R.D. McKenna
2017 Memorial Lecture:
The Growing Problems of Food Allergies and Intolerances
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Dr. Richard D. McKenna

- August 30, 1911 - May 12, 1975
- Received MD from McGill University in 1938
- Trained at the Royal Victoria Hospital and the University of Pennsylvania under Henry Bockus
- Received FRCPS in Internal Medicine in 1947
- Staff/Faculty McGill University 1947-66
- Served as Treasurer of the AGA
- Founded CAG 1961, incorporated Jan 1962 – 1st president
- R. D. McKenna Lecture instituted in 1966, after retiring the McKenna Memorial Lecture was renamed
My Disclosures

• Co-author of “Celiac Disease for Dummies” – royalties
• UpToDate – author of *H. pylori* topics – honorarium
• Ferring, Inc. – Advisory Board – honorarium
• Celimmune – Site PI for a Clinical Trial with anti-IL-15 for Refractory Celiac Disease
A Change in Career

Classification of Adverse Reactions to Food

Adverse food reaction

Immune
- IgE (OAS, Hives, Anaphylaxis)
- Mixed (EoE)

Non-IgE (FPIES, Celiac)
- Cell (Allergic contact dermatitis)

Non-immune
- Metabolic (Lactose intolerance)
- Toxic (Scombroid)
- Pharmacological (Tyramine)
- Other (Mechanical, physiological)

Adapted from Boyce JA et al. JACI.2010;126(6):1105
Prevalence of Food Allergies

• Over 50 million Americans have allergies
• Up to 15 million have “food allergies”
• 1 in 13 children ≤ 18 yrs have food allergies
• $25 billion/year spent on allergies
• Over 85% of ARF are not food allergy
• A fifth of the US population self imposes diet modifications because of perceived ARF
Issues for Consideration as a Gastroenterologist

• Differentiating food allergies from food intolerances
• Why is there an increasing prevalence of celiac disease, peanut allergy, EoE and other food allergic conditions
• Managing eosinophilic food-related GI disorders
• Discuss forms of adverse reactions to wheat
• Consider varying forms of intolerances to milk
• Testing for food allergy and intolerances
• Upsides and downsides of various diets
What to Eat and What Not to Eat?

• Nearly every patient who sees a GI practitioner wants to know is it something they eat and/or is it something they are missing from their diet that is the cause of their GI and other health problems

• The popularity of many types of diets underscore the notion that what we eat is the key to health and wellbeing

• Marketing of food promoting potential health benefits is becoming more common
Good Grains and Bad Grains?

HIS AND HERS “SEX” CEREAL

THE DAILY CONSTITUTIONAL AID
Food and the Digestive Tract: Friend or Foe?

• The average human ingests a large amount of food in their lifetime
  – ~ 60,000 pounds - 27,273 kilograms - 30 tons

• The vast majority benefit from this ingestion but a small percentage develop complications:
  – Food poisoning
  – Food allergies
  – Food sensitivities

• There is a reported increase in food allergies, celiac disease and seemingly of food sensitivities
Biological Variables that Influence the Developing Immunophenotype of an Infant

Brandtzaeg, Nat Rev Gastroenterol Hepatol, 7: 380-400, 2010
Non-Immune Reactions to Food

- Mechanical, physiological
- Food toxicity/poisoning – microbes
- Anaphylactoid (pseudo-allergic) - strawberries
- Pharmacologic – tyramine, sulfates, etc
- Metabolic – lactase insufficiency
- Idiosyncratic – reactions without known cause
- Psychological
Immunological Reactions to Food

• Food hypersensitivity (IgE-mediated)
  • Oral allergy - pollens cross-reacting fruits, vegetables
  • Latex-food allergy – cross-reacting foods (bananas, etc)
• Celiac disease (T-cell mediated)
• Eosinophilic Esophagitis/Gastroenteritis (Eos)
• Food protein enteropathies (mixed)
  • Hypersensitivity
  • Immune complexes
  • T-cells
Peanut Allergy

- Increasing prevalence
- Occurs in 1 in 150-200 individuals
- Varying presentations
- Major cause of anaphylaxis
- Varying dose sensitivity
- Most react on first recognized exposure
- Up to 20% may lose sensitivity
- Associated with other food allergy, atopy
Risk of Anaphylaxis

Food allergy is now the major cause of anaphylaxis in developed countries.

