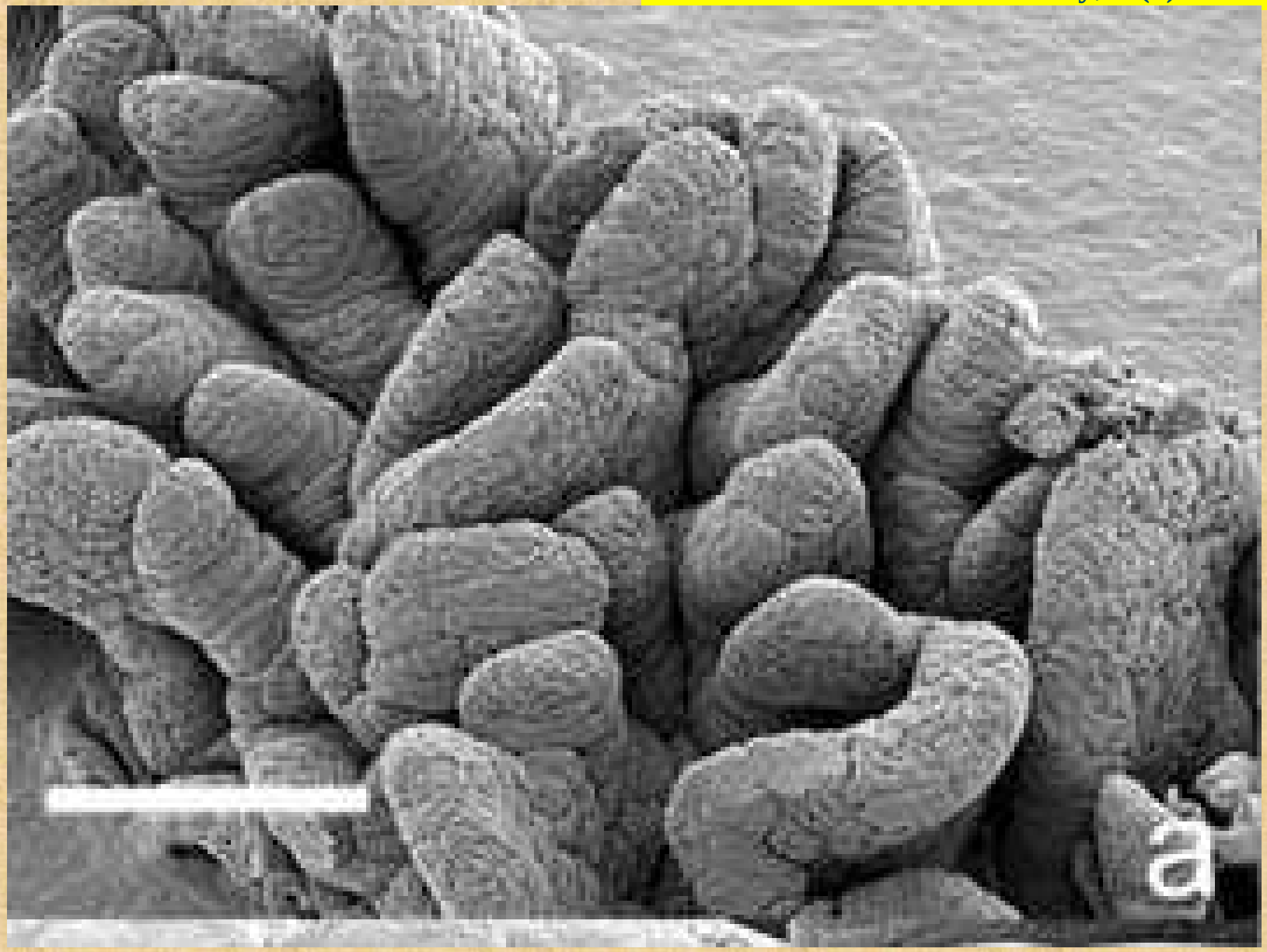
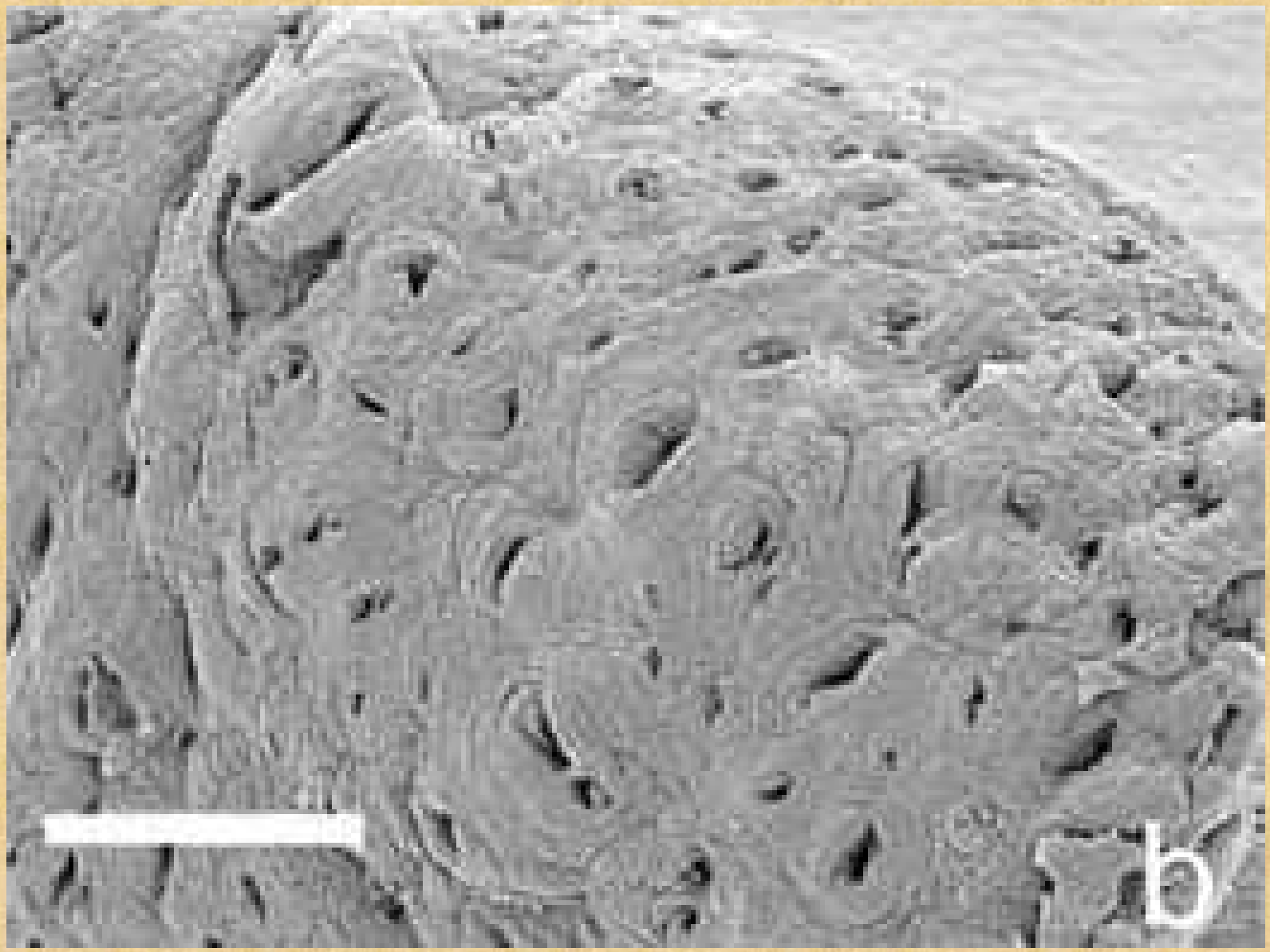
Am J Gastroenterol. 2004 May;99(5):894-904



Am J Gastroenterol. 2004 May;99(5):894-904



Flattened Villous Architecture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The Gluten Summit
A Grain of Truth

Alessio Fasano, MD

-1993 founded the University of Maryland School of Medicine's Division of Pediatric Gastroenterology and Nutrition

-Ten years later, he published the groundbreaking study in the *Annals of Medicine* that established the prevalence rate of celiac disease at 1 in 133 people in the U.S.

-In 1996, Dr. Fasano founded the Center for Celiac Research at the University of Maryland, the first celiac center in the United States.

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

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

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

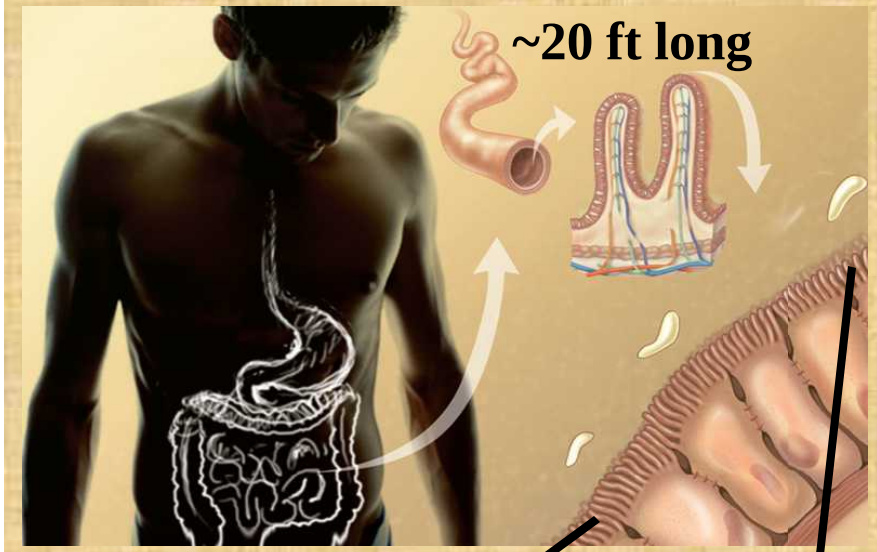
Alessio Fasano, MD

Dr. Fasano, Could you tell us, what is intestinal permeability?

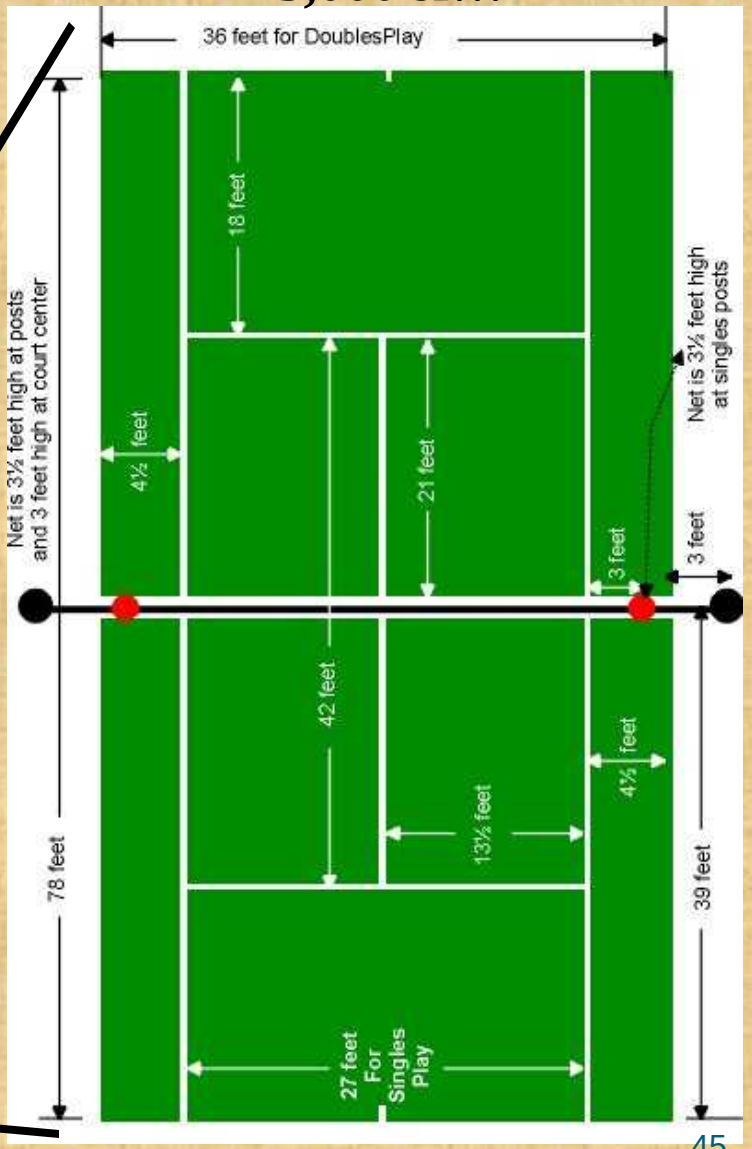
Alessio Fasano, MD

It's one of the key functions of the intestine that I probably think has been the most overlooked over human biology. So, we always were under the impression that the key function of the intestine is to digest and absorb foodstuffs. And, that, of course, is an important function. But, it's not just that. It's much more than that. If we just pay attention to what nature has done in engineering this wonderland system that is the gut's intestinal system, you start to wonder why the anatomy and the physiology is built in that way. And, you start to see, the amplified surface. That means we want to interface with the environment as much as we can.

Intestine: Interesting Facts



~3,000 sf!!!



Alessio Fasano, MD

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

Alessio Fasano, MD

And, when you put all this together, when you connect the dots, you start to wonder, "Well, what else besides digesting and absorbing foodstuffs is the intestine doing?" The key function is to interface with the environment and eventually exchange information, including molecules from the environment that comes in in a very tightly and coordinated and controlled manner. And, the bottom line, the modern biology seems to suggest that the state of health or the state of disease is the combination between what we are--meaning what genetically makes us, the way that we're engineered--and the environment that's around us.

Alessio Fasano, MD

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

Alessio Fasano, MD

And, we knew this for a long time. Evolutionary biologists, they knew that. Clinicians, they knew that. So, you can take identical twins. They have identical genetics. You split [them] at birth. And, one will be grown up in the North Pole and the other one in the Equator. At the end, these kids, even if they are identical twins, they will look totally different, meaning that, again, we are whatever we are at the component of these two worlds: the genes that we're born with and the environment that surrounds us.

Alessio Fasano, MD

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

Alessio Fasano, MD

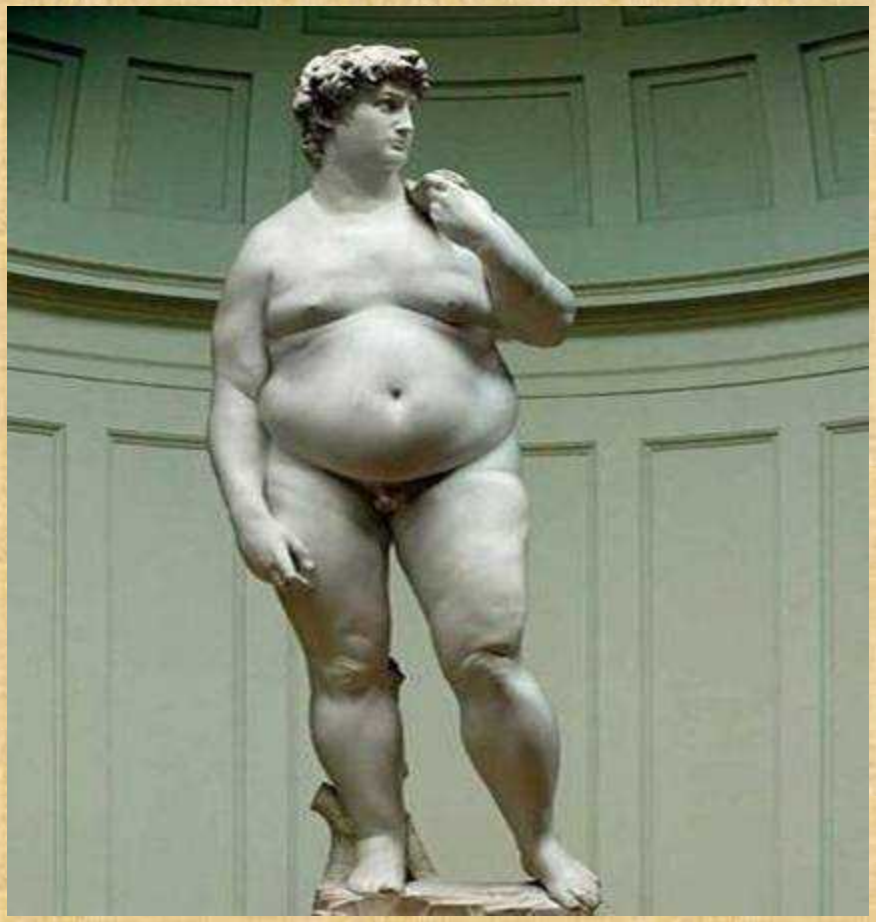
And, if everything goes fine and this traffic is tightly controlled...And, again if you look at what nature did, you really realize that this is an extremely important function of this intestinal permeability, we stay in a state of health. But, if this tightly-controlled trafficking is, for whatever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

Alessio Fasano, MD

So, with Intestinal Permeability, we don't have this tightly-controlled trafficking anymore. But, this uncontrolled trafficking of these molecules. And, depending who we are, on what kind of genetic background we have, we can develop different problems. For example, we can develop food allergies if we are skewed to develop allergies. We can develop autoimmune diseases. We can develop chronic inflammation that can lead to a stroke, Alzheimer's, you name it, cancer. And, all this depends, again, on who we are genetically speaking, and what kind of environment is surrounding us.

Alessio Fasano, MD

So, I think that to make this in even more i ve're born, and, therefore, we have the entire ge like a very precious single marble block. But, wh n this marble block in terms of what kind of scul e environment. So, it can be an environment that you can become the painter Michelangelo's David. Or, you can be in a different environment and the outcome will not be so wonderful. And, that's pretty much the story.



The result of epigenetics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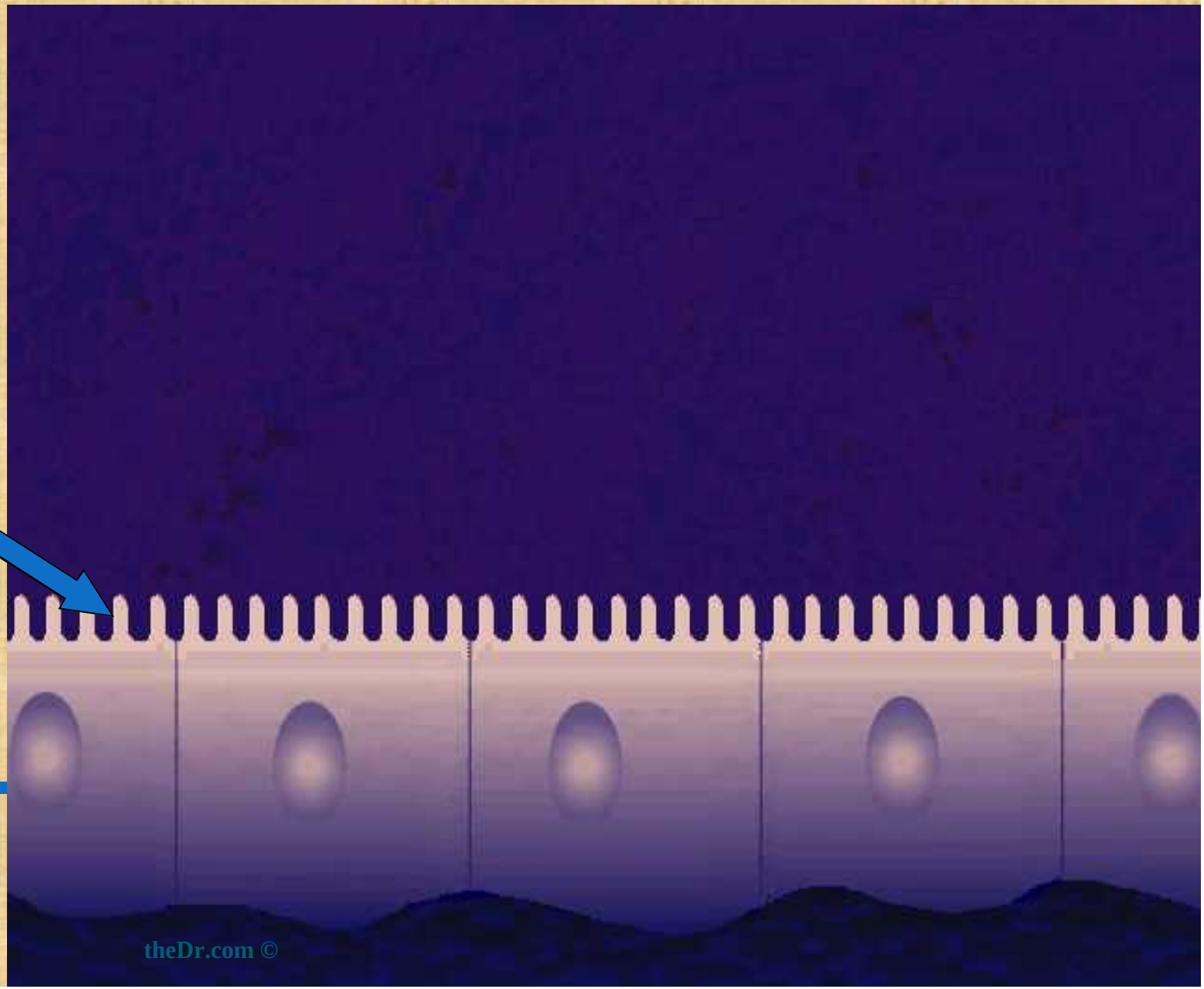
Healthy Gut


Healthy Villi/Good Absorption
Healthy Cell Junctions
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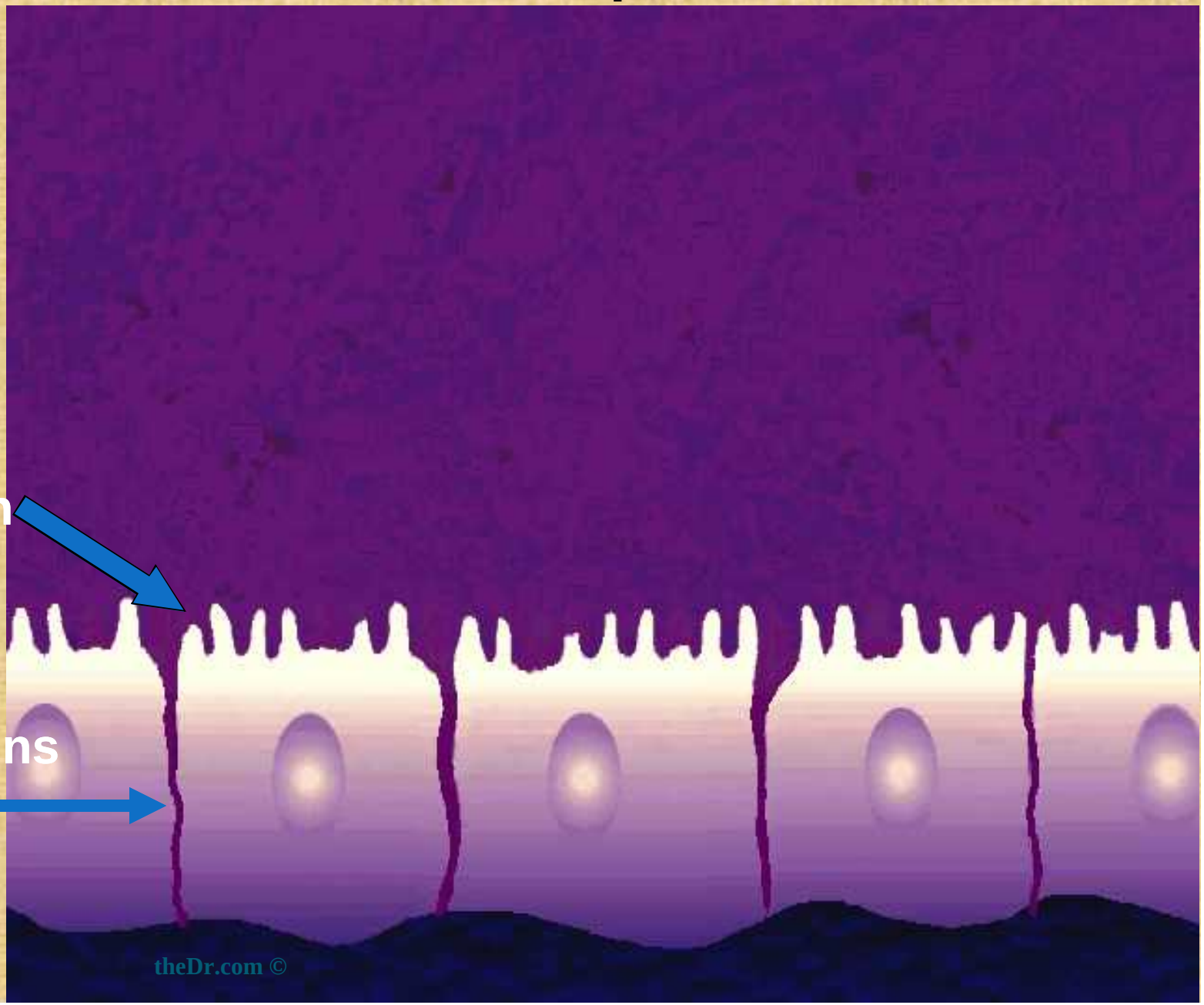
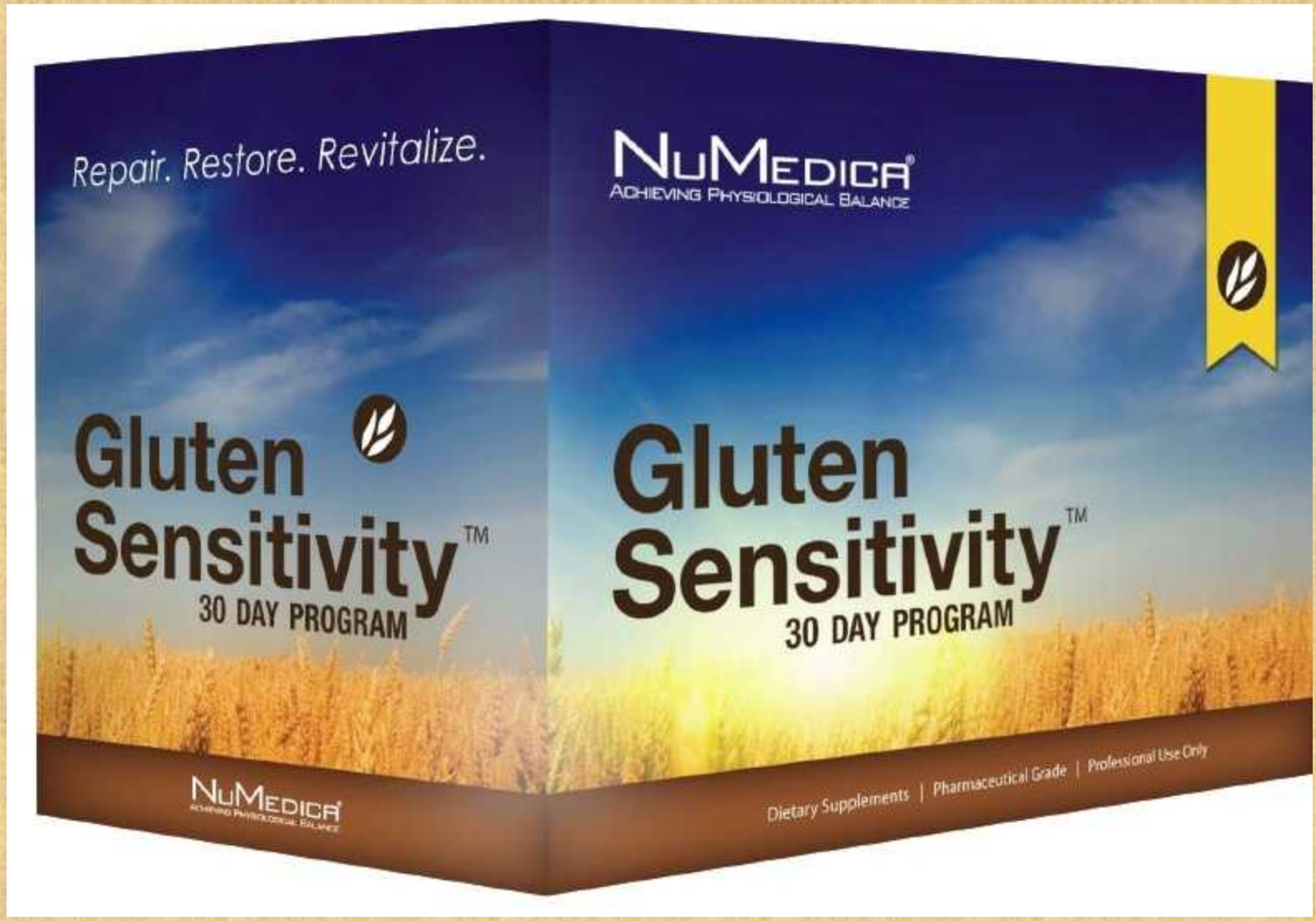
Leaky Gut & Malabsorption



