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Hypothesis

Malfunction of a Hypothetical Evolved Microeukaryote Microbiome: Birth-Initiated Dysregulation of Immune System, Brain, and Gut

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Abstract: Although autoimmune conditions are normally recognised by their physical symptoms, on further investigation signs of neuropsychiatric disease may become apparent. While it is possible that the one actually causes the other, it is noteworthy that a similar correspondence can also be traced to the so-called gut-brain axis, perhaps indicating a deeper relationship between the three nominally independent variables of immune system, brain, and gut. Increasingly, as this "triple plague" of related conditions (autoimmunity, poor mental health, and weight gain) has begun to resemble an avalanche, intense speculation has focused on the so-called microbiome: that collection of unicellular pro- and eukaryotes, viruses and mobile genetic elements present, to a greater or lesser extent, at many sites around and inside the body. Primarily for reasons of accessibility and ease of analysis, most effort has focused on the bacteria, i.e., the bacteriome, but unfortunately with little rationale. By contrast, our work was based on the premiss that the microbiome, "our microbes" has evolved to be an intergenerational part of animal immune systems, helping to protect successive generations of multicellular entities against external microbes. Analysis further suggested that key microbes should be the more flexible microeukaryotes, while the concomitant, diverse, bacteriome is able to express mobile genetic elements. In summary, the evolved nature of these key microbes means that they should be transferred at birth, i.e., as a maternal microbial inheritance working alongside the parental genetic inheritance of the individual. As antigenic information is carried within the body by sentinel cells, the most succinct suggestion would be that intergenerational information is carried by means of a microbial version of such cells, perhaps taken up by the neonate gut as a form of inoculation to become what could be classed as an "immune-gut-brain triangle". If so, it would be their failure in microbe-hostile environments that accounts for the often early-onset epidemiology of what has been termed "dysbiosis": potentially eczema in the infant; autism in toddlers; and type 2 diabetes in primary school children. Significantly, however, in this hypothesis disease is not a problem of the organs themselves, but of their communication with the brain. Accordingly, the so-called placebo effect could be due to a temporary improvement in brain-centred communication.

Keywords: autoimmunity; caesarean section; deep brain stimulation; diabetes; dual inheritance; dysbiosis; gut-brain axis; ingestible sensors; placebo effect; unicellular eukaryotes

1. Introduction: An Avalanche of Illness

Sometime in an early summer's day in about the year 1781, a young (8-year-old) John Bostock famously started to sneeze. As we now know, he continued to sneeze at about the same time every year until, as a well-established medical doctor (with a background in kidney-related conditions), he published his symptoms in 1819 [1] and set out on a search for other sufferers of this *catarrhus aestivus* (i.e., summer catarrh or, more specifically, seasonal allergic rhinitis: hay fever). After asking his medical contacts, by 1828 he published the results of his exhaustive search, enumerating a total of 28 people across the length and breadth of the United Kingdom: and specifically stating that they all belonged to the more well-off elements of society [2]. Contrast this with the situation observed in recent years, with over 40% of United Kingdom teenagers, from all ranks of society, exhibiting symptoms in 2005 [3]. Although no single known explanation adequately accounts for this massive increase in the epidemiology of such disease, it is not for want of trying. David Strachan published his half-serious suggestions concerning both hay fever and asthma in what popularly became known as the "hygiene hypothesis" in 1989 [4], with later extensive studies, carried out by Graham Rook and his collaborators, failing to uncover any external microbial entities (i.e., Rook's "old friends"), that could be associated with these intriguing autoimmune-linked conditions [5].

Similarly, it is instructive to consider the case of Dr Denis Burkitt and his mid-twentieth travels around Africa. Born in 1911, Burkitt attended the same prestigious Edinburgh medical school as John Bostock but, more than a century later, Burkitt had many more medical terms and conditions to memorise than did Bostock. Nevertheless, while he did observe one previously unknown infection, a transmissible sarcoma of the jaw [6], the main point of interest was the unexpected *absence* of disease—specifically, an absence of the chronic, non-communicable conditions that we have become so familiar with today. Focusing on diseases relating to cholesterol metabolism, the circulation, the bowel, obesity, and type 2 diabetes, he published his findings as diseases caused by what he called "Modern, Western Civilization" [7], with a representative sample of specified conditions collected in Table 1. Interestingly, Burkitt thought he detected a pattern. He recognised that the United Kingdom and the United States were at the epicentre of such disease, and that their fibre-poor diet was very different from that of the majority of the traditional societies that he studied. Furthermore, he noted that, as the proportion of fibre in the progressively refined "westernized" diet had steadily dropped over previous years, so the levels of disease had increased. Finally, Burkitt tracked the fate of some groups of such traditional peoples as they migrated from high to low-fibre environments. Significantly, perhaps, he specifically stated that they developed these diseases in *subsequent generations* (author's italics) [7].

