Brain Morsels: Packet 10

The gut microbiome and your brain

The microbiota-gut-brain axis: Mind-altering microorganisms are lurking in your gut!!

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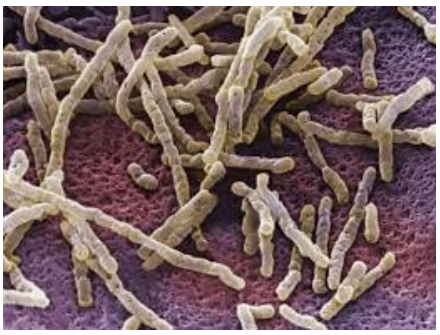
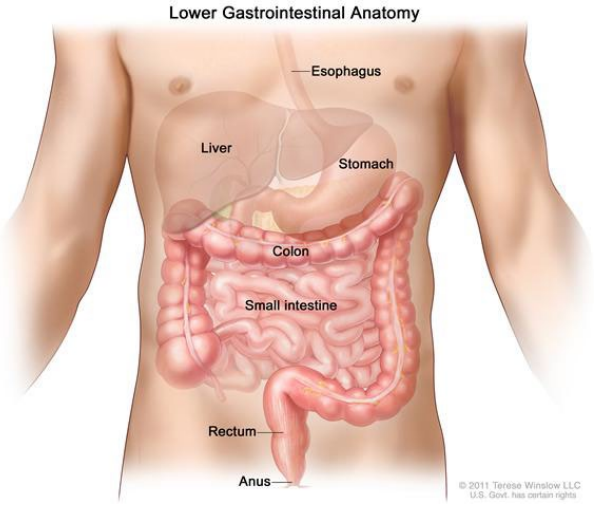


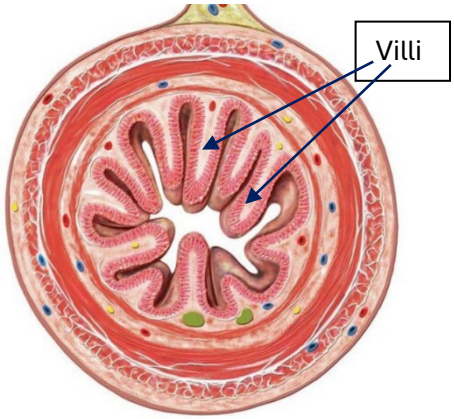
Before we finish talking about nutrition and its importance to the brain, we need to take an excursion to the gut to consider its resident population of microbes. It turns out that there are extraordinary, and until recently, unsuspected linkages among the gut, its microbes, and the brain. Here are the results of three studies, yes, two in mice, that reveal findings that make scientists and physicians incredibly excited when they imagine the possibilities of whole new understandings and therapies for humans.

- Mice with a greater diversity of gut microbes (changed by diet) had greater working memory and less anxiety in a novel environment.
- Timid mice transplanted with gut microbes from adventurous easygoing mice become more adventurous and adventurous mice become more timid.
- Altering gut microbe populations by increasing or decreasing the proportion of certain microbe species has been found to be associated with depression and increased visceral pain, and perhaps with autism, Parkinson's, and Alzheimer's.

The field is new so there is much to explore!

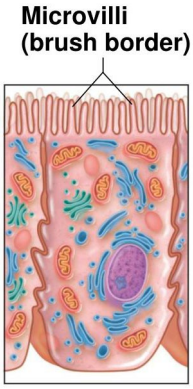
Gut basics





www. sciencephotogallery.com

If you look at a cross-section of the gut, you will find muscles, nerves, blood vessels and lymph vessels forming the outer layer. Inside, the epithelium is thrown into deep folds, called villi.



(c) Absorptive cells

Blood vessels and lymphatic vessels are found in each villus. The outer surface of cells that form the surface of the villi are each extensively folded into what are called microvilli[1]. All this folding creates a huge surface area for processing and absorption of nutrients, which are carried into the bloodstream for distribution to body cells as well as to the brain for those nutrients permitted to enter.

> Trivia to amaze your friends: Estimates suggest that ~50 tons of food pass through our guts over our lifetime.

