



The Gut-Brain Axis

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Definitions

'Microbiota' vs 'Microbiome'

- Microbiota: The microbes living within us
- Microbiome: The collective genome of the Microbiota
- Reason for the confusion: Many of these organisms cannot be cultured and are identified through their genomes



Clarifications

- Microbiota/Microbiome: All parts of the body including the skin
- Enteric (or gut) Microbiota/Microbiome: The microbiota within the digestive system

The Human Microbiota

- 39 trillion microbes (*cf* Human cells in the body: 30 trillion) – *ie* we are outnumbered by 30%
- Enteric microbiota: 10^{14} microorganisms, 2,000 species
- Total mass: approx. 2kg
- Comprise approx. 55% of human faeces



Composition of Microbiota

- **Bacteria** – all animal life depends on bacteria as they possess the genes & enzymes necessary to synthesise Vitamin B12
- **Viruses**
- **Single-celled Eukaryotes**
- These microbes can be detrimental to health but most are beneficial – they are *commensal*



An Aside...

- Until recently, it has been proposed that there are three divisions to the ‘Tree of Life’:
 - **Bacteria:** (single cell, no nucleus, no organelles)
 - **Archaea:** (as bacteria but share genes & metabolic processes with Eukaryota)
 - **Eukaryota:** (Have nuclei & organelles within cells, includes animals and plants)

