How Your Gut Works For You

William T. Cefalu, M.D.
Executive Director
Professor of Diabetes
Pennington Biomedical Research Center
Louisiana State University
U.S. regional concentrations of county-level obesity prevalence

Epidemic is the result of a normal physiology (genetic variability) in a pathoenvironment

Slack T et al. The geographic concentration of U.S adult obesity prevalence and associated social, economic, and environmental factors. Obesity 2013
Obesity: “Epicenter” of Global CardioMetabolic Risk
Diabetes prevalence is ≥11%
Includes 644 counties in 15 mostly southern states

Pre-Diabetes

Type 2 diabetes

Progressive β-Cell Failure

Years from diagnosis

Onset

Diagnosis

Pancreas function

Insulin “inefficiency”

Insulin secretion

Post-Meal glucose

Fasting glucose

“Pre-Diabetes”

PLASMA GLUCOSE

Normal: 99 mg/dl or less
Pre-Diabetes: 100-125 mg/dl
Diabetes: > 126 mg/dl fasting;
> 200 mg/dl (PostPrandial)

Complications of Diabetes

**Macrovascular**

- **Brain**
  - Cerebrovascular disease
    - Transient ischemic attack
    - Cerebrovascular accident
    - Cognitive impairment

- **Heart**
  - Coronary artery disease
    - Coronary syndrome
    - Myocardial infarction
    - Congestive heart failure

- **Extremities**
  - Peripheral vascular disease
    - Ulceration
    - Gangrene
    - Amputation

**Microvascular**

- **Eye**
  - Retinopathy
  - Cataracts
  - Glaucoma

- **Kidney**
  - Nephropathy
    - Microalbuminuria
    - Gross albuminuria
    - Kidney failure

- **Nerves**
  - Neuropathy
    - Peripheral
    - Autonomic
Where Diabetes Drugs Work!

Liver produces Too much glucose

Metformin
TZDs

Glucose absorption

Gut

Pancreas

Sulfonylureas
Meglitinides

Not enough insulin secreted

Insulin doesn’t work well

Muscle and fat

Glucose level

DPP-4=dipeptidyl peptidase 4; TZDs=thiazolidinediones.

Successive dynamic conditions in the GI Tract

- Swallowing of food & saliva
- Gastric enzymes, gastric acid, peristalsis
- Gastric emptying
- Secretion of digestive enzymes
- Bile secretion
- Peristalsis, intestinal transit
- Absorption of dissolved products and water
- Ileum effluent to colon
- Dense active microflora, microbial enzymes
Insulin Deficiency and Glucagon Hypersecretion in Type 2 Diabetes

Defects in diabetes
- Insulin secretion delayed and reduced after a meal
- Glucagon not suppressed after a meal
- Hyperglycemia: fasting and postprandial

What are Incretin Hormones?

Proteins from the gut that increase insulin secretion

- **Glucagon-like peptide-1 (GLP-1)** is a major incretins in humans
- Both are peptide hormones (30 and 42 amino acids)
- Secreted from cells small intestinal mucosa
- Released in response to meal ingestion
- Responsible for the **incretin effect**

GLP-1 positive endocrine L-cells in human small intestine
The Incretin Effect
Insulin release enhanced when you eat a meal

Crossover of Healthy Subjects (n = 6)
- ▲ Oral Glucose
- ○ Intravenous (IV) Glucose

Plasma Glucose (mg/dL)

Insulin Secretion

Mean (SE); *P≤0.05
Data from Nauck MA, et al. J Clin Endocrinol Metab. 1986;63:492-498
INCRETIN (GLP-1) Secretion and Metabolism

Mixed meal

Intestinal GLP-1 release

GLP-1 (7-36) active

Plasma

INCRETIN actions

Deacon CF et al. *Diabetes.* 1995;44:1126-1131
### Continuously Infused Incretins Improves the Defects of Type 2 Diabetes

