Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Highlight

A tale of two microbes☆

Inside you, there are two wolves … one is evil, the other one is good … they are having a terrible fight … This is how a proverb of fuzzy origins[1] starts, which has lately been extensively parodied on the internet. The original version is one of countless moralistic-metaphorical tales about the internal fight between an individual's positive and negative emotions, similar to the depiction as angel-and-demon versions of the same subject in the Western comic culture.

Most religions and mythical beliefs concord on the existence of an immaterial essence of living beings, in charge of the higher, noble mental abilities such as reason, morality, and consciousness – the soul.

My personal experience with the soul is mainly one of linguistic confusion though, as I happened to be born in the south-western region of Germany named Swabia, where the term *Seele* designated not only the ethereal essence of human creatures, but also a local food specialty, more precisely a baguette-shaped bread made from spelt and traditionally coated in large grain salt and caraway. Therefore, when introduced to the idea of the immortal soul, three-year-old me instantly created a very vivid mental image of some sort of luminous, shiny piece of bread stuck inside the human ribcage, which still comes to my mind three decades later, whenever someone mentions souls.

Beyond doubt more attracted to food than metaphysical concepts, I nonetheless entered "soul" into PubMed, out of sheer curiosity. The result exceeded the wildest expectations of the cynical mind, as the second result turned out to be a paper proudly claiming to elucidate the neurobiology of the soul [1]. In a delightful mashup of malarkey and flamboyant scientific terms, "The Soul, as an uninhibited mental activity, is reduced into consciousness by rules of quantum physics" details how the amorphous soul, initially lacking spatial and temporal information, is squeezed into unconscious and mental events by the maturation of the frontal cortex and the rise of γ-aminobutyric acid (GABA) to the rank of main inhibitory neurotransmitter. Quantum physics kick in once the reader is instructed that the universe and the brain share the same structural properties, and that "the universe fills the soul by quantum, and the soul fills the brain by physics".

At this stage I was seriously wondering if I hadn't stumbled by chance across another Alan Sokal affair[2] – back in 1996, the professor of mathematics had managed to get an intentionally nonsensical paper titled "Transgressing the Boundaries; Towards a Transformative Hermeneutics of Quantum Gravity", explaining that the physical reality is no more than a mere social and linguistic construct, published in a renowned academic journal. Sokal's (achieved) goal was to demonstrate the ideological bias and negligence of the editorial process, as well as the thriving anti-intellectual, deconstructionist critique of science.[3]

It is however much more likely that I found an explanation why random strangers in a bar keep trying to convince me that genetic information can be transmitted by the memory of water *via* soundwaves.[4]

Quantum physics aside, the idea of several (im)material entities sharing and controlling one single body is extremely widespread. With time, the concept of a soul has strayed away from the ideological focus and spread into psychology and fiction (often as an equivalent of consciousness), and apparently undergone mitosis. Sigmund Freud for example structured the "psychic apparatus" into the instinct-driven *id*, critical *super-ego*, and realistic, diplomatic *ego* mediating between the two.

Fiction in turn has popularised the individualisation of contrasting emotions, such as in the highly acclaimed 2015 animated movie "Inside Out", where a little girl is piloted by colourful, anthropomorphic personifications of joy, fear, anger & Co. inside her head, and extensively explored the idea of mind coalescence or hive minds: from superorganism like Isaac Asimov's Gaia planet in the *Foundation* series, to aliens overtaking human bodies, typically leading to a fight between two minds over the controls of one organism, for instance in the 2013 *The Host* movie.

Just like the terrible fight between the two wolves inside us, and the pending question "which one will win?". The official answer is "the one you feed", and this leads us straight down the oesophagus to what actually comes closest to the only scientifically proven set of separate entities inhabiting one human body *and* influencing an impressive amount of processes in there. Actually, "Inside you are about two kilograms of microorganisms" would make for a much more accurate start into the proverb, and the conclusion would still hold true.

While the nature and exact location of the soul have been the matter of vehement debate, no doubt persists regarding the identity of countless genera of bacteria, archaea, protists, fungi, and viruses, as well as their presence on almost all body surfaces, with the bowels for headquarters [2]. As a consequence of the last fact, the gut microbiome is the most intensely studied department among the unicellular population of the human body, including its role

☆ Article highlight based on "The microbiota protects against Pseudomonas aeruginosa pneumonia via gd T cell-neutrophil axis in mice" by Li Wang et al.

