Gut – microbiome interactions; implications for human health

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Some key elements

• Textbooks
  – Colon absorbs water and propels feces

• Historical aspects
  – Ancient Egypt
  – Methnickoff and Arbuthnot-Lane
  – Hurst

• Today’s understanding
  – Microbiome
  – Development of immune system
  – Implications for human health
The systemic effect of whdw – the putrefactive principle of faeces

Another [prescription] against a pool [of whdw] generating fever;
his [the patient's] body is heavy, his τ3 lb (cardia? pylorus?) is sick;
his heart is hot, it pulsates;
his covers are heavy on him;
he cannot stand many covers;
he suffers thirst at night
and he tastes [feels] his heart oppressed
like [that of] a man who has eaten fruits of the sycamore(?) tree;
his flesh is weak like [that of] a man whom the road has found.
If he crouches in order to evacuate
(then) his intestines are under pressure
(but) he is not getting along with the evacuation.
Thou shouldst say to him [i.e., concerning such a case];
This is one who is under a pool of whdw in his body;
he tastes [feels] his heart;
he is sick [and] I shall act (on his behalf).
Should it rise in him and become an occlusion
you will have to apply [to him]
remedies against whdw, together with remedies to
destroy whdw.29
"The bird which is called the ibis and which is a native of Egypt, by means of its hooked beak, laves the inside of its body by introducing water into the channel by which it is specially necessary for health that the residiuous food should be discharged"  
Plinius (23-79 A.D.)
Intestinal intoxication

Elie Methnikoff (1845-1916)

Methnikoff: Bacterial toxins from colon responsible for ageing. The colon is a redundant organ and will soon disappear.

Sir William Arbuthnot-Lane (1856-1943)

Lane: I can take it out!
The Unhappy Colon

By Arthur F. Hurst, D.M. Oxon., F.R.C.P. Lond.
Senior Physician to Guy's Hospital, London

No organ of the body is so misunderstood, so slandered, and so maltreated as the colon. Text-books of anatomy are apt to describe it as it is found in the dissecting-room, not as it occurs in a living man. Text-books of physiology describe its motor functions as seen under experimental conditions in animals, and rarely pay sufficient attention to the results of observations made on healthy human beings, and they ignore more or less completely its secretory functions. The colon is slandered every day in the advertising columns of the popular press, which accuse it of sins it never commits, and the mass suggestion which results from constantly reading about the disastrous effects of intestinal intoxication results in most of the lay public and many of the medical profession joining in these slanders. By promoting the sale of purgatives and encouraging the use of various other methods of irritating the colon, these slanders result in maltreatment. No wonder that the colon is unhappy.
Intestinal autointoxification

Many physicians will today laugh of these old theories – but are they completely to be rejected?
The changing pattern of diseases

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

Bach JF. NEJM 2002
Anatomy of mucosal surfaces

• Skin 1 ½ - 2 m².
• Airway mucosa 100 m².
• Intestinal mucosa 3-400 m².

• The mucosal immune system by far the largest compartment.

• 2000 + bacterial species
• Outnumbers own cells by 100
• Large interindividual differences
• 6-7000 kg faeces in a lifetime
• Digests carbohydrates
Human organisms is the home of billions and billions of bacteria, in total one hundred thousand billions \((10^{14})\).

(Norways Oil Fortune (which is saved) is now NOK 4000 billions)

- Small intestine: \(10^{12}\) \((10^{8}-10^{10}/\text{ml})\)
- Colon: \(10^{14}\) \((10^{12}/\text{ml})\)
- Skin: \(10^{11}\) \((10^{3}-10^{9}/\text{cm}^2)\)
Mammalian digestive system

Ruminating herbivores (sheep)
Non-ruminating herbivores (horse)
Omnivores (humans)
Carnivores (dog)

Valeur and Berstad 2008
Why do we have a colon?

• Proteins, fat and mono- and disaccharides readily absorbed (ex lactase-deficiency)

• Complex carbohydrates passes to colon
  – Structural fibre are not fermented
  – Water soluble fibre fermented giving gases (H₂, CO₂, CH₄) and short-chain fatty acids (SCFA)

• Bacterial fermentation gives
  – 5-10 % of human calories, 30-40 % in non-ruminating herbivores and 60-90 % in ruminating
Most metabolites in human plasma is derived from gut bacteria!

Knut E. A. Lundin
Mikrobiology

Classic culture

Microbiomics

- "Genomics" studies of mikrobiology, primarily by means of sequencing (of bakterial-DNA)
- Microbiota: Totality of microbes in a milieu (e.g. intestine)
- Microbiome: Totality of genes in the mikrobiota

<30% of the bacteria in the intestines are cultivable
Main metagenomics applications, from the metagenomic libraries construction and screening, until next generation sequencing, gene count and genome reconstruction.
An integrative approach to study microbial systems.