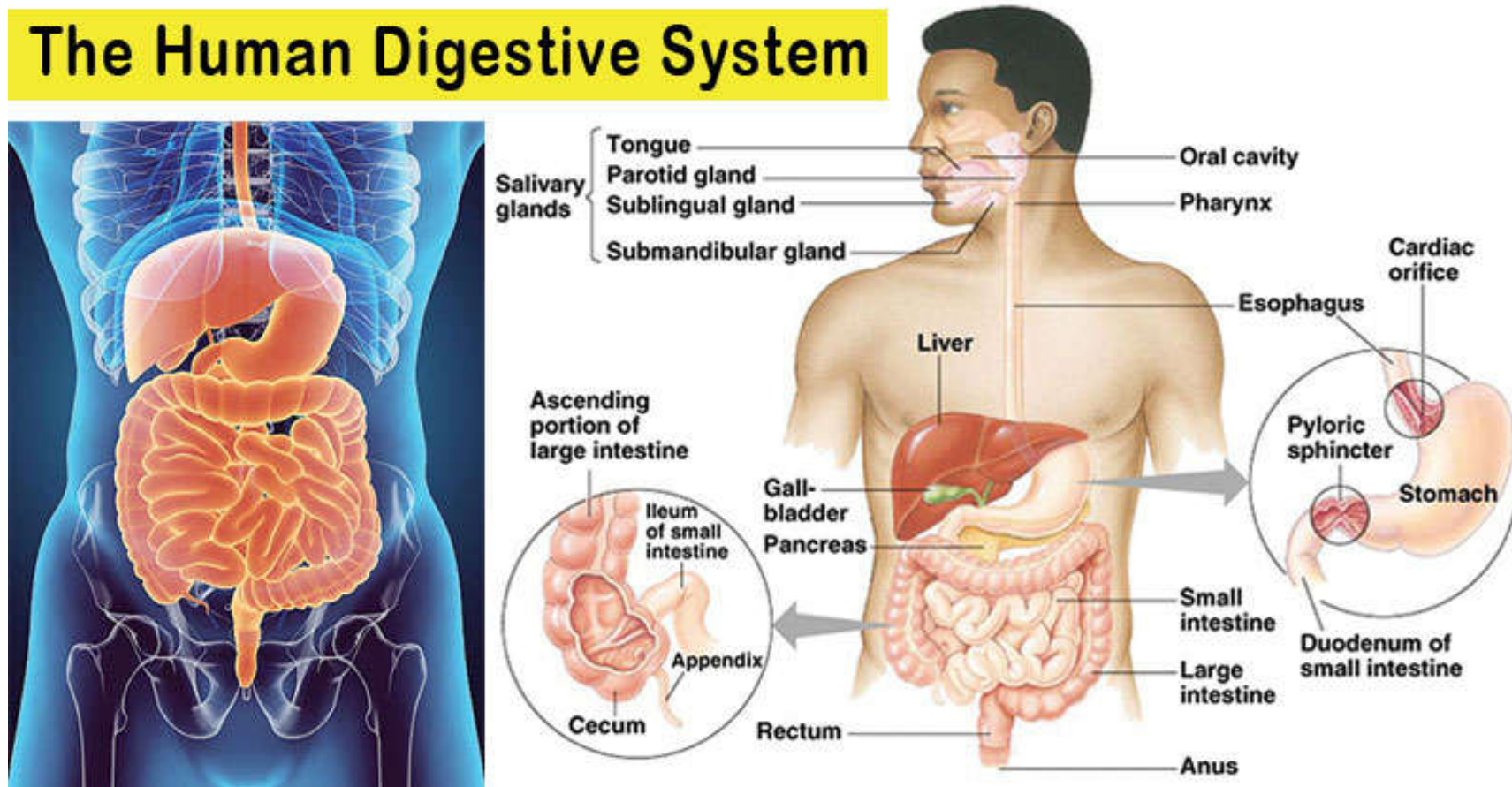


An Aside...

- There is now thought to be a fourth division: ‘Candidate Phyla Radiation’
- These microbes have unusually short genomes and may only be able to live in association with other living organisms
- They exist only in our bodies...

The Digestive System

The Human Digestive System





Another aside...

- After many years of believing that the appendix is a vestigial organ which we have inherited through evolution from ancient ancestors, it has now been established that it has a function.
- It serves over the first three decades of our lives and mediates between our microbiota and our immune system in the development of immunity.



The Human Nervous System

- The Central Nervous System
- The Somatic (Voluntary) Nervous System
- The Autonomic Nervous System
 - The Sympathetic Division ('Fight or Flight')
 - The Parasympathetic Division ('Rest & Digest')
 - The Enteric Nervous System

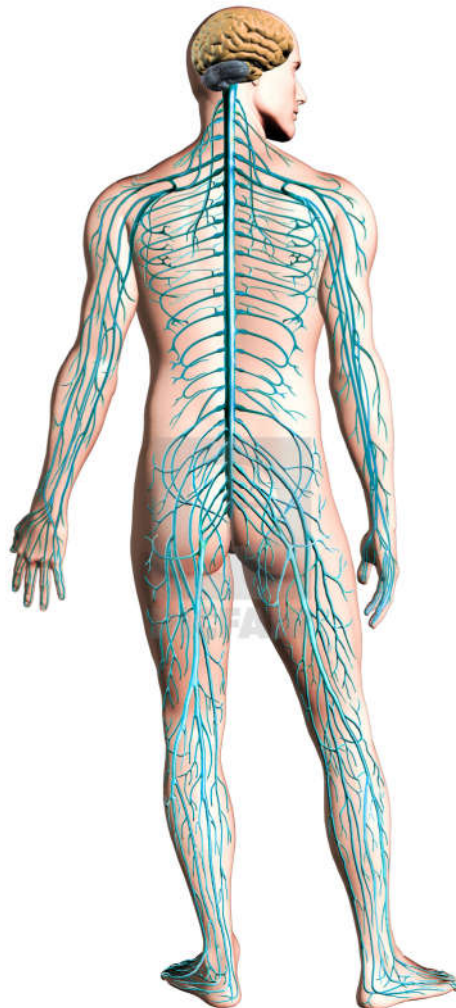


The Human Nervous System

Anatomically:

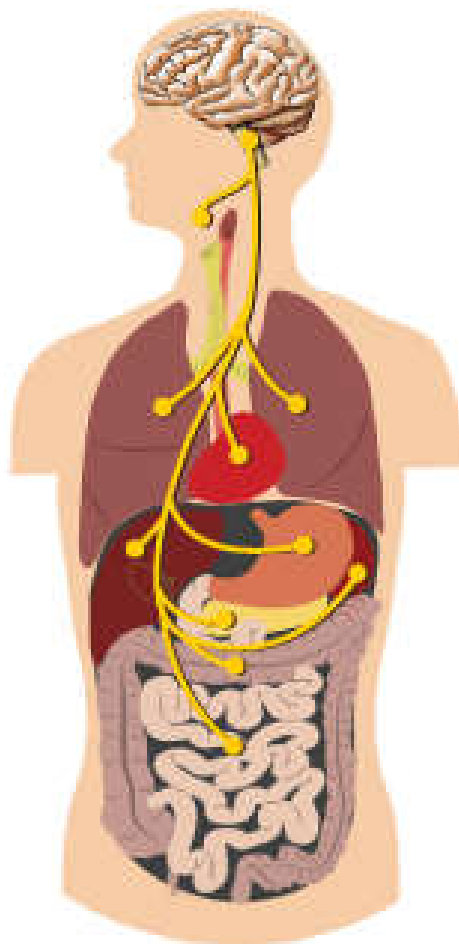
- Spinal Nerves (31 pairs)
- The Vagus Nerve

