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Perspective

The Missing Link: A View of Food in the Age of Obesity

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Abstract: The most visible form of non-communicable disease is, of course, obesity. Sadly, however, there is also a wide range of autoimmune diseases and, increasingly, of mental health and neurodevelopmental conditions that, all-too-often, are not recognised by the sufferers themselves. Another characteristic feature of modern disease is onset in ever-younger individuals. Babies may suffer from eczema, children from autism, and cases of type 2 diabetes in primary school. Alongside this, cancer in under-50-year-olds is best explained by an immunodeficiency problem. The view taken in this article is that such a wide range of diseases points to something missing in the intestinal microbiome of vulnerable people and that, rather than exclusively bacterial in origin, this "missing link" is an intergenerational microeukaryote sentinel cell component of the immune system, possibly one that evolved earlier than the vertebrates themselves. In turn, this implies a "dual inheritance" that, alongside the genetic inheritance of a baby, such sentinel cells are transferred from the intestinal microbiome of the mother to the child at birth. Unlike in normal usage, in this article, the word "dysbiotic", or its derivatives, refers to people having a malfunctioning microbiome from birth, while the corresponding term "eubiotic" refers to the opposite, a person or population who exhibit none of the symptoms of non-communicable disease. Accordingly, a state of eubiosis is best regarded as a theoretical concept in Westernised populations, potentially being restricted to people living outside of modern-dominated environments. In this "missing link" concept it is a failure of a communication network within the growing child, an "immune-gut-brain triangle", rather than the organs themselves, that define the problem. Food, including probiotics, is at the centre of this "triangle", having direct effects on the microbiome, the brain, and the immune system. In addition, we should be able to investigate these relationships more closely with the aid of interkingdom messenger-detecting ingestible sensors.

Keywords: autism; biological handshaking; dysbiosis; eubiosis; exposome; gut-brain axis; holobiont; ingestible sensors; placebo effect; sentinel cells

1. Introduction: A Logical Hypothesis

Having retired from an organic chemistry position within the laboratories of the pharmaceutical industry, in 2016 I turned my attention to the intestinal microbiome as a potential factor in the aetiology of non-communicable disease. However, before deciding on a role for such microbial entities, it was necessary to understand the nature of these chronic conditions in greater depth. Although dealt with in more detail later in the text, it seemed to me that there are three paramount, potentially microbiome-related, features that must be taken into account within an environment dominated by almost universal weight gain:

(1) The relatively recent onset of parallel complaints (a "triple plage"), of which obesity is most visible among the population at large:

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a. Diseases of gut action: irritable bowel syndrome and, potentially, weight gain
b. Diseases of the immune system: atopic and/or autoimmune conditions
c. Diseases of the brain: neurodevelopmental and/or mental health issues

(2) The presence of problems that may be found soon after birth:

a. Neonate: commonly atopic dermatitis
b. Young child: often gut motility issues, potentially autism spectrum disorder
c. Older child to adult: more complex mental health and weight conditions

(3) The near-total absence of such problems in people living their traditional lifestyles, whether due to better food and exercise, or to a relative lack of pollution in their local environment.

There are three vulnerable areas that may lead to problems arising later in life:

(1) In the womb, as the embryo develops according to its parental genetic inheritance
(2) Factors that may be passed from mother to child during the process of birth
(3) Behavioural characteristics, at least partly determined by the society into which the child was born.

Analysis: It seems that the epidemiology of non-communicable disease is more consistent with an environmental problem within modern societies rather than the spread of a genetic disorder itself. Accordingly, as peoples living their traditional lives seem to be largely free from non-communicable disease then it is, perhaps, more likely that the problem follows from some "downstream" combination of birth and behaviour introduced within a relatively recent environmental change. Furthermore, problems in the neonate puts the emphasis on birth as the determining feature, rather than behaviour, while its manifestation as atopic dermatitis strongly suggests that any "factor" passed from mother to child will involve the immune system. Of course, building a hypothesis based on these observations is, of necessity, speculative, but the "missing link" concept of this Article does seem to agree with many clinical and laboratory observations and, gratifyingly, can be extended to a number of potentially beneficial practical suggestions, as will be illustrated in the following Sections.

A Missing Link Hypothesis: As will be illustrated in the bulk of the article, logic implies that the innate immune system of the mother can be extended to cover the transition from one generation to the next. More specifically, a microeukaryote dendritic cell-like entity (more succinctly, a "microbial sentinel cell") could well be passed from the microbiome of the mother to the intestine of the child, potentially helping to distinguish self from non-self. If so, such a system would have evolved, probably via the vertebrates. Indeed, it is worth noting that, while some animals pass their eggs directly through the cloaca, taking any microbiota with them, most mammals have developed so that their birth canal is closely adjacent to the anus. In turn, this ensures at least a degree of contamination of the neonate and, if this hypothesis is correct, the transfer of such microbial sentinel cells could be better described as a faecal inoculation. The "missing link" of the title represents the problems that may arise when these microbial sentinel cells are not transferred at birth. In this hypothesis, therefore, birth may be considered to be the beginning of the development process, incorporating a biological equivalent of the computing term "handshaking": an interaction between the maternal microbiome and the neonate gut wall. Any interruption of this process may lead to the microbial malfunction, and its consequences, that are generically described as "dysbiosis". It is possible to imagine three potential routes to such an interruption, all of which represent aspects of the exposome:

(1) Antibiotics removing, or disabling, key maternal microbes
(2) Caesarean section delivery in an aseptic environment preventing transfer to the child
(3) Prior removal, either by points 1 and 2 above, or by external pollution, leaving subsequent descendants unable to pass microbial sentinel cells on to their children.

Definitions: It is important to note that, in this article, the terms "eubiosis" and "dysbiosis" are defined differently from the usual. (I thank the reviewers for encouraging me to emphasise this distinction early in the article.) Normally, the difference between the two is related to the concept of "balance" in that, while eubiosis represents a stable, "healthy" state, something that causes a drift away from such balance will tend to induce dysbiosis-related symptoms. In this article, by contrast, the focus is on those rare indigenous communities who do not suffer from such diseases. In turn, this implies that these people, as a whole, are eubiotic, while less fortunate populations contain a currently unknown proportion of dysbiotic individuals vulnerable to the onset of non-communicable disease.

A View of Food: As described more fully in the bulk of the article, along with mental and atopic/autoimmune problems, in this hypothesis the development of obesity is a function of a disconnect between the three primarily affected organs: immune system, gut, and brain. Weight gain may be prevented by malabsorption from a diseased gut, or by the development of an eating disorder, to pick just two examples. In other words, an "immune-gut-brain

triangle" may be a better overall description than a "gut-brain axis". Of course, this has immediate consequences for the design of placebo-controlled clinical trials if the "control" is actually the active component. In turn, these phenomena may help explain why people have such a variable response to their food: although there is nothing certain about dysbiosis, in general dysbiotic people are more likely to respond badly, while eubiotic individuals may, perhaps, remain unaffected regardless of the apparent "unhealthiness" of the food in question.

The Age of Obesity: Although these ideas are still tentative it could be that further investigation with, for example, ingestible sensors, will produce more robust definitions. As implied above, however, this version of dysbiosis has at least one unsettling consequence: if searching for healthy controls for a human study, and if dysbiosis applies at a population level, exactly who counts as "healthy"? In a sense, therefore, in a dysbiotic society individual health is an illusion, a state in which the potential for disease has not yet been made manifest. If so, the visible rise of obesity in ever-younger people is a concern.

Evolution: In essence, this article offers a historical perspective that puts the experience of "eubiotic" indigenous peoples in a position as close as possible to the assumed original evolved model of humanity. Accordingly, it is against this model that the majority, "dysbiotic", populations must be compared. Sadly, as noted above, the weakness of this historical approach to non-communicable disease is that it can be hard to distinguish real possibilities from mere speculation and, accordingly, it is important that experimental work to confirm or deny these hypotheses be undertaken as soon as possible.

Practical Opportunities: As outlined in the bulk of the text, I believe that there is sufficient circumstantial evidence to commence laboratory work, and that it should not require the construction of specialist facilities. Although there is nothing technically new, such work will require significant expertise, expense, and effort:

(1) Develop ingestible sensors to offer a real-time view of as-yet-unknown aspects of messenger chemical (semiochemical) communication in the intestine
(2) Explore brain stimulation to offset the effects of dysbiosis-associated intermittent inter-organ communication
(3) Undertake microscopic examination of swabs taken from new-born animals, including consenting humans, in order to directly detect these hypothetical microeukaryote microbial sentinel cells.

2. The Holobiont: The Microbiome as a Co-Factor for Evolution

Along with all the other living entities sharing our planet, *Homo sapiens* is the result of billions of years of evolutionary change. Charles Darwin (1809–1882) set the scene with his eminently sensible observations on the survival of the fittest, later gaining credibility with the principles of heredity outlined by Gregor Mendel (1822–1884). Another line of inquiry started in the 1920s when Frederick Griffith and his team, working on various versions of *Streptococcus pneumoniae*, found that they could transfer lethality to a harmless strain when it was grown in the presence of the degraded remnants of a heat-treated lethal strain [1]. Later work established that Griffith's "transforming principle" was a nucleic acid, rather than a protein, and that eventually fed into the current leading hypothesis that has been called the Modern Synthesis. Interestingly, this so-called "Neo-Darwinism" continues to attract criticism from within the broader field of evolutionary theory but, so far, it reigns supreme [2].

While Darwin was observing his visible creatures, on the opposite end of the size range Louis Pasteur (1822–1895) was starting his fermentation studies. Apart from bread, wine, and the other products of fermentation, in the context of the times it was hard to see anything "good" about microbes and, in due course, the field of bacteriology came of age with the postulates of Robert Koch (1843–1910). However, the germ theory of disease should not be considered to be completely watertight, and it is reasonable to ask: "what would it take to satisfy Koch's postulates in the modern age?" [3]. Indeed, fresh from his Nobel prize in immunology, the zoologist Élie Metchnikoff (1845–1916) was asking whether there was value in the lactobacilli, on the grounds that their consumption in yogurt seemed to be associated with long life. At the time, of course, these questions could not be answered, and the field was clear for the development of antiseptics and antibiotics alongside the improvements in hygiene, sanitation and, if deemed necessary, caesarean section delivery under sterile conditions that has characterised subsequent decades.

Toward the latter half of the 20th century the interrogation of genetic sequences became less expensive and more reliable, allowing us to unlock some of the mysteries of the world we live in. Carl Woese (1928–2012) helped to categorise a "three-domain system" (one of a number of ways to organise the various forms of life), describing the archaea alongside the bacteria as prokaryotes and with the eukaryotes (sometimes spelt as eucaryotes) including animals, plants, and fungi, belonging to the third domain [4] (Figure 1). By the turn of the millennium Woese was publishing his description of what he called the Darwinian threshold: that while multicellular eukaryotes ("above" the threshold) evolve by survival of the fittest, unicellular organisms ("below" the threshold), change by the uptake of mobile genetic elements [5]. In fact, we had long known about this method of bacterial "evolution" because the transforming principle of Griffith and his team was actually *S. pneumoniae* upgrading its

ability to survive in the lung of the mouse [1]. However, such was the excitement surrounding the discovery of nucleic acids as information-transfer systems that this so-called "horizontal gene transfer" of a mobile genetic element seemed to have been quite overlooked. Nowadays, of course, this situation has been brought firmly to our attention by the spread of antibiotic resistance to and from the external environment [6].

Although contemporaneous with Carl Woese, Lynn Margulis (1938–2011), was a very different character. Volatile and combative while he was systematic and phlegmatic, their fractious relationship may have prevented them from grasping the true value of their complementary findings. Margulis' early breakthrough came when she intuitively grasped the relationship between the three domains of life: that the mitochondria-containing eukaryotes are composed of an archaeal "chassis" propelled by a bacterial "engine", assembled so that neither are capable of long-term independent existence. Although her ideas went against the contemporary mainstream view, and proved difficult to publish [7], they were eventually accepted, albeit grudgingly. Not content with this hard-won victory, her next step was to study symbiosis on the multicellular scale, looking at the relationship between the economically important insects and their associated bacteria [8]. Sadly, this form of her "holobiont" (whole biology) concept proved too difficult to be convincingly demonstrated, although it is still being actively pursued [9].

Nevertheless, in the opinion of the Author, Margulis' holobiont approach can usefully be applied as a solution of the seemingly intractable problems facing the world in the modern age: that an antimicrobial-associated disconnect, a "missing link", between body and its attendant microbes leads to dysbiosis, a malfunction of the holobiont. It is likely that these microbes, generically termed "the microbiome", have developed as a defence against the outside world, i.e., that they are primarily a part of our immune system. Equally, while highly diverse intestinal bacteria (i.e., the bacteriome) have been associated with good health, the immune system may operate through microeukaryotes of various forms, under the generic term "sentinel cells". Rather than directly challenging the Modern Synthesis of Neo-Darwinism itself, however, it is probably better to consider a fully functioning, heritable microbiome to be a more flexible, readily modified co-factor for evolution [10]. There is one caveat, that the present Article deals with the enclosed intestinal microbiome of the vertebrates, leaving open the question of whether plants, fungi, or invertebrates also rely on a heritable microbiome (Figure 1).

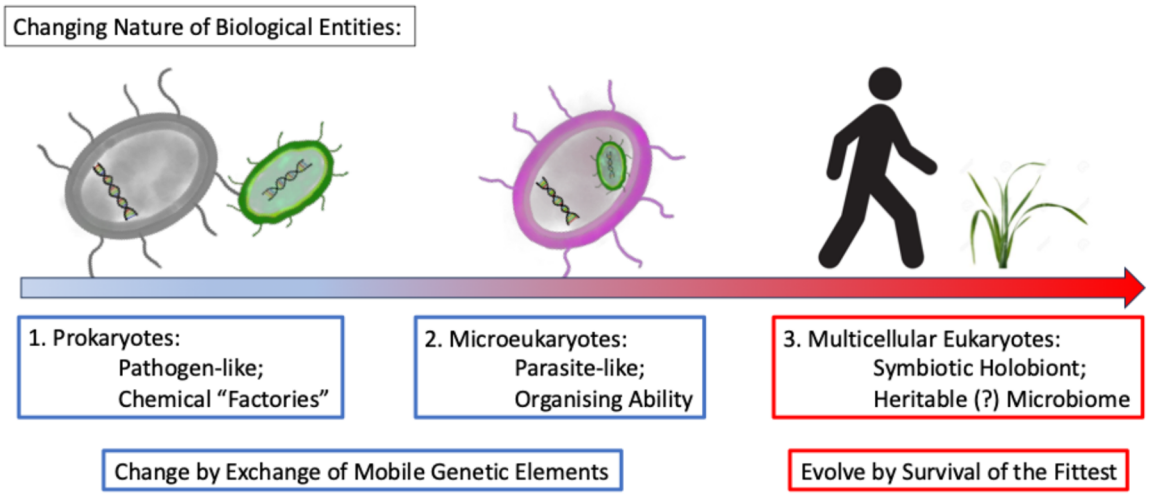

Figure 1. How forms of living entities change over time. Left hand side (blue outline—"below" the Darwinian threshold): Box 1. Carl Woese assembled the "three domain" approach to unicellular life: two prokaryotes: archaea and bacteria, and one microeukaryote [4]. Box 2. Lynn Margulis (writing as Lynn Sagan) showed that the third domain, the microeukaryotes, were derived by symbiosis of the first two [7]. Right hand side (red outline—"above" the Darwinian threshold): Box 3. Margulis later suggested a role for the holobiont as a unit of evolution, a symbiotic combination of multicellular host and microbiome guest, but was unable to prove her argument, at least within the field of evolutionary biology. However, the present Article envisages a Margulis-like holobiont with a heritable microbiome as a co-factor for the survival of vertebrate species. Source: Diagram by the Author.

3. Microbiome Function: Eubiosis versus Dysbiosis

Although, sadly, many practitioners in the field of non-communicable disease still give little credence to the intestinal microbiome, among those that do, a common opinion seems to be that the microbiome is a net provider of bodily energy requirements. In this Article, by contrast, the bulk of the food provided to the fully functioning intergenerational symbiotic intestinal microbiome is used by that entity itself, with any benefits supporting the holobiont as a whole. The gut wall is a go-between, nourished by both sides, and exchanging information about

the state of the body with the brain: health or illness, famine or pregnancy. The "virtuous circle" of Figure 2 illustrates eubiosis, when a child (or vertebrate animal equivalent) is born with a fully functioning microbiome. In return for an appropriate share of the available nutrition, bacteria produce "semiochemicals" (including interkingdom signalling molecules), hormone-like chemicals that activate ultimately brain-controlled mechanisms such as peristalsis in the gut wall. In particular, it will be noted that, in this hypothesis, a eubiotic body avoids obesity by the efficient removal of excess food energy in the form of microbial overgrowth, i.e., by faecal energy excretion (see Section 9) [10].