Table 1. Burkitt's "Some Diseases Characteristic of Modern Western Civilization" [7].

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

However, Burkitt recognised that a subset of these traditional peoples, the Maasai, had long adopted a steppe-dwelling, cattle-rearing lifestyle that did not lead to a high-fibre diet, and yet they did not suffer from these westernized diseases. While he suggested the possibility of some evolved resistance to the negative effects of cholesterol metabolism, he did not follow-up this seemingly important observation. Equally, he admitted that, as far as the immune-related diseases of Table 1 are concerned, that no "acceptable explanation has yet been suggested for their geographical distribution" [7]. Another major gap in Burkitt's studies, though entirely characteristic of mid 20th century science, is the absence of any mention of mental health.

Of course, the controversial ideas of Sigmund Freud cast a long shadow over 20th century attitudes [8], a shock which scientists, arguably, are only just beginning to recover from. Nevertheless, it seems that Freud was right about one practical point at least, that poor mental health can be traced back to early life. The epidemiologist David Barker published an article in 1990 entitled "The fetal and infant origins of adult disease" and, using the subtitle "the womb may be more important than the home" he suggested that the intrauterine environment may be more important for what he called degenerative diseases of later life, including schizophrenia as well as ischaemic heart disease, for example [9]. While Barker's original paper emphasised the role of maternal deprivation, the precise mechanism remains elusive [10]. However, economic arguments are strongly in favour of a "fetal" origin of disease [11]. Probably the most obvious point about the early origin of non-communicable disease, albeit primarily from the immune system point of view, remains the so-called "atopic march" or even "atopic

multimorbidity", the almost-regimented unfolding of such conditions from, for example, babyhood eczema to adolescent hay fever [12]. The exact definition of atopic march can almost certainly be stretched to include both the enigma of the seemingly random appearance of food allergy in childhood [13] and also that of most cases of type 1 diabetes [14]. However, there is a more recent observation with an adult-onset epidemiology: LADA: Latent Autoimmune Disease in Adults [15] (often referred to as "type 1.5 diabetes", or even "double diabetes"). On the whole, the only thing we can be sure of is that autoimmune disease is getting worse over time. These changes are illustrated by Figure 1, in which the above-mentioned individuals are placed in their historical context, as well as stressing the increasing levels of concern as we pass through the 21st century.

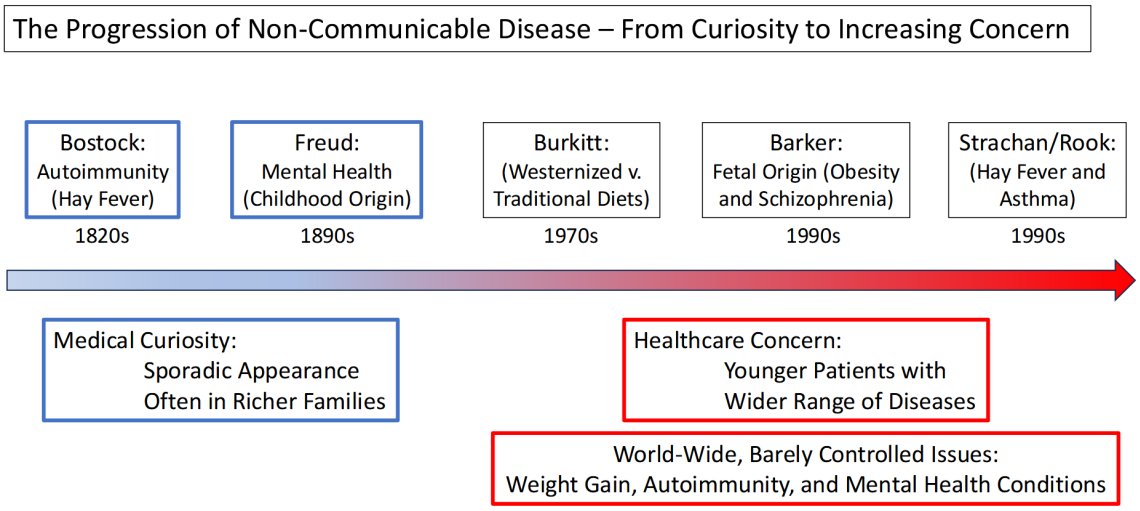

Figure 1. The Progression of Non-Communicable Disease. Left hand side (blue outline): The 19th century findings of Bostock [1] and Freud [8] generated more interest than alarm. Top right (thin outline): The observations of Burkitt [7], Barker [9], Strachan [4], and Rook [5] emphasised growing levels 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.