Those with increased risk include those:

- with past history of anaphylaxis
- with reactions with respiratory tract symptoms
- with reactions to peanuts, tree nuts, fish, seafood
- taking β-blockers or ACE inhibitors
Oral Allergy Syndrome

- Localized IgE - Initial sensitization to pollens results in IgE that cross reacts with fruit and vegetables
- Raw fruit and vegetables
  - Birch pollen – apple, peach, pear, almond, hazelnut, potato, carrot
  - Ragweed pollen – melons, banana, gourd family
  - Mugwort pollen – celery, carrot, spices
  - Grass pollen - tomato
- Itching, ± swelling and/or tingling
- Confined to lips, tongue, roof of mouth and throat
- Affects patients with pollen allergy

Latex – Food Allergy Syndrome

• Sensitization to latex results in IgE that cross reacts with fruit and vegetables
• Exposure to foods give same symptoms as latex
• Natural Rubber Latex contains over 200 proteins, 10 bind IgE (HEV b 1-10)
• Food associations:
  – Kiwi (5)
  – Potato, tomato (7)
  – Avocado, chestnut, banana (6)
Treatment – the 4E’s

- Expert
- Elimination
- Epinephrine
- Education

Eosinophilic Esophagitis (EoE)

- EoE is a clinicopathologic condition defined by:
  - Symptoms
    - Dysphagia
    - Food impaction
    - Heartburn
  - Endoscopy
  - Pathology

Eosinophilic Esophagitis (EoE)

- **ACG Guidelines:** Definition
- Clinicopathologic disorder diagnosed based on both clinical and pathologic information
  - Symptoms related to esophageal dysfunction
  - Eosinophils in esophageal Bx’s > 15 per high power field (HPF)
    - Isolated to esophagus
    - Persists after PPI treatment
  - Secondary causes ruled out

Eosinophilic Esophagitis (EoE) vs Eosinophilic Gastroenteritis (EGE)

- EGE affects upper and lower GI tract
  - Involves the mucosa, muscular layer and/or serosa
  - No change in prevalence, no gender difference
  - Food allergy is much less associated than in EoE
- EoE recognized in the early 1990s, a new disease
  - Prevalence increasing, 56.7/100,000 USA$^2$ (2008-11)
  - Male 65%, mean age 33.5$^2$
  - Incidence 10,000 new cases/yr$^3$

1-Liacouras CA et al. JACI, 128(1):3-20, 2011
2-Dellon, ES, CGH, 12;589, 2014
3-Dellon, ES, Gastroenterol, 147:1238, 2014
Diagnostic Tests for EoE

• Currently the only means to diagnose and follow treatment is esophageal mucosal Bx
• CBC, peripheral eosinophil count
• Patch test not helpful in adults
• Specific IgE levels (RAST, ELISA) not helpful
• Eosinophil markers (investigative)
• Swallowed sponge (studies in progress)
Treatment of EoE: The Three D’s

- **Drugs**
  1) treat with PPI (20-40mg) of any PPI bid for 8 weeks
     - continue if beneficial
  2) Topical steroids (first line)
     - Fluticasone or budesonide (swallowed) x 8 wks
- **Diet** - elimination (first line)
  - Elemental, empiric (6 or 4 food elimination), occasionally targeted
- **Dilation**
  - If persistent esophageal stricture post medical or dietary treatment
    - Type of stricture dictates the modality - Savory, balloon, bougie
Changing Prevalence of Celiac Disease

- Prevalence of up to \( \sim 1:100 \) in most genetically susceptible populations, 0.71% in NHANES study
- Estimated that 15 to 20% of current cases of CD have been diagnosed in the US, not aware of data in Canada
- CD is 4 to 4.5 times more prevalent than 50 yrs ago
- Increase in food allergies and autoimmune diseases as well
- Cause of “CD epidemic” unknown
  - Dietary – grains with increased gluten, increased wheat in diets worldwide
  - Other environmental
  - Microbiota

