

Highlight

To Serve Man^{☆,☆☆}



Food is on everybody's tongue, at least in the developed, slightly bored countries. Radical nutritional convictions are sprouting and blooming more than ever, and vehement debates about protein and vitamin B12 sources are carried out by every available communication tool, with an ardor once reserved to more spiritual issues. Within the scope of the ongoing gluten-, lactose- and GMO-hysteria and the constantly reshaped insights from nutritionists about the contested superiority of vegetal oils and cow milk [2], the members of the different alimentary beliefs battle fervently for their convictions. The spectrum ranges from raw-vegans over vegetarians, high-protein partisans and bio-food addicts to those who extol the hunter-gatherer paleo-diet [3], as the decadence of humanity obviously initiated with sedentariness, agriculture and stock farming. Books, blogs, conferences, camps, festivals and specialized journals and media - they all convey the persuasion that the right food is the right solution for pretty everything, from smooth skin to curing cancer.

It was only a question of time before the intense navel-gazing led a focal plane further, into the universe within us. "If you don't like bacteria, you're on the wrong planet", said the scientist and writer Stewart Brand. Bacteria are everywhere and bacteria have been already everywhere 3.5 billion years before the first multicellular organism appeared [4]. Maybe things started about 2 billion years ago, when an eukaryotic cell swallowed an archaea which subsequently became a mitochondria [5]. For sure, eukaryotic organisms co-evolved over millennia in the constant presence of prokaryotes [4,6]. Actually, 90% of cells of the human body are not human at all and our intestines hold 200 times more non-eukaryotic protein-coding genes than our human genome [7]. Bacteria cover nearly every surface of our body and crowd our guts [8], profoundly changing the perception of the human organism from a defined individual to a walking, super-complex ecosystem [4,9]. Thus, from a democratic point of view, it seems quite legitimate for them to have their

say in the various processes of decision making of their host and comfortable habitat, and in keeping the latter in good shape [1,4].

Consequently, the gut microbiota is by now considered a symbiont part of ourselves [5], has an organ in its own right, both metabolic and endocrine [10,11], and the extent of its acknowledged influence over the human species grows constantly. Following a combination of the modern fixation on our bowels and the recent metagenomics-euphoria, allowing us to sequence mostly everything we can lay our hands on [12,13], the microbiota and its metabolic products [8] are now responsible of a long list of tasks, either as friend or foe [4]. Some are essential for the correct development and operating of the human body – the anatomical development of the intestinal epithelium, vasculature and nervous system [10,14], teaching tolerance to the immune system [9,15], drug metabolism [10], breaking down inaccessible complex plant polysaccharides [7], energy balance [16], vitamin production [8] and excluding pathogens [9,15]. Others correlate with a large panel of diseases – autoimmune diseases [10,14], metabolic disorders [6,8], muscle wasting [16], and even autism-spectrum disorders (ASD), depression and anxiety [15,17].

Nevertheless, the most intriguing and recent assertions are those affirming that the gut microbiota modulate our brain chemistry along the so called *gut-microbiota-brain axis*, thus substantially influencing cognitive functions such as learning, memory and decision making and behavioral outputs like emotional states, motivation and stress processing [4–6,17]. The prosaic insight that the human being is technically no more than a huge, hormone-steered organic machine and that all our noble feelings finally boil down to a finite number of chemical reactions is already rather bad for our self-esteem. The idea of them being moreover orchestrated by a bunch of bacteria might by all means trigger the next existential crisis. Allowedly, considering social interactions, such as kissing and food-sharing, and traditions, like the touching of religious objects, simply as a way to horizontally transfer beneficial microbiota [4,6] somehow lacks the minimal amount of romantic embellishment the human mind requires for operating. Or at least how the bacteria want us to perceive things.

What relativizes the conspiratorial theories is the fact that most observations to date stem from rodent animal models

☆ Article highlight based on "Transcriptome analysis of *Escherichia coli* O157:H7 grown *in vitro* in the sterile-filtrated cecal content of human gut microbiota associated rats reveals an adaptive expression of metabolic and virulence genes" by Guillaume Le Bihan et al. [1].

☆☆ In allusion to: D. Knight, "To serve Man", Galaxy Science Fiction (1950), 1(2):91–97.

[4,9]. Germ-free mice are indeed more stressed and display ASD-like social-cognitive defects but are less anxious, and conversely, depressed and autistic mice harbor altered microbiota [6,10,17]. Remains to prove that humans are as influenceable as mice.

Anyhow, several animal models have provided solid arguments that disadvantageous modifications of the bacterial gut population, or *dysbioses*, can be the cause rather than the consequence of pathologies: for example, the microbiota of obese mice make lean mice put on weight and vice versa [7]. However, the exact quantitative or qualitative alterations responsible of the dysbiotic state remain unclear and controversial. The current consensus is that disease correlates with a loss of diversity and stability of the microbial community [9,10] and rather a shift in the proportions than the appearance or disappearance of different bacterial phyla [5,8,18].