2. The Riddle Within the Enigma: The Microbiome

Fresh from earning his Nobel prize on aspects of the immune system, in the early 20th century Élie Metchnikoff rebelled against the developing idea that all "germs" are bad. Accordingly, he investigated the role of *Lactobacillus* species in the prolongation of life and earned his double soubriquet as both the father of gerontology and the founder of longevity science [16]. More recent probiotic studies continue to excite interest [17] and take their inspiration from Martin Blaser's suggestion that it is the antibiotic-induced disappearance of "ancient" human microbiota that is responsible for many modern non-communicable diseases [18]. Sadly, the above-mentioned work of Rook and his collaborators [5] suggests that the anticipated microbes may prove hard to detect and, of course, Bostock's hay fever clearly pre-dates the arrival of modern antibiotics [1]. Significantly, however, a 2019 article by Harald Brüssow posed a series of relevant statements about so-called "dysbiosis" within the microbiome\probiotic field which, to my knowledge, remain unaddressed. In particular, he bemoans the lack of "ecological and evolutionary reasoning"; of "modified Koch's postulates"; and of the refutational experiments required to fulfil the reasoning of Karl Popper about the nature of the scientific process [19]. Brüssow also mentioned the complexity of microbiome-related datasets that need "sophisticated statistical methods for their analysis". This fact is made clear by a recent publication looking at the "microbiome"—actually exclusively the bacteriome—with respect to (cardiometabolic) "health, nutrition and dietary interventions" [20]. Making use of very extensive databases, albeit time and geographically limited (primarily modern-day Britain and America), they came up with a series of associations which may help with future studies. However, nicely illustrating a problem with the whole field, they echo Brüssow by specifically stating that "causal inference is not possible without prospective cohort studies and interventional clinical trials" [20]. Sensibly, perhaps, attempts are being made to unravel the situation with the aid of artificial intelligence [21]. It will be interesting to see how that develops.

However, there could be a more basic problem that needs to be considered. As noted above, throughout the bulk of the 20th century the term "bacteria" has been synonymous with infectious disease and, as a consequence,

the largely euphemistic terms “microbe” and “microbiome” have been used instead. Of course, owing to the availability of the readily interrogated 16S rRNA gene, the bulk of the work has indeed been done on the bacteriome but, perhaps surprisingly, even Brüssow does not query whether focusing on the bacteria is really the best use of research effort. Accordingly, while other microeukaryote “parasites” may have seemingly beneficial effects on the immune system via the microbiome, such as fungi [22] (or, more specifically, *Candida dubliniensis* [23]), or the arguably greater ambivalence of protists such as *Blastocystis* species [24], unfortunately it is not yet clear if these are the ones sought by either Rook [5], or Blaser [17].

As well as going up a level, from the bacteria to the microeukaryotes, it may also be instructive to go down to the subcellular level of viruses and circular DNA—mobile genetic elements. Sadly, the same “bacterio-centric” constraints apply, with most interest in the potential use of bacteriophages as replacements for antibiotics [25]. However, bacteriophage action is extremely selective and, by pruning overgrowth, they drive bacterial diversity on both large scales, in layers within the sea [26] and, on small scales, in micro-compartments within the soil [27]. Accordingly, phages may contribute to the evolution of mobile genetic elements among the bacteria [28], presumably including the appearance of antibiotic resistance in the wider environment [29]. Similarly, it is likely that potentially valuable signalling molecules, such as dopamine [30], have evolved to be produced by the bacteria-mediated expression of mobile genetic elements. When considering the organising ability of the microeukaryote parasites, such as the effect of *Toxoplasma gondii* on the brain and nervous system of animals [31], this “multilayered” approach gives a new picture of the fully functioning microbiome: that key microeukaryotes coordinate the expression of mobile genetic elements in a diverse bacteriophage-culled bacteriome. This work has recently been summarised in an e-book “Dysbiosis of the Evolved Intestinal Microbiome: Lessons for Health in Future Generations” [32].