*References*

Rubio-Tapa et al, Gastroenterology, 137: 88, 2009
Virta et al, Scand J Gastroenterol, 44:933, 2009
Rubio-Tapia, Am J Gastroenterol, 2012
Who Develops Celiac Disease?
Genetic and Other Factors

• Increased frequency of HLA haplotypes - DR3-DQ2, DR5/7-DQ2, DR4-DQ8
• Other factors involved since most with these haplotypes do not get celiac disease (confer ~40% of risk)

• 70% concordance in twins
• 10-15% prevalence in first degree relatives

• Other genetic factors - genes on chromosomes 5, 16, ?, 6
• GWAS have identified at least 26 celiac genetic risk variants
  — many contain immune-related genes controlling adaptive immune response

• Environmental factors - ? Infectious agents
  — Cytokines released during infection - Affecting APCs (e.g., dendritic cells)
  — Cross-reactive amino acid sequences - Adenovirus, H. pylori
Coexpression Analysis of Genes Mapping to 40 GW Celiac Disease Regions

Immune Gene Clusters

Dubois et al, Nature Genetics, 2010
Risk Factors: The Grains

Darker shaded countries consume more grains. US daily consumption of wheat per individual is moderately high (≈ 24% to 32% of diet).

Wheat consumption

Adapted from Fasano A, Catassi C. Gastroenterology. 2001;120:636-651.
Symptoms and Conditions That Should Prompt Consideration of Celiac Disease

- GI symptoms
- Extraintestinal presentations
- Other inflammatory luminal GI disorders
- First and second degree relatives
- Autoimmune connective tissue disorders
- Autoimmune endocrine disorders
- Miscellaneous conditions
- Hepatobiliary conditions

Changing Picture of Disease

- Classical form less prevalent now
- Average age of diagnosis in 5\textsuperscript{th} decade
- Many are overweight, even super-obese
- Seroprevalence M=F, diagnosis M<F (1: 2 - 3)
- Other presentations are being increasingly recognized:
  - Reproductive problems
  - Neuropsychiatric manifestations
  - Related autoimmune conditions
  - Many others – true associations or chance?
Non-Responsive Celiac Disease (NRCD)

- Usually due to ongoing or recurrent gluten exposure
- Coincident disorders
  - Lactose intolerance
  - Pancreatic insufficiency
  - Small intestinal bacterial overgrowth
  - Microscopic colitis
  - IBS (post-inflammatory or overlap of two common diseases)
- Unrelated to celiac disease – incorrect or additional diagnoses
- Over or erroneous interpretation of the pathology
- Complications of celiac disease
  - Refractory celiac disease
  - Malignancy

Improvement on a Gluten Free Diet:
What Does That Mean? Not always CD

- Placebo response in IBS up to 70%
- Gluten (increased prolamines) is hard to digest, increases stool volume
- Gluten free diet often eliminates other dietary factors – wheat starch
- Potentially other mechanisms explain benefit
- PPV of symptom improvement after gluten withdrawal for celiac disease only 36% in one study

Between Celiac Disease & IBS: The “No Man’s Land” of Gluten Sensitivity

Is it IBS, Celiac Disease or Something in Between?

Non-celiac Gluten Sensitivity

IBS symptoms
- Motility / visceral sensation
- Brain - gut interactions
- Immune activation
- Altered gut microbiome

Spectrum of CD
- Potential / asymptomatic CD
- Symptomatic CD

Non-Celiac Gluten Sensitivity

• Prevalence unknown
  • Varies from 0.548% (NHANES) to 30% of US (Enterolab website)!!
  • Studies reporting prevalence reflect referral bias
• Currently no specific criteria or validated tests for diagnosing NCGS - requires double blind challenge
• Activation of innate immune system (IL-8, IFN-γ, etc), increased permeability, mucosal inflammation, basophil activation but not found in a recent study¹
• Elevated AGA IgA, IgG (up to 50% +AGA IgG)²
• No specific HLA association
• Other proposed mechanisms include immune complex, autoimmune, microbiota, wheat amylase trypsin inhibitors³, toxicity, false neurotransmitters, leaky gut....

