Microbiome and Small Intestinal Bacterial Overgrowth

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The idea that the microbiome existed and played a role in health and disease is not new!
Hepatic Encephalopathy

• Hepatic coma related to the absorption of nitrogenous substances from the intestine

• Abundant coliforms in small intestine of cirrhotics
  Martini et al, Clin Sci 1957;16:35-51

• Antibiotics improve PSE
The Gut Microbiome and the Liver

• Altered gut microbiota first noted in chronic liver disease > 80 yrs ago
  
  *Hoefert, 1921*

• SIBO common in liver disease
  
  – Correlates with severity of liver disease
  – Associated with minimal and overt encephalopathy
  – Increases risk for SBP through translocation
  – Linked to alcoholic liver disease and NAFLD/NASH

For Debate . . .

Diverticular Disease of the Colon: A Deficiency Disease of Western Civilization

NEIL S. PAINTER, DENIS P. BURKITT

British Medical Journal, 1971, 2, 450-454

We present a hypothesis as to the cause of diverticulosis coli which is consistent with its geographical distribution, its recent emergence as a medical problem, and its changing incidence. Diverticulosis appears to be a deficiency disease caused by the refining of carbohydrates which entails the removal of vegetable fibre from the diet. Consequently we consider it to be preventable.

Diverticulosis first became a clinical problem at the turn of the century, and the term “diverticulosis” first appeared in 1914. As recently as 1916 the disease was not important enough to merit a mention in textbooks.1 Though the present incidence of diverticulosis is unknown it is certainly endemic in our aged nations. This dramatic increase in incidence occurred in only 70 years and cannot possibly be explained on a genetic basis. This change might be due to observe error and be apparent rather than real, but we believe that their writings show that the clinicians of the last century were just as capable as those of today of recognizing diverticulosis. We believe that there is another possibility—namely, that the colon’s environment has changed and that diverticulosis are caused by the diet of so-called “civilized” countries.

Historical Impact of Diverticular Disease on Medicine

DIVERTICULOSIS AS A CURiosity

The term “diverticulitis” was used by Fleischman in 1815, Gros in 1845, Cruveilhier in 1849, Rotkranz in 1849, Bieberges in 1857, and Xiebs in 1869 realized that diverticula were acquired and thought they were caused by constipation. The danger of diverticulitis as a cause of infection and perforation was pointed out by Cruveilhier in 1859. He named described vascular fistulae due to diverticulitis.2 Harrison Gripps in 1888 collected 65 perforated diverticula and believed that they were caused by ingested foreign bodies.3 He emphasized that they were usually the result of “inflammatory indigestion” and not of cancer, but he blamed only diverticulitis to the case of Jesus. Chirch in 1853 described peritonitis,4 while Loomis in 1870 recorded peritonitis resulting from diverticulitis.5 Since this complication was still regarded as a surgical curiosity 20 years later it is unlikely that perforated diverticulitis was common at that time.

Our nineteenth-century predecessors described diverticulitis and its complications accurately, but they regarded them as curiosities. Their concept of the pathogenesis of diverticulitis was surprisingly correct, and not until a century later, when enema rectography and pressure recording became available, were diverticula known to be the result of functional obstruction due to the accumulation of the diverticulitis and “little bladders.” These became “hemorrhagic,” with the colonic muscles thrown into ridges of varying thickness before the herniation of the mucosa takes place.11 Modern workers have only confirmed what Gros1 believed—namely, that diverticulitis were caused by obstruction by which the muscular fibres are separated from each other so as to permit the mucous membranes to protrude.12 Haberstock blamed constipation for muscle thickening and for diverticulitis. Lane in 1853 realized that diverticulitis were not caused by obstruction, but that they were produced similarly to that of the last century were just as capable as those of today of recognizing diverticulosis. We believe that there is another possibility—namely, that the colon’s environment has changed and that diverticulosis are caused by the diet of so-called “civilized” countries.

Emergence of Diverticulitis as a Clinical Problem

Gros in 1899 emphasized that diverticulitis led to peritonitis and perforation,13 and this warning was proved true within a decade. Five years later Beer described 18 infected diverticula and stressed that they could cause peritonitis, adhesions, fistulae, and stenosis, but he still believed that they seldom caused symptoms.12 “Diagnosis” such as pediculosis sinistra, peritonitis, and inflammation of appendicitis epiploica. Empson in 1907, still considered the retroperitoneal cells. Even in 1910 Gordon Taylor and Lakin14 were reluctant to attribute peritonitis to diverticulitis, while Moyshin14 15 16 and Mayo et al.17 considered that diverticulitis mimicking cancer was still newsworthy at this time.