So where are all the microbes hanging out? The microbes are mostly bacteria, but the population also includes some viruses and in some cases protozoa and flatworms. They are found in the lumen, the space inside the tubular intestine. They congregate along the wall where they can be more or less protected, often residing deep in the spaces between the villi and between the microvilli.

Humans have about 1000 different species of bacteria in their guts, and thousands of sub-species. The composition of our individual microbial community typically is similar to that of our family's and our social group. It also depends on the quality of our diet (no surprise), what drugs we are taking (especially antibiotics, which wreak havoc on the gut microbes), and even on the quality of our sleep. By one estimate, for every human cell there are 10 microbial cells. In other words, only about 9% of the living cells standing there when I'm in the shower are human cells. I host and transport all the others, and my biology is in constant interchange with theirs. We are a superorganism!

Loss of diversity or proliferation of the 'wrong' microbes can lead to obesity, metabolic syndrome, a variety of chronic diseases, infection. Well, why is that? **What are these microbes normally doing anyway?**

Here's a short list. They

- help to regulate gut movement and leakiness
- metabolize complex lipids (fats) and plant-based complex starches whose nutrients would otherwise be inaccessible
- affect nutrient absorption, including Vitamin K, calcium, iron
- produce vitamins like biotin and folate (both B vitamins)
- neutralize certain drugs and cancer-causing elements in our food
- regulate our energy metabolism
- modify immune responses AND are necessary for development of our immune system in infancy

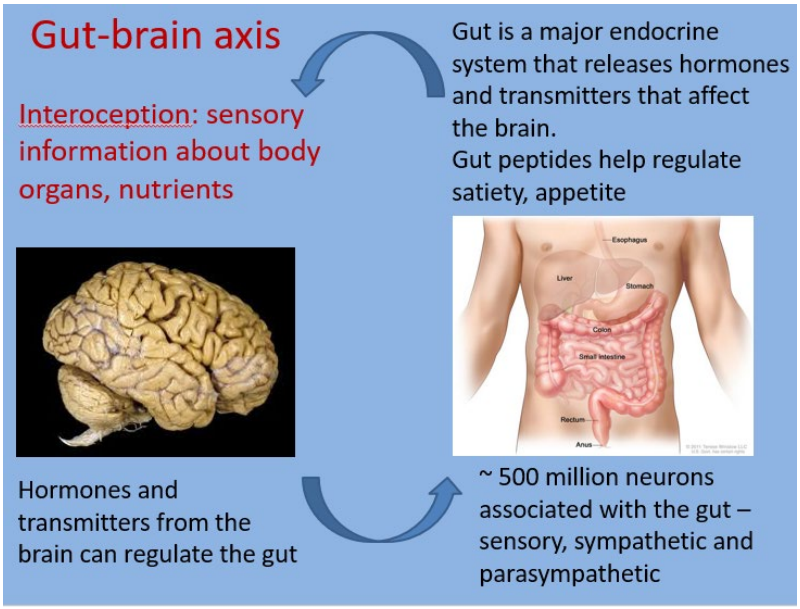
[1] www.slideserve.com/shiri/the-digestive-system-powerpoint-ppt-presentation

- *release factors that influence the brain– neurotransmitters like GABA, serotonin, dopamine, acetylcholine and norepinephrine, as well as stimulating BDNF, a critical brain factor in making new neurons and synapses during fetal brain development*
- *alter weight*
- *alter our stress response*
- *influence mood and cognition*
- *may alter signaling to the brain about the state of the body.*

The last five functions - the ones in italics - clearly involve neuronal networks in the brain.

How does the signaling work?

As the figure on the right shows, the gut and the brain are linked. The brain gets signals from the gut about different organs and the availability of certain nutrients. This is called interoception, sensing the physiological condition of the body relative to the context in which the body is active. Those data also are essential to the process of emotional awareness.



The brain releases appropriate hormones and neurotransmitters that affect the activity of neurons serving the gut to regulate things like gut motility, the permeability of blood vessels, and the level of blood flow to the gut. In response, the gut releases hormones and transmitters that affect the brain. Some of these provide information about satiety and appetite. Much of this bidirectional information flows through a major nerve called the vagus. About 20% of its flow is instructions from the brain to the gut. About 80% is instructions to the brain!