Become A Certifed Gluten Practitioner!

patti@theDr.com

The purpose of the CGP Program is to educate the Healthcare Practitioner and their Staff in recognizing, accurately identifying, testing and comprehensively treating Non-Celiac Gluten Sensitivity (NCGS), Celiac Disease (CD) and related Autoimmune conditions.


Repair. Restore. Revitalize.
Gluten Sensitivity™
30 DAY PROGRAM
NuMedica
Achieving Physiological Balance
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Achieving Physiological Balance
Gluten Sensitivity™
30 DAY PROGRAM
Dietary Supplements | Pharmaceutical Grade | Professional Use Only

Kit Contains

- **Gluten Sensitivity Packs**
- **Gluten Sensitivity GI Restore**
- **Gluten Sensitivity PRP Balance Spray**
- **GS Micellized D3**
- **GS Tri-flora Plus**
- **Gluten Sensitivity Kit Booklet**


NuMedica
Achieving Physiological Balance
GS Micellized D3
1000 IU Per Drop
Soy-Free
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1 Fluid Ounce (30 ml)
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gluten free
NuMedica
Achieving Physiological Balance
GS Tri-Flora™
Multi-Strain Probiotic with
Saccharomyces boulardii
Dietary Supplement
60 Vegetable Capsule
Professional Use Only • Professional Use Only
gluten free
NuMedica
Achieving Physiological Balance
Gluten Sensitivity
GI Restore™
100% Pure Bovine Colostrum
Rich in IgG and PRPs for
Gluten Sensitivity Support*
Dietary Supplement
300 Grams • 30 Servings
Pharmaceutical Grade • Professional Use Only
gluten free
NuMedica
Achieving Physiological Balance
Gluten Sensitivity
PRP Balance™
Immune
Balancing Spray
Dietary Supplement
Pharmaceutical Grade
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Dietary Supplement
Pharmaceutical Grade
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Sensitivity
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A powerful combination
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Gluten Sensitivity Packs™
a powerful combination of five nutritional formulas in convenient daily dose packets. Each packet offers daily support for the maintenance of a healthy immune system, eicosanoid balance and chronic inflammation caused by gluten sensitivity. This formula promotes healthy tissue in the skin, joints, digestive system and nearly every other organ system in the body, and it has been specifically designed to exclude wheat and gluten.
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Gut on FIRE!
Body on Fire

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

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


GLUTEN

CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

Orally Based Diagnosis of Celiac Disease: Current Perspectives

J Dent Res 87(12):1100-1107, 2008

L. Pastore[1]*, G. Campisi[2], D. Compilato[2], and L. Lo Muzio[1]

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J Dent Res 87(12):1100-1107, 2008

ABSTRACT

Celiac disease (CD) is a lifelong immune-mediated [illegible] recurrence of histopathologic changes in the intestinal mucosa after the re-introduction of gluten, is considered for those persons in whom diagnosis remains in doubt. In this paper, we review studies that evaluated: (1) the possibility of using oral mucosa for the initial diagnosis of CD or for local gluten challenge; and (2) the possibility of using salivary CD-associated antibodies as screening tests. Our review shows that orally based diagnosis of CD is attractive and promising, although additional evaluations with standardized collection and analysis methods are needed. There is some evidence of a dissociation between systemic and oral mucosal immune responses in CD. The hypothesis that gluten could stimulate naïve lymphocytes directly in the oral cavity would have important implications for the understanding, diagnosis, and management of CD.

KEY WORDS: celiac disease, diagnosis, oral mucosa, saliva, screening.

Received March 6, 2008; Last revision July 26, 2008; Accepted August 12, 2008

INTRODUCTION

In persons with celiac disease (CD), ingestion of wheat gluten causes small-intestinal mucosal injury. The typical form of the disease is characterized by a malabsorption syndrome (chronic diarrhea, abdominal pain and distention, weight loss). However, it is now evident that most cases of CD are atypical, with extra-intestinal manifestations (*e.g.*, iron-deficient anemia, abnormalities in liver function test) being the predominant, if not the sole, clinical features (Green and Cellier, 2007). Occurrence of long-term complications (autoimmune diseases, cancers) in persons with CD is responsible for a mortality rate higher than that in the general population (Corrao *et al.*, 2001; Peters *et al.*, 2003); this fact justifies gluten

Gluten is the protein fraction of most cereals, including wheat, rye, and barley.

In this paper, we review studies that evaluated: (1) the possibility of using oral mucosa for the initial diagnosis of CD or for local gluten challenge; and (2) the possibility of using salivary CD-associated antibodies as screening tests for the disease.

Etiology of Celiac Disease

Gluten is the protein fraction of most cereals, including wheat, rye, and barley. It is comprised of hundreds of protein components, traditionally classified on the basis of their solubility in alcohol-water solutions, in prolamins (alcohol-soluble), and glutenins (alcohol-insoluble) (Wieser, 2007). Although there is recent evidence that even glutenins could be involved in the pathogenic mechanisms of CD (Dewar *et al.*, 2006; Howdle, 2006), prolamins of wheat, rye, and barley (namely, gliadins, secalins, and hordeins, respectively) are thought to be responsible for triggering CD. A high content of glutamine and proline is a common feature of gliadins, secalins and hordeins, while prolamins of cereals considered to be non-toxic for persons with CD, such as rice and corn, have a lower content of these amino acids (Schuppan, 2000). This particular amino acid composition confers resistance to complete degradation by gastrointestinal proteolytic enzymes, which results in accumulation of peptide fragments rich in glutamine and proline in the lumen of the small intestine (Kagnoff, 2007). An exceptionally immunoreactive 33-mer peptide resistant to digestion by all gastric, pancreatic, and intestinal brush-border membrane proteases has been identified from α-2 gliadin (Shan *et al.*, 2002), and an *in silico* analysis of the gluten proteome has led to the identification of as many as 60 putative peptides that have similar characteristics (Shan *et al.*, 2005).

An 83% concordance rate among monozygotic twins (Nistico *et al.*, 2006) and a 5-15% prevalence of the disease among first-degree relatives of affected persons (Wolters and Wijmenga, 2008) demonstrate a strong genetic susceptibility to CD. In fact, approximately 95% of persons with CD express the human

Table 2. Gluten Content of Various Grains

Food	Total protein	Gliadins (% of total protein)	Glutenins (% of total protein)
Wheat	10-15	40-50	30-40
Rye	9-14	30-50	30-50
Oats	8-14	10-15	~5
Corn	7-13	50-55	30-45
Rice	8-10	1-5	85-90
Sorghum	9-13	>60	
Millet	7-16	57	30
Buckwheat			High

Adapted from: Pizzorno JE, Murray MT, eds. *Textbook of Natural Medicine*. 2nd ed. New York: Churchill Livingstone; 1999:1601.

Expert Rev. Gastroenterol. Hepatol. 6(1), 43–55 (2012)

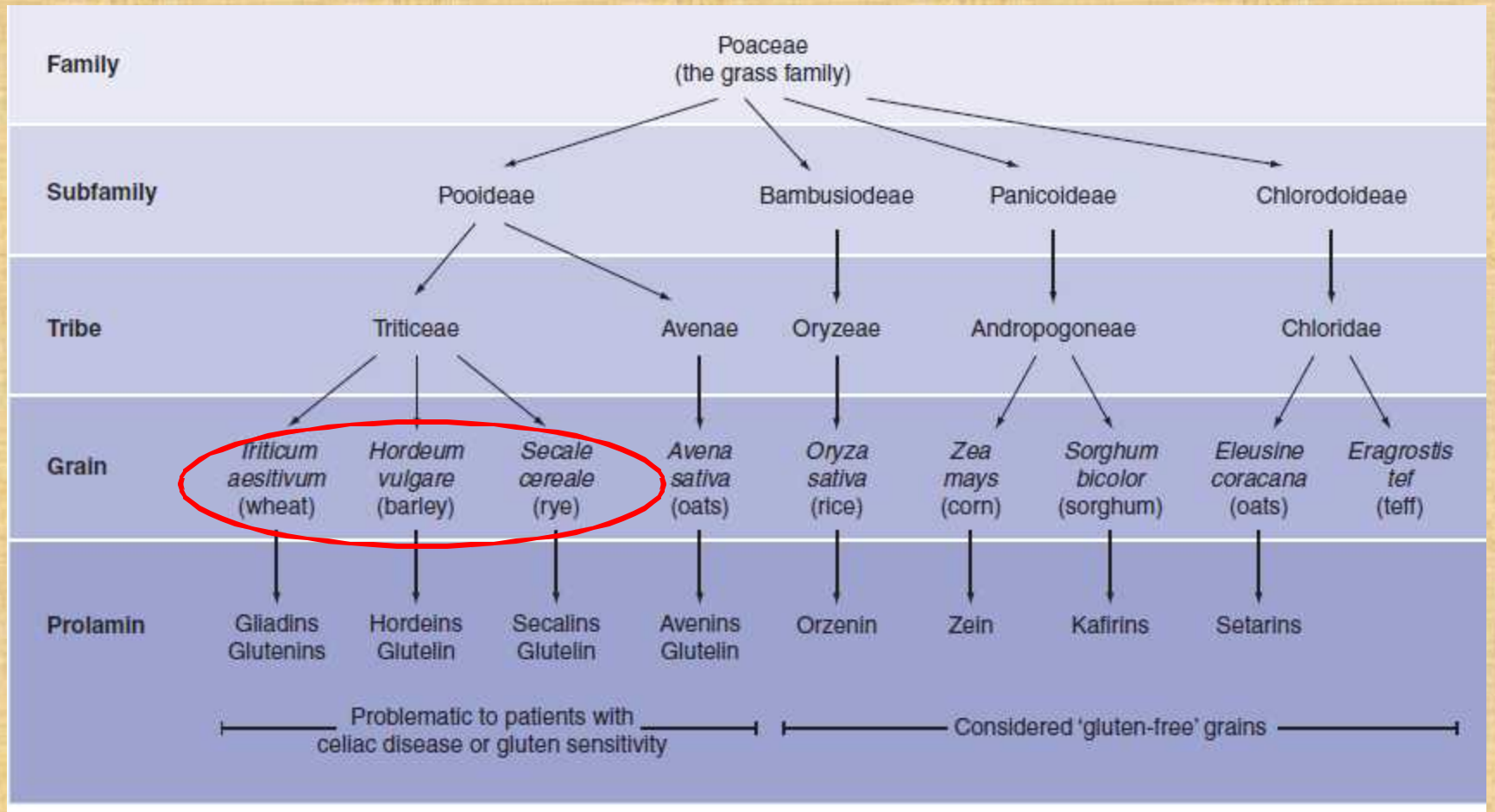
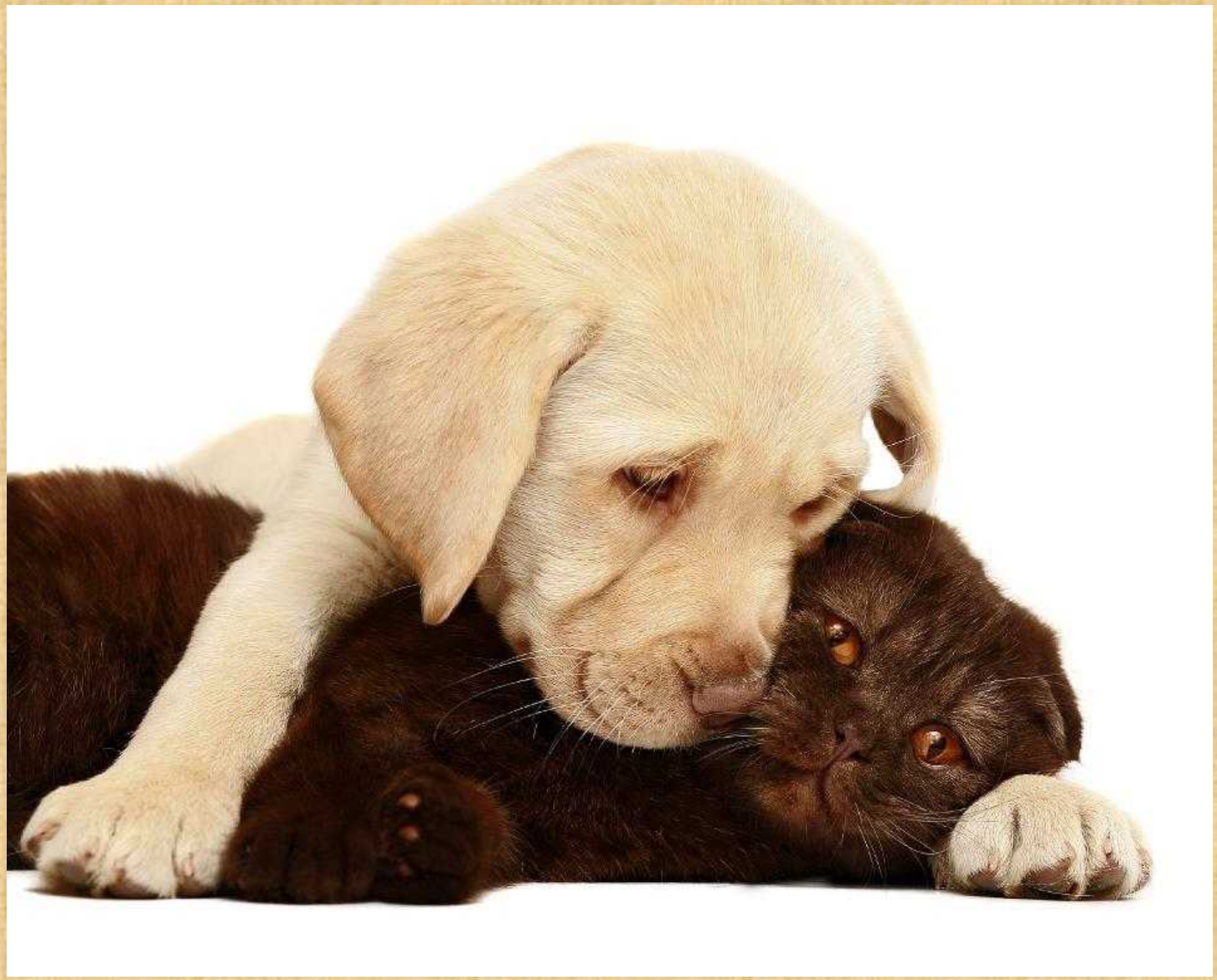


Figure 1. Classification of gluten proteins. Celiac disease and gluten sensitivity patients react to the toxic peptides produced by members of the Triticeae tribe, including the grains of wheat, barley and rye. Some patients also react to the prolamins in oats. Adapted with permission from [39].



The Changing Face of Childhood Celiac Disease in North America: Impact of Serological Testing

Pediatrics 2009;124;1572-1578

WHAT'S KNOWN ON THIS SUBJECT: European data demonstrated that celiac disease is a multisystem disorder, occurring in 0.3% to 1.0% of children. Serological testing facilitates the recognition of children presenting with atypical or extraintestinal symptoms or with celiac disease-associated conditions.

WHAT THIS STUDY ADDS: Serological testing tripled the incidence, quadrupled the age at diagnosis, and led to the recognition of diverse presentations of celiac disease in a North American population. Classic celiac disease predominated in younger children, whereas atypical presentations predominated in older children.

Department of Pediatrics, University of Calgary, Calgary, Canada

KEY WORDS
celiac disease, epidemiology, clinical features, endomysial antibody, serological testing

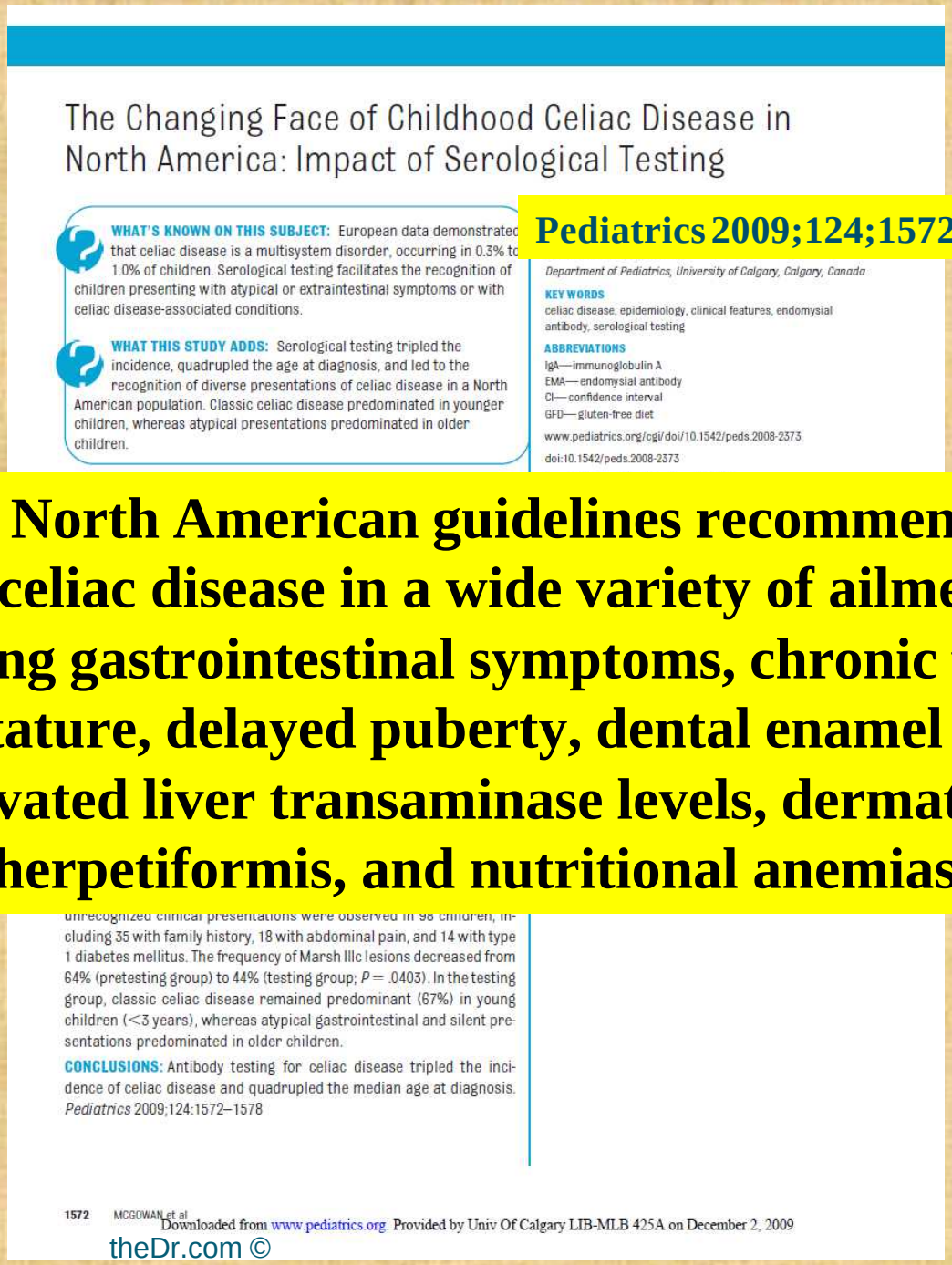
ABBREVIATIONS
IgA—immunoglobulin A
EMA—endomysial antibody
CI—confidence interval
GFD—gluten-free diet

www.pediatrics.org/cgi/doi/10.1542/peds.2008-2373
doi:10.1542/peds.2008-2373

In the past 7 years, 1 in 4 children were diagnosed as having celiac disease in as a result of case-finding of associated conditions,

RESULTS: The median age at diagnosis was 2 years (95% confidence interval: 2–4 years) in the pretesting group ($N = 36$), compared with 9 years (95% confidence interval: 8–10 years) in the testing group ($N = 199$; $P < .001$); the female/male ratios (1.6:1) were similar ($P = .982$). The incidence of celiac disease increased from 2.0 cases per 100 000 children (pretesting group) to 7.3 cases per 100 000 children (testing group; $P = .0256$). The frequency of classic celiac disease presentations decreased from 67% (pretesting group) to 19% (testing group; $P < .001$), but the incidence of classic celiac disease did not differ (0.8 vs 1.6 cases per 100 000; $P = .154$). In the testing group, 13 previously unrecognized clinical presentations were observed in 98 children, including 35 with family history, 18 with abdominal pain, and 14 with type 1 diabetes mellitus. The frequency of Marsh IIIc lesions decreased from 64% (pretesting group) to 44% (testing group; $P = .0403$). In the testing group, classic celiac disease remained predominant (67%) in young children (<3 years), whereas atypical gastrointestinal and silent presentations predominated in older children.

CONCLUSIONS: Antibody testing for celiac disease tripled the incidence of celiac disease and quadrupled the median age at diagnosis. *Pediatrics* 2009;124:1572–1578



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CONCLUSIONS: Antibody testing for celiac disease tripled the incidence of celiac disease and quadrupled the median age at diagnosis. *Pediatrics* 2009;124:1572–1578

Pediatrics 2009;124;1572-1578

Current North American guidelines recommend testing for celiac disease in a wide variety of ailments, including gastrointestinal symptoms, chronic fatigue, short stature, delayed puberty, dental enamel defects, elevated liver transaminase levels, dermatitis herpetiformis, and nutritional anemias.

ORIGINAL CONTRIBUTION

JAMA, Sept 16, 2009,Vol 302, No. 11

Small-Intestinal Histopathology and Mortality Risk in Celiac Disease

Jonas F. Ludvigsson, MD, PhD
Scott M. Montgomery, PhD
Anders Ekbom, MD, PhD
Lena Brandt, BSc
Fredrik Granath, PhD

Context Studies of mortality in celiac disease have not taken small-intestinal pathology into account.

Objective To examine mortality in celiac disease according to small-intestinal histopathology.