"I have no idea what gluten is, either, but I'm avoiding it, just to be safe."
Changes in prevalence and proportions of gluten-related disorders between 2009 and 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence of gluten-related disorders</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-2010</td>
<td>1.3% (95% CI, 0.9-1.6)</td>
<td></td>
</tr>
<tr>
<td>2011-2012</td>
<td>1.8% (95% CI, 1.2-2.4)</td>
<td></td>
</tr>
<tr>
<td>2013-2014</td>
<td>2.4% (95% CI, 1.4-3.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Prevalence of gluten-related disorders**

- **PWAG (people without CD avoiding gluten)**
  - Undiagnosed CD: 72%
  - Diagnosed CD: 12%
  - PWAG: 16%

*DDW 2016 presentation
Impact of Gluten-Free Eating

• The gluten-free (GF) market was expected to reach $15 billion in annual sales by 2016¹

• Portion of households reporting purchases of GF increased from 5% in 2010 to 11% in 2013¹

• Common brands now available as GF

• Increase in labeling of foods as GF that are naturally GF from vodka, water, to meats and poultry

• The Onion reported in April 2014 “14% of Americans now intolerant to word “gluten”

Other “Reasons” for Going Gluten-Free

Weight loss
Leaner
Less bloating
Decrease carbs
No GMOs
More natural
More energy
The Downside of Empiric Diets in Infants and Children

Gluten-Free, Vegan, Dairy-free, Paleolithic, Other diets

Reported adverse outcomes

- Malnutrition
- Deficiencies – vit B12, D
- Tooth and bone disease
- Death in rare instances
- Missed diagnoses
Downsides of Eating Gluten Free?

- Expense, availability
- Travel, dining out
- Increased fat, salt, sugars, calories in processed GF foods
- Exposure to arsenic and other heavy metals with rice flours
- Potential nutritional deficiencies
Does it Matter if it is Celiac Disease or Non-Celiac Gluten Sensitivity?

“She thinks she’s so great cause she has real celiac disease.”
Common Symptoms in Celiac Disease: Overlap with Irritable Bowel Syndrome

- Altered bowel habits
  - Diarrhea, constipation and mixed pattern
- Fatigue
- Borborygmi, flatulence
- Abdominal discomfort or pain
- Weight loss
  - However patients with CD can be overweight and even obese
- Abdominal distention or bloating

Note that there are many other presentations of celiac disease including an asymptomatic state

Cause of IBS: Patients’ Beliefs

Association of Diet, GI Symptoms & IBS

• Romanian study of 193 subjects assessed for eating habits and diet
  – 19.1% met criteria for IBS by Rome III
  – IBS subjects ate more canned food, processed meat, legumes, whole cereals, sweets, fruit compotes

• Swedish study of 197 IBS patients completed questionnaires for food, depression, anxiety, QoL, etc
  – 84% reported symptoms associated with ≥ 1 food
    • 70% carbs – dairy, legumes, apple, flour, plums
    • Histamine-releasing foods – milk, wine/beer, pork
    • Fried or fatty foods

So What do We Know about Dietary Treatments for IBS and Other FGID?

<table>
<thead>
<tr>
<th>Diet</th>
<th>Evidence for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fat</td>
<td>Limited</td>
</tr>
<tr>
<td>Gluten-free</td>
<td>Limited</td>
</tr>
<tr>
<td><strong>Low FODMAP</strong></td>
<td><strong>Increasing data</strong></td>
</tr>
<tr>
<td>Histamine-free diet</td>
<td>Little to none</td>
</tr>
<tr>
<td>Paleolithic</td>
<td>Minimal</td>
</tr>
<tr>
<td>Candida</td>
<td>None</td>
</tr>
<tr>
<td>Elimination</td>
<td>Little to none</td>
</tr>
</tbody>
</table>

Limited evidence overall but for low FODMAP diet studies there are 6 randomized and 7 observational studies\(^1\) plus a recent US RCT\(^3\)

Only 3 of 17 elimination diets met eligibility criteria\(^2\)