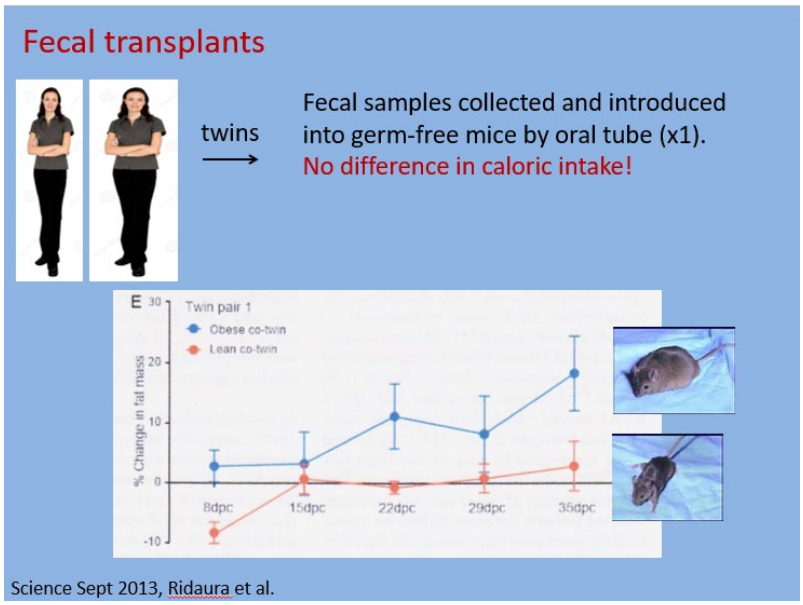
Right, but how do the microbes weigh in on this signaling and affect the brain? Assuming we have a healthy microbial population in the gut, bacteria respond to the presence of particular nutrients and to hormonal and neural signaling by releasing their own signaling molecules, including many of those used by neurons. Those molecules are detected by receptors on the microvillar cells or on specialized neurons and immune cells in the wall of the gut. Those cells in turn respond by releasing factors into the blood stream, eventually reaching the brain. Or, those bacterial signaling molecules directly activate the nerve endings of the vagus nerve or some of the spinal nerves and directly signal the brain.

One thing to understand is that the microbial population is dynamic, in the sense that if you were to sample it in an individual on different days, it would probably be generally similar but also not the same. High stress, changes in diet, use of antibiotics – each of those can affect which species are present. Also understand that our gut's microbial population includes both good and bad species – bad as in if this or these species gain the upper hand in the ongoing bacterial warfare, there is a serious problem. I suspect that many of you have either experienced or known someone who has experienced the misery of "*C. diff*" (*Clostridium difficile*) infection. In many cases, it is life-threatening. With growing understanding of the microbiology of the gut, however, and based on experiments mainly in mice, many patients have been treated successfully with fecal transplants from a family member. In this procedure, fecal matter from the donor is put in a blender and then administered via a tube into the stomach. That sounds rather gross, and there are now pills to deliver the needed good bacteria to repopulate the gut and put down the *C.diff* uprising, but when first tried, the gross aspect paled in the face of need.

One more set of experiments is just so interesting that you need to hear about it. The data strongly support a role for gut bacteria in regulating weight. There was a study called the Missouri adolescent female twin study in which 1,539 female twin pairs (21–32 year-olds) were enrolled. Four pairs were found in which one twin was of normal weight and the other was obese.

The fecal material from each was introduced separately into germ-free mice that were individually caged and fed with a commercial, sterilized mouse chow that was low in fat (4% by weight) and high in plant polysaccharides (LF/HPP). You may wonder why germ-free mice? Well, that way the scientists could control for any internal source of bacteria. It is interesting to note that these germ-free mice were hyper-responsive to stress and had deficits in spatial and working memory tasks, again an indicator that the gut bacteria affect brain function.