3. Colectomy and its Consequences: Key Molecules and Ingestible Sensors

While few people doubt that the levels of interest in the microbiome concept are steadily increasing, one part of the puzzle remains—that modern clinical practise only tentatively accepts the value of microbiome-related probiotics under limited circumstances [17]. Significantly, perhaps, the most widely accepted role for probiotics is in preterm babies, although there is more work to be done [33]. Perhaps the most underrated finding in adults has come from a form of natural “experiment”: that adults suffering a colectomy had no additional symptoms due solely to the lack of a microbiome. Naturally, the replacement of their colon with a stoma bag necessitates a more careful approach to their diet, but their overall health seems not to have been otherwise affected. In particular, neither male nor female fertility was compromised [34], and females could give birth without need for caesarean section delivery [35]. Another significant set of operations is also of interest from a microbiome perspective: those that restrict the stomach for the control of obesity. While such procedures were originally thought to have purely physical effects, unsurprisingly, perhaps, they are clearly associated with microbial changes, and the hunt is on for which effect is the most important [36]. Of course, the other obesity-modifying treatments are the GLP-1 receptor agonists and, although they will undoubtably have an effect on the microbiome (because every variation will induce a change in bacterial constituents), the mechanism(s) involved require more work [37]. Alongside the clinic, there are many studies on genetically well-defined animals. Interestingly, an unexpected observation arose when two sets of homozygous animals were sourced from different suppliers, and the resultant experimental results did not match up. Investigation showed that the two sets of gut microbiomes were not identical, specific bacteria being implicated by FMT (faecal microbiota transplantation) experiments and their effects on the immune system [38]. Of course, this is unlikely to be an isolated occurrence and will inevitably cast doubt on the overall value of such experiments.

One outcome of maternal colectomy is clear, however, that any subsequent children will be born without an evolved microbiome, presumably incorporating bacteria from other sources, along with fungi and other environmentally available microeukaryotes. There is no indication that such children are worse than their peers but, of course, that fact is consistent with one general deduction: that dysbiosis is both widespread and stems from a malfunctioning microbiome from birth. Caesarean section delivery under sterile conditions affords a similar outcome, whose consequences are still being uncovered [39]. It is important to note that, in contrast to fungi and other environmental microeukaryotes, the evolved microeukaryotes implicated by this hypothesis must be passed on from mother to infant and, once lost from one generation, cannot be transferred to the next. In this way, dysbiosis in a few individuals expands through the generations, eventually becoming the avalanche of illness referred to in the Introduction.

In future, the competence of the maternal microbiome will need to be assessed as part of the reversal of current levels of disease. As noted above, it is likely that a fully functioning microbiome will express signalling molecules such as dopamine [30]. Interestingly, ingestible sensors are pill-like miniaturised electronic devices

equipped with sensor and radio transmitter, eminently suitable for real-time monitoring of gut behaviour [40]. In an earlier article we suggested a suitably equipped ingestible sensor for measuring microbiome effectiveness, [41], although the selection of desired signalling molecule has not yet been made [32].

4. The Evolved Microeukaryote Microbiome Hypothesis: Microbial Sentinel Cells

There is one class of cells that may provide a template for a co-evolved, unicellular immune-system assistant, however. The term "sentinel cell" is a generic expression for parasite-like microeukaryotes, such as dendritic cells [42], constrained to act within our own body so that interlopers may be apprehended. The point is that these invaders—or their key antigens—are physically carried to sites operating as part of the adaptive immune system, in order to generate antibodies. In principle, therefore, similar entities could exist inside the fully functioning microbiome, so that antigen-related information could be physically transferred, during the messy process of birth, from the microbiome of the mother to the intestine of her child. In this way, the growing baby could be effectively calibrated against the (maternal) microbial environment into which the child has just been born. Furthermore, it is envisaged that the docking of these hypothetical "microbial sentinel cells" into the gut wall of the neonate would also activate vagal nerve-related growth of the gut-brain axis, in turn allowing full communication between the three directly microbiome-influenced organs: gut wall, brain, and immune system. It is important to note that the three branches of non-communicable disease: immune system; weight gain; and poor mental health have similar epidemiology and may be considered to be a single "triple plague" [32].

The prime exponent of evolutionary symbiosis during the 20th century was Lynn Margulis (1938–2011). Born Lynn Petra Alexander, she published her influential article "On the origin of mitosing cells" as Lynn Sagan in 1967, successfully proposing the cooperation of two prokaryotes to produce a single unicellular eukaryote [43]. Later, in 1990, Margulis and her team were working on a more comprehensive view of symbiosis, the holobiont, in which a multicellular organism forms an evolutionary unit with key microbes [44]. While definitive evidence could not be obtained, alongside Margulis and her collaborators Carl Woese was developing the "Darwinian threshold" concept. In this system, while multicellular entities evolve according to the natural selection principles of Charles Darwin, single cells accumulate their abilities by horizontal gene transfer of mobile genetic elements [45]. Although the holobiont approach may not have met the strict criteria of evolutionary biology, it nonetheless provides a way to understand the vagaries of non-communicable disease.