Design, Setting, and Patients Retrospective cohort study. We collected data from duodenal/jejunal biopsies taken between July 1969 and February 2008 on celiac disease (Marsh stage 3: villous atrophy; n=29 096 individuals) and inflammation (Marsh stage 1-2; n=13 306) from all 28 pathology departments in Sweden. A third cohort consisted of individuals with latent celiac disease from 8 university hospitals (n=3719). Latent celiac disease was defined as positive celiac disease serology in individuals with normal mucosa (Marsh stage 0). Through linkage with the Swedish Total Population

With few exceptions, research has shown an increased risk of death in celiac disease (35-72%)

creased somewhat.

Conclusion Risk of death among patients with celiac disease, inflammation, or latent celiac disease is modestly increased.

JAMA. 2009;302(11):1171-1178 www.jama.com

CELIAC DISEASE IS AN IMMUNE-mediated disorder that is triggered by gluten exposure in genetically sensitive individu-

rological markers has allowed screening of individuals with less marked symptoms; it is therefore possible that earlier studies (based on data until 2000[1,2,4-6,8,10,11]) overestimate the risk of death in celiac disease.

While villous atrophy is usually required for the diagnosis of celiac disease, less is known about the long-term consequences of nonspecific small-intestinal inflammation without villous atrophy. Research on other inflammatory disorders suggests that inflammation may be associated with increased mortality,[12-14] but this has not been investigated for nonspecific inflammation in the small intestine.

Some individuals have positive antibodies but normal small-intestinal mucosa, often referred to as having "latent" celiac disease.[15] Although villous atrophy in small-intestinal biopsy has been the gold standard for a celiac disease diagnosis,[15,16] it has been argued that small-intestinal biopsy can, under certain circumstances, be replaced by celiac disease serology.[17] Positive celiac disease serology has been linked to increased mortality[11]; however, the predictive value and long-term consequences of celiac disease serology in individuals with normal mucosa are unknown.

We used nationwide histopathology data to examine the overall risk of death in individuals with celiac disease and inflammation. Through regional data linkage, we were also able to examine mortality in latent celiac disease.

See also p 1225 and Patient Page.

METHODS

This retrospective cohort study estimated mortality in celiac disease according to small-intestinal histopathology. Nationwide histopathology data were matched with mortality data from government agencies in Sweden.

Author Affiliations: Department of Pediatrics (Dr Ludvigsson) and Clinical Research Centre (Dr Montgomery), Örebro University Hospital, Örebro, Sweden; Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden (Drs Ludvigsson, Montgomery, Ekbom, and Granath and Ms Brandt); and Department of Primary Care and Social Medicine, Charing Cross Hospital, Imperial College, London, England (Dr Montgomery).
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351,403 biopsy reports remained in 287,586 unique individuals

- **celiac disease: 29,148;**
- **latent celiac disease: 3736**
- **inflammation:13,446; and**
- **normal biopsy:244,992**

CELIAC DISEASE IS AN IMMUNE-mediated disorder that is triggered by gluten exposure in genetically sensitive individuals, occurring in about 1% of the West-

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JAMA. 2009;302(11):1171-1178 www.jama.com

This is the largest study of mortality in CD, and the number of deaths (3000) exceeds that of all earlier studies together

CELIAC DISEASE IS AN IMMUNE-mediated disorder that is triggered by gluten exposure in genetically sensitive individu-

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We used nationwide histopathology data to examine the overall risk of death in individuals with celiac disease and inflammation. Through regional data linkage, we were also able to examine mortality in latent celiac disease.

See also p 1225 and Patient Page.

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This retrospective cohort study estimated mortality in celiac disease according to small-intestinal histopathology. Nationwide histopathology data were matched with mortality data from government agencies in Sweden.

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ORIGINAL CONTRIBUTION

JAMA, Sept 16, 2009,Vol 302, No. 11

Small-Intestinal Histopathology and Mortality Risk in Celiac Disease

Jonas F. Ludvigsson, MD, PhD
Scott M. Montgomery, PhD
Anders Ekbom, MD, PhD
Lena Brandt, BSc
Fredrik Granath, PhD

Context Studies of mortality in celiac disease have not taken small-intestinal pathology into account.

Objective To examine mortality in celiac disease according to small-intestinal histopathology.

Design, Setting, and Patients Retrospective cohort study. We collected data from duodenal/jejunal biopsies taken between July 1969 and February 2008 on celiac disease (Marsh stage 3: villous atrophy; n=29 096 individuals) and inflammation (Marsh stage 1-2; n=13 306) from all 28 pathology departments in Sweden. A third cohort consisted of individuals with latent celiac disease from 8 university hospitals (n=3719). Latent celiac disease was defined as positive celiac disease serology in individuals with normal mucosa (Marsh stage 0). Through linkage with the Swedish Total Population

Mortality was increased in all 3 cohorts:

- **HRs were similar in celiac disease (HR, 1.39; 95%)**
- **and latent (negative biopsy) celiac disease (HR, 1.35; 95%)**
- **But was double in patients with inflammation (HR, 1.72; 95%),**

CELIAC DISEASE IS AN IMMUNE-mediated disorder that is triggered by gluten exposure in genetically sensitive individu-

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Cardiovascular disease was the most common cause of death in celiac disease, followed by malignancy

creased somewhat.

Conclusion Risk of death among patients with celiac disease, inflammation, or latent celiac disease is modestly increased.

JAMA. 2009;302(11):1171-1178 www.jama.com

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The highest HRs were seen in the first year after biopsy, with an increased risk of 3.78 for death due to malignancy and 1.86 for CV death.

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ORIGINAL INVESTIGATION

Causes of Death in Patients With Celiac Disease in a Population-Based Swedish Cohort

Ulrike Peters, PhD, MPH; Johan Askling, MD; Gloria Gridley, MS; Anders Ekbom, MD, PhD; Martha Linet, MD

ARCH INTERN MED/VOL. 163, JULY 14, 2003

Background: Patients with celiac disease have an increased risk of death from gastrointestinal malignancies and lymphomas, but little is known about mortality from other causes and few studies have assessed long-term outcomes.

Methods: Nationwide data on 10 032 Swedish patients hospitalized from January 1, 1964, through December 31, 1993, with celiac disease and surviving at least 12 months were linked with the national mortality register. Mortality risks were computed as standardized mortality ratios (SMRs), comparing mortality rates of patients with celiac disease with rates in the general Swedish population.

overall SMR did not differ by sex or calendar year of initial hospitalization, whereas mortality risk in patients hospitalized with celiac disease before the age of 2 years was significantly lower by 60% (95% CI, 0.2-0.8) compared with the same age group of the general population. Mortality risks were elevated for a wide array of diseases, including non-Hodgkin lymphoma (SMR, 11.4), cancer of the small intestine (SMR, 17.3), autoimmune diseases (including rheumatoid arthritis [SMR, 7.3] and diffuse diseases of connective tissue [SMR, 17.0]), allergic disorders (such as asthma [SMR, 2.8]), inflammatory bowel diseases (including ulcerative colitis and Crohn disease [SMR, 70.9]), diabetes mellitus (SMR, 3.0), disorders of

The Swedish Inpatient Registry
-investigated mortality risks > 10,000 CD patients,
-30 years of follow-up,
-examined long-term, cause-specific mortality outcomes (SMR)
-provided further information about the lifetime natural history of CD.

Karolinska Institute, Stockholm, Sweden (Drs Askling and Ekbom). The authors have no relevant financial interest in this article.

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Arch Intern Med. 2003;163:1566-1572

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Cancer of SI (SMR 17.3)
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CELIAC DISEASE is a disorder characterized by permanent intolerance to the protein gluten, which is contained in grains such as wheat, rye, or barley, and manifested by inflammation of the small intestine in genetically susceptible individuals. Typical symptoms include diarrhea and weight loss, but many patients, especially adults, have only mild or atypical symptoms. The widely accepted basis for the diagnosis of celiac disease is a biopsy to confirm the jejunal villous atrophy.[1,2] The prevalence of celiac disease ranges from 0.1 celiac patient per 1000 live births in Denmark, Finland, Germany, Spain, New Zealand, and the United States to approximately 3 per 1000 live births in Ireland.[3-5] In Sweden, a high prevalence of childhood-onset celiac disease has been noted, but it is unclear to what extent this pattern reflects changes in infant exposure to gliadin (eg, through early introduction of cereal drinks).[3,6] The reported prevalence of the disease in the United States seems to be somewhat low in light of the genetic similarities and European ancestry of many white Americans. Since serologic screening tests, such as antigliadin and antiendomysium antibody assays, have become more widely available in the last decade, it now seems that celiac disease is widely underdiagnosed,[7-10] including in the United States.[11-16] Recent population-based screening studies in several European countries have shown that prevalence of celiac disease is much higher (eg, 2 to 10 patients per 1000 individuals) than previously reported,[10,17-20] making celiac disease one of the most common genetically based human diseases.[21,22]

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Diabetes (SMR 3.0)
Disorders of Immune Deficiency (SMR 20.9)
Tuberulosis (SMR 5.9)
Pneumonia (SMR 2.9)
Nephritis (SMR 5.4)

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ORIGINAL INVESTIGATION

Prevalence of Celiac Disease in At-Risk and Not-At-Risk Groups in the United States

A Large Multicenter Study

Alessio Fasano, MD; Irene Berti, MD; Tania Gerarduzzi, MD; Tarcisio Not, MD; Richard B. Colletti, MD; Sandro Drago, MS; Yoram Elitsur, MD; Peter H. R. Green, MD; Stefano Guandalini, MD; Ivor D. Hill, MD; Michelle Pietzak, MD; A... Steven S. Wasserman, PhD

ARCH INTERN MED/VOL 163, FEB 10, 2003

Background: Celiac disease (CD) is an immune-mediated enteropathic condition triggered in genetically susceptible individuals by the ingestion of gluten. Although common in Europe, CD is thought to be rare in the United States, where there are no large epidemiologic studies of its prevalence. The aim of this study was to determine the prevalence of CD in at-risk and not-at-risk groups in the United States.

...tives of patients with biopsy-proven CD, 3236 symptomatic patients (with either gastrointestinal symptoms or a disorder associated with CD), and 4126 not-at-risk individuals.

Results: In at-risk groups, the prevalence of CD was 1:22 in first-degree relatives, 1:39 in second-degree relatives, and 1:56 in symptomatic patients. The overall prevalence of CD in not-at-risk groups was 1:133. All the EMA-positive subjects who underwent intestinal biopsy had lesions consistent with CD.

Conclusions: Our results suggest that CD occurs fre-...

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CD is a much greater problem than has previously been appreciated.

CELIAC DISEASE (CD) is an immune-mediated enteropathy triggered in genetically susceptible individuals by the ingestion of gluten-containing grains (wheat, barley, and rye). The disease is associated with human leukocyte antigen (HLA) DQ2 and DQ8 haplotypes. In the continued presence of gluten, CD is self-perpetuating.[1] Given the undisputed role of gluten in causing inflammation and autoimmunity, CD represents a unique example of an immune-mediated disease for which early serologic diagnosis and dietary treatment can prevent severe, sometimes life-threatening complications.

The advent of new serologic tests, including for antigliadin antibodies (AGA) and anti–endomysial antibodies (EMA), enabled large-scale screening studies in Europe that revealed that CD is one of the most common genetic diseases of humankind, occurring in from 1 of 130 to 1 of 300 individuals in the European general population.[2-5] Recently, several authors have reported data on the prevalence of CD in parts of Africa,[6] South America,[7] and Asia,[8-11] showing that CD is more common than previously thought in these areas as well.

Serologic studies have demonstrated that the clinical manifestations of CD are more protean than previously reported.[12] Numerous clinical manifestations, including typical gastrointestinal symptoms as well as atypical and asymptomatic forms, have been described.[13] Within the US scientific community it is generally held that CD is a rare disorder in the United States.[14,15] However, this perception is unsubstantiated by any large epidemiologic study, and it remains a controversial issue.[16,17]

Author affiliations are listed at the end of this article.

ORIGINAL ARTICLE

Autoantibodies in Gluten Ataxia Recognize a Novel Neuronal Transglutaminase

Marios Hadjivassiliou, MD,[1] Pascale Aeschlimann, BSc,[2] Alexander Strigun, MSc,[2] David S. Sanders, MD,[3] Nicola Woodroofe, PhD,[4] and Daniel Aeschlimann, PhD[2]

Ann Neurol 2008;64:332–343

Objective: Gluten sensitivity typically presents as celiac disease, a chronic, autoimmune-mediated, small-i
Neurological disorders occur with a frequency of up to 10% in these patients. However, neurological dysfuncti
sole presenting feature of gluten sensitivity. Development of autoimmunity directed toward different members of the transglutaminase gene family could offer an explanation for the diversity in manifestations of gluten sensitivity. We have identified a novel neuronal transglutaminase isozyme and investigated whether this enzyme is the target of the immune response in patients with neurological dysfunction.

It is now accepted that gluten sensitivity is a systemic illness that can manifest in a range of organ systems.

detection of anti-gliadin and anti-transglutaminase 2 antibodies to identify a subgroup of patients with gluten sensitivity who may be at risk for development of neurological disease.

Ann Neurol 2008;64:332–343

Celiac disease (CD) is a common T-cell–mediated autoimmune disorder characterized by its linkage to specific human leukocyte antigen (HLA) alleles: HLA-DQ2 and -DQ8. In susceptible individuals, consumption of gluten triggers a $CD4^+$ T-cell response to gliadin, as well as a B-cell response to gliadin and self-antigens.[1] Transglutaminase 2 (TG2) is the autoantigen recognized in the endomysium of the gut by sera from patients with CD.[2] TG2-specific antibodies are almost exclusively found in CD, are characteristic of untreated clinically symptomatic, as well as latent disease, and hence have become accepted as an excellent diagnostic indicator of CD.

TG2 is one of a family of enzymes that covalently cross-link or modify proteins by formation of an isopeptide bond between a peptide-bound glutamine residue and a primary amine, most commonly a lysine residue either within the same or a neighboring polypeptide chain.[3] However, in some instances, TG2 may react with H_2O in preference over an amine, leading to the deamidation of glutamine residues.[4] The biological significance of this latter activity has only recently been established in connection with CD: gliadin proteins, the immunological trigger of gluten sensitivity, are glutamine-rich donor substrates amenable to deamidation.[5] Therefore, TG2 apparently contributes to disease development in at least two ways: first, by deamidating gluten peptides, thereby increasing their reactivity with HLA-DQ2/DQ8, which potentiates the T-cell response[6,7]; and second, by haptenization of self-antigens through cross-linking with gliadins.[8,9] The absence of intestinal T-cell responses to gluten in the majority of individuals carrying HLA-DQ2/DQ8 and the preferential T-cell responses to deamidated gluten fragments in patients with CD indicates that there is tolerance to unmodified gluten peptides. Therefore, acti-

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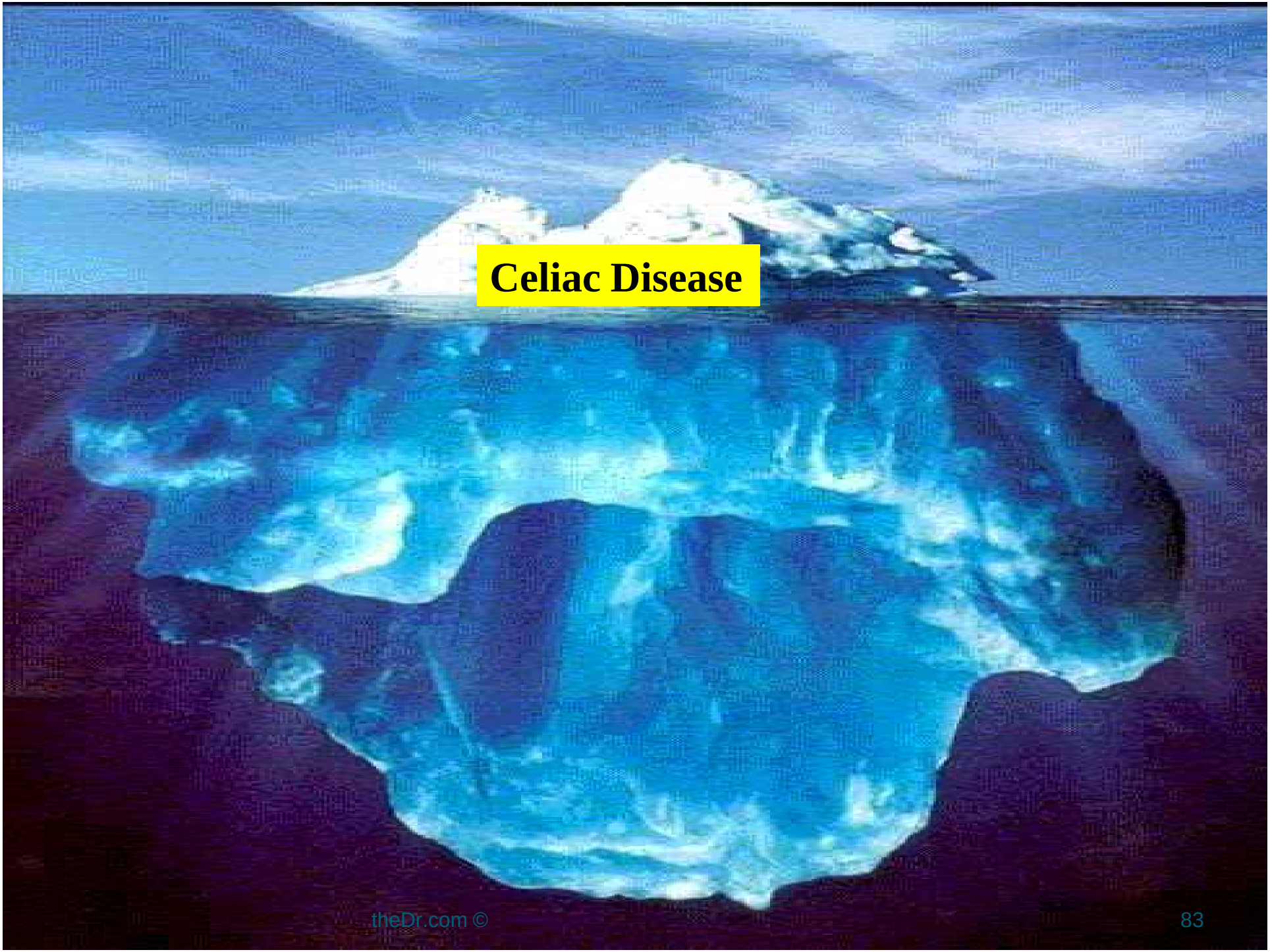
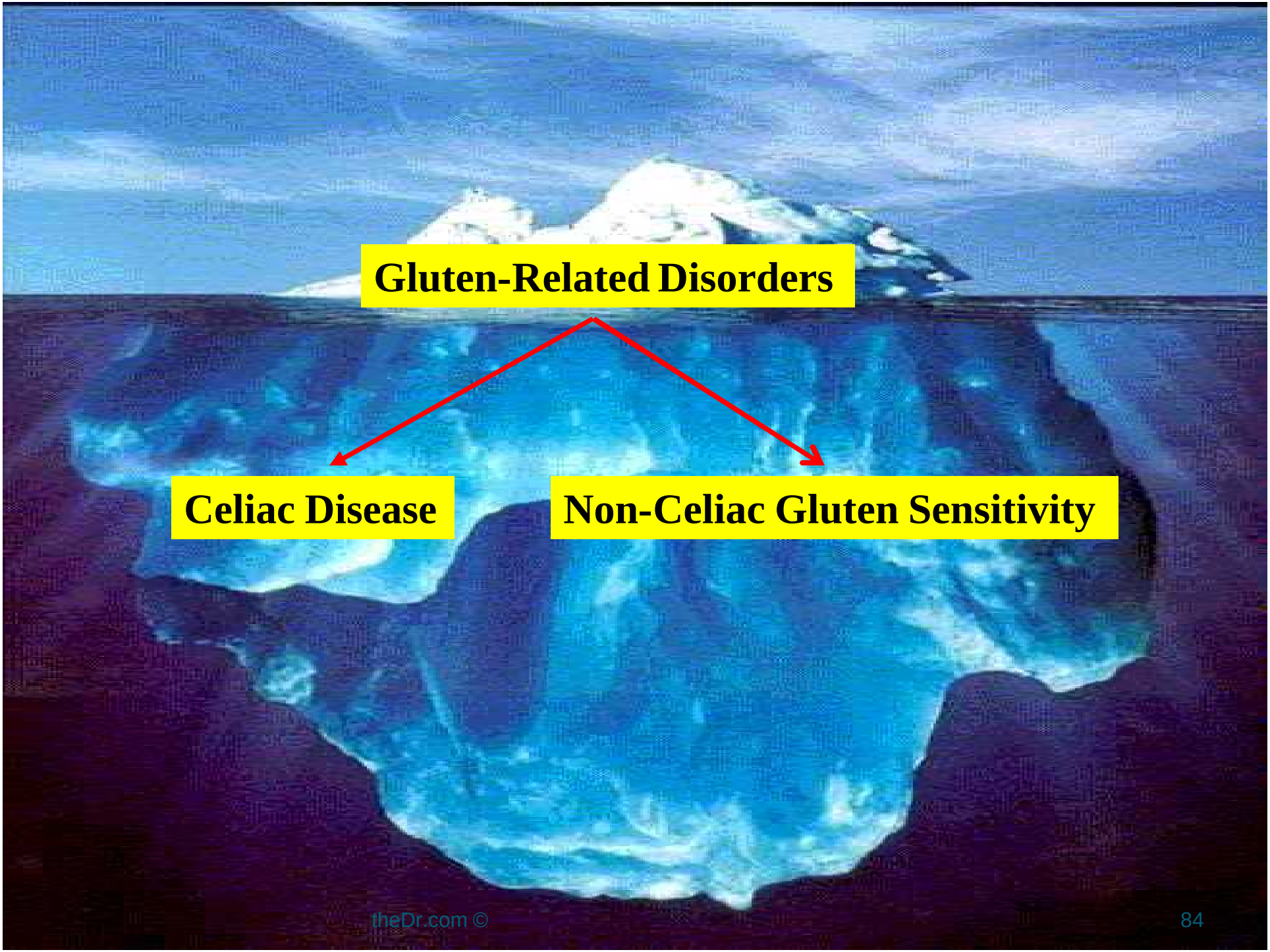
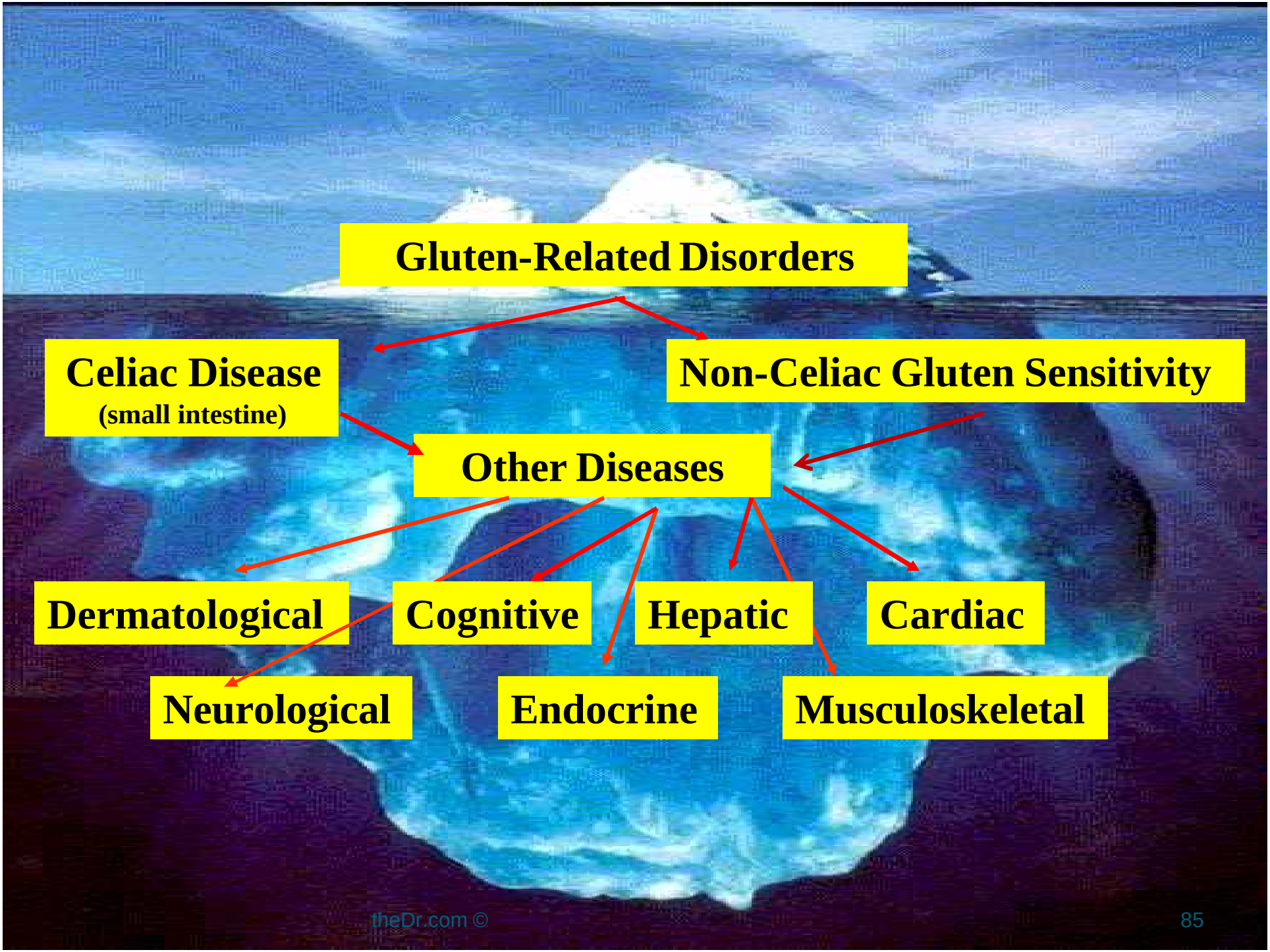