Mechanisms By Which Food Components Cause IBS Symptoms

• Components of food that cause altered pathophysiology and can lead to symptoms:
  – Fiber, fat, histamine, starches/sugars
• Stimulation of mechano- and chemoreceptors
• Release of hormones/peptides
• Alteration of the innate immune system
• In some genetically susceptible individuals food stimulates the adaptive immune system

Physiological Food Reactions

- Large volume meals (overeating) cause distension, promote regurgitation
- Fatty foods delay gastric emptying, alter motility
- Legumes, cruciferous vegetables, garlic, onions, etc, may lead to flatus (farts)
- Non-absorbable or poorly absorbed sugars and carbohydrates can cause diarrhea, bloating, flatulence, etc
- However, intestinal gas is NORMAL (up to 20/day)

What are FODMAPs

Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

• Fructose and fructans
• Sorbitol
• Sucrose
• Lactose

Many foods (grains, starches, fruits, vegetables, lactose, sweeteners) contain FODMAPs

Shepherd SJ, Gibson PR. J Am Diet Assoc. 2006;106:1631
Milk Allergy and Lactose Intolerance

• Cows Milk Protein (CMP) allergy – rare in adulthood
• Symptoms due to lactose malabsorption resulting from lactose deficiency
  – Congenital deficiencies - rare
  – Constitutional lactase insufficiency
    • Genetically programmed decreased in lactase synthesis after weaning
    • Common in native NA, Asians, Africans, those from Mediterranean areas
  – Secondary lactase insufficiency
    • Gastroenteritis, Crohn’s disease, celiac disease
• Most common ARF worldwide  
Management of Lactose Intolerance

- Most individuals with lactose intolerance can tolerate 12-15 g lactose (8-10 oz of milk)
- Yoghurt, hard cheeses are naturally lactose-free
- Lactose better tolerated when taken in small, more frequent amounts and with other foods
- Lactase supplements helpful
- No proven benefit for probiotics, adaptation programs
- Triacylglycerol (fat) content of many milk products can cause GI symptoms unrelated to lactase insufficiency or cows milk protein (CMP) allergy

Pathophysiology of FODMAPs

• Poor absorption in the small intestine
• Osmotic effects in the colon, increased water
• Fermentation with gas production
• Luminal distension
• Effects on microbiota
• Immune modulation
• Alteration of intestinal barrier

Chey, WD, Am J Gastroenterol, 2016, 111, 366
Effect of FODMAPs on Breath Hydrogen

N=29

IBS on High FODMAPs

Controls on High FODMAPs

Low FODMAP

Ong DK et al. J Gastroenterol Hepatol. 2010;25:1366
Recent Canadian Study Suggests Benefits of Low FODMAP Diet

• 40 patients IBS Rome III controlled single blinded study for 3 weeks
  • 19/20 on low FODMAP, 18/20 high FODMAP diet completed
• Significant reduction of IBS symptoms (IBS-SSS)
• Significantly altered metabolic profile in urine (histamine, p-hydroxybenzoic acid, azelaic acid major determinants) and an 8-fold decrease of histamine levels in urine
• Increased Acetinobacteria in the microbiome
• This study suggests a benefit but more studies in different populations with larger numbers are needed to determine the true value of the low FODMAP diet

Overall IBS-QOL Scores

- m-NICE
  - Baseline: 54.3
  - Week 4: 59.4
  - p = 0.03

- Low FODMAP
  - Baseline: 53.4
  - Week 4: 69.3
  - p < 0.0001

Who Benefits From a Low FODMAP Diet?

• Motivated, compliant, educated patients with IBS-D, M, C
• Other functional GI diseases may benefit from a low FODMAP diet
• NCGS and celiac disease patients on a GF diet (eliminates wheat starch with gluten, also some have increased FODMAPs in their diet)
• Low FODMAP diet reported to work better in IBD than IBS patients in one report

The downsides and unknowns of the diet
• Long term effects are not known
• Very stringent restrictions may have adverse effects
• Impact on the individual’s microbiome

1- Maagaard, L, et al, World J. Gastroenterol: 2016, 22; 4009
No Effect of Gluten after Reduced FODMAP Diet in IBS Patients

Foods +/- Gluten Coexist with Nonabsorbed Fructans and Other Saccharides

![Bar chart showing the fructan and GOS content of various foods. The chart includes categories such as rice-brown, rice-white, rice-noodles, gluten-free bread, quinoa-pasta, pasta-gluten free, rice bubbles, cornflakes, wheat-pasta, wheat-bread, rye bread, muesli, wheat-couscous, and haricot beans. The chart also highlights gluten-free products.](chart.png)
Patients Already on Gluten Free Diet: How to Test for Celiac Disease?