The Human Nervous System



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The Vagus Nerve



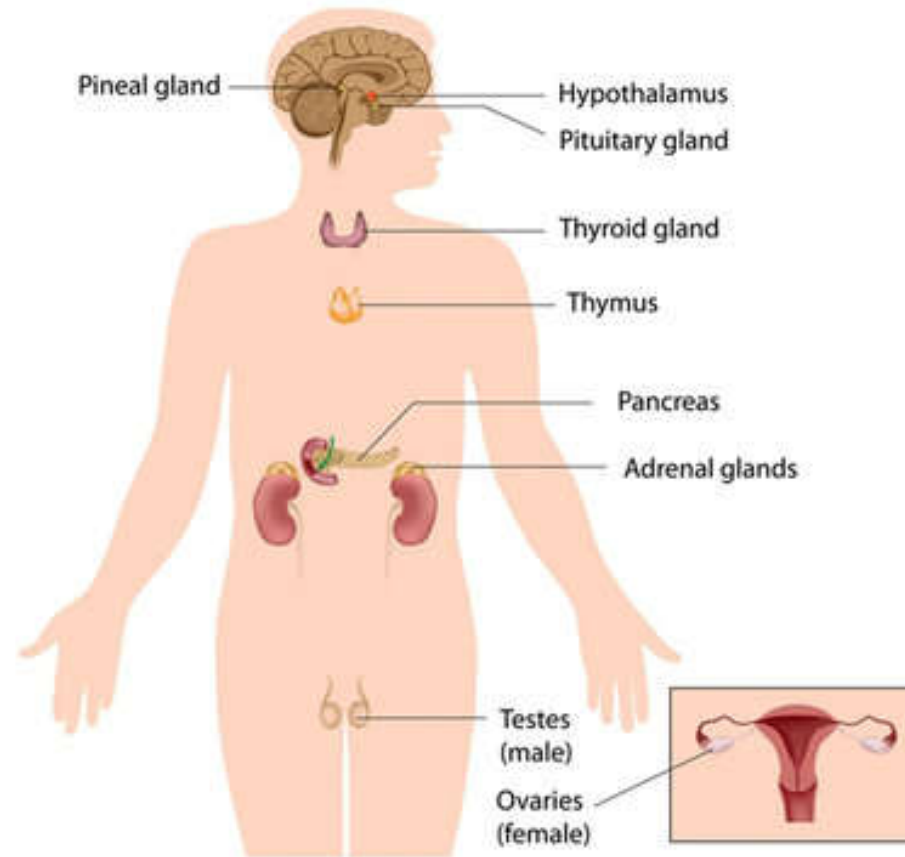
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The Endocrine System

- Made up of glands that produce and secrete hormones – chemical substances produced in the body that regulate the activity of cells or organs
- These hormones regulate:
 - Growth
 - Metabolism
 - Sexual development and function

The Endocrine System



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The Endocrine System

Stress Reaction

- Initiated by the Hypothalamus in the Brain
- Mediated by the Pituitary Gland
- Controls the Adrenal Glands

(Hypothalamic, Pituitary, Adrenal (HPA) Axis)

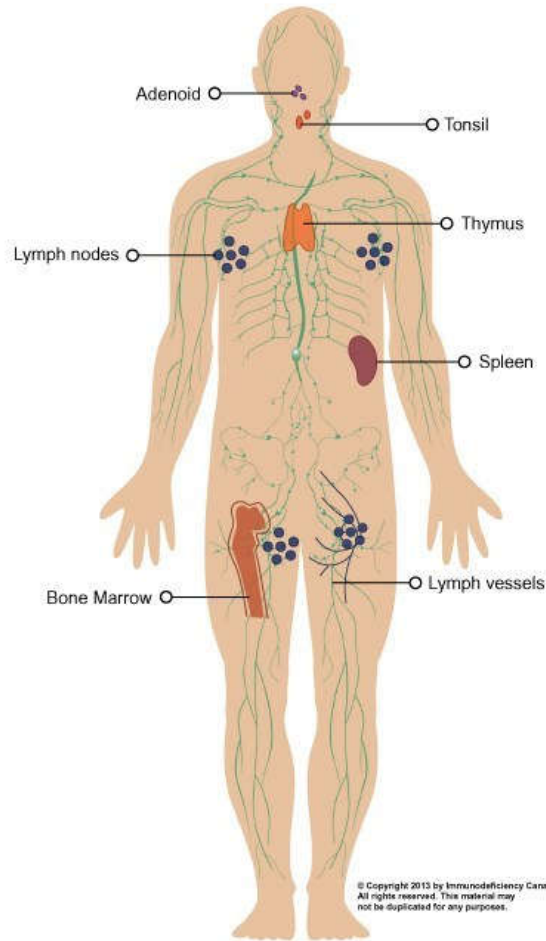
- To produce Cortisol, which circulates in the bloodstream and produces the fight/flight response