Celiac Disease


Gluten-Related Disorders
Celiac Disease
Non-Celiac Gluten Sensitivity


Gluten-Related Disorders
Celiac Disease
(small intestine)
Non-Celiac Gluten Sensitivity
Other Diseases
Dermatological
Cognitive
Hepatic
Cardiac
Neurological
Endocrine
Musculoskeletal

Autoimmunity Reviews 6 (2007) 559–565

Table 1
Celiac disease associated autoantibodies

Anti-endocrine	**Anti-cytoskeleton**
TPO	ARA
TMA	AAA
ATG	SMA
GAD	Anti-desmin
ICA	Anti-collagens
IA-2	CRT
	Anti-bone
Anti-gastrointestinal	
PCA	**Anti-neurological**
AMA	Anti-brain
	Anti-ganglioside
Anti-nuclear	Anti-neuronal
Single-stranded DNA	Anti-blood vessel
Double-stranded DNA	
ENA	
Ro/SSA	

Thyroid

Pancreas

Stomach

SLE

RA

Scleroderma

Sjogrens

AI Liver Diseases

Collagen

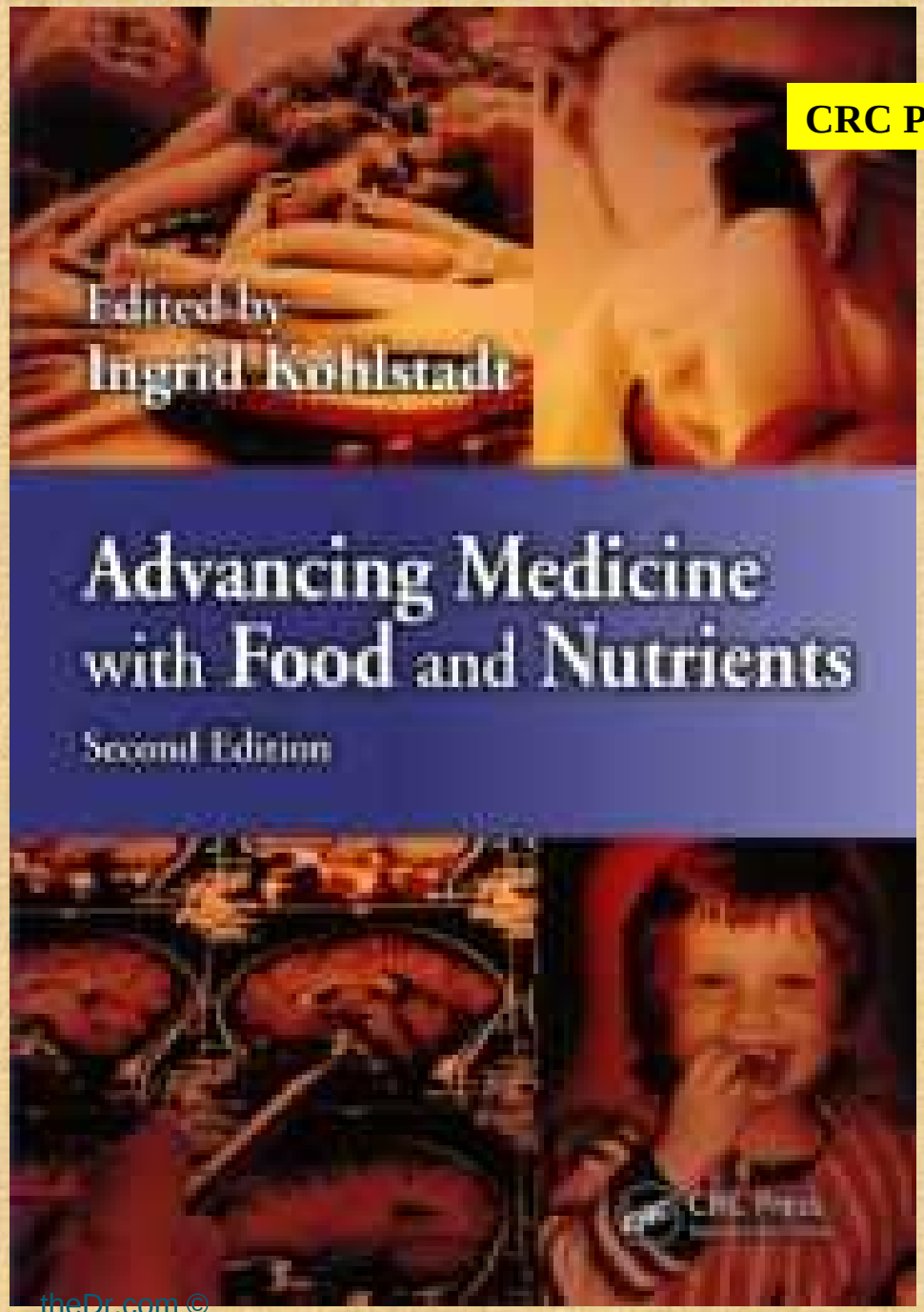
Bone

Brain Tissue

Neurons

Myelin

Blood Vessels



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16 Celiac Disease and Non-Celiac Gluten Sensitivity

The Evolving Spectrum

Thomas O'Bryan, DC, Rodney Ford, MD, MBBS, and Cynthia Kupper, RD

CONTENTS

INTRODUCTION

Underneath the umbrella of gluten related disorders, celiac disease and non-celiac gluten sensitivity have an immune reaction to gluten in common and often present with overlapping clinical symptoms. Differentiating among gluten-related disorders allows clinicians to give patients specific nutritional and other medical recommendations; however, clinical and laboratory diagnosis is complex and evolving as presented in this chapter. Nutrition holds the potential to advance medical care for patients with gluten-related disorders in several ways: A dietary history can prompt diagnosis in a clinical setting. A gluten-free diet is a medical therapy. Nutritional interventions can

TABLE 16.2
Presenting Symptoms of Celiac Disease

General	**Weakness***, lassitude, malaise, weight loss, short stature, failure to thrive
Gastrointestinal	**Diarrhea/constipation**, anorexia, nausea and vomiting, **flatulence and abdominal distension**, **abdominal pain**, **motility disturbance**, glossitis/apthous ulcers
Metabolic	Anemia features, bleeding tendency, edema, **cramps/tetany**, dental enamel hypoplasia, fat malabsorption, nutrient insufficiencies/deficiencies
Musculoskeletal	**Bone pain** and fractures, **myopathy**, **osteopenia/osteoporosis**
Neuropsychiatric	**Depression**, **anxiety**, **schizophrenia**, **paresthesia**, **peripheral neuropathy**, **cerebrospinal degeneration**
Reproductive	Menstrual irregularities, recurrent miscarriages, abnormalities of sperm morphology and motility, infertility, intrauterine growth retardation
Skin	Variety of rashes, petechiae

*bold font indicates symptoms also associated with non-celiac gluten sensitivity

Adapted from Riestra, S., Fernandez, E., Rodrigo, L., Garcia, S. and Ocio, G. 2000; Volta, U., Bellentani, S., Bianchi, F.B., et al. 2001; Volta, U. and Villanacci, V. 2011.

TABLE 16.3
Disorders Associated with Celiac Disease

Autoimmune	Idiopathic	Chromosomal	Miscellaneous
IDDM	Dilated cardiomyopathy	Down syndrome	Female and male infertility,
Antiphospholipid syndrome	**Epilepsy with or without occipital calcifications**	Turner syndrome	IUGR
IgA Nephropathy*		Williams syndrome	Miscarriages
Sjögren's syndrome	Sarcoidosis		
Hashimoto thyroiditis	**Myalgia/Myositis**		Depression
Graves' disease	Hypertransaminasemia		Anxiety
Addison's disease	Atopy		Social phobia
Autoimmune hemolytic disease	Recurrent pancreatitis		**Psychiatric disease (Schizophrenia)**
Myasthenia gravis	**Cerebellar ataxia**		
Autoimmune hepatitis	**Peripheral neuropathy**		Fat malabsorption
Primary biliary cirrhosis	Multiple myoclonus		Nutrient insufficiencies
Primary sclerosing cholangitis	Multiple sclerosis		Nutrient deficiencies
Alopecia	**Brain atrophy**		
Vitiligo	Inflammatory bowel disease		
Psoriases	**Irritable bowel syndrome**		
Dermatitis herpetiformis			
IgA deficiency			
Autoimmune atrophic gastritis			

*bold font indicates symptoms also associated with non-celiac gluten sensitivity
Abbreviation: IDDM: Insulin Dependent Diabetes Mellitus. Adapted from (29, 35)
IUGR: Intrauterine Growth Retardation
Adapted from Volta, U., Bellentani, S., Bianchi, F.B., et al. 2001; Volta, U. and Villanacci, V. 2011.

REVIEW

Vitamin D and autoimmunity: new aetiological and therapeutic considerations

Yoav Arnson, Howard Amital, Yehuda Shoenfeld

Ann Rheum Dis

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

Vitamin D is frequently prescribed by rheumatologists to prevent and treat osteoporosis. Several observations have shown that vitamin D inhibits proinflammatory processes by suppressing the enhanced activity of immune cells that take part in the autoimmune reaction. Moreover, recent evidence strongly suggests that vitamin D supplementation may be therapeutically beneficial, particularly for Th1-mediated autoimmune disorders. Some reports imply that vitamin D may even be preventive in certain disorders such as multiple sclerosis and

Autoimmune diseases are the third leading cause of morbidity and mortality in the industrialized world, surpassed only by cancer and heart disease.

high prevalence rate, the aetiology and pathogenesis of most autoimmune disorders remain obscure and a number of factors have been implicated in their pathogenesis. One of the most recent agents found to be associated with autoimmunity is vitamin D.

Vitamin D has multiple immunosuppressant properties. Supplementation of vitamin D was shown to be therapeutically effective in various animal models such as autoimmune encephalomyelitis,[2 3] collagen-induced arthritis,[4] type 1 diabetes mellitus,[5] inflammatory bowel disease,[6] autoimmune thyroiditis[7] and systemic lupus erythematosus (SLE),[8] and in some models of SLE it prevented disease development. A recent study showed that high circulating levels of vitamin D were associated with a lower risk of future multiple sclerosis.[9]

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PHYSIOLOGY OF VITAMIN D

The classic prominent function of vitamin D is regulation of calcium homeostasis, which is primarily maintained via bone formation and resorption.[10–12] Homeostasis is maintained in addition through the interaction of vitamin D with the parathyroid, kidney and intestinal tissues.[13]

Vitamin D can be ingested orally or can be formed endogenously in cutaneous tissue following exposure to ultraviolent B light.[14] Vitamin D_3 from both sources is metabolised in the liver to 25-hydroxyvitamin D (25(OH)D) which is the major circulati… vitamin … determine vitamin D levels in patients. However, 25(OH)D is biologically inert and requires additional hydroxylation within the kidney to form the biologically active derivative of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). $1,25(OH)_2D$ is a lipid-soluble hormone that interacts with its vitamin D receptors (VDRs) in the small intestine. Its action leads to enhanced expression of the epithelial calcium channel, the calcium-binding

… cells.[16 17] However, in contrast to the renal cells, in antigen presenting cells the enzyme is non-responsive to suppression by either parathyroid hormone or $1,25(OH)_2D$. Instead, it is inducible in the cells by a number of factors such as interferon γ (IFNγ) and is downregulated as the dendritic cell matures.[18]

Vitamin D deficiency is typically found in countries where there is no (or hardly any) ultraviolet light during the winter months and people must rely on the diet as their main source of the vitamin.[19] The optimal level for 25(OH)D for bone health begins at 75 nmol/l (30 ng/ml), with the best concentrations at 90–100 nmol/l (36–40 ng/ml),[20–22] but the vitamin D level required to maintain optimal immune system homeostasis has not yet been established.

VITAMIN D AND THE IMMUNE SYSTEM

Vitamin D interacts with the immune system. It takes part in the regulation and differentiation of the cells of the immune system directly and indirectly. Early reports linking vitamin D metabolism to the prevalence of autoimmune diseases were largely anecdotal and circumstantial. For instance, associations were detected between the

Abbreviations: 1, $25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; GM-CSF, granulocyte-macrophage colony stimulating factor; IFNγ, interferon γ; IL, interleukin; NFκB, nuclear factor κB; SLE, systemic lupus erythematosus; VDR, vitamin D receptor

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CMLS Cellular and Molecular Life Sciences

CMLS, Cell. Mol. Life Sci. 62 (2005) 791–799

Review

Mechanisms underlying celiac disease and its neurologic manifestations

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Autoimmune disorders occur 10 times more commonly in CD than in the general population.

neurologic manifestations of CD have not been elucidated. In this article, the authors review the cellular and play a role in the development of neurologic complications.

Key words. Celiac disease; gluten sensitivity; ataxia; peripheral neuropathy; pathogenesis; neurologic complications; ganglioside antibodies.

Introduction

Celiac disease (CD) has also been termed gluten-sensitive enteropathy because the small intestine is the main target of injury; however, the clinical manifestations are extremely diverse, suggesting the disorder is in fact a multi-systemic disorder [1].

CD is a T-cell-mediated, autoimmune disorder characterized by a close linkage to specific human lymphocyte antigen (HLA) alleles (DQ2 and DQ8) and precipitation by an environmental factor, gluten, which is the term for the storage proteins of wheat. Although gliadin, the alcohol-soluble fraction of gluten, has been most studied, other gluten proteins are probably also toxic to people who have celiac disease. Similar proteins in barley (hordeins) and rye (secalins) are toxic as well [2]. These proteins induce the inflammatory process in the intestine, while withdrawal results in regression of the process [3].

CD is a multi-genetic disorder associated with HLA-DQ2 (DQA1*05/DQB1*02) or DQ8 (DQA1*0301/DQB1*0302). Studies in siblings that have demonstrated a sib recurrence risk of 10% [4] and studies of identical twins in which there is a 70% concordance rate [5] suggest that the contribution of HLA genes in CD is less than 50%. The non-HLA chromosomic region most consistently linked to CD is located on the long arm of chromosome 5 [6, 7].

Other environmental factors, apart from gluten, also appear important for the development of CD. Breast feeding and the timing of gluten introduction in the diet [8], viral infections that promote the secretion of interferon

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Associated autoantibodies in celiac disease

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Abstract

Celiac disease (CD) is a life-long inflammatory autoimmune condition of the gastrointestinal tract affecting genetically susceptible individuals. Several autoimmune disorders are more prevalent in patients and their close relatives and that risk is

Several autoimmune disorders are more prevalent in CD patients and their close relatives and that risk is gluten exposure duration related.

Contents

Abbreviations: AAA, anti-actin antibody; AGA, anti-gliadin antibody; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ARA, anti-reticulin antibody; ATG, anti-thyroglobulin antibody; CRT, calreticulin; ELISA, enzyme-linked immunosorbent assay; EMA, antiendomysium antibodies; ENA, anti-extractable nuclear antigens; GAD, glutamic acid decarboxylase antibodies; GFD, gluten-free diet; HLA, human histocompatibility complex; IAA, anti-insulin antibodies; ICA, islet cell antibodies; IDDM, insulin-dependent diabetes mellitus; IF, immunofluorescence; LKM, anti-liver-kidney microsomal; PCA, anti-gastric parietal cells; SMA, anti-smooth muscle antibody; TG2, tissue transglutaminase 2; TMA, anti-thyroid microsome; TPO, anti-thyreoperoxidase; tTG, tissue transglutaminase.

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GASTROENTEROLOGY 1999;117:297–303

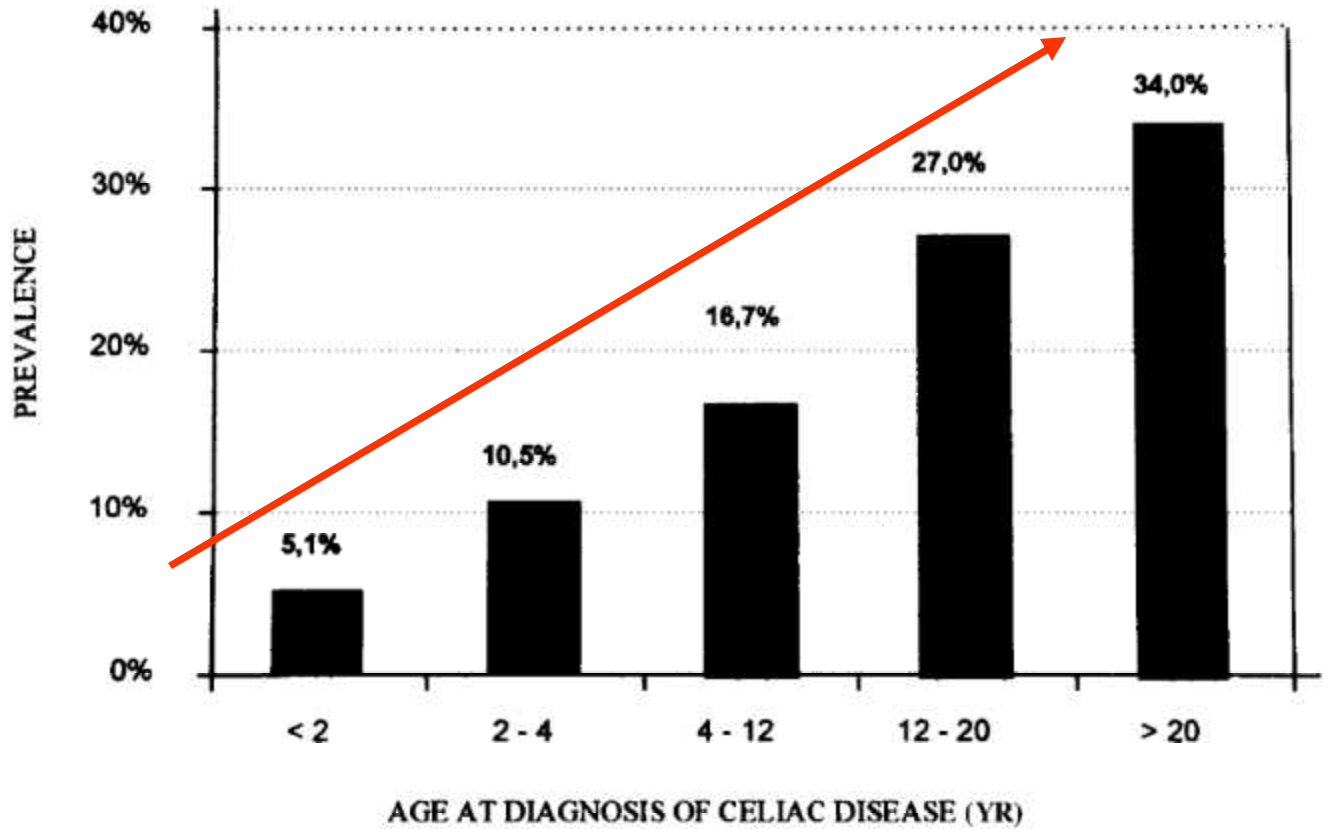

Figure 2. Prevalence of autoimmune disorders according to age at diagnosis of celiac disease (χ^2 for trend = 63.45; P = 0.000001).

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Approx. printed pages:

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Rapid Regression of Psoriasis in a Coeliac Patient after GFD

Case Report

Digestion
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Rapid Regression of Psoriasis in a Coeliac Patient after Gluten-Free Diet

A Case Report and Review of the Literature

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Maria Eugenia D'angelo Di Paola[a] Ludovico Abenavoli[a] Lorenzo Leggio[a]
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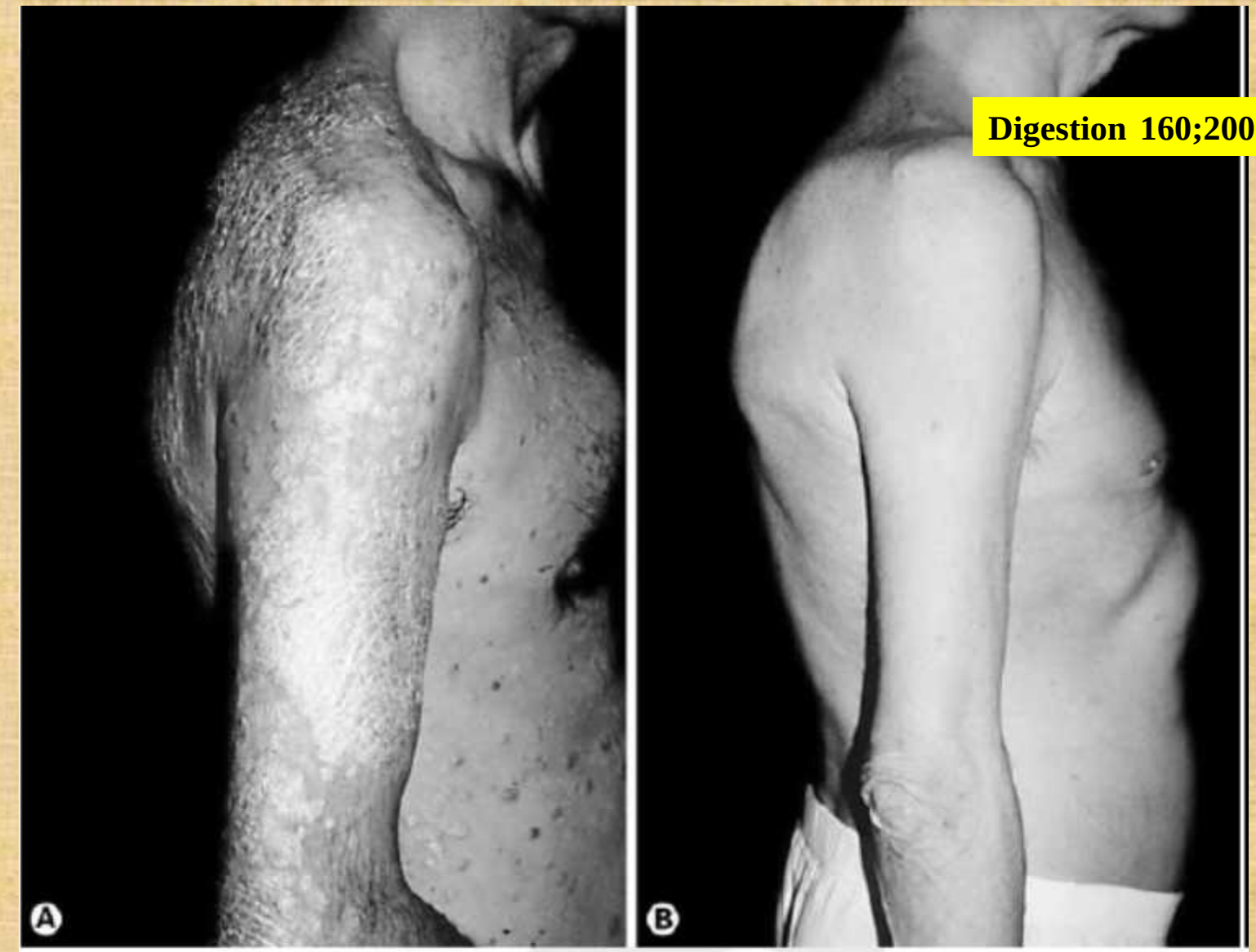

Digestion 160;2003

Fig. 1. Psoriatic skin lesions in the coeliac patient before (**A**) and after 1 month of GFD (**B**). After GFD the skin lesions disappeared.

Gluten sensitivity

Gluten sensitivity as a neurological illness

M Hadjivassiliou, R A Grünewald, G A B Davies-Jones

From gut to brain

J Neurol Neurosurg Psychiatry 2002;72:560–563

That gluten sensitivity is regarded as principally a disease of the small bowel is a historical misconception.

It has taken nearly 2000 years to appreciate that a common dietary protein, introduced to the human diet relatively late in evolutionary terms (some 10 000 years ago), can produce human disease not only of the gut but also the skin and the nervous system. The protean neurological manifestations of gluten sensitivity can occur without gut involvement and neurologists must therefore become familiar with the common neurological presentations and means of diagnosis of this disease.

... disease of a chronic nature is formed".[1]

This extract is from the book on chronic diseases by Aretaeus the Cappadocian, one of the most distinguished ancient Greek doctors of the first century AD. This chapter, entitled "on the coeliac diathesis", was the first description of coeliac disease (from the greek word κοιλιακη meaning abdominal). Aretaeus' books were first published in Latin in 1500 and the new Latin word coeliac was used to translate κοιλιακη. Coeliac disease (CD) remained obscure until 1887 when Samuel Gee gave a lecture entitled *On the coeliac affection*[2] at the Hospital for Sick Children, Great Ormond Street, London. In it he acknowledged Aretaeus' contribution and went on to give an accurate description of CD based on his own clinical observations.