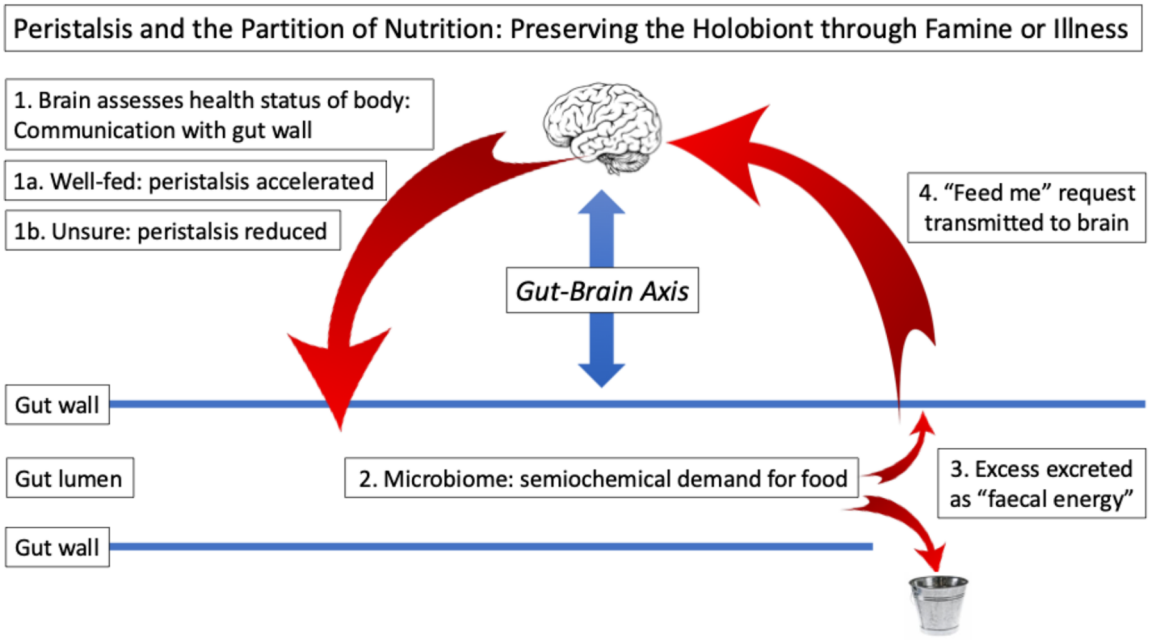

Figure 2. Peristalsis and the partition of nutrition. Box 1. It seems reasonable to suppose that the healthy holobiont allows constant communication along what has been termed the "microbiome-gut-brain axis". Box 1a. If both brain and gut report a healthy body, the acceleration of peristalsis ensures that the microbiome remains well fed. Box 1b. In famine, or if communication is interrupted for any reason, the brain has to assume the worst and slows peristalsis until health and communication is resumed. Box 2. In essence, the microbiome uses messenger chemicals, semiochemicals, to request food from the body, albeit that the message may be modified through the various stages of pregnancy. Box 3. Of course, defecation in humans is a socially charged act, requiring delay until an appropriate level of privacy can be assured. Accordingly, final approval must come from the brain, through the gut-brain axis, before this latter stage of peristalsis can be accomplished. Box 4. This step represents the possibility that eubiotic microbiome-gut-brain communication actually proceeds in two steps, microbiome to gut wall, then gut wall to brain. It could be that the more commonly encountered dysbiosis gives the impression of direct microbiome to brain communication. More studies on wild-born eubiotic animals will be needed to resolve this point. Source: Taken from Smith [10], under CC BY 4.0, used with permission.

As will be seen below, this holobiont interpretation necessitates a dual inheritance in that, not only are the genes of the parents being passed on, but so too is a functioning microbiome. Over the years, however, as humanity has made birth less dangerous to both mother and child, this dual inheritance capability has been lost, and children are increasingly born with dysbiosis, a malfunctioning microbiome. Accordingly, this definition of dysbiosis offers a succinct explanation of the observed "triple plague" of non-communicable disease, in three basic categories:

(1) A kaleidoscope of immune system problems, often first seen as eczema in the baby
(2) So-called "neurodevelopmental" mental health issues, such as autism in the young child
(3) Irritable bowel syndrome and, potentially, obesity, often seen in primary school

On an individual level, of course, while behavioural aspects are most amenable to modification, experience tells us that neither diet nor exercise may be seen as a "magic bullet". In particular, bearing in mind that the degree of holobiont malfunction may well vary at different times, and between different individuals, care must be taken on the quantity as well as the quality of the diet. On the scientific level, more attention must be paid to the fact that, on average, humanity is changing from one generation to the next, that the general idea of the "healthy

control" is not a well-defined concept, and that these phenomena help explain why gene-based twin studies may be less useful than anticipated [10].

So far, we have seen that the concept of the microbiome can be interpreted in the light of the seminal findings of Lynn Margulis [8] and Carl Woese [5], and that diseases related to the microbiome can be understood by dysbiosis, the failure to transfer key components from mother to child in the sanitised conditions of modern birth [10]. While pockets of apparently eubiotic peoples do survive into modern times, such as the Tsimane of the Bolivian Amazon, remarkably resilient to the COVID-19 epidemics [11], the majority of the world population have been born dysbiotic, with dysregulation of biological systems associated with immune system, brain, and gut [12]. Indeed, it is worth noting that, at some point, probably in the mid- to late- 20th century, there will have been a transition in which the results of population-based studies will have changed from representing majority eubiotic to majority dysbiotic individuals.

4. The Intergenerational Intestinal Microbiome: Maternal Microbial Inheritance

The colon, the large intestine, is a mysterious organ. Textbooks tell the reader that it has a three-fold function: to pass water and salts back into the body; to shelter bacteria for the production of vitamins; and to form and expel solid waste. Sadly, the microbiome is not quite ready to take its full place in the textbooks. A recent review on current knowledge about "microbiota dysbiosis" mentions homeostasis (presumably including water and salts) but also notes an ill-defined role in regulating immune function [13]. In the current work it is the prime purpose of the fully functioning microbiome, as a part of the holobiont, to help the next generation survive. In the above scheme (Figure 2), the "eubiotic" microbiome communicates primarily with the gut wall, which acts as an intermediary for further communication, whereas disruption of barrier function [14] is more likely to be an eventual consequence of dysbiosis at birth. By contrast, components such as the short-chain fatty acids acetate, propionate, and butyrate provide energy to the cells lining the intestine, cells which are directly involved in further microbiota-body interactions [15]. The same basic principle may apply to enteroendocrine cells, situated inside the intestinal epithelium and also fuelled by short-chain fatty acids [16]. Unfortunately, as Harald Brüssow has pointed out in a 2020 article: "Problems with the concept of gut microbiota dysbiosis", an equivalent of Koch's postulates has never been formulated for the relationship between "guest" microbiome and "host" body [17]. Overall, therefore, the gap between microbiome-related science and medically relevant textbooks is explained by the need for experimentally testable, falsifiable mechanisms exploring the role of the gut microbiota.

In this Article, a prime function of the vertebrate microbiome is to accumulate information about the maternal microbial environment, eventually passing this information on to her child (either live or via the egg) in what can be best described as a maternal microbial inheritance. Rather than exclusively in the form of live bacteria, this information may come at least partly in the form of mobile genetic elements, such as those responsible for the spread of antibiotic resistance [6]. Another example, mentioned earlier in the text, is the transforming principle uncovered by Griffith and his team [1], illustrating a mobile genetic element with the ability to neutralise bodily defences. However, it must not be thought that such mobile genetic elements are all about pathogens. Since around 2010, researchers have been tracking the flow of carbohydrate-active enzymes (CAZymes), from bacteria feeding on seaweed to bacteria living in human gut microbiomes. Specifically, it seems that enzymes utilised by a marine bacterium, *Zobelia galactanivorans*, have been transferred to bacteria resident in the human gut, presumably by horizontal gene transfer, i.e., without *Z. galactanivorans* itself still being present [18].

As the above CAZyme example illustrates, the role of mobile genetic elements (MGEs) may be more important than the bacteria themselves, potentially spread by bacteriophage-induced bacterial destruction and reassembly within the confines of the intestine. First observed in the sea [19], and more recently, in microscopic spaces in the soil [20], this "viral shunt-like" mechanism allows bacteriophage-produced fragments to be reassembled into new bacteria, picking up MGEs in the process [10]. They have drawn increasing interest in recent years, operating both within microbial populations [21], and between them, from one such MGE to another [22]. Of course, horizontal gene transfer from unicellular into multicellular entities has long been known, but finding plant genes in sap-sucking insects was, nevertheless, a surprise [23].

In evolutionary terms, it could be argued that, after a "skin" (i.e., a multicellular eukaryote partition) has formed to separate one microbial community from another, there would arise a need to coordinate the microbial community with its emerging multicellular entity. Indeed, in all likelihood, the first organ of this newly formed organism would be a nascent immune system. Possibly the most famous case of microeukaryote-induced control is of vertebrate brains by the action of the obligate intracellular protozoan *Toxoplasma gondii*. While there is little doubt about it altering the feline-related behaviour of its rodent intermediate host, the exact details are not clear [24]. Nevertheless, this emphasises the significance of the present-day unicellular eukaryotes, some behaving as guardian "sentinel" cells [25]. Of these, perhaps the most flexible are the dendritic cells of the innate immune

system [26], cells whose function it is to physically transfer antigenic information from the innate to the adaptive immune systems. Indeed, such cells have been found in the earliest extant representative of the vertebrates, the fish [27] and we have suggested that similar "microeukaryote microbial sentinel cells" could exist inside the fully functioning vertebrate microbiome [10]. In this case, their role would be to transfer information from maternal microbiome to neonate gut wall. Interestingly, in the same fashion as the analogy between biological and computer "viruses", there could be a biological equivalent of the computing term "handshaking", the exchange of the "protocols of communication" which takes place prior to the full merger of two electronic devices. Such biological handshaking would be between two evolved chemo-electronic devices, the maternal microbiome on the one hand, and the infant gut wall on the other (Figure 3) [10]. It seems likely that a fully incorporated microeukaryote microbiome would be able to control remote "microbiomes" around the body, such as the skin, for example. Indeed, work on acne vulgaris seemed to establish an "axis" between gut, brain and skin that manifests itself alongside depression and anxiety [28].

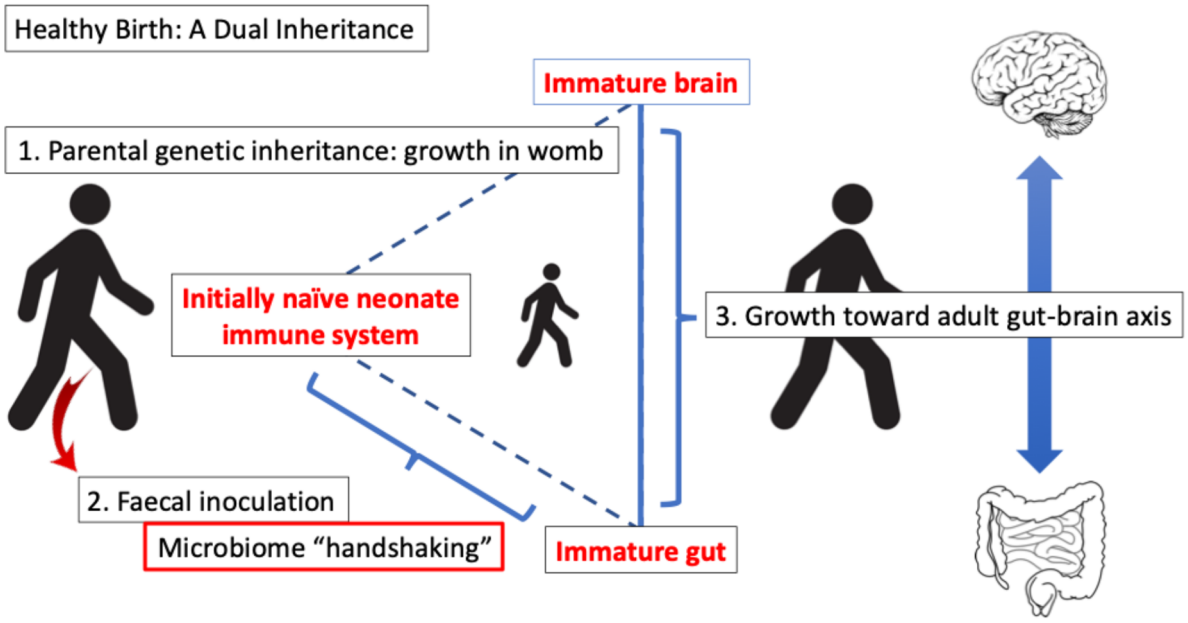

Figure 3. A healthy birth, a dual inheritance. Box 1. The foetus grows according to its parental genetic inheritance, producing an immature brain and gut, along with an initially naïve immune system (red writing). Box 2. Faecal "contamination" is also an "inoculation" by microbial sentinel cells contained within the maternal microbiome, eventually connecting with the neonate gut wall by a biological handshaking process. Box 3. All being well, the brain and gut grow together, interlinked with the immune system, to develop the so-called gut-brain axis. Source: Taken from Smith [12], under CC BY 4.0, used with permission.

In this scheme, "faecal inoculation", the timely transfer of microbial sentinel cells from vertebrate mother to her child at birth (via the egg if appropriate), interacts with the gut wall of the child, effectively calibrating its immune system and initiating growth of the gut-brain axis. The resultant "eubiotic" state (i.e., a fully functioning microbiome) is represented by the above-illustrated "immune-gut-brain triangle". Efficient communication from birth allows the gut and brain to coordinate peristalsis (cf. Figure 2), in addition to providing feedback to guide the growing brain of the infant. Dysbiosis, the absence of a microeukaryote control mechanism from birth, has both mental health and immune system consequences [12], however the most physically obvious corollary is obesity. Although lifestyle modification has been extensively assessed, in recent times our best counter to obesity is to rely on chemical control in the form of the GLP-1 receptor agonists and related substances. In fact, these typically produce a fall of food intake of between 16% and 39% [29]. It is interesting to note, however, that not everyone accepts that the causes of obesity are fully understood. In particular, in his 2022 article entitled "Perspective: Obesity-An Unexplained Epidemic" the influential cardiologist Dariush Mozaffarian has stated that "it is critical for the scientific community to consider and test alternative hypotheses" to explain the causes of obesity [30].

5. Mind the Gap: The Missing Link

As we have seen, in this hypothesis the terms eubiosis and dysbiosis are complementary within the context of the microbiome. In this work, the term dysbiosis implies that, for whatever reason, the "guest" microbiome is

not working efficiently with its "host", the vertebrate animal body. It is important to note, however, that this interaction is fundamentally intergenerational, starting from birth [10]. Accordingly, people born with a fully functioning microbiome are "eubiotic" and, by this definition, are incapable of suffering from microbiome-related non-communicable disease. By contrast, "dysbiotic", being born with a malfunctioning holobiont, requires genetically inherited propensities and inappropriate behavioural tendencies, along with some sort of trigger, to develop actual disorders. For example, is hay fever, a non-contagious autoimmune-related condition, actually a disease or merely a nuisance? In this way we have the bewildering array of observed conditions, of varying degrees of seriousness, each virtually unique to the sufferer themselves.

Unfortunately, there is no general test for dysbiosis in any specific individual, aside from the presence of non-communicable disease itself, so for general discussions terms such as "*Homo sapiens* (eubiosis)" or "*Homo sapiens* (dysbiosis)" may, perhaps, be employed, noting that the lack of italics implies no change in underlying genetic inheritance. The same applies to *Mus musculus*, for example, the standard species of mouse raised for laboratory studies. Again, mice in the wild may be assumed to be *M. musculus* (eubiosis), whereas birth under laboratory conditions would, most likely, afford *M. musculus* (dysbiosis). The difference is not trivial, as illustrated by a recent case in which two sets of genetically identical animals were sourced from different suppliers, but related experimental results were different. Careful FMT (faecal microbiota transplantation) studies identified inflammation-related differences [31]. Needless to say, there will be more such cases, going undiscovered if the animals (probably homogeneously dysbiotic) are sourced from the same supplier.

Interestingly, it is possible to imagine the two components of the holobiont, multicellular body and microbial community, to be an analogy to organelle-containing eukaryotes, in that the genetic functions of both components are pared down to the minimum necessary. Note, however, that that would also imply that neither "body" nor "microbial community" are independently viable in the long term. If true, the observed world-wide fall in fertility rates would have a more fundamental "dysbiotic" explanation than the usually quoted socioeconomic model [32]. Notably, increasing rates of delivery by caesarean section will contribute to ongoing dysbiosis by breaking the maternal microbial inheritance link between generations. A tally published in 2021 indicates that, overall, about 20% of births were by C-section, varying between 5% for sub-Saharan Africa and 42.8% in Latin America, with a projection that, by 2030, a total of about 28% (i.e., 38 million) births will be by this method [33]. It is important to note that an intergenerational microeukaryote microbial sentinel cell would be unique to us and, therefore, cannot be expected to be picked up from the environment. In other words, dysbiosis is irreversible [10].