The overall process may, perhaps, be best envisaged from the beginnings of multicellular life [32]. While a microeukaryote cell presumably developed multicellularity in the context of a mixed microbial community, such as a biofilm, a next step could well be an "inversion" as it formed a multicellular skin and surrounded a select portion of the original microbial community. In turn, this could be looked on as an early microbiome, in which unicellular eukaryotes may well have adapted themselves as primitive sentinel cells, later differentiating into tissue-dwelling and microbiome-dwelling microbial sentinel cells. Of course, the true measure of evolutionary survival is to be able to reproduce and, therefore, to transfer themselves between "mother" and "daughter" down the generations [32]

On the assumption that, at the moment, the presence of a co-evolved microbiome can only be confirmed by the observation of the non-communicable conditions consequent upon its loss, it is important to look for such "indicative" disease in our animal partners. Atopic disease is well known in domestic animals [46], and the ability of antibiotics to accelerate the growth of both farmed mammals and domestic fowl is, likewise, well recognised [47]. Of course, the current need is to reduce antibiotic usage, finally leading to some belated research effort [48]. It is interesting to note that no-one seems to have connected the enlargement of farmed animals in the presence of antibiotics with weight gain and related disease in children and adults.

5. All Being Well: A Dual Inheritance

"Health" is a remarkably difficult state to define. Once we get beyond "absence of disease" an absolute definition requires many words, especially when taking into account living with disability and chronic conditions [49]. In the context of this article, however, perhaps the best approach is to follow Burkitt's observations on people living their traditional lifestyles, including both those eating a high-fibre diet as well as the cattle-rearing, steppe-dwelling Maasai [7]. It is interesting to note that modern-day "health" systems only track disease, whereas the "evolved microbiome" hypothesis requires an intergenerational inheritance of a fully functioning maternal microbiome. Indeed, it is perfectly possible that an ongoing healthy maternal microbiome lineage is still to be found in western-style populations, but without being recognised for what it is.

With their agreement, a community of Tanzanian hunter-gatherers, the Hadza), have been subjected to medical surveillance for a number of years, including so-called "ultra-deep sequencing" of their (bacterial)

microbiome. Unsurprisingly, perhaps, many bacterial strains new to science have been discovered, but their connection to health remains unclear [50]. Similar studies are being performed on the Bolivian Tsimane, a community of hunter-gatherer-farmers. Initial studies, reported from 2017, focused on their low levels of coronary arteriosclerosis [51] while later information emphasised brain health, in spite of high levels of inflammation [52] and, separately, low levels of arterial stiffness [53]. Although their (bacterial) microbiome has been reported [54], in common with other Amazon-basin peoples the modern emphasis remains on their high step-count and low exposure to ultra-processed foods, with the warning that these advantages cannot last [55].

The evolutionary nature of this hypothesis implies a dual inheritance, of both parental genetic and maternal microeukaryote microbiome. Figure 2 illustrates the key features, focusing on those organs most closely associated with dysbiotic disease. In this hypothesis, the development of the foetus remains incomplete, needing to be updated by faecal "inoculation" by microeukaryotes passed on from the maternal microbiome. This inoculation has a twofold function, both calibrating the neonate immune system against the microbial environment experienced by the mother and also activating growth of the gut-brain axis. The result, ideally, is a fully communicating "immune-gut-brain triangle", and the capacity for further environmental adaptation in future generations. The expression "handshaking" is another example, alongside "computer virus" of the overlap between biology and computing: in this context the term biological handshaking is used to define the processes of communication between one chemo-electronic device, the maternal microbiome, and another, the neonate gut wall. A similar process may occur at key points in the life of the organism: puberty; pregnancy; serious illness; and menopause, and these are the times when seemingly new non-communicable diseases may occur. Indeed, it is likely that these vulnerabilities occur because the initial handshaking phase was unsuccessful, although further involvement of the microbiome cannot be ruled out at current levels of knowledge. While the term "mosaic of autoimmunity" encapsulates a given patient in a given time, looking at the wider picture over a longer time frame lends itself to the concept of a more dynamic state of flux: a "kaleidoscope of dysbiosis".