The diverse forms of life

- Life on earth impossible without bacteria
- Bacteria has been around for 2.5 billion years
- All multicellular organisms live in close collaboration with bacteria
- The modern humans developed for approximately 200,000 years ago
- Co-evolved with bacteria
Microbiota = “Normal flora”

- $10^{14}$ bacterier – 10x more than human cells

- J.Lederberg:
  - “…think of each host and its parasites as a superorganism…”
  - “Teach war no more”

(Science 2000)

Cho and Blaser 2012
Human intestinal microbiome

- **Metagenome**
  - 2000 different species, each with 4000 genes
  - Equals ~ 8 millioner gener, that means more than 400 times no of genes in human genome
- **Microbiome large inter-indvidual differences**
- Recently shown 3 stable enterotypes
  - Prevotella
  - Bacteroides
  - Ruminococcus
- Influenced by food
- Enterotypes associated with lean body and with obesity

*Nature 2010, 464:59-65*

A human gut microbial gene catalogue established by metagenomic sequencing
Qin, Li, Raes, et al (MetaHIT consortium)
<table>
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<th>Dysbiosis-Associated Diseases or Conditions</th>
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<tbody>
<tr>
<td>Obesity</td>
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<tr>
<td>Metabolic syndrome</td>
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<tr>
<td>Nonalcoholic steatohepatitis</td>
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<tr>
<td>Inflammatory bowel diseases (Crohn’s disease, ulcerative colitis, pouchitis)</td>
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<tr>
<td>Irritable bowel syndrome, functional bowel disorders</td>
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<tr>
<td>Atherosclerosis</td>
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<tr>
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</tr>
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<td>Asthma</td>
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<tr>
<td>Celiac disease</td>
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See reviews by Bäckhed et al. (2005), Honda and Littman (2012), Ringel and Carroll (2009), and Sartor (2008, 2010).
Patogenesis of inflammatory bowel disease

Major differences
healthy - diseases

- Adaptive immune system
- Innate immune system

Many possibilities for biomarkers (and intervention)

Baumgart and Carding Lancet 2007
Increase in IBD Incidence for Patients Exposed to *Salmonella/Campylobacter*
Induction of Inflammation Changes the Flora: The Chicken-and-Egg Problem

DSS disrupts epithelial barrier
DSS-induced colitis causes a shift in the intestinal microflora towards pro-inflammatory Gram-negative bacteria. During acute colitis *E. coli* increased in wt and TLR-deficient mice (*P<0.05*).
Environmental Factors Determine Disease Expression

Mean age at diagnosis

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The type of fat intake may increase inflammation in the IBD-susceptible host

Saturated high fat diet increased sulphite-reducing sulphite-reducing pathobiont, *Bilophila wadsworthia*
Metagenomic analysis of the human gut microbiota in healthy individuals and IBD
Our new health threat
Obesity epidemic
eat nothing but still gain weight”

An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh¹, Ruth E. Ley¹, Michael A. Mahowald¹, Vincent Magrini², Elaine R. Mardis¹,² & Jeffrey I. Gordon¹
Manipulation with diet
Vancomycin treatment and obesity

Figure 2. Percentage of patients with a major increase (≥10%) in body mass index (BMI), defined as an increase.
FATLOSE trial:
Faecal transplantation from lean subjects to cure metabolic syndrome
Gut microbiome and atherosclerosis

Karlsson et al Nature Comm 2012, shotgun sequencing of gut microbes
Metagenomics and Personalized Medicine

Herbert W. Virgin¹,* and John A. Todd²,*

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Genetic studies

vital explosion in understanding of genetics of IBD

VAS and Crohn
- 2001 two loci (NOD2 and 5q31)
- 2006 one locus (IL23R)
- 2007 seven loci (IRGM, ATG16L1 etc)
- 2008 thirty-two loci

Figure 1. Genes significantly associated with CD (triangles), UC (circles) or both (diamonds) as reported in recent genome wide association, CD meta-analysis and follow-up studies plotted by Odds Ratios of risk allele for UC vs. controls as compared to same/equivalent risk allele for CD vs. controls. Genes listed are those with allele frequencies reported for CD and UC. Data preferentially from largest studies. Gene symbols outside axes lines have significant evidence for UC only or CD only.
GWAS studies complicate previous thoughts on diseases as "single diseases"
Common disease-associated variants cluster in pathways.
Common disease networks
A perfect storm for disease

**A Perfect Storm for Disease**

**Type 1 diabetes**
- Lower IL-2 production and signaling
- Higher frequency of viral infections and type 1 interferon production
- Immune response to presulin and gut antigens
- Changes in metagenome, alterations in Tregs
- Low vitamin D and omega-3 fatty acids
- Altered T cell signaling

**Crohn’s disease**
- Abnormal TH1, TH17, and Treg balance
- Viral and/or bacterial infections that cause disease or trigger genetic phenotypes
- Increased pro-inflammatory cytokine responses
- Changes in metagenome, decreased control of enteric infection
- Decreased Paneth cell function, increased epithelial permeability
- Altered stress responses and autophagy

**Perfect Storms for Developing Crohn’s Disease and Type 1 Diabetes**
Overlapping events and phenotypes driven by metagenetic and environmental processes that, in sum, contribute to the development and pathotype 1 diabetes (A) and Crohn’s disease (B).
Each step influenced by metagenomic interactions

Parental genotype, environment, fetal-maternal interactions, epigenetic effects

→ Infant

Establish normal viral, parasitic, and bacterial microbiome and metagenome

Normal immune system
Immune tolerance
Regulated inflammation
Treg network

Failure to establish normal viral, parasitic, and bacterial microbiome and metagenome

Inflammation & autoimmunity-prone immunity system

Bacteria
Other

Microbial products autoantigens

Type 1 diabetes
Crohn’s disease

Infections, autoantigens

Environmental cofactors
Prospect for future personalized medicine
Can something be done?

Prebiotics
- Food and components promoting "good" intestinal microbiome

Probiotics
- Probiotics are living micro-organisms that, if intake is sufficient, will give a health effect FAO/WHO

Postbiotics
- Components produced by intestinal bacteria with possible health effects

A major breakthrough is eagerly awaited!
Recommended reading

Baeckhed et al., Cell Host and Microbe 2012; 12: 611-622.


Lepage et al., Gut 2013; 62:156-158.

Virgin & Todd, Cell 2012; 147:44-56.