<table>
<thead>
<tr>
<th>T2D Defects</th>
<th>Continuously Infused Incretin</th>
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</thead>
<tbody>
<tr>
<td><strong>Insulin production</strong></td>
<td></td>
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<tr>
<td><strong>First-phase insulin response</strong></td>
<td></td>
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<tr>
<td><strong>Glucagon</strong>; <strong>Liver glucose output</strong></td>
<td><strong>↓</strong></td>
</tr>
<tr>
<td><strong>Stomach emptying</strong></td>
<td><strong>↓</strong></td>
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<tr>
<td><strong>Food intake</strong></td>
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</table>

**Exendin-4**

- From saliva of the Gila Monster
- 53% homologous with GLP-1
- Insensitive to DPP-4
- Full agonist at the GLP-1 receptor
- Metabolically stable – t½ 4-5 hr after sc injection

**Liraglutide**

- Based on human GLP-1 (7-37)
- 97% homologous with GLP-1
- Resistant to DPP-4
- Full agonist at the GLP-1 receptor
- Non-covalent binding to albumin, self-association, slow release from injection site gives prolonged survival time - t½ 12 hr after sc injection

Conserved  Substituted  Additional (relative to human GLP-1 7-37)

Incretins improve glucose in Type 2 diabetes

N = 217; Mean (- SE); $P<0.0001$ from baseline to 30 weeks and baseline to 3 years.

Buse JB et al. Presented at ADA Annual Meeting 2007; Chicago IL. Abstract #0283-OR.
No diet and exercise regimen was provided. 

N = 217; Mean (± SE); P<0.0001 from baseline to 3 years and between 30 weeks and 3 years. 

Buse JB et al. Presented at ADA Annual Meeting 2007; Chicago IL. Abstract #0283-OR.
Where Diabetes Drugs Work!

Liver produces Too much glucose

Gut

Glucose absorption

Metformin

TZDs

Sulfonylureas

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Not enough insulin secreted

Muscle and fat

DPP-4=dipeptidyl peptidase 4; TZDs=thiazolidinediones.
The Human Microbiome
Population of more than 100 trillion microorganisms that live in our gut, mouth, skin and elsewhere in our bodies

There are millions of microbes per square inch on your body

The Microbiome represents over 9 million different genes compared to our paltry 20,000

Thousands of different species on the skin alone

It is estimated that there are more microbes in your intestine than there are human cells in your body!
Microbes and You

- Every part of your body that normally comes in contact with outside world (deep lungs and stomach are exceptions)
- You are “what you eat”
  - Human gut microbes
- “Good” and “bad” microorganisms
Some say we should be killing our bacterial!!

Germ Farm

Scrub 'em!
Microbes and Industry

- **Industry:** Fermentation products (ethanol, acetone, etc.)
- **Food:** Wine, cheese, yogurt, bread, half-sour pickles, etc.
- **Biotech:** Recombinant products (e.g., human insulin, vaccines)
- **Environment:** Bioremediation
  - Bugs+Plus: to digest oil and other petroleum derivatives.
Gut Microbiome

**pH**
- **Duodenum**
  - Proteins
  - Monosaccharide
  - SCFAs
  - Immunomodulation
- **Jejunum**
  - FFAs
  - Calcium/Vit D
  - Vit ADEK
- **Ileum**
  - Vit B12
  - Bile acids
- **Colon**
  - Water
  - SCFAs

**GUT SEGMENT FUNCTION**

**COMPOSITION**
- **Lactobacillus**
  - Streptococcus
  - Density: $10^1-10^3$
- **Enterobacteriaceae**
  - Density: $10^4-10^7$
- **Bacteroides**
  - Bifidobacterium
  - Clostridium
  - Eubacterium
  - Ruminococcus
  - Density: $10^{10}-10^{13}$
Gut Microbiome: Levels of Interaction
Gut Microbiome
Effects noted throughout the Body
Gut Bacteria Detoxify Mercury*

- Gut bacteria demethylate organic mercury forming insoluble free mercury which is excreted
- Mice fed methyl-mercury (toxic)
- Antibiotics added in test group

*Figure 5 in IR Rowland, Toxicol Pathol 1988 16:147-153.
Our microbiome organisms secrete compounds that may determine our future health.