To summarise, this hypothesis suggests that the absence of such cells causes a delay in both immune system calibration and the growth of connections. The net result is illustrated by the dotted lines in Figure 4, below, representing a weakening of communication between immune system, brain, and gut. It is important to note that such "dysbiotic" weakening does not necessarily correspond to overt disease which, kaleidoscope-like, often follows from a change in circumstances, including puberty, pregnancy, giving birth, menopause, infection, or even apparently spontaneously [12]. Immune conditions are particularly susceptible. Autoimmune disease can start very early, with the so-called "atopic march" [34] potentially giving rise to eczema as soon as the first month of a child's life. Conversely, type 1 diabetes, normally thought of as a disease of the young, can remain "latent" until late in adulthood [35]. Very often the precipitating cause is unclear, and even reversible, as in the case of the various relapsing-remitting autoimmune diseases. It has been suggested, for example, that remission may be associated with a high recovery rate of affected tissue, although this is by no means certain and, likewise, the presence of autoantibodies is not necessarily related to overt disease [36]. Finally, while cancer may similarly resolve itself, this rare phenomenon is probably associated with immune system alterations [37].

The transfer of dysbiosis from mother to child is illustrated by Figure 4, indicating that, if key cells are not present in the mother, even a vaginal delivery means that they cannot be passed on to her child. In this way the triple plague mentioned above (Section 3) follows from the breakdown in "biological handshaking" connections between the three organs of brain, gut, and immune system. The fragility of the gut-brain axis is particularly pernicious as brain growth, like the growth of muscles, requires constant input. Accordingly, failure at birth can lead to neurodevelopmental-like diseases, along the lines of autism spectrum disorder, or increase the propensity for conditions such as depression in later life.

While bacteria help to carry mobile genetic elements from maternal microbiome to the neonate, in the womb the foetus is protected by both the innate and adaptive components of the maternal immune system, some of which will be built into the neonate itself. However, the immediate need is for the innate immune system to be working as soon as possible during the birth process, and, for this reason, it seems that the faecal inoculation of Figure 3 will have evolved. It is likely that the distinction between self and non-self is formulated during the handshaking phase and, if so, its absence described by Figure 4 will help account for the increasing levels of immune system problems seen across the world in recent decades [12]. Interestingly, although quorum sensing is normally studied

in bacterial biofilms [38], and bacterial-fungal interactions have gained attention more recently [39], it is possible that dysbiosis is actually precipitated by a critically reduced "quorum-like" concentration of maternal microbial sentinel cells, rather than initiated by their complete absence.

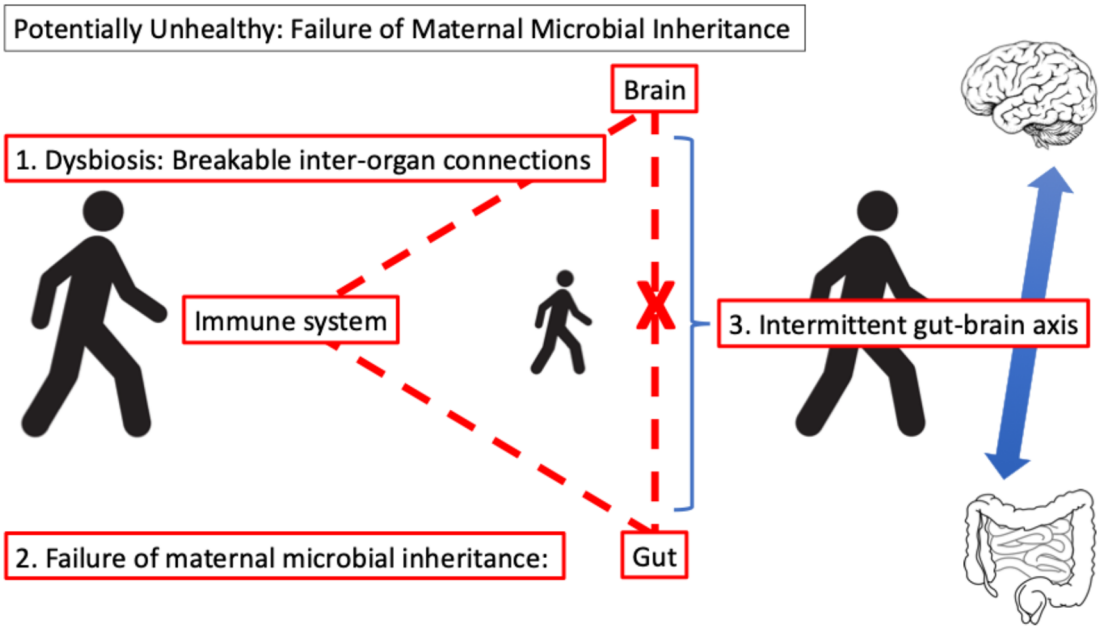

Figure 4. An unhealthy birth, absence of maternal microbial inheritance. Box 1. Although growth inside the womb goes according to plan, healthy connections in the neonate require prior biological handshaking. Box 2. The necessary microbial inheritance may be prevented either by prior disturbance from maternal antibiotic treatment, by interdiction of transfer by C-section delivery in a hospital setting with antiseptics, or by absence due to prior loss in the grandmother or earlier female ancestor. Box 3. Subsequent growth of the brain requires a stable gut-brain axis and, accordingly, intermittent connection may give rise to later "neurodevelopmental" or mental health issues. Source: Adapted from Smith [12], under CC BY 4.0, used with permission.

6. Destroying the Link: Caesarean Section, Colectomy, and Toxins

Currently, the primary explanation for the increase in non-communicable disease remains focused on the idea that our ancestral genetic inheritance is, somehow, incompatible with elements of the modern world. The idea of the exposome, the sum total of all the environmental exposures that will affect our genes over our lifetime, is a massive undertaking [40] that has recently reached its 20th birthday [41]. Interestingly, it was also about twenty years ago when the microbiome field started to become more important, with people such as Martin Blaser beginning to link the presence of non-communicable disease with the use of antibiotics [42]. Accordingly, it seems that both exposome and intestinal microbiome (bacteriome) were simultaneously developed by independent groups with very different philosophies in response to the perceived failure of the human genome project. Sadly, the last twenty years has demonstrated that the bacteriome is at least as complicated as the exposome, neither having reached clinically useful conclusions.

Delivery of babies by C-section under sterile conditions, by separating the baby from its mother's microbes, can be considered as part of the exposome [40], and can reasonably be expected to lead to dysbiosis [43]. Although negative outcomes from C-section delivery are rarely checked, a recent study reported from Taiwan is an exception. Unlike long-term "Westernised" countries, "highly developed" for generations, Taiwan achieved this status only recently in human life terms. Accordingly, a large part of the population may well be eubiotic and a "dysbiotic signal" from C-section delivery should be relatively readily detectable. In fact, as their conclusion states: "higher risk of asthma, allergic rhinitis, atopic dermatitis, respiratory tract infection, and obesity in offspring than those delivered by VD" (VD being vaginal delivery). They go on to say: "among these, obesity has the strongest association with CS" (CS being C-section delivery). Interestingly, they also state: "although this association (i.e., with obesity) was modest, considering the increasing rate of caesarean section in Taiwan, especially elective CS, the modest increase in risks in this study may also translate into a substantial excess burden of morbidity" [44]. The authors' also note that these diseases were diagnosed in childhood, whereas dysbiosis represents a lifetime risk of non-communicable disease.

If C-section delivery is recognised by the exposome model, the next step up, a total colectomy, the complete removal of both gut and microbiome, is more draconian. Paradoxically, however, there is no reported microbiome-specific disease in this population. Although the inconvenience of a stoma bag requires some adjustment, including a more careful approach to food, otherwise life proceeds as normal. Bear in mind that the bulk of people in this position were affected before the largely successful faecal microbiota transplantation methodology came into general use. Accordingly, this older population would have a greater proportion of eubiotic individuals with fewer non-communicable conditions. In turn, this reinforces the idea that the primary function of the microbiome acts at birth [10]. Fertility is not compromised [45] and women can give birth without the need for C-section delivery [46]. Unfortunately, children born to a mother without a microbiome will, of necessity, be born with dysbiosis but, so far, there is no indication that they suffer any more than their peers born into their Westernised, highly developed, dysbiotic environment.

Surprisingly, perhaps, there are certain parts of the world that have scarcely been touched by this "Westernisation" process and, even more surprisingly, some have agreed to cooperate with medical teams without excessive compromise of their own behaviour. It is, however, highly likely that such peoples will use the antibiotics, antiseptics and C-section delivery under sterile conditions that are the hallmarks of Westernised medicine. Accordingly, it will be interesting to see if their health also begins to degrade with each passing generation.

With their permission, the health of the indigenous Bolivian Tsimane and related peoples has been studied since 2002, setting up the Tsimane Health and Life History Project, to be able to test competing hypotheses of human life-history evolution [47]. Of course. the COVID-19 epidemics represented a severe test of their resilience as their peers in other indigenous societies suffered badly. While the Tsimane were offered COVID-19 vaccination, the scattered nature of their communities meant that the early waves of the epidemic travelled too fast for them to be effectively vaccinated. Interestingly, however, a recent extensive report confirmed their remarkably low mortality, with only 1 out of 23 of the deaths expected under normal circumstances. The authors suggest that these people survived due to a "more vigorous and effective immune response to infection" [11]. In this Article the suggestion is that, rather than eubiotic indigenous people having a vigorous response, modern day, largely dysbiotic people suffer badly, for the same reasons that bring about their high levels of autoimmune disease. Unfortunately, the term "vigorous response" is not necessarily helpful and could be used to describe the over-response known as a cytokine storm which, in all-too-many cases, including COVID, leads to the death of the sufferer [48]. What is needed is an accurate immune response and, in this Article, that results from eubiosis, the transfer of a fully functioning microeukaryote sentinel cell microbiome by faecal inoculation during birth [12].

As stated above, the exposome concept is, perhaps, too wide to be useful, even in this age of mass data. Exposure to substances of known toxicity make negative effects more likely, of course. As suggested below, the very early use of toxic cosmetics [49], the later use of pewter eating utensils [50] and, much later, the addition of tetraethyllead to petrol [51], will probably have led to the accumulation of dysbiosis-related health issues cumulating in the 21st century.

7. The Start of the Breakdown: John Bostock and the 19th Century

Like so many people in the modern world, in the early summer of 1781 a child sneezed. Unlike in the modern world, however, John Bostock (1772–1846) found that he was the only one in this situation. Accordingly, in 1819, as an established kidney specialist, he published his symptoms on what he called *catarrhus aestivus* (summer catarrh, currently known as hay fever or seasonal allergic rhinitis) [52]. His colleagues were baffled and, after nine years of patient inquiries, he published his epidemiological findings: that across the length and breadth of the British Isles, there were only 28 cases, specifically stating that they were all from the "highest ranks of society", and none from the poor [53]. While Bostock's was the first example of autoimmune disease reported in the modern style, an archaeological example from 1st century Italy showed evidence of coeliac disease in the skeleton of a young lady from a richly endowed tomb [54]. Interestingly, the authors of this latter paper discuss "predisposing haplotypes" but, although the underlying genetics can indicate the type of condition that may arise, dysbiosis increases the probability that some environmental trigger will eventually bring about actual disease. As indicated above, the ladies from richer families of the times would have been using toxic cosmetics [49] and everybody above a certain class would have had access to toxic metal utensils [50]. Constant, low-level exposure to such metals probably accounts for Bostock's "highest ranks of society" epidemiological findings [10].

Alongside the rise of still-uncommon hay fever, relative riches brought a more visible problem: obesity. William Banting (1796–1878) was born into a family of undertakers to the Kings of England and found that, once he had put on weight, it stayed there. Eventually he tried what we now know as a "low carb" diet, losing significant amounts of weight which, in his case, did not return. He became famous by issuing an open letter in 1869, thus illustrating the

growing need for a solution to obesity, if only among the richer classes of the people of his day [55]. This was an era in which the principles of physics and chemistry were sparking the imagination of the public and a statistician named Adolphe Quetelet (1796–1874) developed a measure that we now know as the body mass index, the BMI (body mass, in kilograms, divided by the square of height in metres). Although intended to compare populations it satisfied demand from an increasingly weighty population and was inevitably adapted, with all its faults, to compare individuals [56]. In this new scientific age an American physician, Lulu Hunt Peters (1873–1930), solved her own obesity problem with the aid of a 1200 kcal diet, publishing her findings in newspaper columns and, eventually, in book form as "*Diet & Health: With Key to the Calories*" (1918). "Counting calories" was here to stay [57].

By the beginning of the 20th century, with the onset of quantum mechanics, that most mathematical of the sciences, physics, was getting complicated. However, perhaps even advanced mathematics pales into insignificance beside the third of the modern non-communicable diseases, poor mental health. In this context, the "distinctive" suggestions of Sigmund Freud (1856–1939) scored a success on at least one count, that problems start from an early age. A second point is that, living and working in Vienna, it was not surprising that he only had rich clients. In fact, as with John Bostock, many were very rich indeed but, in spite (or because) of the unlikely nature of his hypotheses, he seems to have been very successful [58]. Of course, he was not to know about 21st century concepts, of dysbiosis and of the gut-brain axis. In all likelihood the idea of the immune-gut-brain triangle degradation of Figures 3 and 4 would not have surprised him.

8. Dietary Fibre: Denis Burkitt in the 20th Century

Denis Burkitt (1911–1993) attended the same Edinburgh medical school as did John Bostock more than a century earlier, but his curriculum was vastly different, including essentially all the types of non-communicable diseases known today. Posted to Africa in the Second World War, he later returned to that continent, using his skills as a surgeon and taking copious notes. He discovered a cancer of the jaw in children, Burkitt's lymphoma (originally seen as a sarcoma [59]). Burkitt's most perplexing discovery was the fact that the non-communicable diseases that he so painstakingly learned in Edinburgh simply did not exist in many of the peoples he studied. Although Table 1 represents a list of the diseases mentioned by Burkitt as "Some Diseases Characteristic of Modern Western Civilization", it is unlikely that this list is meant to be exhaustive. While some, such as multiple sclerosis, can be looked on as exclusively immune system-related, he considers the bulk of these problems to be curable with sufficient dietary fibre. However, he had no idea about the cause of immune system disease and, consistent with the bulk of 20th century attitudes, he doesn't mention mental health at all [60]. Finally, he states that such Westernised individuals can suffer from several of these diseases at once, a fact which is consistent with the malfunctioning immune-gut-brain triangle model illustrated by Figures 3 and 4 [10]. Indeed, it is feasible that Burkitt's traditional peoples would have resembled the Tsimane of today [11].

Table 1. Burkitt's "Some Diseases Characteristic of Modern Western Civilization" [60].

Appendicitis	Coeliac Disease	Coronary Heart Disease
Deep vein thrombosis	Diabetes, type 2	Diverticular disease
Gall stones	Haemorrhoids	Hiatus hernia
Multiple Sclerosis	Obesity	Pernicious anaemia
Pulmonary embolism	Rheumatoid arthritis	Thyrotoxicosis
Tumours of the bowel	Ulcerative colitis	Varicose veins

Burkitt became convinced that a lack of dietary fibre in "Westernized" diets was the primary cause of non-immune system disease because, much as today, the primary focus on the cause of diabetes was thought to be the overconsumption of sugar and white flour. In fact, Burkitt himself knew that this could not be the whole story because one such people, the Maasai (Masai in his day), lived as cattle-herders on the East African savanna grasslands and, although consuming a Western-style low/medium fibre diet, stayed healthy [60]. Interestingly, in Burkitt's day, as now, a propensity for obesity implies that you have a problem with your diet and, although the focus has shifted from white flour to so-called ultraprocessed foods, the basic principle remains the same. Nowadays, for example, "highly processed" foods may be considered to be addictive [61] while "ultra-processed" represent a modifiable risk factor for dementia, as well as having negative effects on level of attention although, in one study at least, they apparently left memory unaffected [62]. Overall, however, evidence of direct harm is far from satisfactory, with the actual balance of ingredients most likely to be the problem, rather than the processing itself: soft texture and high calorie density often found alongside low dietary fibre and low protein content [63]. In fact, the people described by Burkitt [60] seem very similar to the Tsimane mentioned above [47] and, being

without autoimmune disease, it is likely that they would have similarly survived a COVID-style epidemic [11]. It seems that our problems may run deeper than diet.