With clinical manifestations primarily confined to the gastrointestinal tract or attributable to malabsorption, it was logical to assume that the target organ and hence the key to the pathogenesis of ... the diagnosis of CD. In 1961 Taylor published an immunological study of CD.[3] In his paper he commented that "... an obstacle to the acceptance of the immunological theory of causation has been the lack of satisfactory demonstration of antibodies to the protein concerned". He went on to demonstrate the presence of circulating antibodies against gliadin (antigliadin antibodies), the protein responsible for CD. This provided further evidence that CD was immunologically mediated and that the immune response is not confined to the mucosa of the small bowel. Antigliadin antibodies became a useful screening tool for the diagnosis of CD.

In 1966, Marks *et al*[4] demonstrated an enteropathy in nine of 12 patients with dermatitis herpetiformis,[5] an itchy vesicular skin rash mainly occurring over the extensor aspect of the elbows and knees. The enteropathy had a striking similarity to that seen in CD. It was later shown that the enteropathy and the skin rash were gluten dependent but skin involvement could occur even without histological evidence of gut involvement. This was the first evidence that the gut may not be the sole protagonist in this disease.

THE NEUROLOGY OF COELIAC DISEASE

In 1966 Cooke published a landmark paper on 16 patients with neurological disorders associated with adult CD.[6] This was the first systematic review of the subject after the introduction of diagnostic criteria for CD. Ten of these patients ... changes affecting both the central and peripheral nervous systems. A striking feature was the loss of Purkinje cells with atrophy and gliosis of the cerebellum. All 16 patients had evidence of severe malabsorption as evidenced by anaemia and vitamin deficiencies as well as profound weight loss.

Several case reports followed, primarily based on patients with established CD, often with persisting troublesome

Total number of patients	63
Male to female ratio	44:19
Mean age	48
Neurological diagnosis	
Ataxia	29
Peripheral neuropathy	29
Myopathy	13
Ataxia with myoclonus	0
Myelopathy	4
Dementia (usually with additional features)	6

A review of all such reports (with biopsy proved CD) from 1964 to date shows that ataxia and peripheral neuropathy are the commonest neurological manifestations seen in patients with established CD (table 1). Less common manifestations include inflammatory myopathies[10] and myoclonic ataxia.[11] Isolated dementia is uncommon and most cases tend to have additional neurological features (for example, ataxia or neuropathy). Patients with epilepsy associated with occipital calcifications on CT and CD have been described,[12] mainly in Italy. Most present with epilepsy in

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Screening for Celiac Disease

Despite the unexpectedly high prevalence of celiac disease found in the study by Mäki et al. (June 19 issue),[1] their use of endomysial and tissue transglutaminase antibodies as the sole serologic markers probably underestimated the prevalence of celiac disease in the cohort. One study evaluating endomysial antibodies showed that the sensitivity of this marker was 100 percent in patients with total villous atrophy, but the value plummeted to 31 percent in patients with celiac disease who had partial villous atrophy.[2] Antibodies to tissue transglutaminase likewise correlate with the degree of villous atrophy.[3] Addition of the admittedly less specific gliadin antibodies to the analysis would have increased the detection rate in the study population.

Regarding the accompanying editorial by Fas-

7. West J, Logan RF, Hill PG, et al. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut 2003; 52:960-5.

As Drs. Lebwohl and Green note, we found a high prevalence of celiac disease in the Finnish population. The addition of a gliadin antibody test might
rate. However, recent
antibody tests we use
gliadin antibody test,
As the correspondents also note, endomysial antibody testing in one study had only limited value in screening programs for celiac disease.[4] The same group showed that half their patients who had nonfamilial celiac disease with minor mucosal inflammation were negative for HLA-DQ2 and HLA-

N Engl J Med Oct.23 2003,1673-4

…every time the disease is clinically diagnosed in an adult, that person has for decades had disease in a latent or silent stage...

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Papers

Undiagnosed coeliac disease at age seven: population based prospective birth cohort study

Polly J Bingley, Alistair J K Williams, Alistair J Norcross, D Joe U
Andrew R Ness, Richard W Jones, on behalf of the Avon Longi
Children Study Team

BMJ Vol.328, 7 February 2004 322-3

Division of Medicine, University of Bristol, Southmead Hospital, Bristol BS10 5NB
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Coeliac disease is uncommon in childhood and diagnosed in fewer than 1 in 2500 children in the United Kingdom.[1] Subclinical disease is, however, common in adults, and can be detected by testing for serum IgA antiendomysial antibodies (IgA-EMA).[2] We aimed to establish the prevalence of undiagnosed coeliac disease in the general population at age seven, and to look for associated clinical features.

Participants, methods, and results

We studied children aged 7.5 years participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population based birth cohort study established in 1990.[3] Two stage screening included a

ence in the number of episodes of diarrhoea. Vomiting, abdominal pain, and constipation were not associated with EMA, but more IgA-EMA positive children reported multiple symptoms. Only four children (0.09%; 0.1 to 0.32) were on a gluten-free diet. Of these, three were tTG antibody negative, consistent with effective treatment, and one was IgA-EMA positive (table).

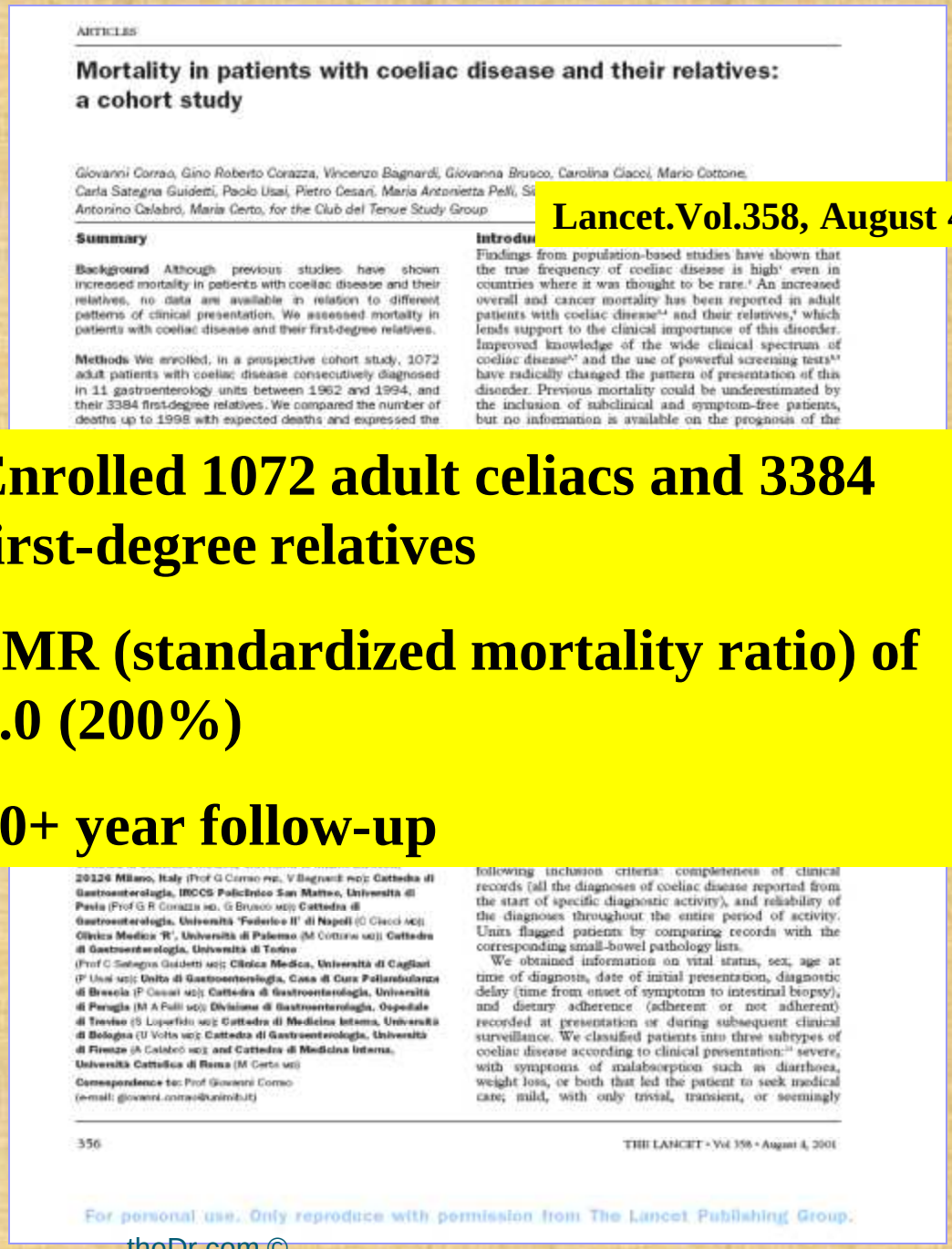
Comment

At age 7, 1% of children were IgA-EMA positive and likely therefore to have subclinical coeliac disease, though less than 0.1% were reported to be on a gluten-free diet. The prevalence of coeliac disease in these

Occult coeliac disease seems to start in childhood, even in those who are subsequently diagnosed as adults. The search for the trigger resulting in the breakdown of immune tolerance to gluten therefore needs to focus on infancy and intrauterine life.

were tTG antibody positive but IgA-EMA negative

	tTG antibody negative controls	IgA-EMA positive	
	Median (interquartile range) (n=5333 children)	Median (interquartile range) (n=54 children)	P value
Measurements taken at age 7.5 years			
Height (cm)	126 (122.4 to 129.6)	122.1 (118.25 to 125.33)	<0.0001
Weight (kg)	25.2 (22.8 to 28.0)	23.4 (21.35 to 25.4)	<0.0001
Standard deviation score for height	0.23 (−0.43 to 0.88)	−0.53 (−1.01 to −0.00)	<0.0001
Standard deviation score for weight	0.18 (−0.45 to 0.86)	−0.36 (−1.01 to 0.28)	<0.0001
Haemoglobin concentration (g/l)	125 (120 to 130)	123 (118 to 127)	0.062
	No (%) (n=4285 questionnaires)	No (%) (n=42 questionnaires)	Odds ratio (95% CI)
Symptoms reported at age 6.75 years			
Any diarrhoea	1450 (34)	21 (50)	1.96 (1.06 to 3.59)
Any vomiting	1933 (45)	23 (55)	1.47 (0.80 to 2.71)
Any stomach pains	2557 (60)	28 (66)	1.35 (0.71 to 2.57)
Any constipation	435 (10)	6 (14)	1.48 (0.62 to 3.52)
≥3 gastrointestinal symptoms	931 (22)	17 (40)	2.45 (1.33 to 4.5)



ARTICLES

Mortality in patients with coeliac disease and their relatives: a cohort study

Giovanni Corrao, Gino Roberto Corazza, Vincenzo Bagnardi, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sategna Guidetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pelli, Si… Antonino Calabrò, Maria Certo, for the Club del Tenue Study Group

Lancet.Vol.358, August 4, 2001

Summary

Background Although previous studies have shown increased mortality in patients with coeliac disease and their relatives, no data are available in relation to different patterns of clinical presentation. We assessed mortality in patients with coeliac disease and their first-degree relatives.

Methods We enrolled, in a prospective cohort study, 1072 adult patients with coeliac disease consecutively diagnosed in 11 gastroenterology units between 1962 and 1994, and their 3384 first-degree relatives. We compared the number of deaths up to 1998 with expected deaths and expressed the

Enrolled 1072 adult celiacs and 3384 first-degree relatives

SMR (standardized mortality ratio) of 2.0 (200%)

20+ year follow-up

20126 Milano, Italy (Prof G Corrao *mr*, V Bagnardi *mr*); **Cattedra di Gastroenterologia, IRCCS Policlinico San Matteo, Università di Pavia** (Prof G R Corazza *mr*, G Brusco *ms*); **Cattedra di Gastroenterologia, Università 'Federico II' di Napoli** (C Ciacci *ms*); **Clinica Medica 'R', Università di Palermo** (M Cottone *ms*); **Cattedra di Gastroenterologia, Università di Torino** (Prof C Sategna Guidetti *ms*); **Clinica Medica, Università di Cagliari** (P Usai *ms*); **Unità di Gastroenterologia, Casa di Cura Follanbulanza di Brescia** (P Cesari *ms*); **Cattedra di Gastroenterologia, Università di Perugia** (M A Pelli *ms*); **Divisione di Gastroenterologia, Ospedale di Treviso** (S Loperfido *ms*); **Cattedra di Medicina Interna, Università di Bologna** (U Volta *ms*); **Cattedra di Gastroenterologia, Università di Firenze** (A Calabrò *ms*); **and Cattedra di Medicina Interna, Università Cattolica di Roma** (M Certo *ms*)

Correspondence to: Prof Giovanni Corrao (e-mail: giovanni.corrao@unimib.it)

following inclusion criteria: completeness of clinical records (all the diagnoses of coeliac disease reported from the start of specific diagnostic activity), and reliability of the diagnoses throughout the entire period of activity. Units flagged patients by comparing records with the corresponding small-bowel pathology lists.

We obtained information on vital status, sex, age at time of diagnosis, date of initial presentation, diagnostic delay (time from onset of symptoms to intestinal biopsy), and dietary adherence (adherent or not adherent) recorded at presentation or during subsequent clinical surveillance. We classified patients into three subtypes of coeliac disease according to clinical presentation:[15] severe, with symptoms of malabsorption such as diarrhoea, weight loss, or both that led the patient to seek medical care; mild, with only trivial, transient, or seemingly

ARTICLES

Mortality in patients with coeliac disease and their relatives: a cohort study

Giovanni Corrao, Gino Roberto Corazza, Vincenzo Bagnardi, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sategna Guidetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pelli, Si… Antonino Calabrò, Maria Certo, for the Club del Tenue Study Group

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Methods We enrolled, in a prospective cohort study, 1072 adult patients with coeliac disease consecutively diagnosed in 11 gastroenterology units between 1962 and 1994, and their 3384 first-degree relatives. We compared the number of deaths up to 1998 with expected deaths and expressed the comparison as standardised mortality ratio (SMR) and relative survival ratio.

Findings 53 coeliac patients died compared with 25·9 expected deaths (SMR 2·0 [95% CI 1·5–2·7]). A significant excess of mortality was evident during the first 3 years after diagnosis of coeliac disease and in patients who presented with malabsorption symptoms (2·5 [1·8–3·4]), but not in those diagnosed because of minor symptoms (1·1 [0·5–2·2]) or because of antibody screening (1·2 [0·1–7·0]). SMR

Introdu

Findings from population-based studies have shown that the true frequency of coeliac disease is high[1] even in countries where it was thought to be rare.[2] An increased overall and cancer mortality has been reported in adult patients with coeliac disease[3,4] and their relatives,[5] which lends support to the clinical importance of this disorder. Improved knowledge of the wide clinical spectrum of coeliac disease[6,7] and the use of powerful screening tests[8,9] have radically changed the pattern of presentation of this disorder. Previous mortality could be underestimated by the inclusion of subclinical and symptom-free patients, but no information is available on the prognosis of the new forms of coeliac disease. Additionally, the reported 1·9-fold[3] and 3·4-fold[4] increases in mortality might be excessive because some patients with a less favourable outcome, such as those with refractory sprue and intestinal lymphoma, were probably enrolled in those series.[10] The finding that the mortality excess is mainly accounted for by deaths occurring within a short time after diagnosis[3] indirectly lends support to this possibility.

We did a prospective study to find out whether differences in patterns of clinical presentation of coeliac

Adherence to gluten-free diet						
Likely	627 (59%)	3794	5	10·5	0·5 (0·2–1·1)	0·16
Not likely	155 (15%)	998	26	4·3	6·0 (4·0–8·3)	<0·0001
Uncertain	290 (27%)	1652	22	11·1	2·0 (1·2–3·0)	0·005
				Test for heterogeneity:		<0·0001

SMR=standardised mortality ratio. *Unknown in 68 patients (clinical records lacking this information) and not applicable in 67 patients with symptomless disease. Test for trend does not include this category.

Table 1: **Demographics, clinical features, and overall mortality of patient cohort**

Gastroenterologia, Università 'Federico II' di Napoli (C Ciacci MD); **Clinica Medica 'R', Università di Palermo** (M Cottone MD); **Cattedra di Gastroenterologia, Università di Torino** (Prof C Sategna Guidetti MD); **Clinica Medica, Università di Cagliari** (P Usai MD); **Unità di Gastroenterologia, Casa di Cura Follanbulanza di Brescia** (P Cesari MD); **Cattedra di Gastroenterologia, Università di Perugia** (M A Pelli MD); **Divisione di Gastroenterologia, Ospedale di Treviso** (S Loperfido MD); **Cattedra di Medicina Interna, Università di Bologna** (U Volta MD); **Cattedra di Gastroenterologia, Università di Firenze** (A Calabrò MD); **and Cattedra di Medicina Interna, Università Cattolica di Roma** (M Certo MD)

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the diagnoses throughout the entire period of activity. Units flagged patients by comparing records with the corresponding small-bowel pathology lists.

We obtained information on vital status, sex, age at time of diagnosis, date of initial presentation, diagnostic delay (time from onset of symptoms to intestinal biopsy), and dietary adherence (adherent or not adherent) recorded at presentation or during subsequent clinical surveillance. We classified patients into three subtypes of coeliac disease according to clinical presentation:[10] severe, with symptoms of malabsorption such as diarrhoea, weight loss, or both that led the patient to seek medical care; mild, with only trivial, transient, or seemingly

ARTICLES

Mortality in patients with coeliac disease and their relatives: a cohort study

Giovanni Corrao, Gino Roberto Corazza, Vincenzo Bagnardi, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sategna Guidetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pelli, Si… Antonino Calabrò, Maria Certo, for the Club del Tenue Study Group

Lancet.Vol.358, August 4, 2001

Summary

Background Although previous studies have shown increased mortality in patients with coeliac disease and their relatives, no data are available in relation to different patterns of clinical presentation. We assessed mortality in patients with coeliac disease and their first-degree relatives.

Methods We enrolled, in a prospective cohort study, 1072 adult patients with coeliac disease consecutively diagnosed in 11 gastroenterology units between 1962 and 1994, and their 3384 first-degree relatives. We compared the number of deaths up to 1998 with expected deaths and expressed the

Death was most significantly affected by diagnostic delay, pattern of presentation, and adherence to the GFD…Non-adherence to the GFD, defined as eating gluten once-per-month increased the relative risk of death 6-fold.

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…diagnosis, between Jan 1, 1962, and 31 Dec, 1994, at 11 gastroenterology units. These units, evenly distributed through Italy, were selected from those participating in the Italian Club del Tenue study in accordance with the following inclusion criteria: completeness of clinical records (all the diagnoses of coeliac disease reported from the start of specific diagnostic activity), and reliability of the diagnoses throughout the entire period of activity. Units flagged patients by comparing records with the corresponding small-bowel pathology lists.

We obtained information on vital status, sex, age at time of diagnosis, date of initial presentation, diagnostic delay (time from onset of symptoms to intestinal biopsy), and dietary adherence (adherent or not adherent) recorded at presentation or during subsequent clinical surveillance. We classified patients into three subtypes of coeliac disease according to clinical presentation:[10] severe, with symptoms of malabsorption such as diarrhoea, weight loss, or both that led the patient to seek medical care; mild, with only trivial, transient, or seemingly

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Eric Petersen / The Livingston Enterprise

Case Study

An environmental exposure affecting the brain

Inspector Clouseau

CASE REPORT

White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease

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H. Herfarth
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SUMMARY: CD is an autoimmune-mediated disorder of the gastrointestinal tract. Initial symptom presentation is variable and can inclu
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Am J Neuroradiol. 2010 May;31(5):880-1

ABBREVIATIONS: ALS = amyotrophic lateral sclerosis; CD = celiac disease; FLAIR = fluid-attenuated inversion recovery; IgA = immunoglobulin A

A 32-year-old man with a 1-year history of balance difficulties presented with 1 week of worsening symptoms, including hand tremors and gait disturbance.

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Initial diagnostic considerations included ALS and Friedrich ataxia. Electromyelography findings of the right upper and lower extremities were normal. Total spine MR imaging and CT findings of the chest, abdomen, and pelvis were normal. CSF findings for herpes simplex virus, human herpesvirus 6 cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and Venereal Disease Research Laboratory test were negative, but +4 oligoclonal bands were noted. Findings were negative for paraneoplastic antibodies. Ataxia work-up included a positive antiendomysial antibody titer of 1:160. Duodenal biopsies yielded crypt hyperplastic villous atrophy with numerous intraepithelial lymphocytes, most consistent with gluten-sensitive enteropathy.

The patient started a strict gluten-free diet with improvement of symptoms during the next several months. Repeat brain MR imaging (23 months after initial presentation) revealed resolution of initial abnormalities (Fig 2). Continued physical therapy and a gluten-free diet have been prescribed.

viduals by ingestion of foods containing gluten, such as wheat, rye, and barley. Consumption of triggering foods leads to an autoimmune-mediated inflammatory response in the small intestine, resulting in villous atrophy and malabsorption.[3] The most common presenting symptoms include diarrhea, steatorrhea, weight loss, iron deficiency anemia, and abdominal distension.

The diagnosis is sometimes difficult to make given that not all patients present in the same manner and that symptoms overlap other gastrointestinal disorders. Half of patients have iron deficiency anemia or osteoporosis, without diarrhea. Diagnostic evaluation for CD consists of antibody testing and duodenal biopsy.[4] The most sensitive and specific antibodies for its confirmation are tissue transglutaminase IgA and endomysial IgA antibodies. Due to the low specificity compared with tissue transglutaminase and endomysium antibodies, gliadin antibodies should no longer be used in the diagnostic work-up for CD. Duodenal biopsies are still the criterion standard for tissue diagnosis and reveal villous atrophy[5] and increased intraepithelial lymphocytes.[6]

Neurologic findings associated with CD disease were initially reported in 1966 by Cooke and Smith.[7] Most common symptoms are ataxia and neuropathy, followed by epilepsy, ALS and multiple sclerosis-like symptoms, isolated motor neuron disorders, sensory ataxia, and dizziness. These complications may arise as consequences of vitamin and mineral deficiencies. Other authors discuss a potential pathophysiologic role of antigliadin antibodies in a neurotoxic autoimmune process.[8]

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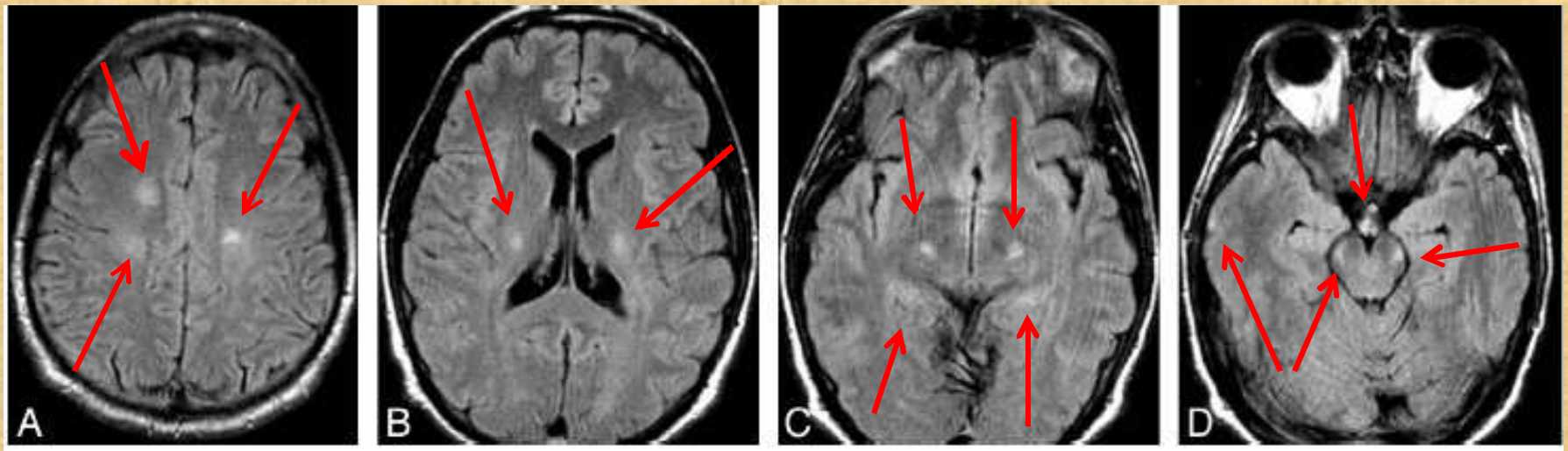

Fig 1. FLAIR images from initial brain MR imaging demonstrate abnormal increased signal intensity in the white matter of the centra semiovale and bilateral corticospinal tracts.

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have been associated with CD, including Down syndrome, insulin-dependent diabetes mellitus, IgA deficiency, and rheumatoid arthritis.[1]

Symptoms are precipitated in genetically predisposed individuals by ingestion of foods containing gluten, such as wheat, rye, and barley. Consumption of triggering foods leads to an autoimmune-mediated inflammatory response in the small intestine, resulting in villous atrophy and malabsorption.[3] The most common presenting symptoms include diarrhea, steatorrhea, weight loss, iron deficiency anemia, and abdominal distension.