Dr. Tilling, of Leeds, first saw the disease in 1880 when no one was familiar with it, but by 1908 he could describe all its complications, and in 1917 he published his classic description of diverticulitis disease. Even so, the condition was still not mentioned in textbooks in 1929. 18 19

Diverticulitis surprised even surgeons of repute early in the century, but by 1926 Sir John Blund-Sutton remarked that: “In the last ten years, acute diverticulitis is recognized with the same certainty as appendicitis and is a newly discovered bane of elders.20-22”

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5. Gripps, H.: Lancet 1888, 1, 43.
Fig. 4. Diagrammatic representation of possible relationship between diet and cancer of the bowel.

Stomach; not such a hostile place!

Bacteria in the Stomach

- Bottcher and Letulle 1875
- Klebs 1881
- Bizzozero 1893
- Salomon 1896
- Krienitz 1906
- Edkins 1921
- Doenges 1938
- Freedberg and Barron 1940
- Gorham 1940

Hunt RH 2012
Helicobacter Pylori

Warren and Marshall 1983
(Jaworski 1899)
Why has there been this explosion in interest in the microbiome?

• Arrival of molecular methods
  – High throughput sequencing
  – Metagenomics
  – Metabolomics
• Informatics
Fraher MH, O’Toole PW, Quigley EM. Nat Rev Gastroenterol 2012; 9:312-22
Interpreting the Methods

• High throughput sequencing - what’s there

• Metagenomics - what they could do

• Metabolomics, Metatranscriptomics - what they actually produce
What is the Microbiome?

- The totality of microorganisms and their collective genetic material present in or on the human body or in another environment
- Microorganisms + their genomes
Other Commonly Used Terms

- **Microbiota**: The assemblage of microorganisms (bacteria, archaea or lower eukaryotes...) present in a defined environment.

- **Metagenome**: The collection of genomes and genes from the members of a microbiota.

- **Metabolome**: The metabolic products of the microbiome.
What influences the Microbiota?

• Age
  – Early life
  – Old age
• Geography
• Diet
• Exposures:
  – Antibiotics
  – Disease
  – Proton Pump Inhibitors (PPIs)
The Microbiota in Health

• Prevents colonization by pathogens
• “Educates” the immune system

**Metabolic Role**
- Caloric salvage
- Produces
  - Short Chain Fatty Acids
  - Arginine, Glutamine
  - Vit K and Folate
- Participates in drug metabolism
  - e.g. activates 5-Aminosalicylic acid

• Deconjugates Bile Acids
Microbiota-Gut-Brain Axis
Microbiome and the ENS

Kabouridis and Pachinis
JCI 2015;125:956-64
Gut-Brain Axis – two-way traffic!
Microbiota in Disease: Well Established

• Enteric infections and infestations
• *Helicobacter pylori*
• Antibiotic-associated diarrhea
  – *Clostridium difficile*-associated disease (CDAD)
• Small Intestinal Bacterial Overgrowth
• Gut Microbiota and the Liver
  – Portal-Systemic Encephalopathy
  – Spontaneous Bacterial Peritonitis
• Biliary and pancreatic sepsis
Small Intestinal Bacterial Overgrowth
Original Definitions Focused on Maldigestion

- “a bacterial flora qualitatively resembling that found in the large intestine and faeces”
- “the occurrence of a bile salt tolerant flora consisting of both aerobic bacteria such as *E coli* and *S faecalis* and anaerobic bacteria such as *Bacteroides* and *Bifidobacteria*

Drasar and Shiner *Gut* 1969;56:71-9
Modern Definitions of SIBO focus on bacterial populations