Not surprisingly, perhaps, the apparently bizarre nature of non-communicable disease continued to perplex scientists long after the end of the 19th century. The public health epidemiologist David Strachan published a paper in 1989 which seized the attention of the general public as the Hygiene Hypothesis: "Hay fever, hygiene, and household size" [64]. His insight was that something in the external environment helps to calibrate our immune system to distinguish self from non-self, harmless from harmful. Later, the immunologist Graham Rook picked up the challenge of finding these hypothetical co-evolved external agents which he termed "Old Friends". Sadly, his search proved fruitless [65]. A few hours' drive down the M3 motorway from London brings one to Southampton where, almost simultaneously with David Strachan, the clinical epidemiologist David Barker was penning his paper: "The fetal and infant origins of adult disease". His studies led to the term "Fetal Origins Hypothesis", including schizophrenia in the range of non-communicable diseases that seem to start *in-utero* [66]. The situation at the end of the 20th century is summarised by Figure 5, illustrating a dawning appreciation of the danger.

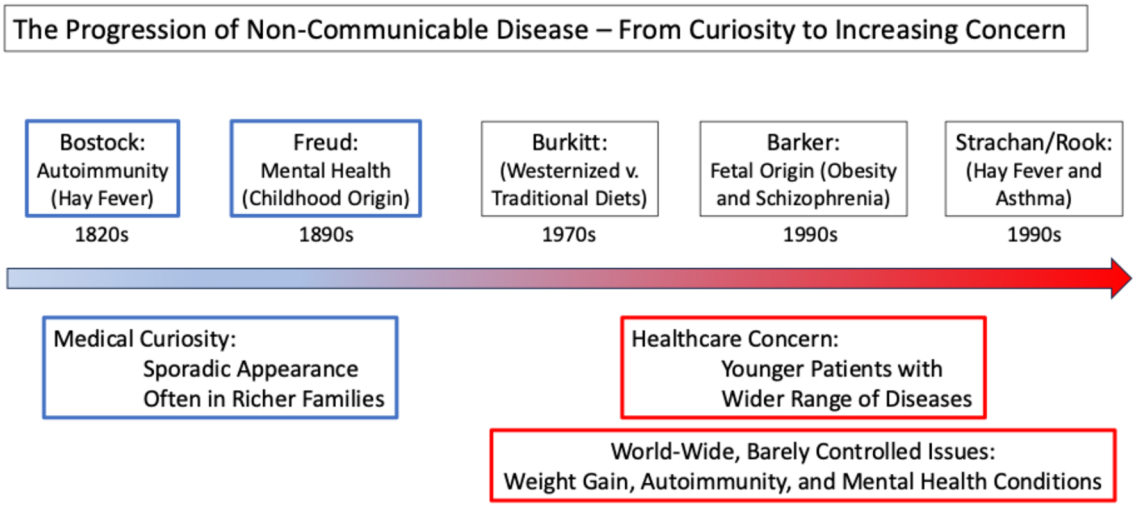

Figure 5. The progression of non-communicable disease. Left hand side (blue outline): the 19th century findings of. John Bostock [52] and Sigmund Freud [58] generated more interest than alarm. Top right (thin outline): The observations of Denis Burkitt [60], David Barker [66], David Strachan [64] and Graham Rook [65], emphasised growing levels of concern as the 20th century progressed. Bottom right (red outline): By the 21st century increasing levels of strain were becoming evident as ever-younger patients with more complex conditions were putting health services at risk of collapse across the world. Source: Taken from Smith [12], under CC BY 4.0, used with permission.

9. Food and Exercise in the 21st Century: Faecal Energy Excretion

In the year 2007 the official sounding "British Nutritional Foundation (BNF)", actually an industry advocacy body, was celebrating its 40th anniversary. Their researchers estimated that food energy consumption peaked in the 1950s at 2660 kcal/person/day. Paradoxically, intake in 2007 had slumped to only 1750 kcal/person/day, during which time people had, on average, got noticeably heavier. Although without any supporting evidence, they suggested that this fall is "in line with declining levels of physical activity", connecting the problem with access to motor cars, television viewing, and computer gaming [67]. Interestingly, a 200-year anniversary edition of the New England Journal of Medicine (published in 2012) reported that, in their 1912 issue, the Journal was anticipating a future epidemic of obesity based on the spread of labour-saving devices such as lifts and, indeed, the ubiquitous automobile [68]. While there is little doubt that we have been getting heavier, our understanding of biology, chemistry and physics seems to give us only two choices: either we eat too much, regardless of the researches reported by the BNF, or we "burn" too little, by doing insufficient physical activity. Significantly, the product of metabolic "burning" is carbon dioxide, which can most efficiently be measured within enclosed cage environments. Sadly, these are not representative of normal behaviour, at least at the population level.

Water is composed of two elements, both of whom have stable isotopes: hydrogen with hydrogen-2 (also known as deuterium), and oxygen with oxygen-18. Normally, of course, water is freely absorbed by the body and just as freely lost, so the addition of an aliquot of water containing a known amount of hydrogen-2 would allow the measurement of the rate of loss of water, by mass spectrometry, as the body goes about its normal business. By contrast, the addition of a portion of oxygen-18 labelled water would lead to a greater rate of loss as oxygen

atoms are lost both as water and as carbon dioxide. Accordingly, addition of an aliquot of doubly labelled water, with known amounts of both hydrogen-2 and oxygen-18, gives a measure of total energy expenditure (TEE) by mass spectrometric comparison of the rates of loss of deuterium versus oxygen-18. After initial studies on smaller animals, eventually mass spectrometry became accurate enough for this technique to be used on humans [69].

While the British Nutritional Foundation (BNF) researchers were collating information for their 2007 article, a very different set of researchers, Klaas Westerterp and John Speakman, were collating their results on the other side of the North Sea, in the city of Maastricht, Netherlands. Their aim was to document the above isotopically labelled experiments determining total energy expenditure across the previous 20 years. This time period was chosen because, firstly, the data was available from earlier measurements on the population of Maastricht itself and, secondly, because the period saw a steep rise in the prevalence of obesity in both Europe and in America. In a carefully argued paper, in the light of the health issues facing the world, their conclusions were spectacular. These were published in 2008 and are worth repeating in full: "As physical energy expenditure has not declined over the same period that obesity rates have increased dramatically, and daily energy expenditure of modern man is in line with energy expenditure in wild mammals, it is unlikely that decreased expenditure has fuelled the obesity epidemic" [70]. Although they also point out that estimates of energy intake are largely self-reported, and therefore unreliable, in the present Article it is considered unlikely that the BNF could be so far out in their estimation. Could it be that both are right, that, by some unknown mechanism, while the energy used in activity has remained essentially the same over this time, food intake has sharply decreased, and yet obesity has increased?

Although faeces clearly contain chemical energy, with one exception the general assumption has been that its contribution to the overall energy balance is negligible. While this may be true in present-day dysbiotic societies, it may not be true of the eubiotic societies of earlier times. Accordingly, a better picture of overall energy balance may be expressed by Equation (1):

$$\text{Energy intake} = \text{Energy used (converted to carbon dioxide, } CO_2\text{)} + \text{Energy excreted (faeces)} \quad (1)$$

Please note that this equation relates to a steady state for an individual. As dysbiosis sets in across a society as a whole, however, a decrease in faecal energy excretion leads to a steady weight gain, not completely captured by a single equation.

The most logical explanation for the drop between the estimated average 1950s energy intake (2660 kcal/day) and that of the 2000s (1750 kcal/day) is a substantial fall in faecal energy excretion which, of course, few researchers measure [10]. Interestingly, neither of the two primary models of obesity emerging from the past decade, the "energy balance model (EBM)" and the "carbohydrate-insulin model (CIM)" mention faecal energy excretion, instead presenting mechanistic options in ever-greater depth [71]. The key test for any model is experimentation and, for equation 1, the experiment has, in a sense, already been done. Among the many observations made by Denis Burkitt was a comparison between the stool consistency and average faecal weight of the peoples living their traditional lives, free from non-communicable disease, compared to people suffering from what he termed "Diseases Characteristic of Modern Western Civilization" [60]. Burkitt states that these former people "often average 400–500 g of soft, unformed stool daily" whereas people eating what he called "low residue diets", by which he means people living in Westernised societies, produce "under 150 g of firm, formed stool" [60]. More recent work (reported in 2015) gives a figure of 130 g/person/day for high income countries [72], the apparent drop since Burkitt's day perhaps representing the increase in levels of dysbiosis over the intervening decades. The dramatic difference between these two sets of people is illustrated in Figure 6. As mentioned earlier, however, when Burkitt refers to "traditional" diets he means high dietary fibre, whereas he recognised that the Maasai, living their traditional lives, ate a relatively low residue diet and yet stayed healthy [60].

Interestingly, recent research has shown that transit time and stool energy density varies considerably with enterotype-related gut microbiome ecosystem variations, at least among Western-type obese individuals [73]. While there is little doubt that the gut microbiome does influence energy metabolism in humans, there remains considerable confusion as to exactly how this feat is achieved. A common expression is the "harvesting" of energy from the gut microbiome, with little consideration of faecal energy excretion [74]. Of course, it is possible that traditional peoples with lower levels of obesity, such as the Tsimane [75] and the African Hadza [76], who exhibit high microbial diversity, may show different enterotype correlations and greater levels of faecal energy excretion. On the whole, it seems reasonable to suppose that peoples living their traditional lives free from non-communicable disease should, most likely, be classed as eubiotic, with a fully functioning microbiome from birth, whereas the "Westernised" peoples who are prone to suffer from such diseases are dysbiotic. Significantly, the data published by the BNF in 2007 [67] strongly suggests that we have been increasingly dysbiotic between the 1950s and the 21st century. It remains an open question as to how many of the more recent scientific studies should be reinterpreted in the light of this hypothesis [10].

One example is an article, published in 2020, with the title "Role of energy excretion in human body weight balance" [77]. One interesting fact about this article is the absence of any mention of the microbiome, or even that stools contain bacteria. This is an example of a common problem: that the interpretation of an observation will vary with the context of its times. Indeed, the isotopic labelling experiments of Westerterp and Speakman mentioned above [70] ought to have been seminal, however, without a scheme such as Figure 2, above, there was no context into which these results could have been inserted. Accordingly, although moderate physical exercise certainly has its benefits, it cannot adequately offset reduced faecal energy excretion, and the concept of "energy harvest" is still falsely believed (in my opinion, apart from the shared value of short-chain fatty acids, see Section 4) to be a function of the intestinal microbiome [74].

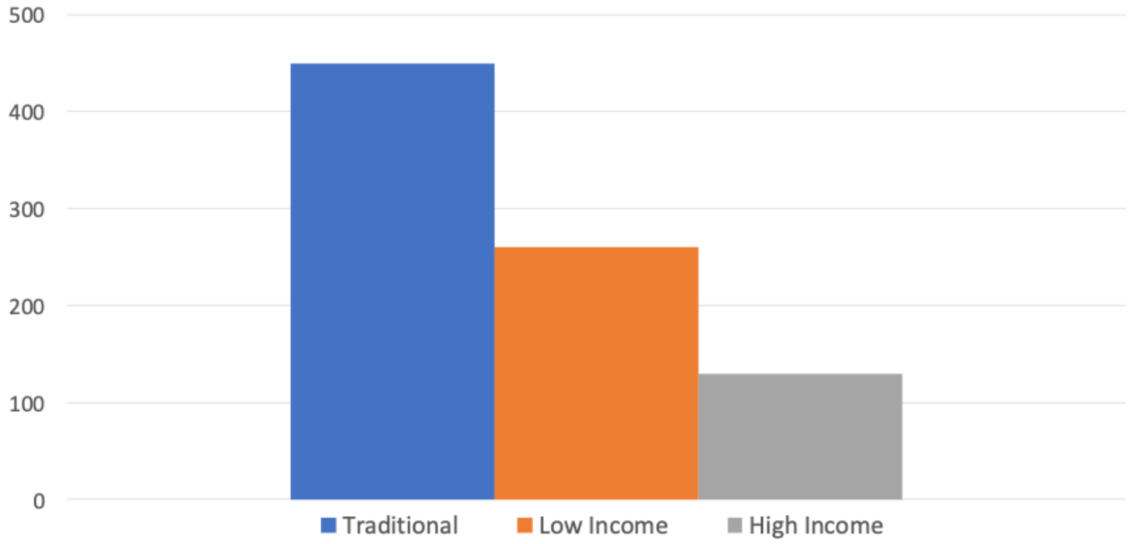

Figure 6. Faecal weight versus type of society. The columns on the left and right correspond to the faecal weights of people living in Burkitt's "traditional" and "Modern, Western Civilization", respectively, with the left-hand column corresponding to the 400–500 g range of Burkitt's figures [60]. The centre column represents the data provided by Rose [72] (income levels according to the Human Development Index), approximately an average of the other two. Source: Author's compilation based on data from Burkitt [60] and Rose [72] (previously reported by Smith [10], under CC BY 4.0, used with permission).

10. Dysbiosis 1: Obesity and Energy Compensation

While the above discussions cover the last 50 years or so, the case of William Banting, discussed above [55], is a reminder that the problem extends back 200 years or more. While the probable negative effects of antibiotics, antiseptics, and delivery of babies by sterile caesarean section have been discussed above, sentinel cells have an obligation to seek out, identify, and deal with any novel microscopic objects that may pose a threat. In this context, colourful heavy metal salts have been used as the basis for cosmetics for many years [49] and it seems feasible that sub-acute poisoning will have depleted populations of microbial sentinel cells prior to childbirth. Indeed, we can take this hypothesis even further back in time, to the palaeolithic "Venus" figurines, statuettes of women of ample bulk who, rather than the usual suggestion of being fertility symbols [78], could have been actual women affected by dysbiosis following the use of such early cosmetics by their mothers. Whatever the reason, sadly, we will never know what the ladies themselves thought about it.

Later, eating implements were made out of toxic metal alloys, generically referred to as "pewter" [50], possibly contributing to the damaged microbiome of the mother of the ancient Italian lady referred to earlier [54], as well as the mothers of Bostock, Banting, and other rich families of more modern ages. Later still, tetraethyl lead was added as an anti-knock agent to petrol, along with 1,2-dibromoethane as scavenger, leading to the spraying of microscopic particles of lead[II] bromide around the environment. It took many years before this all-too-obviously toxic process was stopped [51] but epidemiology suggests that, once microbial sentinel cells are reduced below a critical value (which may be zero), they are not recovered from one generation to the next. Accordingly, dysbiosis has steadily increased, generation by generation, throughout current "Westernised" populations [10].

To understand the extent and speed of calorie uptake due to dysbiosis, consider the numbers provided by the 2007 edition of the British Nutritional Foundation [67], i.e., a 1950s intake of 2660 kcal/day compared to their recent (2007) intake of 1750 kcal/day, an "average" person with the latter levels of dysbiosis trying to eat like their

eubiotic 1950s grandparents would be absorbing an extra 910 kcal/day. Another way of looking at the same figures is that, in the 1950s, eubiotic people would have been excreting an extra 910 kcal/day in their faeces, compared to relatively "dysbiotic", low faecal output, people in 2007. It is in this context that the dangers of so-called ultra-processed diets must be realised. Reporting in 2019, a closely supervised crossover study was carried out in which two groups of weight-stable adults were allowed to eat what they liked for 2 weeks, either of "ultra-processed" or of "more normally representative" food for a further 2 weeks, the two groups swapping over in the halfway stage. In other words, the two groups ate either "normal" followed by processed, or vice versa. The result was clear: both groups gained weight in the "ultra-processed" period of eating, perhaps suggesting that, as anticipated, more heavily processed foods are simply easier to eat [79].

In this context, many of the facts we consider to be indicative of *Homo sapiens* in general were established in the "eubiotic" mid-19th century, including body temperature. Accordingly, while 37 °C has been accepted for many decades, in the late 20th century physicians began to suspect that this number was wrong, and that the actual number was 36.5 °C. Loath to disbelieve their own eyes, naturally they made the assumption that the earlier researchers were simply wrong. However, an extensive study by Myroslava Protsiv and colleagues confirmed that both readings were right, for their respective date of measurement, and suggested a monotonic decrease of 0.03 °C per birth decade. In the opinion of these authors, the drop in body temperature reflects improvements in sanitation and the use of antibiotics, with a corresponding decrease in chronic inflammation [80], essentially the same argument as was used for the Tsimane [11].

In fact, the logic of rising obesity implies a reduction in body temperature due to what has been called "energy expenditure compensation". Clearly, any excess of energy expenditure over intake offers a risk of starvation, triggering emergency saving from some other source, as described in an influential 2021 paper [81]. Sadly, the concept of energy expenditure compensation is not widely understood, prompting one of the authors, Lewis Halsey, to offer a seemingly personalised "Bob" article, describing an oft-observed problem: the plateauing of otherwise successful weight loss programmes under apparently identical conditions of low food intake and high exercise. His explanation is that, when an energy deficiency is detected, body weight is defended by the reduction of energy expenditure on "some other biological processes" [82], possibly including body temperature.