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Neurologic findings associated with CD disease were initially reported in 1966 by Cooke and Smith.[7] Most common symptoms are ataxia and neuropathy, followed by epilepsy, ALS and multiple sclerosis-like symptoms, isolated motor neuron disorders, sensory ataxia, and dizziness. These complications may arise as consequences of vitamin and mineral deficiencies. Other authors discuss a potential pathophysiologic role of antigliadin antibodies in a neurotoxic autoimmune process.[8]

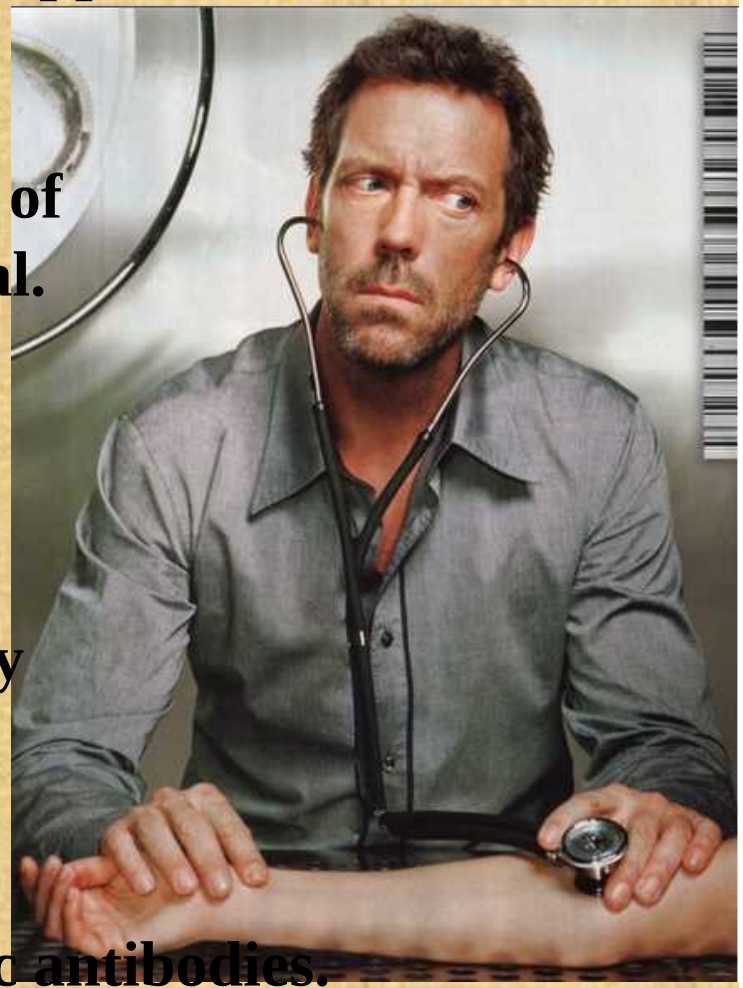
Amyotrophic lateral sclerosis (ALS), often referred to as "Lou Gehrig's Disease," is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to their death.

Neuromuscular examination revealed :

- **Electromyelography findings of the right upper and lower extremities were normal.**

- **Total spine MR imaging and CT findings of the chest, abdomen, and pelvis were normal.**

- **CSF findings for herpes simplex virus, human herpesvirus 6 cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and Venereal Disease Research Laboratory test were negative, but 4 oligoclonal bands were noted.**



- **Findings were negative for paraneoplastic antibodies.**

Clin Rheumatol (2005) 24: 76–78

- **Difficulty walking (Ataxia) work-up included a positive antiendomysial antibody titer of 1:160 (high)**
- **Duodenal biopsies yielded crypt hyperplastic villous atrophy with numerous intraepithelial lymphocytes, most consistent with gluten-sensitive enteropathy.**

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

CASE REPORT

White Matter Lesions Suggestive of Amyotrophic Lateral Sclerosis Attributed to Celiac Disease

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SUMMARY: CD is an autoimmune-mediated disorder of the gastrointestinal tract. Initial symptom presentation is variable and can inclu
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discovered, and CD was confirmed by upper gastrointestinal endoscopy with duodenal biopsies. MR imaging findings suggestive of ALS improved after gluten-free diet institution.

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ABBREVIATIONS: ALS = amyotrophic lateral sclerosis; CD = celiac disease; FLAIR = fluid-attenuated inversion recovery; IgA = immunoglobulin A

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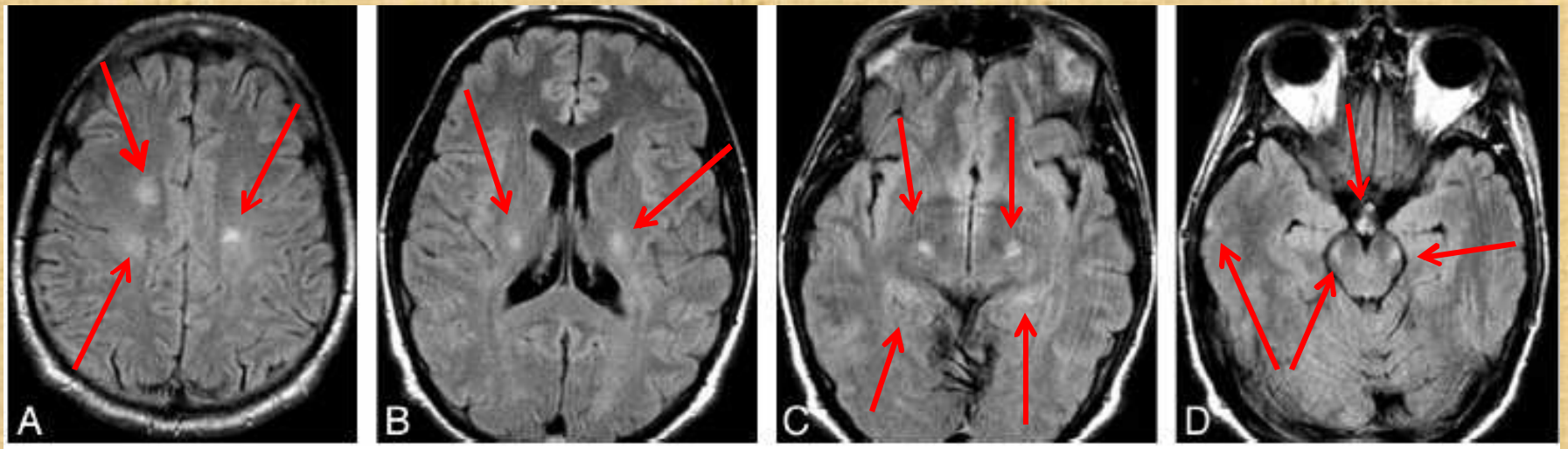

Fig 1. FLAIR images from initial brain MR imaging demonstrate abnormal increased signal intensity in the white matter of the centra semiovale and bilateral corticospinal tracts.

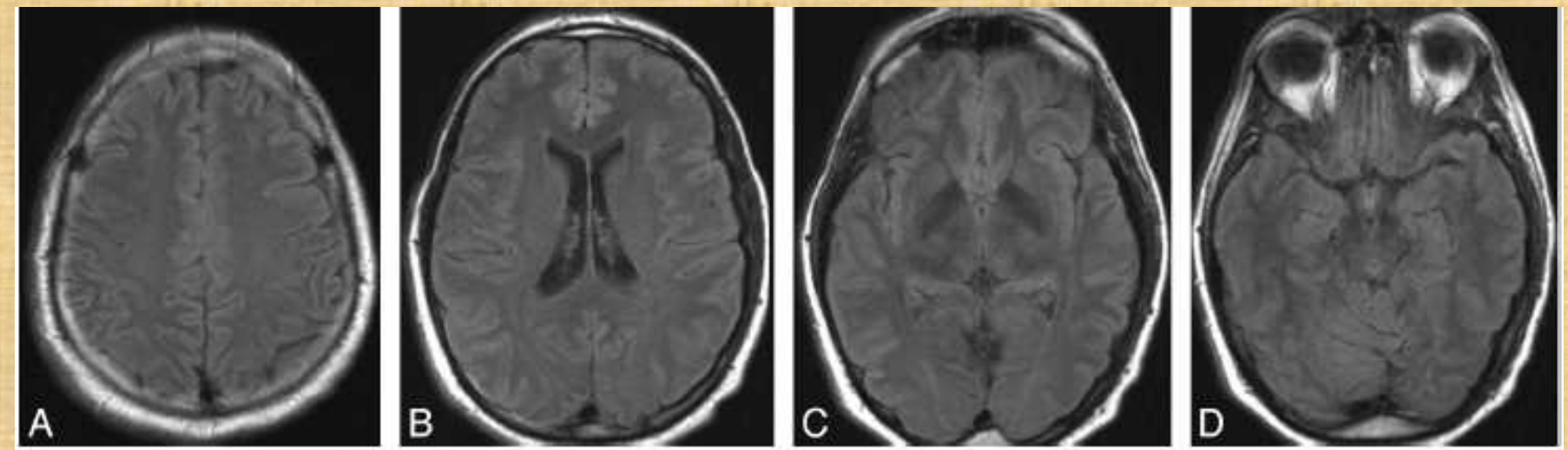

Fig 2. Follow-up FLAIR images after a gluten-free diet show complete resolution of signal-intensity abnormalities.

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His symptoms and MR imaging lesions improved and resolved, respectively, on appropriate treatment of CD.

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

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Regional Cerebral Hypoperfusion in Patients with Celiac Disease

Giovanni Addolorato, MD, Daniela Di Giuda, MD, Giuseppe De Rossi, MD, Venanzio Valenza, MD, Marco Domenicali, MD, Fabio Caputo, MD, Antonio Gasbarrini, MD, Esmeralda Capristo, MD, Giovanni Gasbarrini, MD

Am J Med,March 1, 2004,312-7

BACKGROUND: Neurological and psychiatric disorders occur in approximately 10% of patients with celiac disease. Although some of these alterations respond to a gluten-free diet, the etiology of these abnormalities is uncertain. Because of a case report that cerebral hypoperfusion in a celiac patient resolved after a gluten-free diet, we studied brain perfusion changes in untreated celiac patients, treated celiac patients, and healthy controls.

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RESULTS: Of the 15 untreated celiac patients, 11 (73%) had at least one hypoperfused brain region, compared with only 1 (7%) of the 15 celiac patients on a gluten-free diet and none of the controls ($P = 0.01$). Cerebral perfusion was significantly lower ($P < 0.05$) in untreated celiac patients, compared with healthy controls, in 7 of 26 brain regions. No significant differ-

Single Photon Electron Computed Tomagraphy (SPECT scan)

-15 untreated adult celiac patients

-15 treated (1 year) adult celiac patients

-24 non-celiac healthy adult volunteers

(18). Some of these alterations, such as cerebellar ataxia,

the Ethics Committee of the Università Cattolica del Sacro Cuore in Rome, Italy; all subjects provided informed consent. A group of 19 newly diagnosed adult patients affected by the classic form of celiac disease was enrolled consecutively in the study during a 1-year period. Four of these patients refused to undergo SPECT examination because they suffered from claustrophobia; the remaining 15 patients (9 women and 6 men; mean [± SD] age, 37 ± 9 years) were studied. We excluded patients with endocrine disorders, abuse of alcohol or other substances, consumption of psychotropic drugs, and secondary causes of villous atrophy. The diagnosis of celiac disease was based on the presence of antigliadin and an-

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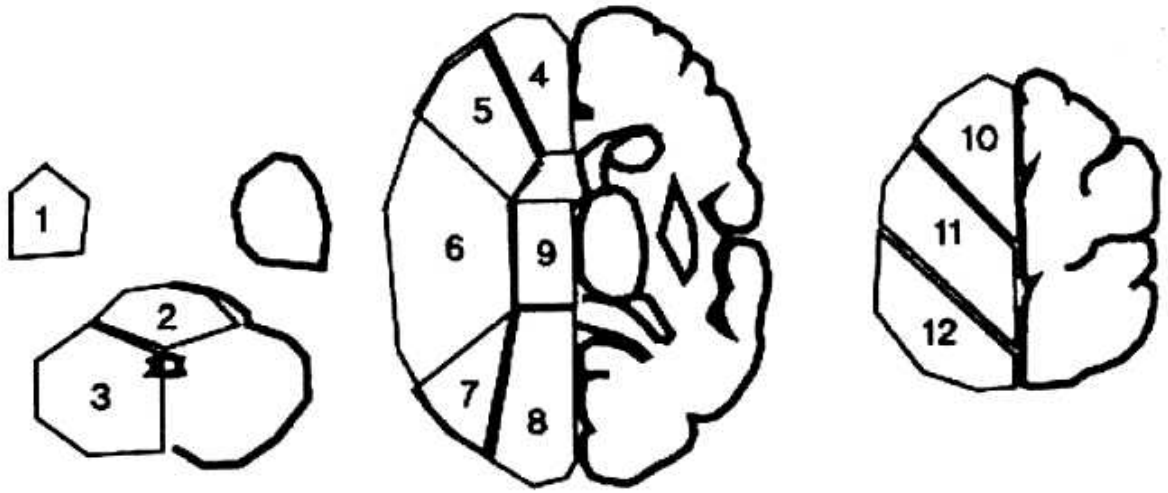

Figure 1. Predetermined regions of interest (20). Selected brain regions are shown on the left of each diagram. 1: anterior temporal region; 2: pons; 3: cerebellar lobe; 4: anterior frontal region; 5: middle frontal region; 6: sylvian area; 7: temporo-parieto-occipital region; 8: occipital region; 9: thalamus area; 10: superior frontal region; 11: central region; 12: parietal region.

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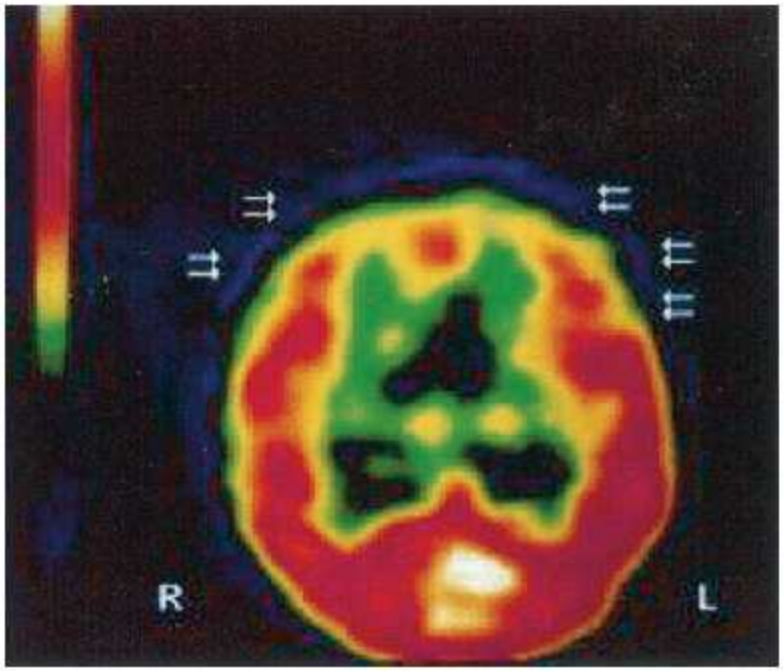
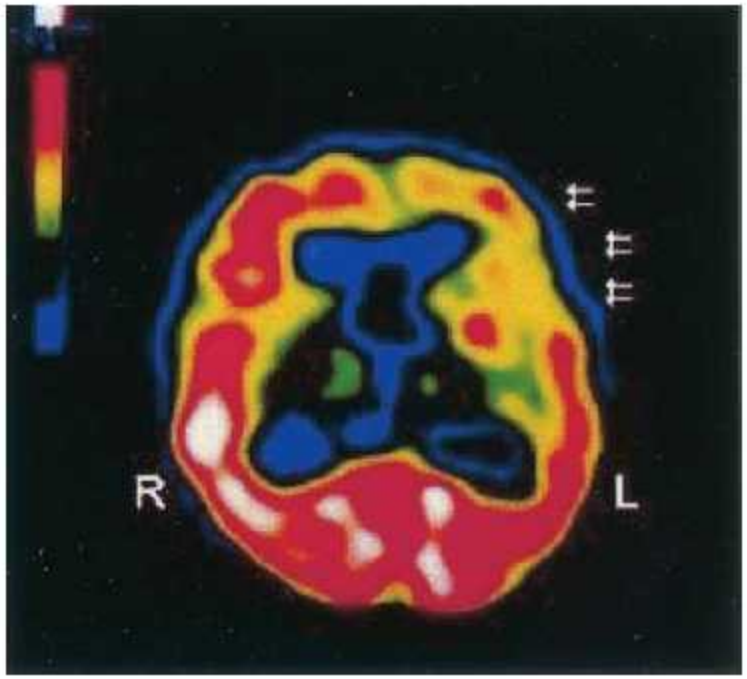
Brain Hypoperfusion in Celiac Disease/Addolorato et al





Cerebral Hypoperfusion at basal ganglia level in untreated celiac patients (double arrows) appear “less red” and “thin” and “yellow”

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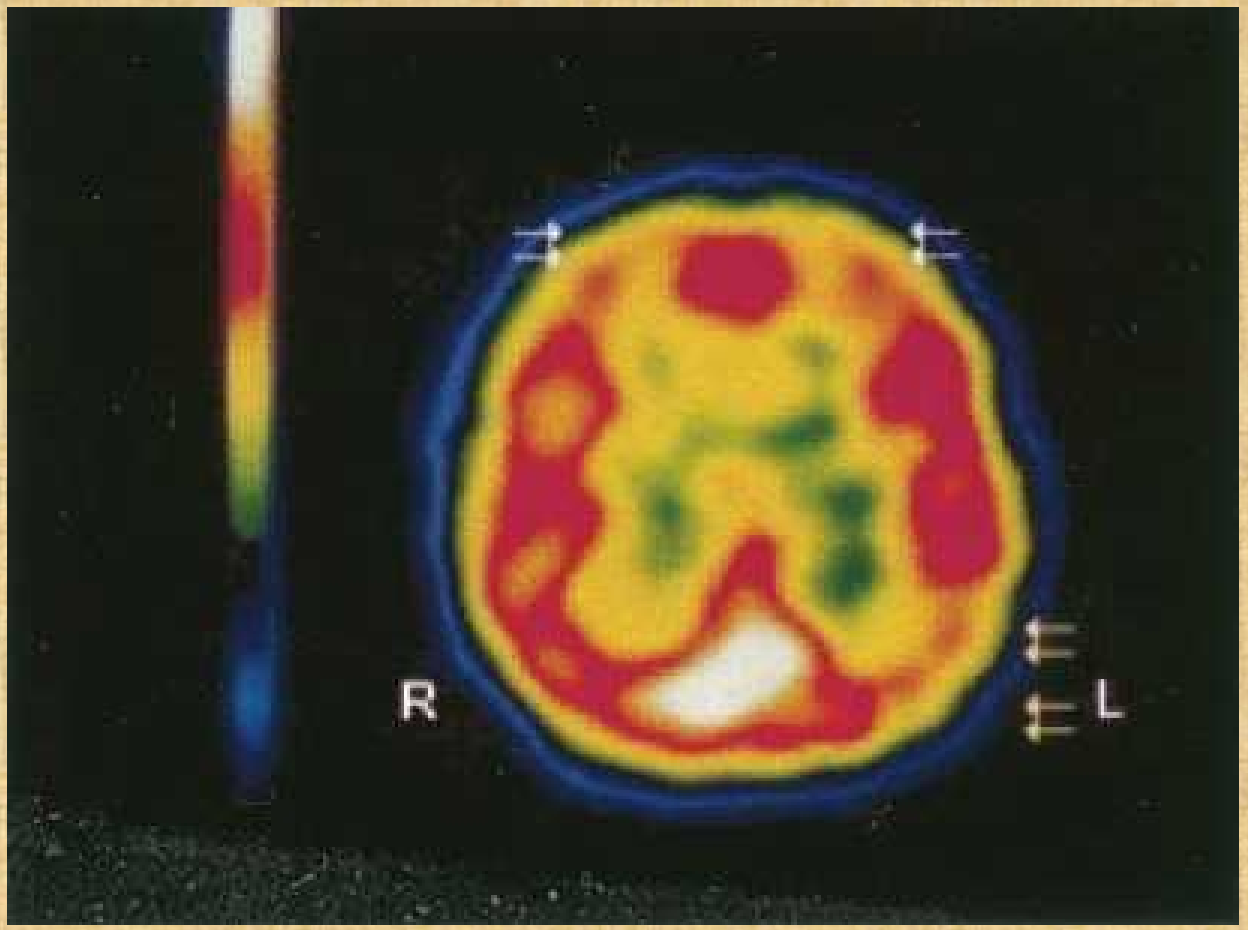

Circumcised areas of decreased tracer uptake (hypoperfusion) can be seen in bilateral superior frontal regions (double white arrows) in an untreated celiac patient

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No blood flow abnormalities were found in the healthy control subjects.

Of the 15 untreated celiac patients, 11 (73%) had at least one hypoperfused brain region (median 4;range 1 to 10),

…while only 1 of 15 (7%) celiac patients on a gluten-free diet had hypoperfusion.

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High levels of anxiety were common in the untreated celiac patients 11/15 (73%)…

Depression was more common in untreated celiac patients 10/15 (67%).

scribed (4–6).

Several neurological, psychiatric, and affective disorders occur in celiac patients. In particular, cerebellar ataxia (7,8), peripheral neuropathies (9), epileptic seizures and intracranial calcifications (10), isolated brain vasculitis (11), brain atrophy and dementia (12), myoclonus and posterior column demyelization (13), schizophrenia (14), depressive syndrome (15–17), and anxiety disorders (15–17) have been reported. These complications occur in approximately 8% to 10% of celiac patients (18). Some of these alterations, such as cerebellar ataxia,

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ten-free diet (14). Given that case report, the aim of the present study was to investigate brain perfusion changes in untreated celiac patients, comparing them with treated celiac patients and healthy subjects.

METHODS

Patients and Controls

The study protocol complied fully with the guidelines of the Ethics Committee of the Università Cattolica del Sacro Cuore in Rome, Italy; all subjects provided informed consent. A group of 19 newly diagnosed adult patients affected by the classic form of celiac disease was enrolled consecutively in the study during a 1-year period. Four of these patients refused to undergo SPECT examination because they suffered from claustrophobia; the remaining 15 patients (9 women and 6 men; mean [± SD] age, 37 ± 9 years) were studied. We excluded patients with endocrine disorders, abuse of alcohol or other substances, consumption of psychotropic drugs, and secondary causes of villous atrophy. The diagnosis of celiac disease was based on the presence of antigliadin and an-

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Association Between Migraine and Celiac Disease: Results From a Preliminary Case-Control and Therapeutic Study

Maurizio Gabrielli, M.D., Filippo Cremonini,
Cristiano Padalino, M.D., Marcello Candelli,
Mario Giacovazzo, M.D., Giovanni Gasbarri

Department of Internal Medicine, and Department of Pathology, Catholic University of the Sacred Heart, Gemelli Hospital, Rome; and Department of Internal Medicine, La Sapienza University, Rome, Italy

Am J Gastroenter,Vol.98,No.3 2003 626-9

OBJECTIVES: Subclinical celiac disease (CD) has been associated with various neurological disorders, the most common being neuropathy and cerebellar ataxia. The aims of the present study were to assess the following: 1) the prevalence

CD is often asymptomatic, the detection rate can be increased by using serology, i.e., the antiendomysial antibody test (1, 2).

Migraine is the most frequent subtype of primary head-

All patients with both migraine and CD showed evident abnormalities in regional cerebral blood flow…the gluten free diet strongly affected the abnormalities of regional cerebral blood flow. In fact, the second study showed a significant improvement in brain perfusion in all patients

patients. Such reduction in uptake completely resolved at follow-up.