The main question is, how exactly do the bacteria talk to brain and body? There is certainly no shortage of plausible theoretical explanations [4,15,17]. Apart from being in direct contact with the epithelial cells of the intestines and members of the immune system, signaling mainly through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and nucleotide binding oligomerization domains (NODs) [9,10], the microbiota sits at the source and the control center of a plethora of diffusible signaling molecules which can reach virtually any cell of the organism *via* the blood stream and the lymphatic system [15,16]. Among the metabolites of gut bacteria feature GABA, tryptophan, serotonin, histamine and dopamine, all well-known neurotransmitters or precursors of the latter [4,6]. After supervising the nutrient uptake, are bacteria also restricting the availability of neurotransmitters, thus directly influencing behavior and cognition [10,14]? It remains however unclear, to what extent the microbial metabolites diffuse and which section of the nervous system is primarily targeted. Some claim that they affect mainly the neurons of the enteric nervous system (ENS), including the vagus nerve [6,17], others that they smoothly cross the blood brain barrier [8].

The other main powerful tool in the imaginary hands of gut bacteria are called short fatty acids (SCFAs), the principal end products of their metabolism after the fermentation of dietary fibers [4,10]. SCFAs, such as acetate, propionate and butyrate, diffuse passively and bind to PRRs and G protein-coupled receptors [7,8], subsequently inducing immune tolerance [14], modulating the release of neuropeptides including serotonin and peptide YY [10] and decreasing inflammation through inhibition of NF- κ B activation [8].

On the host side, the molecular crosstalk [5] seems to involve two currently quite popular domains – noncoding RNAs and epigenetics. The previous issue of this column already dealt with the key role of microRNAs (miRNAs) in the interaction of the host organism and various pathogens [19]. In the special case of the gut microbiota, bacteria-

induced host miRNAs are probably essential to fine-tune and buffer the otherwise binary response of the immune system in order to balance tolerance with barrier function [15]. Epigenetics, the adjustment of gene expression and cell fate without modifying the DNA sequence, in turn, are essential for the diversification of the immune system. It turns out that some gut microbes deliver some epigenetic effector proteins, carrying the fancy name of *nucleomodulins*, starting with the SCFA butyrate, a potent inhibitor of histone deacetylases (HDACs) [6,8]. Remembering the part of the microbiota in educating the host immune system, the theoretically possible link is quickly established [14]. Epigenetic mechanisms also underlie the plastic changes in the brain, shaping cognition and behavior. Theoretically, HDAC inhibition and the control of histone acetylase substrates by the gut bacteria could favor transcription in neurons, memory consolidation and neuroprotection [6]. Theoretically.

Needless to say that mankind in turn claims the control over its inhabitants. After providing our bodies with the right diet, it is now time to provide them with the right bacteria. In 1908, Elie Metchnikoff got the Nobel Prize for correlating the longevity of Bulgarians with their penchant for fermented milk and showing that *Lactobacillus*-containing yogurt reduced the number of toxin-producing bacteria in the gut [8,9]. 105 years later, we got Shakira suggestively shaking her hips for the football World Cup and the Activia® advertising clip.

An individual's initial microbiota seems to be a matter both of genes and environment. On the one hand, a recent study on twin pairs highlighted the existence of the gene-dependent, highly heritable taxa Christensenellaceae and their link with body-mass index [20], on the other hand, factors like the mode of delivery, breast milk *versus* formula feeding [10,14], the use of antibiotics, geographical origin, stress and infections [5,8] further modulate the composition of our intestinal inhabitants. Now, an entire business is growing around their manipulation, including prebiotics, probiotics, antibiotics and even psychobiotics [6,16,17], despite that the European Food Safety Authority (EFSA) just refused the health claims of marketed probiotics for lack of substantial proof of effectiveness. At least, *Lactobacilli* & Co. obtained the curious title of organisms “Generally Regarded as Safe” (GRAS) [9]. Even the 2000-year old technique of fecal microbiota transplantation is gaining in popularity and has proven to be quite efficient in treating recurrent *Clostridium difficile* infection and multiple sclerosis [11,21], as well as in avoiding, in form of an ostensibly read article, any attempt of conversation from your train or plane neighbor.

Beyond doubt, our microbes, spectators of evolution and ontogeny, have still a lot to tell, if they agree. In order to tell apart causality from the secondary effect of sociality, larger metagenome-wide association studies (MGWAS) are needed [4,5,10], larger cohorts and the inclusion of differences in the microbial population according to their location in the gastrointestinal tract into analyses [9,10,17]. Among the countless

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