Weight gain should not be thought of only in adult terms. In an echo of the "fetal origins" hypothesis of Barker [66] in 2019 Sandercock and Cohen reported a series of measurements on different tranches of 10-year-old schoolchildren in the years 1998, 2008, and 2014. While height, girth, and weight all showed an increase from one tranche to the next, and the BMI (body mass index) remained the same, measures of strength such as sit-ups and handgrip declined between each batch, possibly suggestive of fat penetration inside the muscles. Unsurprisingly, perhaps, Sandercock and Cohen (reporting in a sports journal) simply suggested that more time be devoted to school sports [83]. A similar problem of inappropriate growth may lie behind the current myopia epidemic, affecting an astonishing one third of children across the world [84]. In a similar fashion to the findings of Sandercock and Cohen, if the eyeball also grows in proportion to height and weight, but the focal length remains the same, then myopia automatically results.

Indeed, weight gain should not only be thought of in human terms. Since the development of antibiotics farmers have noticed that prolonged low-level use in young, growing animals increases their bulk, and hence their market value. The leading theory was that microorganisms actually competed with the animals for food [85], although it is interesting to note that nobody seems to have commented on the likely effect of antibiotics on growing human children. Equally, of course, farmed animals are slaughtered while still young and, accordingly, longer-term negative effects were never noticed. In today's world the use of antibiotics in animals are considered a threat of antibiotic resistance in people, stimulating the search for alternatives [86]. Whatever the vertebrate, physical changes going from a state of eubiosis to one of dysbiosis are summarised in Figure 7.

Illustrating the direct effect of diet on the brain, 29 young male volunteers were split into two groups, one asked to increase their calorie consumption with an additional 1500 kcal/day with readily available "high-caloric ultra-processed snacks" for 5 days, the other acting as control. The treated group both increased liver fat and were found to have disrupted brain insulin action lasting longer than the course of treatment [87]. It is interesting to note the persistent association between these foods and disrupted immune-system function [88]. Significantly, these and similar studies are all consistent with the idea of a malfunctioning immune-gut-brain triangle [10]. The suggestion in this Article is that, if this experiment were to be repeated with "eubiotic" individuals, although weight gain may well be noted, levels of energy excretion would also be expected to rise, thus maintaining an acceptably healthy weight. Overall, we have a potential explanation for what has been happening in recent decades: as dysbiosis became more common, so people ate fewer calories but excreted less energy in their faeces, leaving the proportion of obese people at least the same, if not actually increasing. It is important to note, however, that this

process is not constipation, which represents a change in bowel habit [89], but rather a problem stemming from early childhood [10].

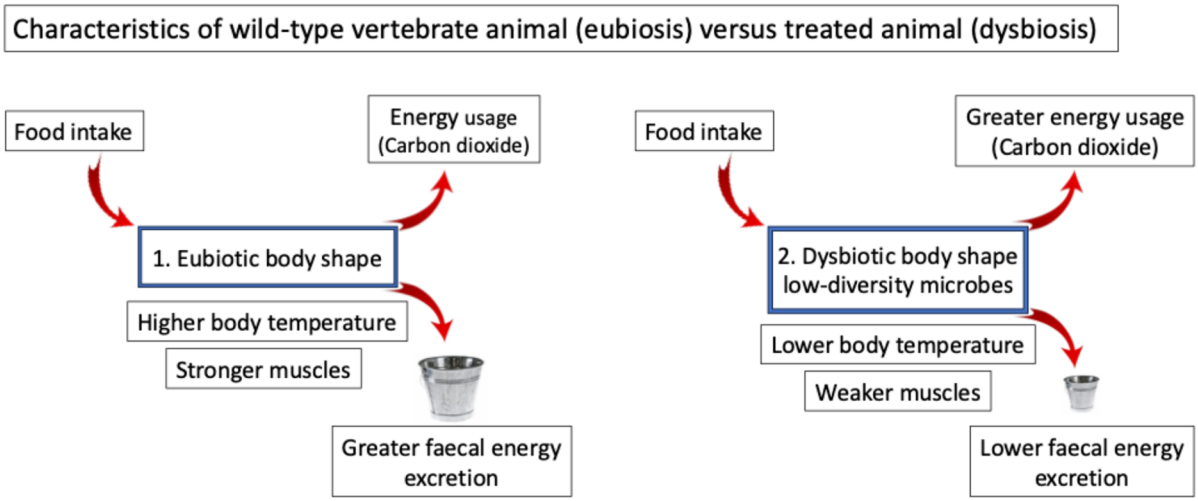

Figure 7. Energy flow diagrams in eubiotic (left hand side) versus dysbiotic (right hand side) animals (including humans). For an adequate food intake into an otherwise healthy body, the relatively slim eubiotic body shape, Box 1, will be associated with greater faecal mass excretion (Burkitt, 1973 [60]); higher body temperature (Protsiv et al., 2020 [80]); and stronger muscles (Sandercock et al., [83]). By contrast, the dysbiotic body shape of Box 2 will be taller, wider, and heavier, but with weaker muscles (Sandercock et al., 2019 [83]); lower body temperature (Protsiv et al., 2020 [80]); and lower faecal mass excretion (Burkitt, 1973 [60]) with, presumably, a higher usage of energy commensurate with moving a heavier body weight (Careau et al., 2021 [81]). While, in humans and our pet animals, dysbiosis will be associated with negative health outcomes (see text), of course in farm animals the greater weight carries economic benefits when slaughtered at the appropriate moment (Gaskins et al., 2002 [85]). Source: Diagrammatic compilation by the Author.

11. Dysbiosis 2: Coordination of Immune System, Gut, and Brain

While weight gain, potentially leading to obesity, is the most visible form of dysbiosis (even though not in itself an actual disease), sometimes "dysbiotic" people remain slim. One example is coeliac disease, in which an immune system-related problem prevents the absorption of food, even if the individuals are themselves unaware of the condition [90]. Illustrating the overall degradation of the immune-gut-brain triangle of Figures 3 and 4, coeliac disease can co-exist with psychiatric conditions [91]. Perhaps the most surprising consequence of the failure of the gut-brain axis is the observed association between autism-like conditions and joint hypermobility [92]. Probably the best explanation is that interoception, the knowledge that the brain has of the body [93], actually works through the gut, interfering with the last steps of both fine tuning the formation of the joints and aspects of brain function [10]. As noted previously, people who have experienced a total colectomy do not seem to suffer any additional diseases due to the lack of an intestinal microbiome, retaining fertility [45], and are able to give birth relatively normally [46]. They must, however, be careful when eating [94]. Indeed, although a person with dysbiosis can eat normally, the reduction in the rate of peristalsis means that too great a portion may be absorbed into the body, risking eventual obesity and its complications [10].

Covered by the deliberations of the not-for-profit Rome Foundation [95], Functional Gastrointestinal Disorders (FGID) constitute a huge area of study which, probably, ought to have a closer relationship with the psychiatric sciences such as the American Psychiatric Association [96]. Functional gastrointestinal disorders have also been termed "disorders of gut-brain interaction" (DGBI) and have been linked to obesity, albeit by mechanisms that not yet been elucidated [97]. Irritable bowel syndrome (IBS) is one of the major types of FGID and, along with others, may also carry psychiatric comorbidities. Its relationship to the gut bacteriome has recently been reviewed and, although some grounds for optimism were reported, none were definitive [98]. Although not strictly covered by the Rome Foundation, the effect of stress on the glucocorticoid-HPA (hypothalamus-pituitary-adrenal) axis may link cortisol levels with obesity, albeit that "the link between stress and obesity is complex and multifaceted, influenced by physiological, affective, cognitive and behavioural stress response mechanisms" [99]. Would a fuller understanding of dysbiosis help to unravel these difficulties?

As with Burkitt's "Some Diseases Characteristic of Modern Western Civilization" (Table 1), the examples above should not be treated as a comprehensive list. Indeed, there are at least two examples of Burkitt's work,

hiatus hernia and varicose veins, that can be included under the general category of "coordination". While Burkitt ascribes these two conditions to what he calls "faecal arrest", it must be noted that defecation is a socially charged act, under normal circumstances requiring input from the brain. It can easily be seen that a dysbiotic failure of the gut-brain axis may prevent such communication, leading to straining and an increase in intra-abdominal pressure, of up to 200 mm of mercury according to Burkitt's paper [60]. Perhaps something similar happens in disorders of menstrual flow, helping to account for the observation that dysmenorrhea is ameliorated by diet, maybe involving what the authors call "cycle-syncing" [100]. It is likely that dysbiosis also affects hormonal coordination, potentially leading to premenstrual syndrome (PMS), or its more severe version, premenstrual dysphoric disorder (PMDD), both of which are ill-defined and marginally diet modified [101]. Along similar lines, endometriosis is another poorly defined condition, characterised by chronic inflammation and, although benign (if severe), is remarkably reminiscent of malignancy. As with cancer, however, its relationship with nutrition is controversial and requires more well-designed, randomised trials [102].

12. Walking the Narrow Path: Dietary Dilemmas

Comprehensive, reliable information on fundamentally behavioural matters such as calorie intake and levels of exercise are normally hard to come by, while data on faecal weight and energy excretion are next to impossible. Fortunately, as described in Sections 9 and 10, we do have reasonably reliable data from the start of the 21st century obesity crisis, both in terms of calorie intake, from the British Nutritional Foundation [67], and energy usage developed from doubly labelled water methodology [70]. Accordingly, we can draw some deductions as, granted that there was no significant change in energy use through exercise (Sections 8 and 9), the drop of 910 kcal/person/day must correspond to a fall in average faecal energy excretion over that period (see Equation (1), Section 9). Sadly, in spite of intensive research, whether carried out via genes or by the bacterial microbiome, obesity rates remain stubbornly high, with few options remaining [103]. What to do?

Although it is not the purpose of this Article to propose specific diets, some general points are worth mentioning. The 20th century led to significant debate over the role of diet, especially saturated fat, on the initially American epidemic of heart disease. As it began to bite into their way of life, so teams of researchers began to scour the world for clues. Eventually they settled on areas of southern Europe and the Mediterranean, with their emphasis on (the largely unsaturated) olive oil, fish and vegetables, and their low rates of heart disease, and a dietary phenomenon was born. Comparing a Mediterranean diet with a more straightforwardly low-fat diet, the CORDIOPREV study (CORonary Diet Intervention with Olive oil and cardiovascular PREvention) seems to have finally convinced most people that the low-fat diet was inferior [104]. In fact, a better expression may be Mediterranean-style diet [105], more recent studies having emphasised the herbs and spices of the menu [106].

It is important to note, however, that the primary benefits of olive oil are associated with the polyphenol-rich, expensive extra-virgin style, with its pale green colour, characteristic taste, and effects on the gut microbiota [107]. Of course, the Mediterranean-style dietary concept is increasingly popular, both in improving quality of life of adults [108] and in slowing the rate of age-related macular degeneration [109]. In principle, alongside the classic high-fibre diet, there are ways in which cheaper carbohydrates can contribute directly to the growth of the gut microbiota, by processing readily digestible cooked starch into so-called resistant starch. In turn, this makes it difficult for the digestive enzymes to engage with the resultant molecular fibres affording, in theory, a beneficial health impact [110].

In the absence of the probably health-giving polyphenols, questions surrounding fats are hard to settle, but a medium-term (8 year) study on nearly fifty thousand post-menopausal women, reported in 2006, seems to have provided a definitive answer: that there was no cardiovascular benefit, either from the reduction of heart disease or stroke, from a specifically low-fat diet [111]. Alongside this, a similarly convincing comprehensive meta-analysis, reported in 2025, stated that there were tangible benefits to be gained from low-carbohydrate diets (i.e., necessarily high-fat), although raised low-density lipoprotein levels were noted with the more ketogenic dietary versions [112]. The third macronutrient, protein, raises more dose-related questions but with even fewer definitive studies, a recent example being the lack of negative effects when older individuals without prior kidney disease ate a higher protein intake [113]. Of course, much of the protein-based interest refers to cosmetic body building or supplementation to counter the effects of ageing or medication, important areas that, in the opinion of the authors of a recent article, require better-designed experiments [114]. Finally, micronutrients need to be kept under consideration. A comprehensive report included 480,825 dieting adults over six studies, singling out iron and vitamin D deficiencies, but also mentioning calcium and protein. Causality of deficiencies due specifically to the use of GLP-1 agonist agents could not definitively be established. Significantly, these authors state that paediatric studies were excluded, thus suggesting where more problems will lie in the near future [115].

Unfortunately, there are those who, often through no fault of their own, stray from the narrow path. As noted above (Section 10), perhaps the most obvious way is when an individual with uncomplicated dysbiosis (i.e., without additional conditions) tries to eat like their eubiotic grandparents and, therefore, absorbing too much nutrition—obesity being the most likely consequence. Another common cause of unexpected problems is food intolerance (alongside the potentially deadly food allergy). A recent comprehensive overview calls for greater effort to develop validated tests for these ill-defined conditions, thereby encouraging correspondingly less reliance on patient self-diagnosis [116]. Carbohydrate-related intolerance may be treated by the low-FODMAP diet, a (hopefully) temporary exclusion of "Fermentable Oligosaccharide, Disaccharide, Monosaccharide, and Polyol" constituents from the diet, even though the evidence of their net benefit is far from conclusive [117].

Finally, possibly the most famous of the named lifestyles (after the Mediterranean) is that associated with the so-called Blue Zones. A recent article presents a method of validating debatably extreme ages by documentary cross-checking. The claim is to (usually) eliminate errors due to "fraud, honest mistakes, poor memory, or identity switches, especially between homonymous siblings", sensibly looking for "valuable insights into human health from investigating the long-lived people who live there" [118]. Although a laudable aim in its own right, the claim for valuable insights must be modified in the light of this "Missing Link" hypothesis: that "Blue Zone" people, like the Tsimane [11] and, indeed like the original consumers of the Mediterranean diet, could well have been born eubiotic, risking high infant mortality but with a fully functioning sentinel cell microbiome. In itself, of course, this does not guarantee long-life, and any insights gained from such Blue Zones may well be useful, but they cannot necessarily be translated directly to people born with dysbiosis.

13. Seeking the Elixir: Probiotics and Polyphenols

Although coined earlier, Denis Burkitt popularised the expression "dietary fibre" throughout the latter half of the 20th century [119], believing that a lack of such fibre could be associated with several seemingly very different diseases (Table 1) [60]. Although what has been called "Burkitt's hypothesis" fell out of favour toward the end of the century, increasing realisation of the relevance of the gut microbiome to the immune system later rekindled that interest, drawing attention to the theoretical concept of a dietary fibre deficiency [120]. Attempts are underway to improve the otherwise too-simple classification of dietary fibre into soluble and insoluble, expressing health effects in terms of the rate of their fermentation by human intestinal bacteria [121]. Significantly, the earliest feeding a baby experiences includes microbe-specific oligosaccharides in breast milk [122], along with bacteria [123] some of which, interestingly, are also found in the "crop milk" that pigeons of both sexes feed to their squabs (pigeon chicks) [124], implying a system that evolved prior to the vertebrates themselves. Of course, wide-ranging attempts are also underway to correlate gut microorganisms (invariably bacteria) with health via dietary interventions [125], among which we can include studies on fermented foods [126]. Alongside these observations, there is a relentless, long-term, on-going search for a single, patentable living entity, or one of their "postbiotic" derivatives, that will achieve some desirable health outcome. Increasingly, probiotics come in a "synbiotic" combination with so-called prebiotics, often specifying a select form of dietary fibre to support a chosen function [127]. Nevertheless, it remains possible that probiotics, or even their postbiotic fragments, are effective by engaging with the immune system of the recipient and, therefore, temporarily stimulating both gut and brain [10].

The emphasis on genes has led us astray in the vexing question of dietary supplements. In an attempt to counter rising levels of non-communicable disease, researchers applied modern understanding of medical science to the study of ancient remedies (which may themselves have developed to counter their own problems of dysbiosis-induced non-communicable disease). Turmeric is a case in point. Having identified the major yellow component, curcumin, they then noted that it was not readily bioavailable. Nevertheless, after significant effort an extract of black pepper, piperine, was found to enhance absorption [128]. Armed with this information, many studies have been carried out, and some successes noted, a recent example being the reduction of concomitant depression in type 2 diabetes [129]. Alongside success, however, a "growing" problem has also been noted: turmeric (probably curcumin)-induced liver injury, ten cases being reviewed between 2011 and 2017 (reported in 2023), including one death [130]. Of relevance in this context is a review entitled "The essential medicinal chemistry of curcumin", published in 2017, providing evidence that "curcumin is an unstable, reactive, nonbioavailable compound and, therefore, a highly improbable lead" [131]. This ongoing toxicity problem is fundamentally due to our belief that pharmaceutically relevant activity can only follow from bioavailable compounds, knowing nothing about the microbiome. Instead, the activity of turmeric and similar foods may stem largely from non-bioavailable polyphenolic tannins, with their potential ability to activate otherwise unresponsive, potentially dormant microbiota [10].