CONCLUSIONS: Our results suggest that a significant proportion of patients with migraine may have CD, and that a gluten free diet may lead to a improvement in the migraine in these patients. (Am J Gastroenterol 2003;98:625–629. © 2003 by Am. Coll. of Gastroenterology)

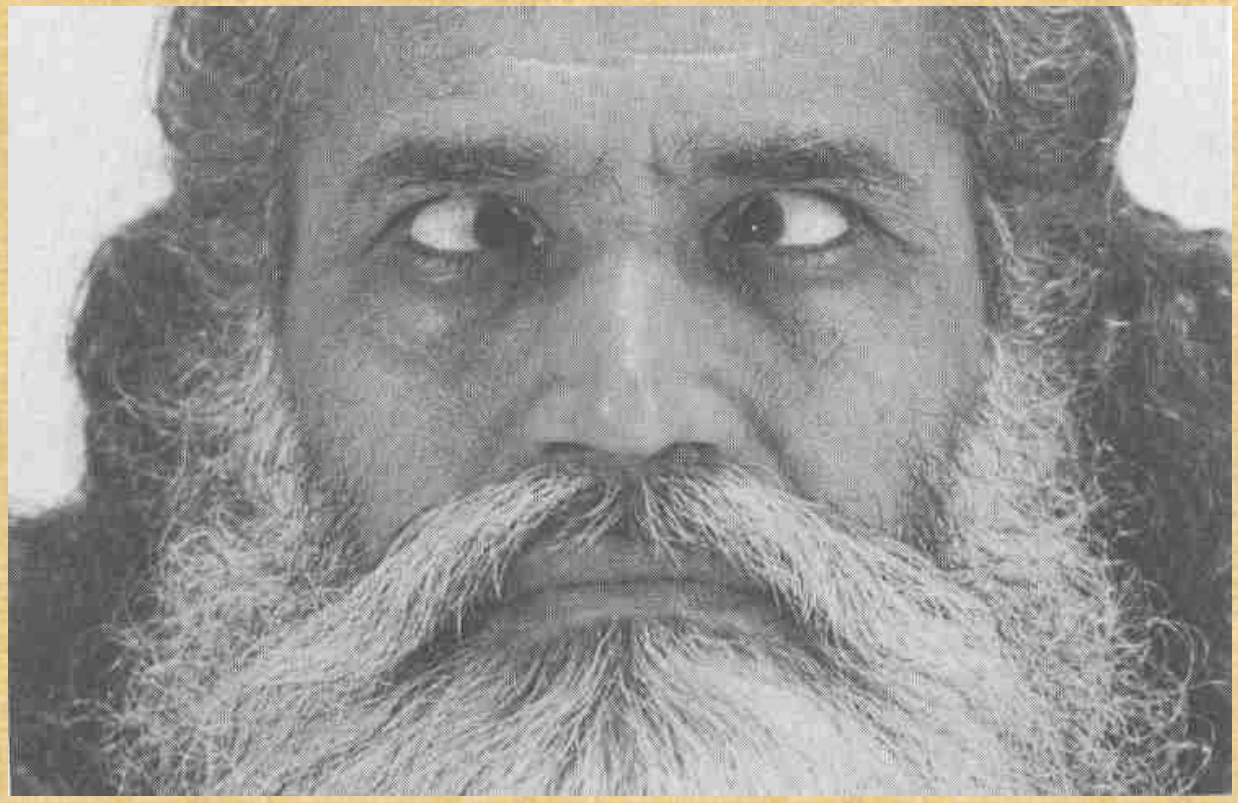
INTRODUCTION

Epidemiological studies using serology tests have shown celiac disease (CD) to be more common than previously realized, showing a prevalence in Europe of 0.33%. Because

headache free intervals, revealing clear interhemispheric asymmetry in the upper frontal and occipital regions (8). Other investigators reported no significant asymmetries in regional cerebral blood flow in patients with migraine outside or during the attacks (9). Moreover, a recent report showed a region of severe hypoperfusion of the left frontal area in a patient with CD and schizophrenic symptoms that both completely resolved after a gluten free diet (10).

The aims of the study were: 1) to assess the prevalence of CD in patients with migraine by means of serology and intestinal biopsy samples and to compare this prevalence with that of a control group; 2) to determine whether SPECT abnormalities are present in migraine patients with CD, and

HOW MANY HAVE SUSPECTED GLUTEN SENSITIVITY OR CELIAC DISEASE, RAN THE BLOOD PANEL, IT COMES BACK NEGATIVE AND YET YOU FELT BETTER ON A GLUTEN FREE DIET?



IT'S THE TESTS!!!!!!!!!!!!!!!!

Alimentary Pharmacology & Therapeutics

Immunoglobulin A autoantibodies against transglutaminase 2 in the small intestinal mucosa predict forthcoming coeliac disease

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SUMMARY

Background
Reliable markers of early developing coeliac diseases are needed. Coeliac autoantibodies in the serum or Marsh I inflammation may be indicators of subsequent coeliac disease.

Aim
To investigate whether determination of intestinal transglutaminase 2-

cytes were assessed as indicators of developing coeliac disease.

Results
Seventeen patients had developed coeliac disease: 13 in the autoantibody-positive group, three in the Marsh I group and one in the Marsh 0 group. At baseline, intestinal coeliac autoantibody deposits had a sensitivity and specificity of 93% and 93% in detecting subsequent coeliac disease, CD3+ 59% and 57%, $\gamma\delta$+ 76% and 60%, and villous tip intraepithelial lymphocytes 88% and 71%, respectively.

Conclusions
Endomysial antibodies with normal histology indicates early developing coeliac disease. Transglutaminase 2-targeted intestinal autoantibody deposits proved the best predictor of subsequent coeliac disease.

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Blood tests for IgA endomysial (EmA) and transglutaminase 2 (TG2) antibodies are powerful tools in disclosing celiac disease with overt villous atrophy..

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Seronegative Celiac Disease: Increased Prevalence with Lesser Degrees of Villous Atrophy

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Negative Blood Tests in Celiac Disease occur. Antibody positivity correlates with more severe villous atrophy, and not mode of presentation.

Commentary

Can histological damage influence the severity of coeliac disease? An unanswered question

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Digestive and Liver Disease 39 (2007) 30–32

Recent literature data showed that serology (not only EMA, but also anti-tTG) seems to be ineffective in detecting most of patients affected by subclinical/silent disease.

Coeliac disease (CD) is a typical chronic inflammatory disease of the gut in which most of the immunopathogenetic events are now well known. Despite this, CD remains an elusive condition and is frequently cited as one of the most under recognised medical diagnoses. This is because CD often exists in a subclinical or silent form, or shows symptoms that do not immediately suggest an origin in the gastrointesti-

fore, found a certain correlation between clinical appearance of the disease, serology and degree of histological damage.

In this issue of *Digestive and Liver Disease*, Brar et al. [9] investigated retrospectively a cohort of 499 adults CD patients, assessing both the clinical presentation and the degree of mucosal damage. They found that majority had silent CD (56%) and total villous atrophy (65%); on the other hand, they found a significant trend over time for a greater proportion of patients presenting as subclinical/silent CD and having partial villous atrophy (although not statistically significant). Finally, they found that female patients with total villous atrophy were at higher risk for osteopenia and lower haemoglobin values.

The results of this study seem to be disappointing, since histological damage does not seem to influence the severity of the disease. Moreover, the large number of CD patients enrolled seems to reinforce the results. But some points deserve further comments for clinical practice.

Despite the large number of patients studied, this is a retrospective study and suffers from this drawback. Some literature data, collected as prospective studies, found that subclinical/silent CD is associated with slight/mild rather than severe damage [4,6]. On the other hand, Brar et al.

been clearly shown that the quality of life of the symptomatic gluten-sensitive cases with Marsh I–II lesions could be dramatically improved by imposing a gluten-free diet [10,13]. Considering this, we cannot exclude that the histological spectrum lesion from Marsh I to Marsh IIIa may be now considered as the main histological damaged recognised in clinical practice despite the results of Brar et al.

But the most important question for clinical practice raising from these studies is why some CD patients are asymptomatic or show atypical symptoms with mild–moderate (Marsh I–IIIa) histological damage, whilst other are symptomatic with severe (Marsh IIIb–c) damage. Unfortunately, this question is also still unaddressed.

Even assessing the correlation between clinical presentation of CD, serology and age, there are conflicting results. A recent study found patients with subclinical/silent CD as generally younger, seronegative and with mild–moderate histological damage [7]. On the other hand, a more recent study found that EMA-negative CD patients were older, and had

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N Engl J Med Oct.23 2003,1673-4

Screening for Celiac Disease

Despite the unexpectedly high prevalence of celiac disease found in the study by Mäki et al. (June 19 issue),[1] their use of endomysial and tissue transglutaminase antibodies as the sole serologic markers probably underestimated the prevalence of celiac disease in the cohort. One study evaluating endomysial antibodies showed that the sensitivity of this marker was 100 percent in patients with total villous atrophy, but the value plummeted to 31 percent in patients with celiac disease who had partial villous atrophy.[2] Antibodies to tissue transglutaminase likewise correlate with the degree of villous atrophy.[3] Addition of the admittedly less specific gliadin antibodies to the analysis would have increased the detection rate in the study population.

Regarding the accompanying editorial by Fasano[4] on screening for celiac disease, the health implications of silent celiac disease are not clear. Al-

As Drs. Lebwohl and Green note, we found a high prevalence of celiac disease in the Finnish population. The addition of a gliadin antibody test might have increased the detection rate. However, recent articles indicate that the autoantibody tests we used are more sensitive than the gliadin antibody test,[1,2] as we reported previously.[3] As the correspondents also note, endomysial antibody testing in one study had only limited value in screening programs for celiac disease.[4] The same group showed that half their patients who had nonfamilial celiac disease with minor mucosal inflammation were negative for HLA-DQ2 and HLA-DQ8.[5] This finding is contrary to our experience.

More research is needed to determine whether

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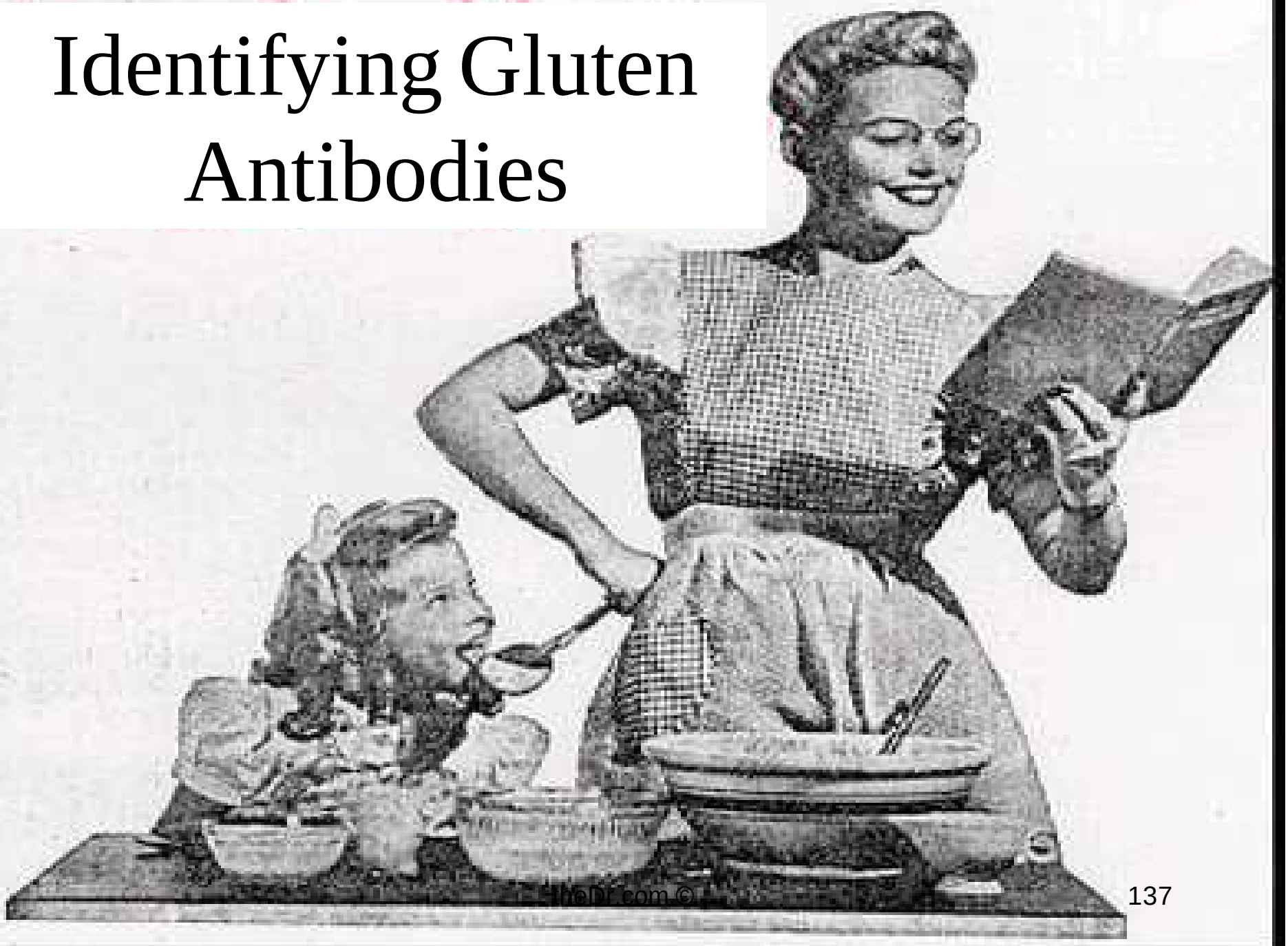
Identifying Gluten Antibodies



CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

Orally Based Diagnosis of Celiac Disease: Current Perspectives

J Dent Res 87(12):1100-1107, 2008

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ABSTRACT

Celiac disease (CD) is a lifelong immune-mediated

tests are used to screen at-risk individuals, although a firm diagnosis requires demonstration of characteristic histopathologic findings in the small-intestinal mucosa. A gluten challenge, with a repeat biopsy to demonstrate recurrence of histopathologic changes in the intestinal mucosa after the re-introduction of gluten, is considered for those persons in whom diagnosis remains in doubt. In this paper, we review studies that evaluated: (1) the possibility of using oral mucosa for the initial diagnosis of CD or for local gluten challenge; and (2) the possibility of using salivary CD-associated antibodies as screening tests. Our review shows that orally based diagnosis of CD is attractive and promising, although additional evaluations with standardized collection and analysis methods are needed. There is some evidence of a dissociation between systemic and oral mucosal immune responses in CD. The hypothesis that gluten could stimulate naïve lymphocytes directly in the oral cavity would have important implications for the understanding, diagnosis, and management of CD.

KEY WORDS: celiac disease, diagnosis, oral mucosa, saliva, screening.

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INTRODUCTION

In persons with celiac disease (CD), ingestion of wheat gluten causes small-intestinal mucosal injury. The typical form of the disease is characterized by a malabsorption syndrome (chronic diarrhea, abdominal pain and distention, weight loss). However, it is now evident that most cases of CD are atypical, with extra-intestinal manifestations (*e.g.*, iron-deficient anemia, abnormalities in liver function test) being the predominant, if not the sole, clinical features (Green and Cellier, 2007). Occurrence of long-term complications (autoimmune diseases, cancers) in persons with CD is responsible for a mortality rate higher than that in the general population (Corrao *et al.*, 2001; Peters *et al.*, 2003); this fact justifies gluten

higher than previously reported, and yet probably lower than the actual prevalence, since many atypical cases remain undiagnosed (Mearin *et al.*, 2005). Consequently, there is a need for discovering the submerged part of the "celiac iceberg".

In this paper, we review studies that evaluated: (1) the possibility of using oral mucosa for the initial diagnosis of CD or for local gluten challenge; and (2) the possibility of using salivary CD-associated antibodies as screening tests for the disease.

Etiology of Celiac Disease

Gluten is the protein fraction of most cereals, including wheat, rye, and barley. It is comprised of hundreds of protein components, traditionally classified on the basis of their solubility in alcohol-water solutions, in prolamins (alcohol-soluble), and glutenins (alcohol-insoluble) (Wieser, 2007). Although there is recent evidence that even glutenins could be involved in the pathogenic mechanisms of CD (Dewar *et al.*, 2006; Howdle, 2006), prolamins of wheat, rye, and barley (namely, gliadins, secalins, and hordeins, respectively) are thought to be responsible for triggering CD. A high content of glutamine and proline is a common feature of gliadins, secalins and hordeins, while prolamins of cereals considered to be non-toxic for persons with CD, such as rice and corn, have a lower content of these amino acids (Schuppan, 2000). This particular amino acid composition confers resistance to complete degradation by gastrointestinal proteolytic enzymes, which results in accumulation of peptide fragments rich in glutamine and proline in the lumen of the small intestine (Kagnoff, 2007). An exceptionally immunoreactive 33-mer peptide resistant to digestion by all gastric, pancreatic, and intestinal brush-border membrane proteases has been identified from α-2 gliadin (Shan *et al.*, 2002), and an *in silico* analysis of the gluten proteome has led to the identification of as many as 60 putative peptides that have similar characteristics (Shan *et al.*, 2005).

An 83% concordance rate among monozygotic twins (Nistico *et al.*, 2006) and a 5-15% prevalence of the disease among first-degree relatives of affected persons (Wolters and Wijmenga, 2008) demonstrate a strong genetic susceptibility to CD. In fact, approximately 95% of persons with CD express the human

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REVIEW

Celiac disease: how complicated can it get?

Jennifer May-Ling Tjon · Jeroen van Bergen · Frits Koning

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As modern wheat varieties contain up to 100 different gluten proteins in a single wheat variety, and many of these are implicated (as the trigger) in (developing) CD.

be explained by the fact that gluten peptides can be presented in HLA-DQ2 and HLA-DQ8 molecules on antigen presenting cells. Gluten-specific $CD4^+$ T cells in the lamina propria respond to these peptides, and this likely enhances cytotoxicity of intraepithelial lymphocytes against the intestinal epithelium. We propose a threshold model for the development of celiac disease, in which the efficiency of gluten presentation to $CD4^+$ T cells determines the likelihood of developing celiac disease and its complications. Key factors that influence the efficiency of gluten presentation include: (1) the level of gluten intake, (2) the enzyme tissue transglutaminase 2 which modifies gluten into high affinity binding peptides for HLA-DQ2 and HLA-DQ8, (3) the HLA-DQ type, as HLA-DQ2 binds a wider range of gluten peptides than HLA-DQ8, (4) the gene dose of HLA-DQ2 and HLA-DQ8, and finally,(5) additional genetic polymorphisms that may influence T cell reactivity. This threshold model might also help to understand the development of refractory celiac disease and lymphoma.

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2009). Clinical manifestations vary according to age group: infants and young children present with diarrhea, abdominal distention, and failure to thrive, whereas adults that develop CD not only present with diarrhea, but also with silent manifestations such as anemia, osteoporosis, or neurological symptoms (Green and Cellier 2007). Immunohistochemistry of the small intestine of patients shows villous atrophy, crypt hyperplasia, and elevated levels of intraepithelial lymphocytes (IELs). The only therapy until now is a gluten-free diet, which will normalize the clinical and histological manifestations and allows the patients to live an otherwise normal life.

A small percentage of adult-onset CD patients develop a primary or secondary resistance to a gluten-free diet (Fig. 1). This condition is called refractory celiac disease (RCD) and is characterized by persisting villous atrophy and elevated levels of IELs. Currently, RCD is subdivided into two subtypes: RCD type I (RCD I) and RCD type II (RCD II) that both display clinical and histological resistance to a gluten-free diet (Daum et al. 2005). RCD II, however, is associated with the presence of an aberrant IEL population that lacks surface T cell receptor (TCR)-CD3 expression, but contains intracellular CD3ε and has clonal TCRγ-gene rearrangements (Cellier et al. 1998). These aberrant IELs can gain chromosomal abnormalities and develop into surface TCR-$CD3^-$ lymphoma cells (Deleeuw et al. 2007; Verkarre et al. 2003). RCD II is

GASTROENTEROLOGY 2002;122:1729–1737

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 KOOY,* PETER VAN VEELEN,* ARNOUD DE RU,* DIANA HARRIS,* WILLEMIEN BENCKHUIJSEN,* 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 α-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.[1–3] The large majority of patients express the HLA-DQ2 [DQ(α1*0501, β1*02)] and/or -DQ8 [DQ(α1*03, β1*0302)] molecules. This has been solved by the finding that the enzyme tissue transglutaminase (tTG), the target of the endomysium-specific antibodies in CD patients,[10] can modify GLU peptides by conversion of glutamine residues into glutamic acid (termed deamidation[11]), 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 deamidation.[12–18] 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[16] and 2 independent studies showed that all HLA-DQ2 patients respond to a particular α-GLIA peptide.[12,13] 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[12,13,15,16,18] 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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CLINICAL RESEARCH

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This may help to prevent disease development in individuals at risk.

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 α-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.**

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respond to the α-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.

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Although some patients respond to one set of peptides, others respond to different sets of peptides.

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 α-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.[1–3] The large majority of patients express the HLA-DQ2 [DQ(α1*0501, β1*02)] and/or -DQ8 [DQ(α1*03, β1*0302)] molecules, which has been solved by the finding that the enzyme tissue transglutaminase (tTG), the target of the endomysium-specific antibodies in CD patients,[10] can modify GLU peptides by conversion of glutamine residues into glutamic acid (termed deamidation[11]), 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 deamidation.[12–18] 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[16] and 2 independent studies showed that all HLA-DQ2 patients respond to a particular α-GLIA peptide.[12,13] 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[12,13,15,16,18] 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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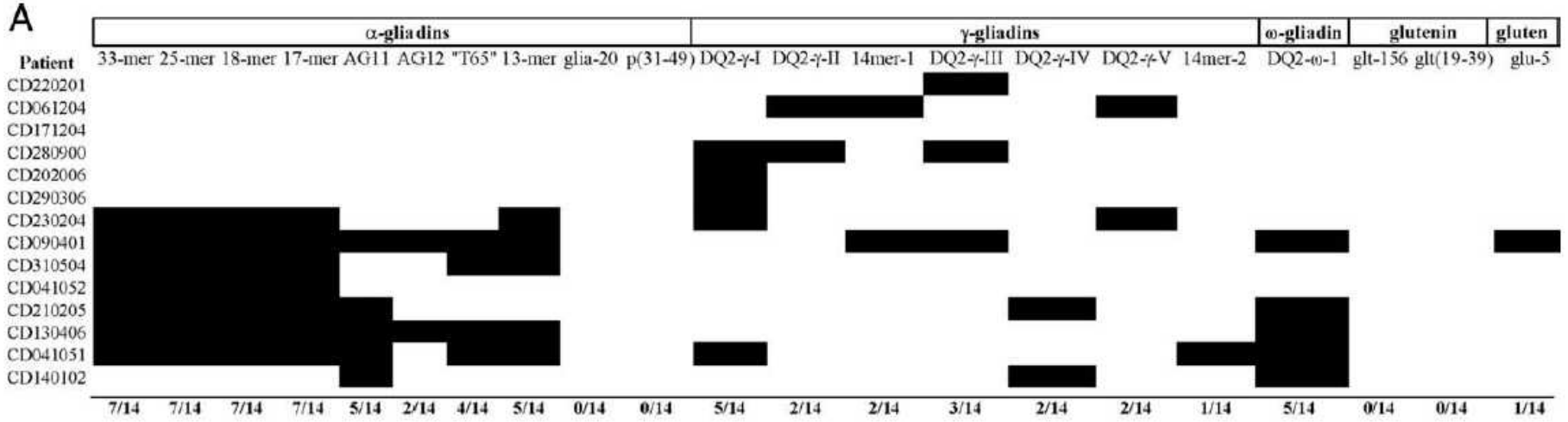

Epitopes / Patients	Novel DQ2 gluten epitopes								
	Glia-α20	Glia-γ30	Glt-17	Glt-156	Glu-5	Glu-21	Glia-γ1	Glia-α2	Glia-α9
LP		■							
JB	tTG								
JP					■				
MB					■				
SV		■				no tTG	tTG		
NP				tTG	■			tTG	
NV			tTG	tTG					
MS			tTG	tTG			tTG		
RR		■	tTG	tTG			tTG	tTG	
KL	■	■			■			tTG	tTG
DB	tTG				■			tTG	
SB					■			tTG	tTG
NB							tTG	tTG	tTG
BD								tTG	tTG
LS								tTG	tTG
MaB							tTG		
Adult1					■				
Adult2		■							
Adult3								tTG	tTG
Adult4	tTG				■		tTG	tTG	tTG

GASTROENTEROLOGY 2002;122:1729–1737

Figure 6. Overview of the T-cell responses against the known DQ2 epitopes. TCCs and lines of young and adult patients were tested against the DQ2 epitopes characterized in the present study and the previously published epitopes Glia-α2(62-75) PQPQLPYPQPQLPY, Glia-α9(57-68) QLQPFPQPQLPY, and Glia-γ1 (138-153) QPQQPQQSF-PQQQRPF.[13,15] The *black boxes* represent stimulation of the T cells by the epitope. The effect of deamidation of the epitope on the T-cell response is indicated in the individual boxes. tTG indicates requirement of deamidation for recognition, and no tTG indicates blocking of the response by deamidation of the peptide. The remaining responses are (largely) indifferent to deamidation.

GASTROENTEROLOGY 2002;122:1729–1737

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 KOOY,* PETER VAN VEELEN,* ARNOUD DE RU,* DIANA HARRIS,* WILLEMIEN BENCKHUIJSEN,* 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

Our present results indicate that CD patients are capable of responding to a large array of gluten peptides.

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 α-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.[1–3] The large majority of patients express the HLA-DQ2 [DQ(α1*0501, β1*02)] and/or -DQ8 [DQ(α1*03, β1*0302)] molec-

affinity ligands for HLA-DQ2 and -DQ8. This paradox has been solved by the finding that the enzyme tissue transglutaminase (tTG), the target of the endomysium-specific antibodies in CD patients,[10] can modify GLU peptides by conversion of glutamine residues into glutamic acid (termed deamidation[11]), 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 deamidation.[12–18] 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[16] and 2 independent studies showed that all HLA-DQ2 patients respond to a particular α-GLIA peptide.[12,13] 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[12,13,15,16,18] 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

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Intestinal T Cell Responses to Gluten Peptides Are Largely Heterogeneous: Implications for a Peptide-Based Therapy in Celiac Disease[1]

Alessandra Camarca,* Robert P. Anderson,† Gianfranco Mamone,* Olga Fierro,* Angelo Facchiano,* Susan Costantini,* Delia Zanzi,‡ John Sidney,§ Salvatore Auricchio,‡ Alessandro Sette,§ Riccardo Troncone,‡ and Carmen Gianfrani[2]*

The identification of gluten peptides eliciting intestinal T cell responses is crucial for the design of a peptide-based immunotherapy in celiac disease (CD). To date, several gluten peptides have been identified to be active in CD. In the present study, we investigated the recognition profile of gluten immunogenic peptides in adult HLA-DQ2$^+$ celiac patients. Polyclonal, gliadin-reactive T cell lines were generated from jejunal mucosa and assayed for both proliferation and IFN-γ production in response to 21 peptides from wheat glutenins and α-, γ-, and ω-gliadins. A magnitude analysis of the IFN-γ responses was performed to assess the hierarchy of peptide potency. Remarkably, 12 of the 14 patients recognized a different array of peptides. All α-gliadin stimulatory peptides mapped the 57–89 N-terminal region, thus confirming the relevance of the known polyepitope 33-mer, although it was recognized

The great majority of patients reacted to a particular set of peptides.