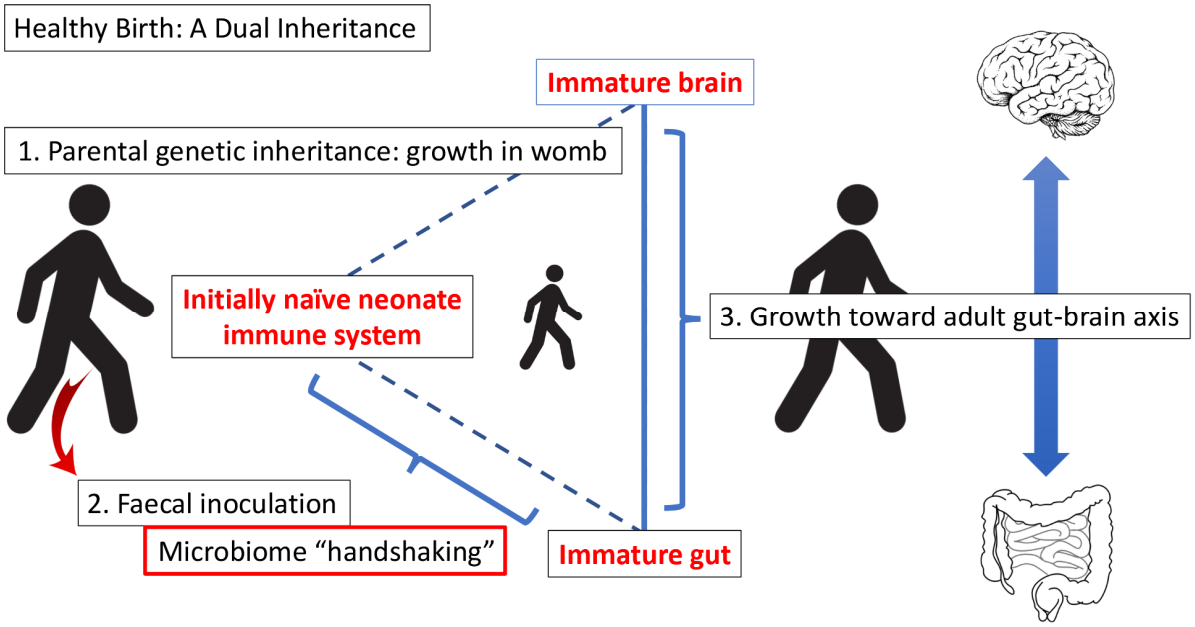

Figure 2. A healthy birth, a dual inheritance. Box 1. The foetus grows according to its parental genetic inheritance, producing an immature brain and gut, along with an initially naïve immune system (red writing). Box 2. Faecal "contamination" is also an inoculation by microbial sentinel cells contained 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.

6. What Went Wrong…? A Kaleidoscope of Conditions

While Blaser's hypothesis—that antibiotic-driven loss of key microbiota is ultimately responsible for the bulk of non-communicable disease [17]—has driven much speculation, the failure to find obvious candidates for key immune-modulating microbes, in spite of extensive searching [5], is discouraging. Nevertheless, the virtually explosive spread of hay fever (seasonal allergic rhinitis), from Bostock's "well-off" 28 people in the early 19th century [2] to the millions of the early 21st [3], strongly suggests an environmental factor in addition to any genetic

susceptibility. However, while hay fever, an essentially harmless condition, attracts relatively little funding, the same cannot be said of the equally mysterious, but far more serious, coeliac disease.

This non-communicable disease, an allergic response to a variety of related cereal proteins ("gluten"), has a variable presentation but may give rise to malnutrition. Its incidence lies between 0.7 and 1.5% of the overall population but is currently increasing by about 7.5% per year [56] (i.e., approximately doubling every decade). In common with other systemic autoimmune diseases, coeliac disease may present with extra-intestinal manifestations, such as dermatitis herpetiformis [57] and has also been associated with psychiatric and neurological symptoms [58], in common with other systemic autoimmune diseases [59]. Coeliac disease is almost invariably associated with specific haplotypes, which are assumed to have been generated as the early hunter-gatherers became cereal farmers, and which have been traced back at least 2,000 years: to the case of a young lady interred by a rich family in 1st century CE Italy [60].

Clearly, Blaser's "antibiotic-driven" hypothesis cannot apply to Bostock's hay fever, but an alternative explanation, also applicable to the Ancient World, may be suggested. Since earliest times, humans have had an association with caves and, therefore, with readily mined but toxic heavy-metal ores. Equally, of course, humans have long had a desire to beautify themselves with cosmetics and the use of lead derivatives—black lead sulfide, white lead carbonate, and red lead oxides—were well documented in Bostock's day [61]. In a similar fashion, the more well-off members of society could well have been eating with pewter utensils—an alloy of tin and lead, among other potentially toxic heavy metals [62]. Finally, although there is no direct information of autoimmune disease in prehistoric times, the presence of statuettes potentially representing obese females, the so-called "Venus figurines", have been discovered at intervals by archaeological excavation [63]. Although nothing can be confirmed, these could be evidence for non-communicable disease in palaeolithic times. Miniature ceramic bottles potentially containing cosmetic lead-derived residues have indeed been found, dating back as far as the 5th millennium BCE [64].