- **Culture**
  - $> 10^5$ Total
  - $> 10^3$ Colonic

- **Breath Tests**
  - d-Xylose
  - Glucose
  - Lactulose

- **Response to therapy**

```c.f.u.’s per ml
  jejunal fluid```
## Culture vs Breath Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Culture Positive</th>
<th>Culture Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Breath Hydrogen Test</td>
<td>5/8</td>
<td>2/12</td>
</tr>
<tr>
<td>Lactulose Breath Hydrogen Test</td>
<td>13/19</td>
<td>9/16</td>
</tr>
</tbody>
</table>

Pathogenesis

• **Defenses against SIBO**
  – Gastric acid
  – Intestinal motility
  – Intact ileo-cecal valve
  – Immunoglobulins
  – Bacteriostatic properties of pancreatic and biliary secretions

• **Causes**
  – Achlorhydria
  – Motility disorders e.g. scleroderma
  – Anatomical defects e.g. fistula, resection, strictures
  – Immune deficiencies
  – Pancreatic exocrine deficiency
Putting it in Perspective

• Retrospective review of 675 duodenal aspirates
  – 8% positive overall
  • Predictors
    – Older age
    – Steatorrhoea
    – Narcotic use
    – IBD
    – Small bowel diverticula
    – Pancreatitis
  – 2% of IBS positive for SIBO

Another view!

• Prospective review of 320 duodenal aspirates
  – 19.4% positive overall (68% had IBS)
    • Predictors
      – IBS
      – Type II DM
      – PPI use
      – Not having gastritis

  – 38% of IBS positive for SIBO
    • 60% D-IBS
    • 27% non D-IBS

SIBO Consequences: Direct

- $B_{12}$ malabsorption - mucosal changes
- Bile acid deconjugation
- Mucosal injury
  - Loss of b.b. enzymes
  - Altered permeability
  - PLE
- Intraluminal protein digestion
- Enterotoxins
SIBO Consequences: Indirect

• Nutritional effects
• Translocation; systemic sepsis
• Other systemic effects
  – Liver
  – Reactive arthropathy
  – Other “auto-immune” disorders
• Immune-mediated enteropathy
SIBO Consequences: Symptoms

• None
• Those of malnutrition or specific deficiencies
• Steatorrhea
• Diarrhea, especially in the elderly
• Bloating
• Flatulence
• Abdominal discomfort
• Weight loss
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Non-specific
Clinical Syndromes

- **Malabsorption syndrome ("Classic" SIBO)**
- **Altered permeability**
  - Enhanced absorption of Vitamin K₁ impact on warfarin dose
    
    Giuliano et al. Thromb Res 2010;126:12-7

- **Flora-immune engagement**
  - Normal flora
  - Abnormal flora
    - Mucosal
    - Systemic

- **Metabolic activity**
  - Obesity
  - NAFLD

- "Functional" symptoms: IBS
Diagnostic Approaches

Quantify

Measure Products of Fermentation

Assess Consequences
Diagnosis

- No gold standard
- No community values
- Aspirate and culture
  - Proximal only
  - Will not detect un-culturables
  - Invasive
  - Diagnostic thresholds based on jejunal not duodenal aspirates
Diagnosis

• **Breath tests**
  – Non-invasive
  – Significant issues with false positives and negatives
    • Sensitivity 70-90%
    • Specificity 40-100%
      – Glucose more accurate but proximal only
      – 15-27% do not produce hydrogen with lactulose

• **Jejunal biopsy**
  Chandra et al. Ind J Gastroenterol 2010;29:226-30

• **Molecular**
  – In development
Therapy of SIBO

- Correct cause
- Nutritional replacement
- Prokinetics
- Antibiotics
  - Short course
  - Repeated
  - Continuous, rotating
- Prebiotics
- Probiotics

Few Trials
Microbiota in disease: Postulated

- GERD
- Functional dyspepsia (FD)
- Diverticulitis
- Necrotizing enterocolitis (NEC)
- Inflammatory bowel disease (IBD)
  - Ulcerative colitis (UC)
  - Crohn’s disease
  - Pouchitis
- Irritable bowel syndrome (IBS)
- Celiac disease
Microbiota in disease: Postulated

- Liver disease
  - Cirrhosis
  - NAFLD and NASH
  - PBC and PSC
  - HCC
- Obesity and metabolic syndrome
- Auto-immune disease
- Cardiovascular disease
- Neurological diseases (e.g. Parkinson’s disease)
NAFLD
NASH

The Microbiota and Cardiovascular Disease

Wang et al, Nature 2011

Microbiota

Predict risk for CVD
The Microbiota and Cardiovascular Disease

Rak and Rader, Nature 2011
Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease

Problems with Clinical Studies of the Microbiome in Disease

• Single point in time
  – State vs Trait
  – Influence of therapy

• Do not account for diet

• Do we really know what is normal?

• Sampling
Summary

- Microbiome is important in health and disease
- Host-microbiome interactions in man are complex and far from completely understood
- Diet is a major modulator of the microbiome
- Associations with disease are tantalizing and clearly suggested by animal models but it remains to be shown that they are causal in man
- Many possibilities for new therapeutics