[1] Some claim them to be Cherokee, but this is most certainly just another great example of the "Detroit rule": https://www.smbc-comics.com/comic/2012-10-25.

[2] https://en.wikipedia.org/wiki/Sokal_affair.

[3] At least the latter hasn't much changed over a quarter of a century, I fear.

[4] True story. It also involves e-mails.

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in development, physiological functions, and disease [3,4]. Namely two processes have made the headlines over the past decades – first its involvement with the education and upkeep of the host immune system, inflammation control, and autoimmunity prevention [5]; second the "gut–brain axis", comprising the role of the microbiota in behaviour, mood, and neurodegenerative diseases [6].

But as seemingly all roads lead to the gut, more and more connections come into sight, including the "gut-lung" axis, which stands at the centre of the highlighted article by Jilin Yu's team in this issue of *Microbes & Infection* [7]. Here, the authors demonstrate that antibiotic pre-treatment in mice causes dysbiosis of the gut microbiota and impairs the host immune response to *Pseudomonas aeruginosa*, one of the leading causes of nosocomial infections, notably hospital-acquired pneumonia [8].

Coincidentally, since the start of the ongoing COVID19 pandemic, pneumonia has been on the tip of everyone's tongue, as one of the main complications caused by the novel coronavirus consists in severe pneumonia and acute respiratory failure [9]. That said, pneumonia had already quite the portfolio, even before SARS-CoV-2 entered the stage – with approximately 4.5 million cases and 4 million deaths worldwide per year, it is the currently deadliest infectious disease [10,11].

This aside, the present study by Wang et al. adds several valuable new elements to previous studies regarding the gut-lung connection [11–13].

Namely the fact that the authors do not observe any changes in the composition of the lung microbiome following antibiotic treatment is of particular interest, as this seems to have been a point of dispute in previous studies. For instance, Schuijt et al. published a study advocating for the existence of the gut-lung axis in 2016, where they depleted the gut microbiota in mice with an antibiotic cocktail and then infected the animals with *Streptococcus pneumoniae*, the pathogen responsible for half of all pneumonia cases [11]. Compared to controls, these mice displayed higher bacterial dissemination, inflammation, organ damage, and mortality. Faecal microbiota transplantation (FMT) from untreated animals resulted in the normalisation of the infection and inflammatory status. Additionally, the authors observed that alveolar macrophages derived from mice pre-treated with antibiotics exhibited a reduced ability to phagocytose *S. pneumoniae*, as well as a reduced responsiveness towards lipoteichoic acid and lipopolysaccharides. The report received [14], and addressed [15], some criticism for not verifying any potential impact of the antibiotic treatment or the FMT on the lung microbiota, leading thus to a "premature invocation of a gut-lung axis", shifting the debate to the actual existence of the lung microbiota itself.

As a matter of fact, the respiratory tract was considered sterile until quite recently [16], when the overall gain of interest in the microbial populations hosted by the human body promoted researchers to screen other organs than the intestines for inhabitants [17], the lung being one of the latest recruits [18].

Studies converge so far on the presence of a low density microbial population, principally bacteria, displaying a considerable heterogeneity between individuals and lung regions. What mixture counts as healthy is still a matter of debate, but in any case, it is expected to change in, and potentially modulate, the lung affected by cigarette smoke, chronic obstructive pulmonary diseases, asthma, fibrosis, and lung cancer [16,17,19].

However, both the small amounts of microorganisms in the lung and the reduced accessibility of the lower respiratory tract, especially in studies on human subjects, represent obvious technical hurdles for the routine assessment of the lung microbiota [16]. Wang et al. themselves advise caution regarding their results, quoting the difficulties involved in sampling the lungs for microbiota sequencing [7].

As expected, human studies related to the gut-lung axis are yet rare [13]. Shimizu et al. performed a randomized controlled trial in 2018 in order to determine if the administration of synbiotics would benefit mechanically ventilated patients with sepsis. The treatment reduced significantly the incidence of enteritis, as fairly expected, but also of ventilator-associated pneumonia [20], although the methodology encountered some scepticism [21]. Moreover, Shenoy et al. examined both the gut and lung microbiota in HIV-infected patients with pneumonia. Interestingly, they found that the gut, but not the lung microbiota, composition correlated with CD4 cell counts, and thus diseases severity, prompting them to hypothesise that the intestinal microbiome modulates peripheral immune function and response to lung infection [22].