Celiac disease (CD)[3] is a common food-sensitive enteropathy in humans. In CD patients, the ingestion of wheat gluten, and of homologous proteins of barley and rye, induces pronounced T cell-mediated inflammatory reactions, mainly in the small intestine (1). The marked genetic association with HLA class II genes and the isolation of gluten-reactive, HLA-DQ2/DQ8-restricted CD4$^+$ T cells from the intestinal mucosa of celiac patients have highlighted the key role of the adaptive T cell response in the CD lesion (2–6).

Despite the efforts of several laboratories to define relevant gluten epitopes (2, 3, 5, 6), the characterization of the complete repertoire of peptides involved in the pathogenesis of CD remains a daunting task because of the great heterogeneity of gluten proteins (7). So far, several T cell stimulatory peptides from α-gliadin, γ-gliadin, and glutenins have been identified using mass spectrometry analysis or by screening large peptide libraries (5, 6, 8–10). Furthermore, only in recent years has the key role of tissue transglutaminase (TG2) been elucidated in deamidating gluten peptides to facilitate their binding to HLA-DQ2 and -DQ8 molecules (11, 12). These findings led to an important step forward in the knowledge of CD pathogenesis, and also to the identification of immunogenic gluten peptides on the basis of their susceptibility to be deamidated by TG2 (Ref. 13 and G. Mamone, A. Camarca, O. Fierro, F. Addeo, G. Mazzarella, S. Auricchio, R. Troncone, and C. Gianfrani, manuscript in preparation).

Despite the large number of immunogenic gluten peptides so far identified, Arentz-Hansen et al. showed that intestinal T cell responses in HLA-DQ2$^+$ Norwegian CD patients are mainly focused on two overlapping peptides spanning the 57–68 and 62–75 region of α-gliadin (8). Remarkably, Khosla and coworkers demonstrated that a single 33-mer peptide encompassing the 57–89 N-terminal region of certain α-gliadin proteins displayed the optimal T cell stimulatory capacity in a cohort of adult Scandinavian subjects (14). This 33-mer peptide, encompassing six copies of three reported T cell epitopes (DQ2-α-I, DQ2-α-II, and DQ2-α-III), is resistant to gastrointestinal proteolysis, does not require intracellular processing for presentation, and binds efficiently to HLA-DQ2. Collectively, these chemical and immunological properties add further weight to the contention that this 33-mer peptide is the immunodominant T cell stimulatory gluten peptide in HLA-DQ2$^+$ CD patients (15, 16). Parallel studies have shown that following consumption of wheat-containing food, gluten-reactive T cells secreting IFN-γ transiently circulate in peripheral blood of previously "gluten-free" celiac patients (17). By this innovative approach, the screening of a peptide library spanning the entire

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[3] Abbreviations used in this paper: CD, celiac disease; B-LCL, EBV-lymphoblastoid cell line; iTCL, intestinal T cell line; PT, peptic-tryptic; TCC, T cell clone; TG2, tissue transglutaminase.

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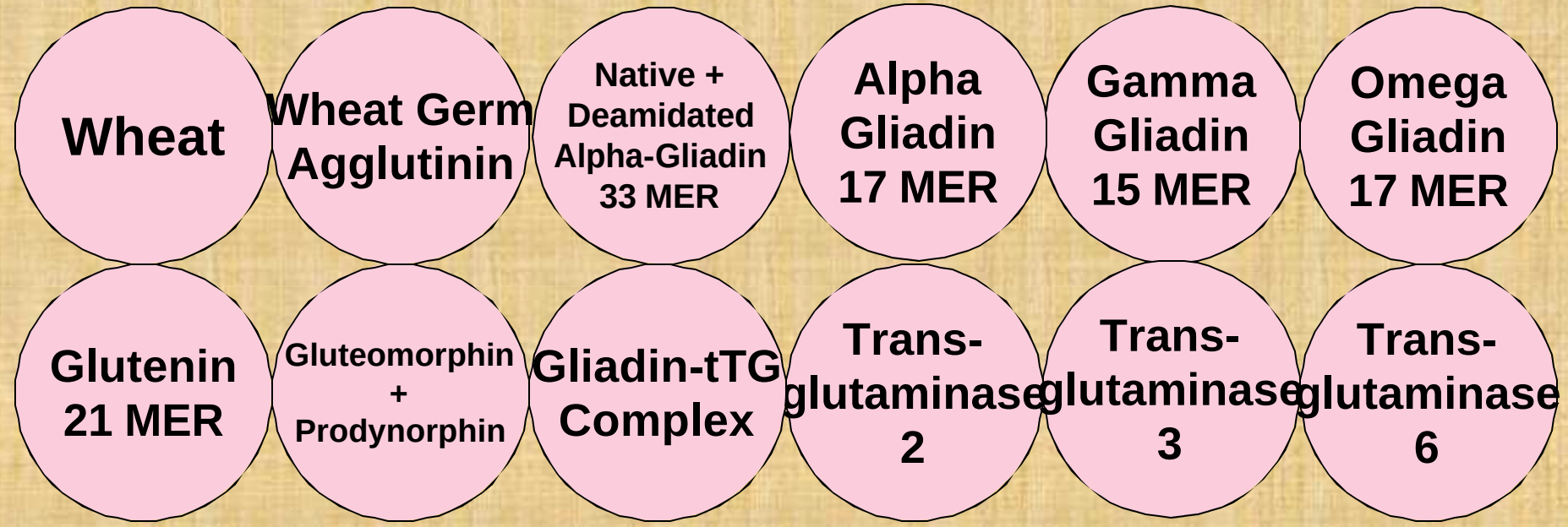

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REVIEW

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

J R Soc Med 2011 104: 510

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DECLARATIONS

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

Summary

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.

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

Introduction

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

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.[12] 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%.[13] 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% arise 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,[14] 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.[1,3,15] Balas and Bohen,[16] Grant[17] and Wratschko[18] 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

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Long-Term Mortality in People With Celiac Disease Diagnosed in Childhood Compared With Adulthood: A Population-Based Cohort Study

Masoud Solaymani-Dodaran, M.D., Ph.D., M.P.H., Joe West, M.B., Ph.D., M.R.C.P., and Richard F.A. Logan, M.B., M.Sc., F.R.C.P.
University of Nottingham, Division of Epidemiology and Public Health, Medical School, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom

INTRODUCTION: To explore whether the excess mortality in celiac disease is related directly to the disease and

Childr **WHY???** **had a threefol** **rtality.**

95% CI 1.21–8.67), and cerebrovascular disease (two deaths, SMR 10.03, 95% CI 1.21–36.00).

CONCLUSIONS: Children diagnosed with celiac disease had a threefold increased risk of long-term mortality. This is in marked contrast to the experience of adult celiac disease where the long-term increase of mortality was modest. The increased mortality in children from external causes may reflect behavioral change associated with coping with a chronic disease and its treatment.

(Am J Gastroenterol 2007;102:864–870)

INTRODUCTION

Various studies have found that celiac disease still confers about a 1.3- to 2-fold increase in all-cause mortality compared with the general population (1–6). It is unclear how much this increase is related to celiac disease itself and how much the increase might be only indirectly related via various associated conditions. In addition, there has been speculation that the duration of gluten exposure prior to diagnosis has long-term adverse effects and therefore contributes to mortality (6). If the mortality increase is directly the result of celiac disease and/or the duration of preceding gluten exposure, then celiac disease diagnosed in childhood might be expected to be associated with a lesser increase of mortality than adult diagnosed disease (3, 4).

Previous studies have been unable to precisely estimate the mortality in children with celiac disease mainly because of lack of long-term follow-up (5–8). In adults most of the excess mortality in celiac disease has previously been reported as resulting from malignant disease (6). As children with celiac disease are mostly diagnosed around the age of 1–3 yr they have little long-term gluten exposure, assuming they are compliant with a gluten-free diet. It is plausible then that children may be protected in some way from the excess malignant risk that is apparent in adults.

To examine whether there are differences in the long-term mortality experience of people diagnosed with celiac disease as children and as adults we have analyzed further data from the Lothian celiac disease cohort. As this study has good quality follow-up we have been able to examine cause-specific mortality over many years following diagnosis compared with the general population.

METHODS

Participants

Our study cohort was originally set up in 1979 through an attempt to identify all cases of celiac disease diagnosed in the Lothian region of Scotland. Details of the recruitment process have been published previously (2, 9). In brief, the following sources were used to identify celiac cases: the records of gastrointestinal units of all the hospitals in the region including the Edinburgh Royal Infirmary, Western General Hospital, and Royal Hospital for Sick children up to December 1981; The Scottish Hospital Inpatient Statistics for the years 1961–1977; all the existing regional histopathology records in the

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THE NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Celiac Disease — How to Handle a Clinical Chameleon

Alessio Fasano, M.D.

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible persons. The disease is associated with HLA-DQ2 in 90 to 95 percent of cases and with HLA-DQ8 in 5 to 10 percent of cases and is self-perpetuating in the continued presence of gluten.[1] It is the interplay between genes (both HLA and other types) and environment (i.e., gluten) that leads to the intestinal damage that is typical of the dis-

characteristic of the early phase of celiac disease[2] and the subsequent abnormal passage of gluten into the lamina propria. The protein is deamidated by tissue transglutaminase in the lamina propria and is then recognized by antigen-presenting cells bearing HLA-DQ2 or DQ8, thereby triggering the autoimmune reaction of celiac disease.[3] Given the undisputable role of gluten in causing inflammation and immune-mediated tissue damage, celiac disease represents a unique model of autoimmunity in which, in contrast to all other autoimmune diseases, a close genetic association with HLA-DQ2, DQ8, or both; a highly specific humoral autoimmune response (autoantibodies against tissue transglutaminase); and most important, the triggering environmental factor (gluten) have all been identified. This information provides the rationale for the treatment of the disease based on complete avoidance of gluten-containing grains, a task complicated by the lack of a clear food-labeling policy.

and the United States.[5] The clinical presentation of this condition can range from the typical syndrome of malabsorption (chronic diarrhea, weight loss, and abdominal distention) to symptoms and conditions that can affect any organ system (Table 1).[6] Since the onset of celiac disease may be atypical or

tissue transglutaminase antibodies — combined with HLA typing, the authors screened a cohort of children whose serum samples had been collected seven years earlier. Fifty-six had positive serologic tests; only 10 (18 percent) of whom had been given a diagnosis of celiac disease between the serum

Table 1. Atypical Clinical Manifestations of Celiac Disease.

Diabetes
Anemia
Osteoporosis or other bone diseases
Chronic fatigue
Autoimmune disorders
Gastrointestinal cancer
Dermatitis herpetiformis
Behavioral changes
Irritable bowel
Miscarriage
Neurologic symptoms (including ataxia)

2568

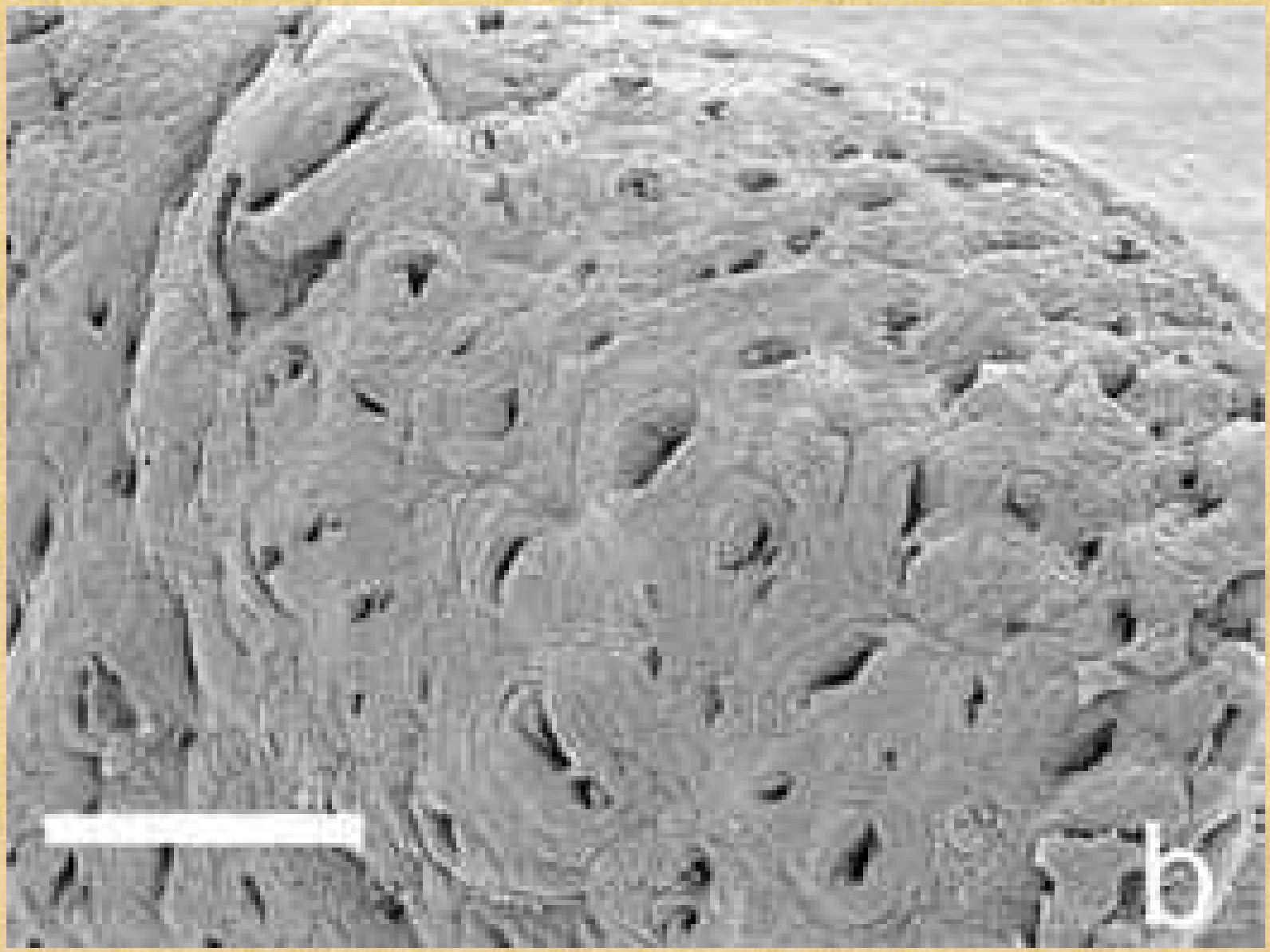
N ENGL J MED 348;25 www.NEJM.ORG JUNE 19, 2003

NEJM 348;25 June 19,2003

Celiac Disease is one of the most common lifelong disorders in both Europe and the US


visuals:unlimited

Am J Gastroenterol. 2004 May;99(5):894-904



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Body on Fire

- **Elimination Diet**
- **Probiotics**
- **Vitamin D**
- **Glutamine**
- **EPA/DHA**
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Note: There are many other beneficial anti-inflammatories that can be used. These are foundational recommendations

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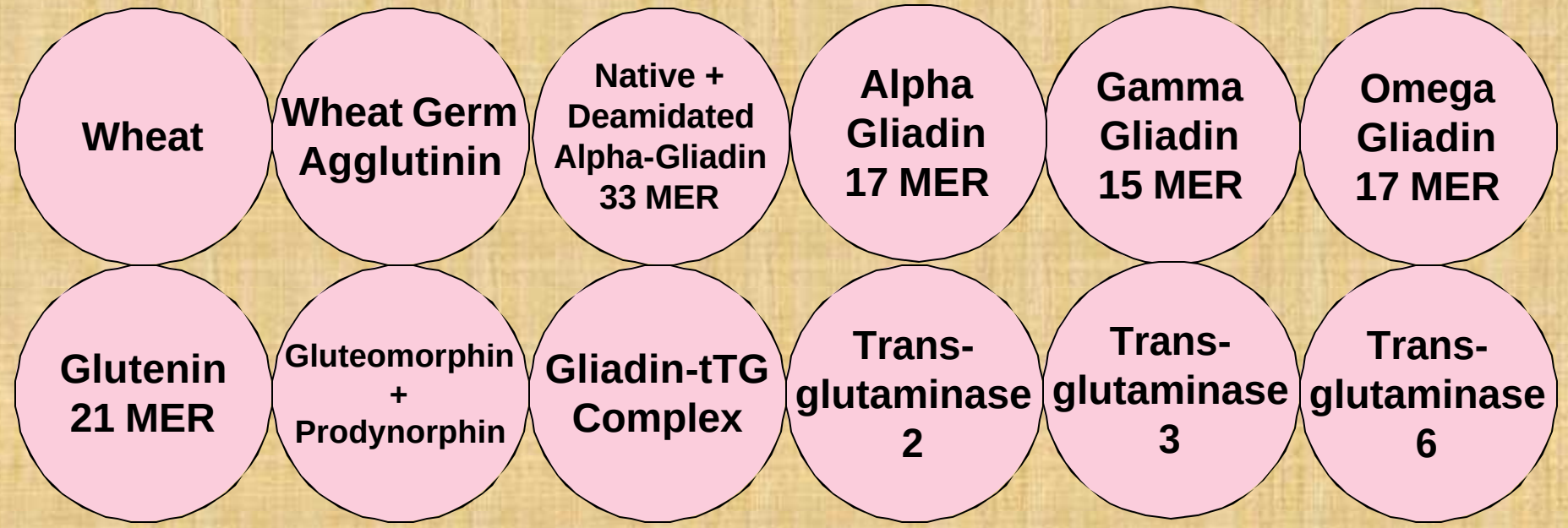

Undiagnosed coeliac disease at age seven: population based prospective birth cohort study

Polly J Bingley, Alistair J K Williams, Alastair J Norcross, D Joe Unsworth, Robert J Lock, Andrew R Ness, Richard W Jones, on behalf of the Avon Longitudinal Study of Parents and Children Study Team

Division of Medicine, University of Bristol, Southmead Hospital, Bristol BS10 5NB
Polly J Bingley *reader*
Alistair J K Williams *research associate*
Alastair J Norcross *research assistant*

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BMJ Vol.328, 7 February 2004 322-3

Occult coeliac disease seems to start in childhood, even in those who are subsequently diagnosed as adults. The search for the trigger resulting in the breakdown of immune tolerance to gluten therefore needs to focus on infancy and intrauterine life.

Coeliac disease is uncommon in childhood and diagnosed in fewer than 1 in 2500 children in the United Kingdom.[1] Subclinical disease is, however, common in adults, and can be detected by testing for IgA antiendomysial antibodies (IgA-EMA). We used these to establish the prevalence of undiagnosed coeliac disease in the general population at age seven and to look for associated clinical features.

Participants, methods, and results

We studied children aged 7.5 years participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population based birth cohort study established in 1990.[2] Two stage screening included a

ence in the number of episodes of diarrhoea. Vomiting, abdominal pain, and constipation were not associated with EMA, but more IgA-EMA positive children (table).

Comment

At age 7, 1% of children were IgA-EMA positive and likely therefore to have subclinical coeliac disease, though less than 0.1% were reported to be on a gluten-free diet. The prevalence of coeliac disease in these

were tTG antibody positive but IgA-EMA negative

	tTG antibody negative controls	IgA-EMA positive	
	Median (interquartile range) (n=5333 children)	Median (interquartile range) (n=54 children)	P value
Measurements taken at age 7.5 years			
Height (cm)	126 (122.4 to 129.6)	122.1 (118.25 to 125.33)	<0.0001
Weight (kg)	25.2 (22.8 to 28.0)	23.4 (21.35 to 25.4)	<0.0001
Standard deviation score for height	0.23 (−0.43 to 0.88)	−0.53 (−1.01 to −0.00)	<0.0001
Standard deviation score for weight	0.18 (−0.45 to 0.86)	−0.36 (−1.01 to 0.28)	<0.0001
Haemoglobin concentration (g/l)	125 (120 to 130)	123 (118 to 127)	0.062
	No (%) (n=4285 questionnaires)	No (%) (n=42 questionnaires)	Odds ratio (95% CI)
Symptoms reported at age 6.75 years			
Any diarrhoea	1450 (34)	21 (50)	1.96 (1.06 to 3.59)
Any vomiting	1933 (45)	23 (55)	1.47 (0.80 to 2.71)
Any stomach pains	2557 (60)	28 (66)	1.35 (0.71 to 2.57)
Any constipation	435 (10)	6 (14)	1.48 (0.62 to 3.52)
≥3 gastrointestinal symptoms	931 (22)	17 (40)	2.45 (1.33 to 4.5)

THE NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Celiac Disease — How to Handle a Clinical Chameleon

Alessio Fasano, M.D.

NEJM 348;25 June 19,2003

Multiple studies suggest that patients with celiac disease should be treated, whether or not they have symptoms or associated conditions.

Table 1. Atypical Clinical Manifestations of Celiac Disease.

Diabetes
Anemia
Osteoporosis or other bone diseases
Chronic fatigue
Autoimmune disorders
Gastrointestinal cancer
Dermatitis herpetiformis
Behavioral changes
Irritable bowel
Miscarriage
Neurologic symptoms (including ataxia)


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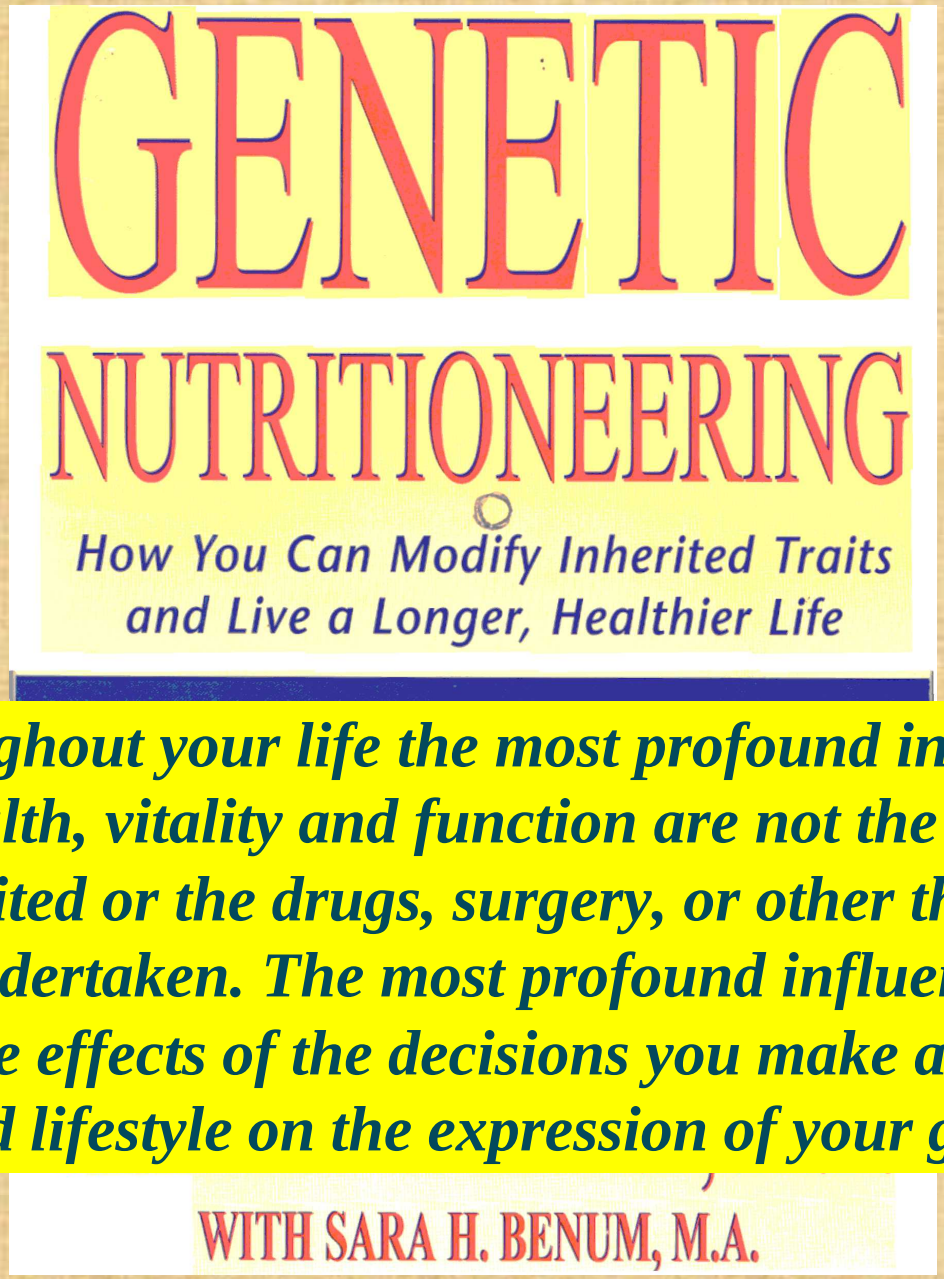

"Throughout your life the most profound influences on your health, vitality and function are not the Doctors you have visited or the drugs, surgery, or other therapies you have undertaken. The most profound influences are the cumulative effects of the decisions you make about your diet and lifestyle on the expression of your genes."


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