It is possible to envisage a low-level but continuous ingestion of toxic microparticles, from either cosmetics or cutlery, but without triggering the symptoms of acute poisoning. Engagement with microbial sentinel cells could, potentially, lead to their eventual disappearance. In the absence of sequestration, toxic heavy metals can only be removed by defecation, a process known to be slowed by such metals. Indeed, in parts of the world, constipation is considered to be a sign for testing, especially in children [65]. In his comparison of traditional peoples with "Western Civilization", Denis Burkitt provided information on stool weights: "often average 400–500 g of soft, unformed stool daily" compared to "under 150 g of firm, formed stool" [7], data which is largely confirmed by more recent studies [66]. Accordingly, it is tempting to suggest that the diseases of "modern Western Civilization" (Table 1) reported by Burkitt are indeed related to lead poisoning, especially in the knowledge that the 1970s, when Burkitt was reporting, was the peak use of leaded petrol in most high-income countries [67]. Encouraged by increasing levels of various neurodevelopmental brain disorders since the beginning of the 21st century, the concept of the exposome has been promulgated, which includes essentially all sources of non-endogenous interactions with individual genetic backgrounds. Needless to say, this is a very wide field indeed, with the (mostly) bacterial microbiome only a small part of it [68]. It could be that this microeukaryote microbiome hypothesis will help to make exposome-based arguments more cogent.

7. …and How to Fix It: The Central Role of the Brain

The current situation is, perhaps, best represented by Figure 3, the immune-gut-brain triangle, in which the three organs most susceptible to dysbiosis, the brain (poor mental health); the gut (associated with irritable bowel syndrome and/or weight gain); and the immune system (autoimmunity and cancer in people younger than 50-year-old) are connected by dotted lines representing incomplete communication (effectively "connectivity dysbiosis", perhaps temporarily ameliorated by placebo-like activation). The concept of a gut-brain axis is most obvious, with much work on the vagal nerves and the so-called gut-brain axis [69]. However, the interaction between nerves and immune system is coming increasingly into focus, as is nerve-brain maturation, its links with autism and schizophrenia [70] and the implications for neurogenesis [71]. Finally, the immune system has been suggested to be part of the communication pathway between gut and brain [72], however, this study posits a direct connection between gut microbiota and brain, thus failing to explain how people seem to stay healthy after a total colectomy, at least as far as fertility is concerned [34].

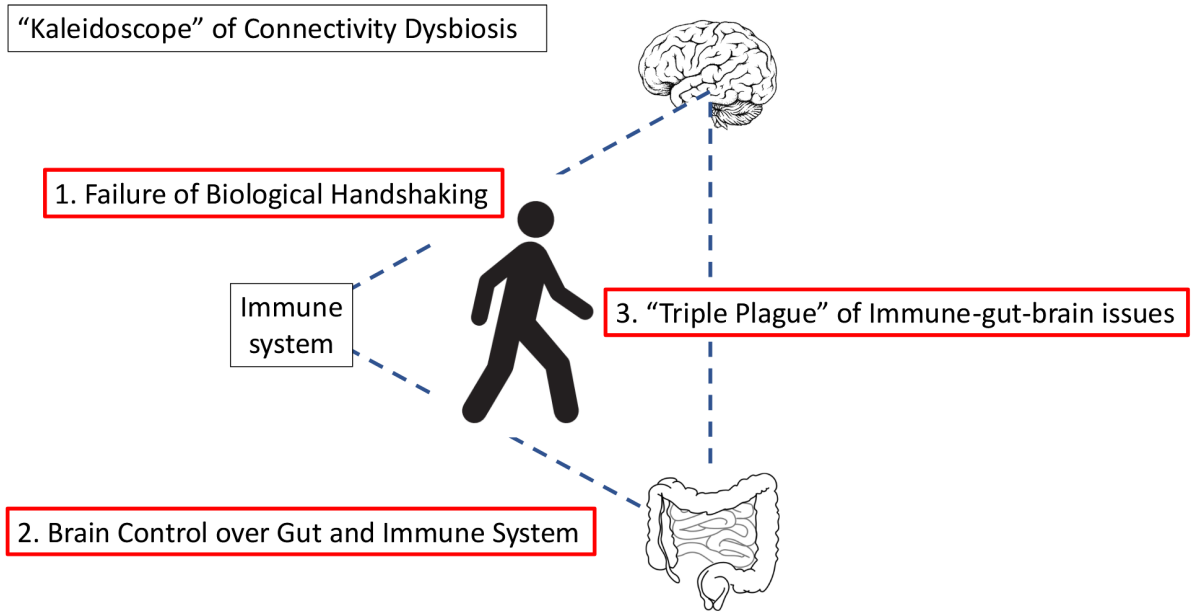

Figure 3. A kaleidoscope of connectivity dysbiosis. Box 1. The failure of biological handshaking, for whatever reason, results in poor inter-organ communication (represented by dotted lines). Box 2. After the biological handshaking process, the brain interacts with both immune system and gut wall. Box 3. The intermittent nature of communication between the three vertices leads to issues with brain, gut, and immune system, resulting in a "triple plague" of non-communicable diseases with a common underlying cause.