- Depends on duration and stringency of the GFD
  - if truly on a GFD for many years it is difficult to prove CD
  - many patients on a self-taught GFD are not truly or continually gluten-free
- Serology can take over a year to normalize
  - Check TTG IgA +/- DGP IgA, IgG
- Histology can take several years plus to become normal

If an undiagnosed patient wants an assessment for possible CD assess with serological tests, HLA DQ2/8 and EGD with biopsies within the first year on a GFD

- Absence of HLA DQ2.2, 2.5 or 8 effectively excludes CD now or in the future

Sugal, E, et al, Digestive & Liver Disease, 42:352, 2010
Crowe, SE. In The Clinic : Celiac Disease, Ann Int Med,2011 154:ITC5-14,
How to Evaluate for Causes of Adverse Reactions to Food

- History - ? co-factors (exercise, drugs)
- Assess for lactose intolerance
- Assess for SIBO
- Skin testing for food allergens
- Diet diary
- Hypoallergenic diet trial
- Endoscopy and biopsy

- CBC, eosinophil count
- Quantitative immunoglobulins
- Specific IgE levels (RAST, ELISA)
- Serum IgG to foods – No longer accepted
- Celiac serology and/or HLA DQ assay
- Other tests for non-IgE mediated reactions

Bischoff & Crowe, Gastroenterology, 128: 1089, 2005
DeGaetani & Crowe, CGH, 8: 755, 2010
Alternate Tests for Food Sensitivity and Non-Celiac Gluten Sensitivity

- **LabCorp** – NCGS screen = IgG to native gliadin
- **ALCAT** – Gut Heath Profile (tests specific genetic predisposition to celiac disease as well as antibody testing and immune system activation to food sensitivities), also leukocyte assays for food sensitivities*
- **Cyrex** – Intestinal antigen permeability screen, Wheat/Gluten proteome reactivity/autoimmunity, Cross-reacting foods & food sensitivities (IgG & IgA)*
- **Enterolab** – various stool panels (food Abs, gene tests, celiac Abs)
- **Genova Diagnostics** (Great Smokies Diagnostic Lab) – Blood for IgG4 to food, for celiac & gluten sensitivity, saliva for gliadin sensitivity
Alternate Tests for Food Allergy or Food Intolerance

- **Many labs** – food allergies, IgG to food antigens*
- **Cyrex, ALCAT** – as per previous slide*
- **MRT/LEAP** – Measures release of immune mediators (histamine, cytokines, etc) via changes to the liquid/solids ratio of a blood sample after incubation with specific food, additive, or chemical*
- **Applied kinesiology** – patient holds putative allergenic food while muscle strength is tested by the practitioner*
- **Electrodermal skin testing** - machine measures electrical resistance at acupuncture points when allergen is placed in the electrical circuit*

* Expert NIH panel “recommends not using” this test for routine diagnosis of food allergy

*Boyce JA et al. JACI.2010;126(6):1105*
Food Intolerances & Allergies

Take Home Messages

• Food ingestion is a significant factor in causing symptoms in patients with IBS and other FGID
• Culprits are often comfort foods (sweets/starches, fatty foods, histamine containing foods)
• Lactose in lactase deficient patients
• Non-celiac gluten sensitivity in some but may be due to coexisting dietary wheat starch
• Bacterial overgrowth, dysbiosis
• The low FODMAP diet does provide some benefit but difficult to adhere to long-term
• A minority will have food allergy or celiac disease – an overlap of common diseases (IBS affects 15% of the US population, 1% with celiac disease and 2-4 % of adults have food allergy)
“Something’s just not right—our air is clean, our water is pure, we all get plenty of exercise, everything we eat is organic and free-range, and yet nobody lives past thirty.”