The fecal material of the mice receiving the obese twins' fecal material was compared to that from the normally weighted twins. In the material of those that had received an "obese" transplant, researchers found expression of microbial genes associated with the stress response while the "lean" transplants had expression of genes associated with normal digestion. Those data alone have implications for human health if the data

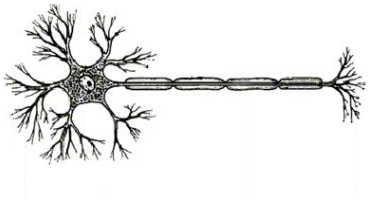


are robust in humans, not just in mice. But most remarkably, the mice receiving the "obese" transplant became obese even though there was no difference in caloric intake![2]

Summary

Your gut microbes are important. Feed them well with the kind of diet described in Packet 9, and ensure that your diet is rich in probiotic foods like kefir, sauerkraut, miso, pickled vegies and yogurt. You *could* take probiotic supplements, but they are not regulated by the FDA and you typically get somewhere between 4 and 12 bacterial species – common ones but are they the ones you need? Again, consuming natural probiotic foods delivers the bacteria in a natural context, what our bodies have evolved to expect.

Oh, and get enough sleep, and try to keep your stress levels down!



Puzzles

Puzzle 1

Which word is the odd one out? It's not the obvious one with only 3 letters!

Snug	Live
Dam	Grid
Pans	Trap
Keep	Rats

Puzzle 2

How many holes does this shirt have?

[2] Ridaura VK et al. (2013) *Science* 341:1241214. doi: 10.1126/science.1241214.

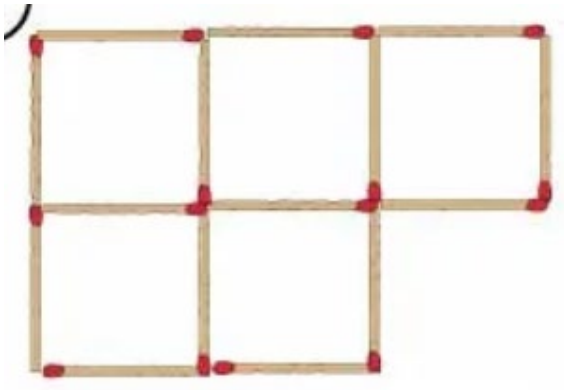
Puzzle 3

What is the next letter in this series?

O,T,T,F,F,S,S,…

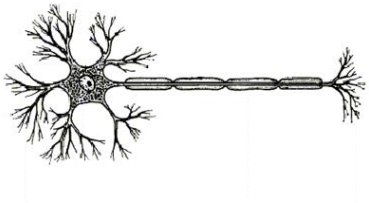
Puzzle 4

Remove only 3 matches to leave 3 squares.



Puzzle 5

Two sons and two fathers went fishing. They all caught 1 fish each. Only 3 fish were caught. How is this possible?



Answers on the following page

Answers

Puzzle 1

Grid. All the other words are a word when spelled backwards.

Puzzle 2

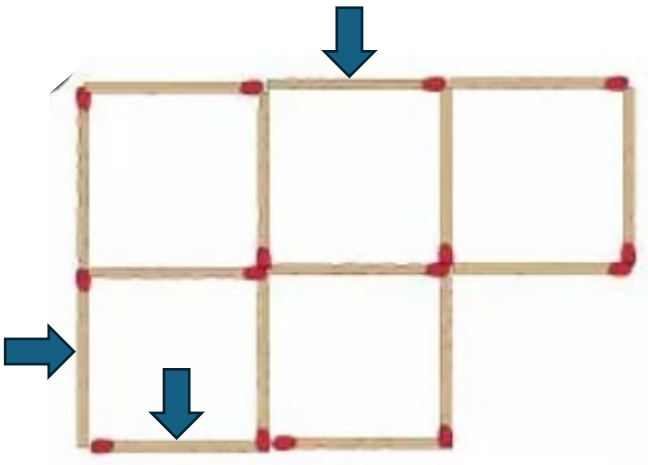
There are 10 holes – 7 in the shirt front, and the neck, arm and bottom-of-the-shirt holes.

Puzzle 3

"E" – **O**ne, **T**wo, **T**hree, **F**our, **F**ive, **S**ix, **S**even, **E**ight

Puzzle 4

Remove the matchsticks indicated by the arrows.



Puzzle 5

Grandfather, father, son

Note: these puzzles come from ESLvault.com