Indeed, once considered toxic antinutrients [132], tannins have slowly become accepted as valuable food components for flavour, astringency, and health benefits even if, in 2025, they still use the expression "antioxidant" that requires "bioavailability" [133]. A slightly more recent, 2026, review of habitual coffee drinkers looks beyond caffeine at the faecal bacterial microbiome, but still mentions specific molecular constituents and microbes, and their individual effects on the gut-brain axis [134]. The idea of collective action, of non-specific improvements in the growth of the gut microbiome [10], has not yet been brought fully into consideration.

14. Next Steps: Ingestible Sensors and Brain Stimulation

While this sentinel cell microbiome seems to explain much, if not all, of the epidemiology of non-communicable disease, the true test of a valuable hypothesis is to provide useful approaches to the solution of pressing problems. Viable options include ingestible sensors [10] and, possibly, stimulation of the brain in areas that may be related to the control of either peristalsis or the immune system [12].

(1) Can Food be Medicine? Alongside the quality of food, the propensity for its over-absorption in dysbiotic societies poses serious questions relating to quantity, how much should be eaten. Related to this, the issues surround the monitoring of childhood growth [83], with its all-too-apparent threat of obesity, are positively urgent. Adolescence is a particularly dangerous time, with increased freedom of dietary choice during a vulnerable period of neurodevelopment [135]. For all ages, a "food is medicine program", set up in America to provide theoretically healthy food for low-income families vulnerable to non-communicable disease, needs more information before it can be shown to be effective [136]. Similarly, while efforts in the field of personalised nutrition have managed to improve biomarkers, they did not exert much influence on the relevant statistics such as weight and blood pressure modification [137]. Regarding the microbiome itself, there is sufficient data available, of sufficient complexity, to make analysis by Artificial Intelligence useful, if not actually compulsory. Not surprisingly, this effort is now underway, the aim being to "accelerate innovations in personalised medicine and deepening our understanding of host-microbiome relationships" [138]. On the whole, it seems that a combination of analysis and blood-borne biomarkers may not be good enough to predict wider health benefits. It may prove helpful to probe directly inside the gut contents with the use of ingestible sensors [10].

(2) Plumbing the Depths (Ingestible Sensors): Perhaps the most direct way of accessing information about the status of the intestinal microbiome is to make use of the established technology of ingestible sensors. The basic principle is of a capsule, small enough to be swallowed, loaded with a specific detector and enough microelectronics enabling it to capture precise information about the environment in which it finds itself. As a recent review puts it "understanding the complex interplay between microbiome, host and dietary substrate... is pivotal in the correct interpretation of gastrointestinal tract physiology in health and disease". This same article goes on to point out that, although successful, "few ingestible devices have reached clinical practice to date, partly due to the novelty of the information they provide and also due to the challenges of adding this novel technology to established clinical paradigms" [139]. Indeed, presumably for these reasons it seems that the promise of such technology has not advanced far since our earlier article, published in 2020 [140]. Accordingly, the situation remains essentially the same, that ingestible sensors can be used as a research tool to assess microbiome efficiency by the detection and monitoring of key interkingdom signalling molecules [10]. Unfortunately, it remains unclear as to what these hypothetical molecules actually are, in spite of a wide range of contenders. The two-way communication between gastrointestinal hormones and gut microbiota provide many options [141] and, likewise, a variety of monoamine derivatives seem, somehow, to interfere with a selection of nervous system diseases [142]. The investigation of microbiome function may be the primary future use for ingestible sensor technology.

(3) Dysbiotic versus Eubiotic Populations: The most readily available human populations for exploration by ingestible sensor live in Westernised nations but, as these suffer from a range of dysbiosis-related problems, it will be hard to be sure of the general validity of the results [10]. The ideal populations will belong to those peoples born eubiotic, i.e., without non-communicable, Burkitt-style Westernised diseases [60]. As examples, both the microbiome-diverse Tsimane [75] and the Hadza [76] have been mentioned in the text, but other peoples will be available. Alongside human cooperation, as laboratory animals may be dysbiotic [31], wild-born boar may, perhaps, be encouraged to participate with discrete ingestible sensors hidden in their food, capable of being monitored remotely [12]. By contrast, employing the long standing Amboseli Baboon research project [143] would pose the interesting question of whether these intelligent animals could be bribed to knowingly swallow whole capsules [12].

(4) Tweaking the Triangle (Brain Stimulation): Activation of the immune-gut-brain triangle, either from the action of probiotics on the immune system or of polyphenols on the gut microbiota, strongly resembles the

so-called "placebo effect". This effect is normally considered to be a sign of failure, as indicated by the expression "no better than placebo", however, currently there is a recognition that they offer potential strategies for the enhancement of patient care [144]. Similarly, current understanding of the placebo effect as "psycho-neuro-endocrine-immunological" offers applications beyond pain therapy [145] and clearly resembles the present immune-gut-brain triangle concept [10]. Accordingly, the involvement of placebo effects in non-communicable disease implies that such effects could, perhaps, be replicated "to order" by direct or by transcranial brain stimulation. Parkinsons's disease has been shown to be responsive to deep brain stimulation by implanted electrode [146], for example, for which the technology is rapidly maturing [147]. Of course, it would be more useful with non-invasive means, such as is under investigation for depression [148]. Indeed, while the relationship of obesity with depression strongly suggests that one causes the other [149] this "missing link" microbial sentinel cell hypothesis implies a deeper link between the two [10]. Hopefully regular treatment with an appropriate form of non-invasive brain stimulation will be effective in relieving obesity by the stimulation of peristalsis, potentially alongside other non-communicable diseases such as mental health and autoimmune conditions [12].

15. Finding the Needle in the Haystack: Can We Reintroduce the Missing Link?

While an explanation of the epidemiology of non-communicable disease is one thing, the prevention of such disease in future generations is of the greatest importance. To do this, it will first be necessary to isolate such cells and then to show that they can be successfully reintroduced at birth. Finally, it would be necessary to demonstrate that such diseases would indeed be banished from future populations.

(1) Where to look: While faeces constitute a good source of bacteria, this is actually an overgrowth, a waste product, and should not contain viable microbial sentinel cells. Indeed, it is possible that such cells are only generated in the later stages of pregnancy, perhaps not before the embryo is nearly complete. Likewise, distribution of microbial sentinel cells across the neonate may well be random, each cell trying to make its own way to the intestine of the child. If so, the chance of picking them up by a swab would be quite high, with little chance of harm to the baby. Of course, this is only true if the mother herself does not suffer from dysbiosis, even if symptom-free, in which case these cells would not be present. Accordingly, the cooperation of peoples such as the above-mentioned Tsimane [75] and Hadza [76] would be appreciated, and may be absolutely necessary. As far as possible, any help provided by such peoples should be compensated for, possibly by the mechanisms developed for cancer treatment-related ethnobotanical knowledge [150].

(2) Catching them: While their shape is unknown, they are likely to resemble dendritic cells and should, therefore, be able to move, searching either for the mouth or, indeed, for the anus. Such active movement would naturally make them easier to detect, with AI-assisted microscopic examination of swabs taken during birth hopefully leading directly to candidate microbial sentinel cells, when the process of identification could begin.

(3) Other animals: In principle, these cells should be present throughout the vertebrates, Burkitt himself stating that non-communicable diseases are "rare or unknown in undomesticated animals". Apart from farm or pet animals, one exception may be the heavily polluted English populations of the European hedgehog, *Erinaceous europaeus*, potentially having been poisoned by extensive use of leaded petrol throughout the latter half of the 20th century [10]. Nowadays all European hedgehog species are under threat, but the common theme is that, as with many human societies, "there remains a comprehensive lack of knowledge of populations, ecology and threats" [151].

(4) Reintroduction of Microbial Sentinel Cells: In principle, once these cells have been identified, along with a suitable eubiotic maternal donor, a transfer by swab from her child to that of a nearby dysbiotic mother should lead to a healthy, eubiotic child ready for future growth. Of course, every step of this process will need to be optimised, and it is likely that the initial detection of such microbial sentinel cells would be only the beginning of a major campaign to reverse the decades-long epidemic of non-communicable disease. Among various practical questions perhaps the most theoretically important is whether such cells must come charged with a suitable antigen or whether they would trigger the biological handshaking process referred to earlier (Sections 4 and 5) without the need to carry a specific antigen.

Finally, it is important to note that analysis, in the shape of ingestible sensors, amelioration, via brain stimulation (Section 14), and prevention, reintroducing the missing link, should be pursued independently. Even if the reintroduction concept cannot be brought to fruition, the immune-gut-brain triangle hypothesis seems to be accurate. In addition, thought must be given to the whole antimicrobial/caesarean section policy which, alongside pollution, probably lies at the heart of the problem.

16. A Faustian Pact: Reflections on the Modern World

The idea that you can't get something for nothing, often encapsulated in the saying "there's no such thing as a free lunch", is widely accepted, but the social and economic environment in which the human race has made for itself openly encourages the flouting of this principle. The consequence is known as the "tragedy of the commons" in which, in the absence of world-wide strong government, everybody must participate. We see this in the depletion of natural resources, such as fossil fuels or rare elements, and in the resultant pollution. Likewise, as the toxicity of lead is well-known, its use in petrol was careless at the very least, but its effect on the hitherto unknown microbiome could not easily have been predicted. Similarly, everyone wants the best for themselves and their family, so the overuse of antimicrobial and C-section technology is not a surprise. In fact, the same applies to the use of antibiotics to accelerate the growth of animals for food, but here the current constraint is avoiding the development of antibiotic resistance.

In principle, of course, it should be the other way around, so that we should encourage the use of antibiotics for animals and develop microbiome-preserving alternatives for people. Only in this way can we be sure of creating a stable, eubiotic society. In fact, it may be that we are already part of the way there. Although there is a clear fall in fertility rates across the world [32], it could be that this problem is restricted to the increasing portion of the population more severely affected by dysbiosis (see Section 5). If so, the prevention of the problem at source will, over time, lead to a healthy set of maternal microbial lineages. At this point it is worth repeating that, as illustrated by the twin diagrams of Figures 3 and 4, the change from *H. sapiens* (eubiotic) to *H. sapiens* (dysbiotic) is not affected by genetic inheritance but rather by an individual's maternal microbial inheritance. Equally, it is clear that a diverse bacteriome is critical to eubiosis, but it could be that, much as key messages can be transmitted more-or-less regardless of the make of a mobile phone, it is the transmission of mobile genetic elements through the inherited microbiome that is the key element. In other words, any search for single, "good" bacteria may be misplaced.

Surprisingly, there may be upsides to the existence of dysbiosis, potentially playing a major role in the development of modern civilisation. Granted that a malfunctioning gut-brain axis prevents input to guide the developing brain, ongoing growth may be directed to increasing intellectual ability, potentially leading to the disturbing phenomenon described as savant syndrome. Sketched out in Figure 4 and probably representing one extreme of autism spectrum disorder, this condition leaves prodigious skills within a badly malfunctioning body [152]. Fortunately, this situation is currently exceptional, and many "gifted" people exhibit variations on the twin themes of intellectual ability and eccentricity. Interestingly, among the cave-dwelling species, members of the genus *Homo* are blessed with binocular vision, nimble fingers and curiosity. Once fire was tamed, it was only natural to test its properties by putting readily available minerals inside it. In this way, they would observe the colour change from black galena (lead(II) sulfide) to the bright reddish colour of the various oxides of lead. Brighter than ochre, these would have been traded as early cosmetics [49], at least among the rich. Alongside any tendency to weight gain (cf. Venus figurines, Section 10 [78]), the resultant dysbiosis may well have led to a sharpening of the intellect, putting our genus on the path to domination. In this context, the last word should be left to Arne Dietrich who, in 2014, published an entertaining article entitled "The mythconception of the mad genius". In this writing, aided by the impossibility of defining either "mad" or "genius" Dietrich came to the conclusion that it is not necessary to be mad to be a genius [153]. However, if we may employ a popular idiom, perhaps we can alter Dietrich's conclusion a little and say: "you don't have to be mad to be a genius, but it helps…".

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Use of AI and AI-Assisted Technologies

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References

1. Griffith, F. The Significance of Pneumococcal Types. *J. Hyg.* **1928**, *27*, 113–159. https://doi.org/10.1017/s0022172400031879.
2. Hancock, Z.B.; Lehmberg, E.S.; Bradburd, G.S. Neo-darwinism still haunts evolutionary theory: A modern perspective on Charlesworth, Lande, and Slatkin (1982). *Evolution* **2021**, *75*, 1244–1255. https://doi.org/10.1111/evo.14268.
3. Segre, J.A. What Does It Take to Satisfy Koch's Postulates Two Centuries Later?: Microbial Genomics and *Propionibacteria acnes*. *J. Investig. Dermatol.* **2013**, *133*, 2141–2142. https://doi.org/10.1038/jid.2013.260.
4. Woese, C.R.; Kandler, O.; Wheelis, M.L. Towards a natural system of organisms: Proposal for the domains Archaea, Bacteria, and Eucarya. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 4576–4579. https://doi.org/10.1073/pnas.87.12.4576.
5. Woese, C.R. On the evolution of cells. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 8742–8747. https://doi.org/10.1073/pnas.132266999.
6. Larsson, D.G.J.; Flach, C.F. Antibiotic resistance in the environment. *Nat. Rev. Microbiol.* **2022**, *20*, 257–269. https://doi.org/10.1038/s41579-021-00649-x.
7. Sagan, L. On the origin of mitosing cells. *J. Theor. Biol.* **1967**, *14*, 255–274. https://doi.org/10.1016/0022-5193(67)90079-3.
8. Margulis, L. Symbiogenesis and symbionticism. In *Symbiosis as a Source of Evolutionary Innovation: Speciation and Morphogenesis*; MIT Press: Cambridge, MA, USA, 1991; pp. 49–92.
9. Kohl, K.D. Through the microbial looking glass: Our shifting understanding of the holobiont and microbes as mediators of organismal biology. *Integr. Comp. Biol.* **2025**, *65*, 727–735. https://doi.org/10.1093/icb/icaf059.
10. Smith, D. *Dysbiosis of the Evolved Intestinal Microbiome: Lessons for Health in Future Generations*; MDPI AG: Basel, Switzerland, 2025. https://doi.org/10.3390/books978-3-7258-1523-4.
11. Inchauste, L.; de Lamballerie, X.; Priet, S.; et al. Exceptionally low mortality despite widespread COVID-19 infection among Indigenous Tsimane and Moseten of Bolivia. *Soc. Sci. Med.* **2026**, *404*, 119493. https://doi.org/10.1016/j.socscimed.2026.119493.
12. Smith, D. Malfunction of a Hypothetical Evolved Microeukaryote Microbiome: Birth-Initiated Dysregulation of Immune System, Brain, and Gut. *J. Mosaic Autoimmun.* **2026**, *2*, 2. https://doi.org/10.53941/jmai.2026.100002.
13. Hou, K.; Wu, Z.X.; Chen, X.Y.; et al. Microbiota in health and diseases. *Signal Transduct. Target. Ther.* **2022**, *7*, 135. https://doi.org/10.1038/s41392-022-00974-4.
14. Martel, J.; Chang, S.H.; Ko, Y.F.; et al. Gut barrier disruption and chronic disease. *Trends Endocrinol. Metab.* **2022**, *33*, 247–265. https://doi.org/10.1016/j.tem.2022.01.002.
15. Fusco, W.; Lorenzo, M.B.; Cintoni, M.; et al. Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. *Nutrients* **2023**, *15*, 2211. https://doi.org/10.3390/nu15092211.
16. Chao, J.; Coleman, R.A.; Keating, D.J.; et al. Gut Microbiome Regulation of Gut Hormone Secretion. *Endocrinology* **2025**, *166*, bqaf004. https://doi.org/10.1210/endocr/bqaf004.
17. Brüssow, H. Problems with the concept of gut microbiota dysbiosis. *Microb. Biotechnol.* **2020**, *13*, 423–434. https://doi.org/10.1111/1751-7915.13479.
18. Hehemann, J.H.; Correc, G.; Barbeyron, T.; et al. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. *Nature* **2010**, *464*, 908–912. https://doi.org/10.1038/nature08937.
19. Wilhelm, S.W.; Suttle, C.A. Viruses and Nutrient Cycles in the Sea. *BioScience* **1999**, *49*, 781–788. https://doi.org/10.2307/1313569.
20. Kuzyakov, Y.; Mason-Jones, K. Viruses in soil: Nano-scale undead drivers of microbial life, biogeochemical turnover and ecosystem functions. *Soil Biol. Biochem.* **2018**, *127*, 305–317. https://doi.org/10.1016/j.soilbio.2018.09.032.
21. Haudiquet, M.; de Sousa, J.M.; Touchon, M.; et al. Selfish, promiscuous and sometimes useful: How mobile genetic elements drive horizontal gene transfer in microbial populations. *Philos. Trans. R. Soc. B* **2022**, *377*, 20210234. https://doi.org/10.1098/rstb.2021.0234.
22. Lang, A.S.; Buchan, A.; Burrus, V. Interactions and evolutionary relationships among bacterial mobile genetic elements. *Nat. Rev. Microbiol.* **2025**, *23*, 423–438. https://doi.org/10.1038/s41579-025-01157-y.
23. Gilbert, C.; Maumus, F. Multiple Horizontal Acquisitions of Plant Genes in the Whitefly *Bemisia tabaci*. *Genome Biol. Evol.* **2022**, *14*, evac141. https://doi.org/10.1093/gbe/evac141.
24. Johnson, H.J.; Koshy, A.A. Latent Toxoplasmosis Effects on Rodents and Humans: How Much is Real and How Much is Media Hype? *mBio* **2020**, *11*, e02164-19. https://doi.org/10.1128/mbio.02164-19.
25. Danilova, N. The evolution of immune mechanisms. *J. Exp. Zool. Part B Mol. Dev. Evol.* **2006**, *306B*, 496–520. https://doi.org/10.1002/jez.b.21102.
26. Banchereau, J.; Briere, F.; Caux, C.; et al. Immunobiology of Dendritic Cells. *Annu. Rev. Immunol.* **2000**, *18*, 767–811. https://doi.org/10.1146/annurev.immunol.18.1.767.
27. Zhao, C.; Lin, G.; Cheng, K.; et al. Swimming Through Dendritic Cell Biology: Insights from Fish Models. *Immunol. Rev.* **2025**, *336*, e70067. https://doi.org/10.1111/imr.70067.