Another interesting point of the highlighted paper is the focus on neutrophils as a target population of the antibiotic pre-treatment [7]. Indeed, most previous studies have primarily examined the behaviour of alveolar macrophages, the resident pulmonary immune cells, following the disturbance of the intestinal microbiome [11], omitting the recruitment of circulating members of the host immune system upon pulmonary infection. Evidence for the importance of a healthy gut microbiome for adequate neutrophil development can be found in a study by Deshmukh et al. from 2014, where pregnant mice were exposed to antibiotics, leading to a reduced number and diversity of the neonate intestinal microbes. The new-borns displayed in addition fewer circulating and bone marrow neutrophils and granulocyte/macrophage-restricted progenitor cells compared to controls, as well as an impaired host defence and increased susceptibility to *Escherichia coli* and *Klebsiella pneumoniae* [23]. Fittingly, Wang et al. observe less neutrophil recruitment in the *P.* aeruginosa-infected lungs of mice that had been subjected to antibiotic pre-treatment [7]. Hence, neutrophils are good candidates for at least one cellular intermediate between the physically separate gut and lung, migrating either through blood or lymph inside the so-called "mucosal immune system" [17,24]. Upstream of neutrophils, the authors identified the lack of activation and expansion of γδ T-cells, in charge of producing the pro-inflammatory IL-17 cytokine [7]. γδ T-cell abundance is the highest in the gut mucosa [25], where dendritic cells sample antigens from the gut lumen to stimulate the proliferation and expansion of T-cells [17], and although it is yet unclear which specific antigens drive their activation, it is tempting to speculate that at least some derive from the intestinal microbiome. In accordance with the present results, Deshmukh et al. also observed a reduction of IL-17-producing cells in the antibiotic-treated mouse intestine [23].

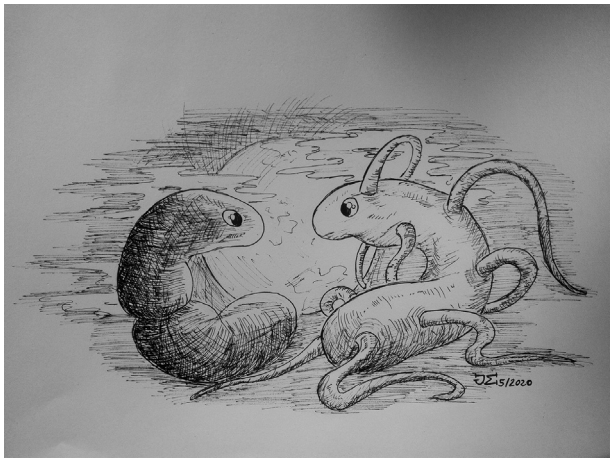
To note, the road from gut to lung might very well be a two-way street. Coopersmith et al. showed in 2003 that pneumonia-induced sepsis by *P. aeruginosa* in mice caused apoptosis and impaired proliferation of gut epithelial cells [26], which in turn would quite probably impact on the intestinal microbiome [17].

Should feeding the right microbes thus also be part of respiratory tract-related therapies? Probably, claims the literature. Although concrete proof has still to be delivered, prospects are good for healthy diets and probiotics to reduce asthma risk, support chemotherapy, and curtail lung infections [16,17].

At least, "food for the soul" makes much more sense now.

1. Background
   - Pneumonia affects 4.5 million individuals and causes 4 million deaths every year
   - It accounts for 15% of all deaths of children under 5 years old
   - *Pseudomonas aeruginosa* is a Gram-negative bacterium causing disease in plants and animals, and notably nosocomial infections in humans
   - The bacterium's ability to form biofilms accounts for its enhanced drug resistance abilities

2. In a nutshell
   - Antibiotic treatment of mice prior to *Pseudomonas aeruginosa* infection doubled the mortality rates and led to appreciably higher bacterial burden
   - Substantial alterations of the gut, but no the lung microbiota is observed in antibiotic pre-treated mice, including a decrease of microbial diversity, and an increase in the abundance of Proteobacteria
   - TNF-α as well as IL-6 protein and mRNA levels were reduced, and IL-10 levels elevated in the antibiotic treatment group
   - IL-17 levels are lower in pre-treated mice, leading to a reduced production Cxcl1/2, and thus fewer neutrophils in their lungs
   - Antibiotics decreased the steady state percentage of γδ T17 cells and prevented their activation and expansion upon *P. aeruginosa* infection, as well as their IL-17 production
   - Blocking γδT cells in mice with antibodies closely mimicked the phenotype of antibiotic-treated animals



Conflict of interest

The author declares no conflict of interest.

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