The Immune System

- Phagocytes in pursuit of Pathogens
- Carried through the network of lymphatic vessels in lymph fluid
- Broken down in the Lymph Nodes...
- ...and removed by the Spleen

The Immune System



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The Gut-Brain Axis

- The *Enteric Nervous System* consists of a mesh-like network of nerves along the whole length of the digestive system with its own reflexes independent of the brain or spinal cord
- It is now considered to be a third division of the Autonomic Nervous System – a ‘second brain’



The Gut-Brain Axis

- There is two-way connection between the Central Nervous System and the Enteric Nervous System
- The mechanisms involve neural, immune system & endocrine mediators
- The gut microbiota influence these interactions
- The emotional & cognitive functions of the brain connect with our intestinal functions



Influence of Gut Microbiota

Changes in the Gut Microbiota may cause:

- *Clostridium difficile* infection
- Irritable Bowel Syndrome (IBS)
- Autoimmune & allergic diseases
- Obesity & Metabolic Disorders
- Neuropsychiatric Disorders such as Autism

Everensel *et al* (2015)



Brain, Gut & Emotions: Origins

- In language: ‘He’s got guts...’; ‘I’ve got a gut feeling...’; ‘I’m gutted...’
- William Beaumont and Alexis St Martin
 - Digestion is chemical
 - Mood affects the rate of digestion

William Beaumont (1785-1853)



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Unexpected Relationships...

- Human milk has higher diversity of sugars compared with other mammals
- *Infants can't digest these sugars*
- Microbes in our microbiota can
- The metabolic products are essential for normal brain development



From Gut Microbiota to Brain (1)

Hepatic Encephalopathy

- ...a spectrum of neuropsychiatric disorders in patients with liver dysfunction...
- Oral antibiotics lead to dramatic improvement

From Gut Microbiota to Brain (2)

Studies on germ-free animals

- Demonstrate an exaggerated stress response (increased ACTH & Cortisol)
- ‘Microbial colonisation’ of the gut leads to normalization
- ...and increase in serotonin & related metabolites in the limbic system



From Brain to Gut Microbiota (1)

- Psychological stressors affect the composition and total biomass of the enteric microbiota
- Likely to be mediated in parallel by autonomic nervous system & neuro endocrine systems



From Brain to Gut Microbiota (2)

- The Brain has a prominent role in the control of gut functions – motility, secretion of acid, bicarbonates & mucus, intestinal fluid handling and mucosal immune response

Gut Microbiota & Depression

- Many examples in rodent models, *eg*
- *Campylobacter jejuni* administered to rats induces anxiety-like behaviour
- Experimentally elevated HPA-axis response and depression-like behaviour in rats can be reversed by administering *Bifidobacterium infantis*.



What can we conclude for Humans?

- Study involving people with major depression
 - Reduced diversity of microbiome identified
 - Bacteria transferred to rats
 - Rats displayed increased anxiety response

Ilya Mechnikov



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Benefits of Fermented Milk?

- Ilya Mechnikov won the Nobel Prize in 1908 for establishing a link between longevity amongst Bulgarians and the fermented milk products they consumed

Probiotics and Prebiotics

- In principle, 'probiotics' could be used to alter balance within the gut microbiota
- In practice, its difficult to get them past the hostile environment of the stomach
- 'Prebiotics' (nutrients which encourage the growth of probiotics already in the gut may be easier



Conclusion

- Two-way links between the brain and Enteric Nervous System
- Some evidence to support that this extends to the gut microbiota
- Can the brain influence the microbiota?
- Can the microbiota influence our brains – and thus our behaviour?

Where is it going?

- Enormous amount of research to (1) better understand the role of the gut microbiota and (2) devise therapies to improve health, especially mental health
- ***Postscript*** New research (*The Guardian*, 26th June 2019) suggests link between the gut and Parkinson's Disease...

Sources

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