28. Bowe, W.P.; Logan, A.C. Acne vulgaris, probiotics and the gut-brain-skin axis—Back to the future? *Gut Pathog.* **2011**, *3*, 1. https://doi.org/10.1186/1757-4749-3-1.
29. Christensen, S.; Robinson, K.; Thomas, S.; et al. Dietary intake by patients taking GLP-1 and dual GIP/GLP-1 receptor agonists: A narrative review and discussion of research needs. *Obes. Pillars* **2024**, *11*, 100121. https://doi.org/10.1016/j.obpill.2024.100121. Erratum in *Obes. Pillars* **2024**, *12*, 100136.
30. Mozaffarian, D. Perspective: Obesity—An unexplained epidemic. *Am. J. Clin. Nutr.* **2022**, *115*, 1445–1450. https://doi.org/10.1093/ajcn/nqac075.
31. Burberry, A.; Wells, M.F.; Limone, F.; et al. C9orf72 suppresses systemic and neural inflammation induced by gut bacteria. *Nature* **2020**, *582*, 89–94. https://doi.org/10.1038/s41586-020-2288-7.
32. Aitken, R.J.; Norman, R.J. Epidemiology of falling fertility: The contribution of social, environmental, and genetic forces. *Fertil. Steril.* **2026**, *125*, 187–196. https://doi.org/10.1016/j.fertnstert.2025.04.048.
33. Betran, A.P.; Ye, J.; Moller, A.B.; et al. Trends and projections of caesarean section rates: Global and regional estimates. *BMJ Glob. Health* **2021**, *6*, e005671. https://doi.org/10.1136/bmjgh-2021-005671.
34. Mrkić Kobal, I.; Plavec, D.; Vlašić Lončarić, Ž.; et al. Atopic March or Atopic Multimorbidity—Overview of Current Research. *Medicina* **2023**, *60*, 21. https://doi.org/10.3390/medicina60010021.
35. Santoso, C.; Wei, Y.; Ahlqvist, E.; et al. Autoimmune diseases and the risk and prognosis of latent autoimmune diabetes in adults. *Diabetologia* **2025**, *68*, 331–341. https://doi.org/10.1007/s00125-024-06303-4.
36. Elkoshi, Z. New insights into the phenomenon of remissions and relapses in autoimmune diseases and the puzzle of benign autoantibodies in healthy individuals. *Front. Immunol.* **2025**, *16*, 1522356. https://doi.org/10.3389/fimmu.2025.1522356.
37. Radha, G.; Lopus, M. The spontaneous remission of cancer: Current insights and therapeutic significance. *Transl. Oncol.* **2021**, *14*, 101166. https://doi.org/10.1016/j.tranon.2021.101166.
38. Liu, D.; Lu, Y.; Li, Z.; et al. Quorum Sensing: Not Just a Bridge Between Bacteria. *MicrobiologyOpen* **2025**, *14*, e70016. https://doi.org/10.1002/mbo3.70016.
39. Zhou, Y.; Tang, L.; Chen, D.; et al. Analysis and engineering of quorum sensing-based communications between bacteria and fungi. *mBio* **2026**, *17*, e3838–25. https://doi.org/10.1128/mbio.03838-25.
40. Wan, M.; Simonin, E.M.; Johnson, M.M.; et al. Exposomics: A review of methodologies, applications, and future directions in molecular medicine. *EMBO Mol. Med.* **2025**, *17*, 599–608. https://doi.org/10.1038/s44321-025-00191-w.
41. Wild, C.P. The exposome at twenty: A personal account. *Exposome* **2025**, *5*, osaf003. https://doi.org/10.1093/exposome/osaf003.
42. Blaser, M.J.; Falkow, S. What are the consequences of the disappearing human microbiota? *Nat. Rev. Microbiol.* **2009**, *7*, 887–894. https://doi.org/10.1038/nrmicro2245.
43. Inchingolo, F.; Inchingolo, A.D.; Palumbo, I.; et al. The Impact of Cesarean Section Delivery on Intestinal Microbiota: Mechanisms, Consequences, and Perspectives—A Systematic Review. *Int. J. Mol. Sci.* **2024**, *25*, 1055. https://doi.org/10.3390/ijms25021055.
44. Chua, W.C.; Chen, Y.L.; Yen, C.F.; et al. Long-term health outcomes of children born by cesarean section: A nationwide population-based retrospective cohort study in Taiwan. *J. Formos. Med. Assoc.* **2025**, *124*, 1034–1038. https://doi.org/10.1016/j.jfma.2024.09.024.
45. Druvefors, E.; Myrelid, P.; Andersson, R.E.; et al. Female and Male Fertility after Colectomy and Reconstructive Surgery in Inflammatory Bowel Disease: A National Cohort Study from Sweden. *J. Crohn's Colitis* **2023**, *17*, 1631–1638. https://doi.org/10.1093/ecco-jcc/jjad079. Correction in *J. Crohn's Colitis* **2024**, *18*, 978.
46. Baggio, S.; Pomini, P.; Zecchin, A.; et al. Delivery and pregnancy outcome in women with bowel resection for deep endometriosis: A retrospective cohort study. *Gynecol. Surg.* **2015**, *12*, 279–285. https://doi.org/10.1007/s10397-015-0901-9.
47. Gurven, M.; Stieglitz, J.; Trumble, B.; et al. The Tsimane Health and Life History Project: Integrating anthropology and biomedicine. *Evol. Anthropol. Issues News Rev.* **2017**, *26*, 54–73. https://doi.org/10.1002/evan.21515.
48. Karki, R.; Netea, M.G.; Diorio, C.; et al. Cytokine storm. *Nat. Rev. Dis. Prim.* **2026**, *12*, 1. https://doi.org/10.1038/s41572-025-00677-4.
49. McMullen, R.L.; Dell'Acqua, G. History of Natural Ingredients in Cosmetics. *Cosmetics* **2023**, *10*, 71. https://doi.org/10.3390/cosmetics10030071.
50. Hull, C. *Pewter*; Bloomsbury: New York, NY, USA, 2008.
51. Needleman, H.L. The Removal of Lead from Gasoline: Historical and Personal Reflections. *Environ. Res.* **2000**, *84*, 20–35. https://doi.org/10.1006/enrs.2000.4069.
52. Bostock, J. Case of a Periodical Affection of the Eyes and Chest. *J. R. Soc. Med.* **1819**, *10 Pt 1*, 161–165. https://doi.org/10.1177/09595287190100p111.
53. Bostock, J. Of the Catarrhus Æstivus, or Summer Catarrh. *J. R. Soc. Med.* **1828**, *14 Pt 2*, 437–446. https://doi.org/10.1177/09595287280140p204.

54. Gasbarrini, G.; Rickards, O.; Martínez-Labarga, C.; et al. Origin of celiac disease: How old are predisposing haplotypes? *World J. Gastroenterol.* **2012**, *18*, 5300–5304. https://doi.org/10.3748/wjg.v18.i37.5300.
55. Banting, W. Letter on Corpulence, Addressed to the Public. *Obes. Res.* **1993**, *1*, 153–163. https://doi.org/10.1002/j.1550-8528.1993.tb00605.x.
56. Eknoyan, G. Adolphe Quetelet (1796–1874) the average man and indices of obesity. *Nephrol. Dial. Transplant.* **2008**, *23*, 47–51. https://doi.org/10.1093/ndt/gfm517.
57. Jou, C. The Progressive Era Body Project: Calorie-Counting and "Disciplining the Stomach" in 1920s America. *J. Gilded Age Progress. Era* **2019**, *18*, 422–440. https://doi.org/10.1017/s1537781418000348.
58. Borch-Jacobsen, M.; Shamdasani, S. *The Freud Files: An Inquiry into the History of Psychoanalysis*; Cambridge University Press: Cambridge, UK, 2012.
59. Burkitt, D.P. A sarcoma involving the jaws in African children. *Br. J. Surg.* **1958**, *46*, 218–223. https://doi.org/10.1002/bjs.18004619704.
60. Burkitt, D.P. Some diseases characteristic of modern Western civilization. *BMJ* **1973**, *1*, 274–278. https://doi.org/10.1136/bmj.1.5848.274.
61. Gearhardt, A.N.; DiFeliceantonio, A.G. Highly processed foods can be considered addictive substances based on established scientific criteria. *Addiction* **2023**, *118*, 589–598. https://doi.org/10.1111/add.16065.
62. Cardoso, B.R.; Steele, E.M.; Brayner, B.; et al. Ultra-processed food intake, cognitive function, and dementia risk: A cross-sectional study of middle-aged and older Australian adults. *Alzheimer's Dement. Diagn. Assess. Dis. Monit.* **2026**, *18*, e70335. https://doi.org/10.1002/dad2.70335.
63. Magkos, F.; Forde, C.G.; Robinson, E. Ultraprocessed foods and obesity: Interpreting the evidence. *Science* **2026**, *392*, 1020–1022. https://doi.org/10.1126/science.aef3495.
64. Strachan, D.P. Hay fever, hygiene, and household size. *BMJ* **1989**, *299*, 1259–1260. https://doi.org/10.1136/bmj.299.6710.1259.
65. Rook, G.A.W. The old friends hypothesis: Evolution, immunoregulation and essential microbial inputs. *Front. Allergy* **2023**, *4*, 1220481. https://doi.org/10.3389/falgy.2023.1220481.
66. Barker, D.J. The fetal and infant origins of adult disease. *BMJ* **1990**, *301*, 1111. https://doi.org/10.1136/bmj.301.6761.1111.
67. Foster, R.; Lunn, J. 40th Anniversary Briefing Paper: Food availability and our changing diet. *Nutr. Bull.* **2007**, *32*, 187–249. https://doi.org/10.1111/j.1467-3010.2007.00648.x.
68. Jones, D.S.; Podolsky, S.H.; Greene, J.A. The Burden of Disease and the Changing Task of Medicine. *N. Engl. J. Med.* **2012**, *366*, 2333–2338. https://doi.org/10.1056/nejmp1113569.
69. Schoeller, D.A.; van Santen, E. Measurement of energy expenditure in humans by doubly labeled water method. *J. Appl. Physiol.* **1982**, *53*, 955–959. https://doi.org/10.1152/jappl.1982.53.4.955.
70. Westerterp, K.R.; Speakman, J.R. Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals. *Int. J. Obes.* **2008**, *32*, 1256–1263. https://doi.org/10.1038/ijo.2008.74.
71. Flier, J.S. Moderating "the great debate": The carbohydrate-insulin vs. the energy balance models of obesity. *Cell Metab.* **2023**, *35*, 737–741. https://doi.org/10.1016/j.cmet.2023.03.020.
72. Rose, C.; Parker, A.; Jefferson, B.; et al. The Characterization of Feces and Urine: A Review of the Literature to Inform Advanced Treatment Technology. *Crit. Rev. Environ. Sci. Technol.* **2015**, *45*, 1827–1879. https://doi.org/10.1080/10643389.2014.1000761.
73. Boekhorst, J.; Venlet, N.V.; Procházková, N.; et al. Stool energy density is positively correlated to intestinal transit time and related to microbial enterotypes. *Microbiome* **2022**, *10*, 223. https://doi.org/10.1186/s40168-022-01418-5.
74. Montenegro, J.; Armet, A.M.; Willing, B.P.; et al. Exploring the Influence of Gut Microbiome on Energy Metabolism in Humans. *Adv. Nutr.* **2023**, *14*, 840–857. https://doi.org/10.1016/j.advnut.2023.03.015.
75. Sprockett, D.D.; Martin, M.; Costello, E.K.; et al. Microbiota assembly, structure, and dynamics among Tsimane horticulturalists of the Bolivian Amazon. *Nat. Commun.* **2020**, *11*, 3772. https://doi.org/10.1038/s41467-020-17541-6.
76. Carter, M.M.; Olm, M.R.; Merrill, B.D.; et al. Ultra-deep sequencing of Hadza hunter-gatherers recovers vanishing gut microbes. *Cell* **2023**, *186*, 3111–3124. https://doi.org/10.1016/j.cell.2023.05.046.
77. Lund, J.; Gerhart-Hines, Z.; Clemmensen, C. Role of Energy Excretion in Human Body Weight Regulation. *Trends Endocrinol. Metab.* **2020**, *31*, 705–708. https://doi.org/10.1016/j.tem.2020.06.002.
78. Dixson, A.F.; Dixson, B.J. Venus Figurines of the European Paleolithic: Symbols of Fertility or Attractiveness? *J. Anthropol.* **2011**, *2011*, 569120. https://doi.org/10.1155/2011/569120.
79. Hall, K.D.; Ayuketah, A.; Brychta, R.; et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. *Cell Metab.* **2019**, *30*, 67–77.e3. https://doi.org/10.1016/j.cmet.2019.05.008. Erratum in *Cell Metab.* **2019**, *30*, 226; Erratum in *Cell Metab.* **2020**, *32*, 690.
80. Protsiv, M.; Ley, C.; Lankester, J.; et al. Decreasing human body temperature in the United States since the Industrial Revolution. *eLife* **2020**, *9*, e49555. https://doi.org/10.7554/elife.49555.