The relative proportion of bacterially-produced short chain fatty acids (SCFA) differed significantly between stool of healthy adults and individuals with colorectal cancer.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0070803
Helicobacter pylori and Ulcers

- Ulcers were thought to be caused by stress or poor diet
- Disruptions to the human microbiome caused by a Helicobacter pylori that is not normally present or does not cause troubles (early 1980s).
- A Nobel Prize for Medicine was given to Robin Warren & Barry Marshall in 2005 for their discovery
Diseases Caused by Microbes

*Bacillus anthracis*  
*Anthrax*

*Borrelia burgdorferi*  
*Whooping cough (pertussis)*

*Brodetella pertussis*  
*Lyme disease*

*Chlamydia trachomatis*  
*Trachomas (blindness), etc.*

*Clostridium botulinum*  
*Botulism*

*Clostridium perfringens*  
*Gas gangrene & food poisoning*

*Clostridium tetani*  
*Tetanus*

*Corynebacterium diphtheriae*  
*Diphtheria*

*Escherichia coli*  
*Typhoid fever*

*Gardinerella vaginalis*  
*Vaginitis*

*Helicobacter pylori*  
*Stomach ulcer*

*Haemophilus influenzae*  
*Lung, ear infection, meningitis*

*Klebsiella pneumoniae*  
*Atypical pneumoniae*

*Legionella spp.*  
*Legionnaire’s disease*

*Listeria monocytogenes*  
*Damage to fetus*
The gut micro biome may play a role in weight management and contribute to obesity.
Disruptions to the gut microbiome

• **Diet:** eg High fat diet is associated with altering bacteria number and type

• **Disease states:** Mainly association studies (causal direction unclear) for diabetes, some cancers, obesity, “irritable bowel”, others

• **Antibiotics:** Effects are immediate and potentially long lasting, especially important for children

• **Bariatric Surgery:** Rapid changes in food intake, metabolism (including reversal of T2diabetes), fat mass, inflammation, microbiome composition.
Gut Microbiome differs in individuals with and without diabetes

<table>
<thead>
<tr>
<th>Intestinal bacterial phyla</th>
<th>Increase in T2DM</th>
<th>Decrease in T2DM</th>
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</thead>
<tbody>
<tr>
<td><em>Firmicutes</em></td>
<td></td>
<td><strong>x</strong></td>
</tr>
<tr>
<td><em>Bacteroidetes</em></td>
<td></td>
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<th>Intestinal bacterial species</th>
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<tr>
<td><em>Roseburia</em></td>
<td><strong>x</strong></td>
<td></td>
</tr>
<tr>
<td><em>Eubacterium halii</em></td>
<td><strong>x</strong></td>
<td><strong>x</strong></td>
</tr>
<tr>
<td><em>Faecalibacterium prauznitzii</em></td>
<td><strong>x</strong></td>
<td><strong>x</strong></td>
</tr>
<tr>
<td><em>Lactobacillus gasseri</em></td>
<td><strong>x</strong></td>
<td><strong>x</strong></td>
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<tr>
<td><em>Streptococcus mutans</em></td>
<td><strong>x</strong></td>
<td><strong>x</strong></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td><strong>x</strong></td>
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Our gut hosts billions of microorganisms which contain more than 150 times the genetic diversity of the human genome.

The micro-biome performs digestive and metabolic functions, and “evolves” over our life course.

The micro-biome “talks” to the liver, the brain, organs controlling metabolism, inflammation and the immune system.

The micro-biome is affected by what we put into our mouths.
...and finally,

_Eat food, mostly plants, not too much_

_Michael Pollan, “What to eat”_
“Eat and Drink the Rainbow”