81. Careau, V.; Halsey, L.G.; Pontzer, H.; et al. Energy compensation and adiposity in humans. *Curr. Biol.* **2021**, *31*, 4659–4666.e2. https://doi.org/10.1016/j.cub.2021.08.016.
82. Halsey, L.G. Why did Bob stop losing weight? We need to talk about energy expenditure compensation. *Biol. Lett.* **2025**, *21*, 20250275. https://doi.org/10.1098/rsbl.2025.0275.
83. Sandercock, G.R.H.; Cohen, D.D. Temporal trends in muscular fitness of English 10-year-olds 1998–2014: An allometric approach. *J. Sci. Med. Sport* **2019**, *22*, 201–205. https://doi.org/10.1016/j.jsams.2018.07.020.
84. Liang, J.; Pu, Y.; Chen, J.; et al. Global prevalence, trend and projection of myopia in children and adolescents from 1990 to 2050: A comprehensive systematic review and meta-analysis. *Br. J. Ophthalmol.* **2025**, *109*, 362–371. https://doi.org/10.1136/bjo-2024-325427.
85. Gaskins, H.R.; Collier, C.T.; Anderson, D.B. Antibiotics as growth promotants: Mode of action. *Anim. Biotechnol.* **2002**, *13*, 29–42. https://doi.org/10.1081/abio-120005768.
86. Low, C.X.; Tan, L.T.H.; Ab Mutalib, N.S.; et al. Unveiling the Impact of Antibiotics and Alternative Methods for Animal Husbandry: A Review. *Antibiotics* **2021**, *10*, 578. https://doi.org/10.3390/antibiotics10050578.
87. Kullmann, S.; Wagner, L.; Hauffe, R.; et al. A short-term, high-caloric diet has prolonged effects on brain insulin action in men. *Nat. Metab.* **2025**, *7*, 469–477. https://doi.org/10.1038/s42255-025-01226-9.
88. Tian, T.; Hong, T.; Tian, T.; et al. Association between ultra-processed foods consumption and systemic immune-inflammation biomarkers in US Adults: Cross-Sectional results from NHANES 2003–2023. *Hum. Nutr. Metab.* **2025**, *42*, 200339. https://doi.org/10.1016/j.hnm.2025.200339.
89. Forootan, M.; Bagheri, N.; Darvishi, M. Chronic constipation. *Medicine* **2018**, *97*, e10631. https://doi.org/10.1097/md.0000000000010631.
90. Doyle, J.B.; Silvester, J.; Ludvigsson, J.F.; et al. Advances in the pathophysiology, diagnosis, and management of celiac disease. *BMJ* **2025**, *391*, e081353. https://doi.org/10.1136/bmj-2024-081353.
91. Alkhiari, R. Psychiatric and Neurological Manifestations of Celiac Disease in Adults. *Cureus* **2023**, *15*, e35712. https://doi.org/10.7759/cureus.35712.
92. Glans, M.R.; Thelin, N.; Humble, M.B.; et al. The Relationship between Generalised Joint Hypermobility and Autism Spectrum Disorder in Adults: A Large, Cross-Sectional, Case Control Comparison. *Front. Psychiatry* **2022**, *12*, 803334. https://doi.org/10.3389/fpsyt.2021.803334.
93. Chen, W.G.; Schloesser, D.; Arensdorf, A.M.; et al. The Emerging Science of Interoception: Sensing, Integrating, Interpreting, and Regulating Signals within the Self. *Trends Neurosci.* **2021**, *44*, 3–16. https://doi.org/10.1016/j.tins.2020.10.007.
94. Utrilla Fornals, A.; Costas-Batlle, C.; Medlin, S.; et al. Metabolic and Nutritional Issues after Lower Digestive Tract Surgery: The Important Role of the Dietitian in a Multidisciplinary Setting. *Nutrients* **2024**, *16*, 246. https://doi.org/10.3390/nu16020246.
95. Drossman, D.A. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. *Gastroenterology* **2016**, *150*, 1262–1279.e2. https://doi.org/10.1053/j.gastro.2016.02.032.
96. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Association: Arlington, VA, USA, 2013. https://doi.org/10.1176/appi.books.9780890425596.
97. Mahadeva, S. Obesity and functional gastrointestinal disorders: What is the link? *J. Gastroenterol. Hepatol.* **2023**, *38*, 344–345. https://doi.org/10.1111/jgh.16158.
98. Shaikh, S.D.; Sun, N.; Canakis, A.; et al. Irritable Bowel Syndrome and the Gut Microbiome: A Comprehensive Review. *J. Clin. Med.* **2023**, *12*, 2558. https://doi.org/10.3390/jcm12072558.
99. Lengton, R.; Schoenmakers, M.; Penninx, B.W.J.H.; et al. Glucocorticoids and HPA axis regulation in the stress–obesity connection: A comprehensive overview of biological, physiological and behavioural dimensions. *Clin. Obes.* **2024**, *15*, e12725. https://doi.org/10.1111/cob.12725.
100. Sergio, E.; Compher, C.; Mumford, S.L. Investigating the association between diet and primary dysmenorrhea: A systematic review. *F&S Rev.* **2026**, *7*, 100112. https://doi.org/10.1016/j.xfnr.2026.100112.
101. Oboza, P.; Ogarek, N.; Wójtowicz, M.; et al. Relationships between Premenstrual Syndrome (PMS) and Diet Composition, Dietary Patterns and Eating Behaviors. *Nutrients* **2024**, *16*, 1911. https://doi.org/10.3390/nu16121911.
102. Neri, L.C.L.; Quintiero, F.; Fiorini, S.; et al. Diet and Endometriosis: An Umbrella Review. *Foods* **2025**, *14*, 2087. https://doi.org/10.3390/foods14122087.
103. Ahmed, S.K.; Mohammed, R.A. Obesity: Prevalence, causes, consequences, management, preventive strategies and future research directions. *Metab. Open* **2025**, *27*, 100375. https://doi.org/10.1016/j.metop.2025.100375.
104. Delgado-Lista, J.; Alcala-Diaz, J.F.; Torres-Peña, J.D.; et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): A randomised controlled trial. *Lancet* **2022**, *399*, 1876–1885. https://doi.org/10.1016/s0140-6736(22)00122-2.
105. Davis, C.; Bryan, J.; Hodgson, J.; et al. Definition of the Mediterranean Diet; A Literature Review. *Nutrients* **2015**, *7*, 9139–9153. https://doi.org/10.3390/nu7115459.

106. Garza, M.C.; Pérez-Calahorra, S.; Rodrigo-Carbó, C.; et al. Effect of Aromatic Herbs and Spices Present in the Mediterranean Diet on the Glycemic Profile in Type 2 Diabetes Subjects: A Systematic Review and Meta-Analysis. *Nutrients* **2024**, *16*, 756. https://doi.org/10.3390/nu16060756.
107. Millman, J.F.; Okamoto, S.; Teruya, T.; et al. Extra-virgin olive oil and the gut-brain axis: Influence on gut microbiota, mucosal immunity, and cardiometabolic and cognitive health. *Nutr. Rev.* **2021**, *79*, 1362–1374. https://doi.org/10.1093/nutrit/nuaa148.
108. Godos, J.; Guglielmetti, M.; Ferraris, C.; et al. Mediterranean Diet and Quality of Life in Adults: A Systematic Review. *Nutrients* **2025**, *17*, 577. https://doi.org/10.3390/nu17030577.
109. Keenan, T.D.L.; Hébert, M.; Chew, E.Y.; et al. What Should Patients with Age-Related Macular Degeneration Eat? *Am. J. Ophthalmol.* **2026**, *288*, 12–21. https://doi.org/10.1016/j.ajo.2026.04.003.
110. Baptista, N.T.; Dessalles, R.; Illner, A.K.; et al. Harnessing the power of resistant starch: A narrative review of its health impact and processing challenges. *Front. Nutr.* **2024**, *11*, 1369950. https://doi.org/10.3389/fnut.2024.1369950.
111. Howard, B.V.; Van Horn, L.; Hsia, J.; et al. Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* **2006**, *295*, 655–666. https://doi.org/10.1001/jama.295.6.655.
112. Feng, S.; Liu, R.; Thompson, C.; et al. Effects of carbohydrate-restricted diets and macronutrient replacements on cardiovascular health and body composition in adults: A meta-analysis of randomized trials. *Am. J. Clin. Nutr.* **2025**, *122*, 1461–1478. https://doi.org/10.1016/j.ajcnut.2025.09.012.
113. Rinde, L.B.; Hopstock, L.A.; Lundblad, M.W.; et al. Higher habitual protein intake is not linked to decline of iohexol-measured GFR in adults ≥ 40 years. *Clin. Kidney J.* **2026**, *19*, sfag235. https://doi.org/10.1093/ckj/sfag235.
114. French, S.J.; Kanter, M.; Maki, K.C.; et al. The harms of high protein intake: Conjectured, postulated, claimed, and presumed, but shown? *Am. J. Clin. Nutr.* **2025**, *122*, 9–16. https://doi.org/10.1016/j.ajcnut.2025.05.002.
115. Urbina, J.; Salinas-Ruiz, L.E.; Valenciano, C.; et al. Micronutrient and Nutritional Deficiencies Associated With GLP-1 Receptor Agonist Therapy: A Narrative Review. *Clin. Obes.* **2026**, *16*, e70070. https://doi.org/10.1111/cob.70070.
116. Zingone, F.; Bertin, L.; Maniero, D.; et al. Myths and Facts about Food Intolerance: A Narrative Review. *Nutrients* **2023**, *15*, 4969. https://doi.org/10.3390/nu15234969.
117. Bellini, M.; Tonarelli, S.; Nagy, A.; et al. Low FODMAP Diet: Evidence, Doubts, and Hopes. *Nutrients* **2020**, *12*, 148. https://doi.org/10.3390/nu12010148.
118. Austad, S.N.; Pes, G.M. The validity of Blue Zones demography: A response to critiques. *Gerontologist* **2025**, *65*, gnaf246. https://doi.org/10.1093/geront/gnaf246.
119. Cummings, J.H.; Engineer, A. Denis Burkitt and the origins of the dietary fibre hypothesis. *Nutr. Res. Rev.* **2018**, *31*, 1–15. https://doi.org/10.1017/s0954422417000117.
120. O'Keefe, S.J. The association between dietary fibre deficiency and high-income lifestyle-associated diseases: Burkitt's hypothesis revisited. *Lancet Gastroenterol. Hepatol.* **2019**, *4*, 984–996. https://doi.org/10.1016/s2468-1253(19)30257-2.
121. Opperman, C.; Majzoobi, M.; Farahnaky, A.; et al. Beyond soluble and insoluble: A comprehensive framework for classifying dietary fibre's health effects. *Food Res. Int.* **2025**, *206*, 115843. https://doi.org/10.1016/j.foodres.2025.115843.
122. Porro, M.; Kundrotaite, E.; Mellor, D.D.; et al. A narrative review of the functional components of human breast milk and their potential to modulate the gut microbiome, the consideration of maternal and child characteristics, and confounders of breastfeeding, and their impact on risk of obesity later in life. *Nutr. Rev.* **2023**, *81*, 597–609. https://doi.org/10.1093/nutrit/nuac072.
123. Du, Y.; Cheng, J.; Xie, R.; et al. The triad of maternal gut-breast milk-infant gut microbial transmission in early life as a critical pathway for microbial inheritance. *Gut Microbes* **2025**, *17*, 2574928. https://doi.org/10.1080/19490976.2025.2574928.
124. Ding, J.; Liao, N.; Zheng, Y.; et al. The Composition and Function of Pigeon Milk Microbiota Transmitted from Parent Pigeons to Squabs. *Front. Microbiol.* **2020**, *11*, 1789. https://doi.org/10.3389/fmicb.2020.01789. Correction in *Front. Microbiol.* **2021**, *12*, 641828.
125. Asnicar, F.; Manghi, P.; Fackelmann, G.; et al. Gut micro-organisms associated with health, nutrition and dietary interventions. *Nature* **2025**, *650*, 450–458. https://doi.org/10.1038/s41586-025-09854-7.
126. Sampsell, K.; Marcolla, C.S.; Tapping, S.; et al. Current Research in Fermented Foods: Bridging Tradition and Science. *Adv. Nutr.* **2025**, *16*, 100554. https://doi.org/10.1016/j.advnut.2025.100554.
127. Smolinska, S.; Popescu, F.D.; Zemelka-Wiacek, M. A Review of the Influence of Prebiotics, Probiotics, Synbiotics, and Postbiotics on the Human Gut Microbiome and Intestinal Integrity. *J. Clin. Med.* **2025**, *14*, 3673. https://doi.org/10.3390/jcm14113673.
128. Rolfe, V.; Mackonochie, M.; Mills, S.; et al. Turmeric / curcumin and health outcomes: A meta-review of systematic reviews. *Eur. J. Integr. Med.* **2020**, *40*, 101252. https://doi.org/10.1016/j.eujim.2020.101252.
129. Yaikwawong, M.; Jansarikit, L.; Jirawatnotai, S.; et al. Curcumin reduces depression in obese patients with type 2 diabetes: A randomized controlled trial. *Nutrients* **2024**, *16*, 2414.

130. Halegoua-DeMarzio, D.; Navarro, V.; Ahmad, J.; et al. Liver Injury Associated with Turmeric—A Growing Problem: Ten Cases from the Drug-Induced Liver Injury Network [DILIN]. *Am. J. Med.* **2023**, *136*, 200–206. https://doi.org/10.1016/j.amjmed.2022.09.026.
131. Nelson, K.M.; Dahlin, J.L.; Bisson, J.I.; et al. The Essential Medicinal Chemistry of Curcumin. *J. Med. Chem.* **2017**, *60*, 1620–1637. https://doi.org/10.1021/acs.jmedchem.6b00975.
132. Savolainen, H. Tannin content of tea and coffee. *J. Appl. Toxicol.* **1992**, *12*, 191–192. https://doi.org/10.1002/jat.2550120307.
133. Cosme, F.; Aires, A.; Pinto, T.; et al. A Comprehensive Review of Bioactive Tannins in Foods and Beverages: Functional Properties, Health Benefits, and Sensory Qualities. *Molecules* **2025**, *30*, 800. https://doi.org/10.3390/molecules30040800.
134. Boscaini, S.; Bastiaanssen, T.F.S.; Moloney, G.M.; et al. Habitual coffee intake shapes the gut microbiome and modifies host physiology and cognition. *Nat. Commun.* **2026**, *17*, 3439. https://doi.org/10.1038/s41467-026-71264-8.
135. Young, H.A.; Gaylor, C.M.; Brennan, A.; et al. Diet and the Developing Brain: A Systematic Review of Nutritional Influences on Adolescent Cognitive and Academic Outcomes. *Adv. Nutr.* **2026**, *17*, 100648. https://doi.org/10.1016/j.advnut.2026.100648.
136. Seligman, H.K.; Angell, S.Y.; Berkowitz, S.A.; et al. A Systematic Review of "Food Is Medicine" Randomized Controlled Trials for Noncommunicable Disease in the United States: A Scientific Statement from the American Heart Association. *Circulation* **2025**, *152*, e32–e46. https://doi.org/10.1161/cir.0000000000001343.
137. Martinsen, T.; Brennan, L. Key evidence for personalised nutrition: A review of randomised controlled trials. *Food Funct.* **2026**, *17*, 646–658. https://doi.org/10.1039/d5fo02969d.
138. Zhou, T.; Zhao, F. AI-empowered human microbiome research. *Gut* **2026**, *75*, 1432–1446. https://doi.org/10.1136/gutjnl-2025-335946.
139. Thwaites, P.A.; Yao, C.K.; Halmos, E.P.; et al. Review article: Current status and future directions of ingestible electronic devices in gastroenterology. *Aliment. Pharmacol. Ther.* **2024**, *59*, 459–474. https://doi.org/10.1111/apt.17844.
140. Smith, D.; Jheeta, S. Measuring Microbiome Effectiveness: A Role for Ingestible Sensors. *Gastrointest. Disord.* **2020**, *2*, 3–11. https://doi.org/10.3390/gidisord2010002.
141. Zhao, X.; Qiu, Y.; Liang, L.; et al. Interkingdom signaling between gastrointestinal hormones and the gut microbiome. *Gut Microbes* **2025**, *17*, 2456592. https://doi.org/10.1080/19490976.2025.2456592.
142. Ma, S.; Yu, J.; Fu, J.; et al. Determination and Application of Nineteen Monoamines in the Gut Microbiota Targeting Phenylalanine, Tryptophan, and Glutamic Acid Metabolic Pathways. *Molecules* **2021**, *26*, 1377. https://doi.org/10.3390/molecules26051377.
143. Alberts, S.C.; Altmann, J. The Amboseli Baboon Research Project: 40 Years of Continuity and Change. In *Long-Term Field Studies of Primates*; Springer: Berlin/Heidelberg, Germany, 2012; pp. 261–287. https://doi.org/10.1007/978-3-642-22514-7_12.
144. Bagnis, A.; Meeuwis, S.H.; Haas, J.W.; et al. A scoping review of placebo and nocebo responses and effects: Insights for clinical trials and practice. *Health Psychol. Rev.* **2025**, *19*, 409–447. https://doi.org/10.1080/17437199.2025.2471792.
145. Ortega, Á.; Salazar, J.; Galban, N.; et al. Psycho-Neuro-Endocrine-Immunological Basis of the Placebo Effect: Potential Applications beyond Pain Therapy. *Int. J. Mol. Sci.* **2022**, *23*, 4196. https://doi.org/10.3390/ijms23084196.
146. Wójcik, R.; Dębska, A.; Zaczkowski, K.; et al. Deep Brain Stimulation for Parkinson's Disease—A Narrative Review. *Biomedicines* **2025**, *13*, 2430. https://doi.org/10.3390/biomedicines13102430.
147. Frey, J.; Cagle, J.; Johnson, K.A.; et al. Past, Present, and Future of Deep Brain Stimulation: Hardware, Software, Imaging, Physiology and Novel Approaches. *Front. Neurol.* **2022**, *13*, 825178. https://doi.org/10.3389/fneur.2022.825178.
148. Xiao, Y.; Dong, S.; Pan, C.; et al. Effectiveness of non-invasive brain stimulation on depressive symptoms targeting prefrontal cortex in functional magnetic resonance imaging studies: A combined systematic review and meta-analysis. *Psychoradiology* **2024**, *4*, kkae025. https://doi.org/10.1093/psyrad/kkae025.
149. Dębski, J.; Przybyłowski, J.; Skibiak, K.; et al. Depression and Obesity—Do We Know Everything about It? A Narrative Review. *Nutrients* **2024**, *16*, 3383. https://doi.org/10.3390/nu16193383.
150. Ryan, J.C. Toward an Ethics of Reciprocity: Ethnobotanical Knowledge and Medicinal Plants as Cancer Therapies. *Humanities* **2014**, *3*, 624–644. https://doi.org/10.3390/h3040624.
151. Gazzard, A.; Macdonald, D.W.; Rasmussen, S.L. Conservation concern for Europe's hedgehog species (Erinaceidae): Current statuses, issues and needs. *Biol. Conserv.* **2025**, *304*, 111033. https://doi.org/10.1016/j.biocon.2025.111033.
152. Tan, M.Y.E. Savant syndrome and autism spectrum disorder: A literature review. *Asia Pac. J. Dev. Differ.* **2025**, *12*, 332–347.
153. Dietrich, A. The mythconception of the mad genius. *Front. Psychol.* **2014**, *5*, 79.