Rather than the organs themselves, the key point seems to be that communication is the problem, that, following the failure of the "handshaking" process of Figure 2, neurogenesis remained incomplete during the transition into adulthood. Granted that, as stated above, the microbiome has little role in the adult, the emphasis lies in the growth of the brain, in turn requiring adequate input through the nerves. Perhaps the best way to look at the situation is to say that inadequate input determines the direction of brain growth, rather than the extent, and that this dichotomy determines the type of neurodevelopmental disease that may result. Although the effect on brain shape can often be observed, of course changes are invariably interpreted in the light of an individual's genetic inheritance, rather than any dual inheritance, "handshaking", interpretations [73]. It is important to note, however, that a change in brain shape may not result in a reduction of ability, as demonstrated by the rare phenomenon of savant syndrome, in which people suffering from, for example, potentially severe autism spectrum disorder may still exhibit abilities in excess of their general functioning level, indeed potentially greater than those of the bulk of the population [74]. Changes in the brain are known to take place in stages, perhaps being more clearly defined by the science of "structural topology", the neural connectivity of the brain. A recent article illustrated four major turning points, starting at nine years, presumably preparing for puberty, and at 32, 66, and 83 years [75]. Interestingly, the total data set corresponded to about 4 000 individuals ranging from zero to 90 years old. Of course, this time period includes ever-increasing levels of dysbiosis, and it would be interesting to know if these results were affected.

In a similar fashion, placebo effects are both profound and surprising, are often associated with expectation, conditioning, and contextual cues [76] and can affect both immune and endocrine systems [77]. However, it has long been known that expectation is not necessary for a placebo-like effect to occur, so that, when such trials were carried with the full knowledge of the patient, apparently there was still an improvement compared with no treatment at all [78]. Interestingly, deep brain stimulation has grown in importance in recent years, with no sign of slowing down [79]. One of its major uses is in the control of motor disturbance [80], and we have suggested that obesity may be a consequence of the brain-moderated rate of peristalsis through the small intestine during digestion [32]. Once the brain is fully accepted as being involved in immune system control, it seems that non-communicable disease in general could already be on the way to being a solved problem.

8. Plugging the Gap: Supplementation with Microbial Sentinel Cells

The essence of this evolved microeukaryote microbiome hypothesis is that immune system information is somehow passed from maternal microbiome to neonate intestine at birth. It is further hypothesised that the agents

of this transfer, tentatively termed microbial sentinel cells, have disappeared from at least a large proportion of the population under the combined stress of pollution, antibiotic overuse, and delivery of babies by caesarean section under sterile conditions [32]. As mentioned above, FMT, faecal microbiota transplantation, is regarded as a safe and potentially effective way of reversing the damage caused by overgrowth of *Clostridioides difficile* (previously known as *Clostridium difficile*) [81]. Likewise, the form of FMT delivered at birth after caesarean section delivery, variously referred to as vaginal inoculation, microbirthing, or vaginal seeding, is still under investigation to reduce the potential long-term dangers to the child associated with caesarean section delivery [82]. It is interesting to consider that emergency C-sections carried out "in the field" are likely to introduce far more faecal contamination than would ever be considered in a hospital. Of course, in earlier days, before the current prevalence of non-communicable conditions, it is reasonable to suppose that microbial sentinel cells would have been far more common. In fact, considering their microeukaryote nature, such cells would be expected to actively seek out the mouth and intestine of the neonate.

While the microbiome is normally considered to include both prokaryotes (bacteria and archaea) and seemingly accidental microeukaryotes (such as fungi), largely for reasons of experimental convenience (specifically the readily interrogated 16S rRNA gene), the focus is mostly on the bacteria. By contrast, this hypothesis regards the primary role of bacteria as carriers of mobile genetic elements and the faecal bacteriome as overgrowth, excreted because it is excess to requirements, but unlikely to contain microbial sentinel cells [32]. Instead, such cells, representing an intergenerational component of the immune system, may only multiply in the pregnant female, ready to be transferred to the neonate at the time of birth (or carried with the egg in non-mammal vertebrates). Rather than a swarm of such cells, each identifying a separate antigen, it may be that, while the bulk of such information is built into the foetus during growth, microbial sentinel cells have evolved both to carry any updates, and also to initiate growth of gut-brain communication [32]. Taking the hypothesis to its logical conclusion, the prevention of non-communicable disease in the infant can be realised by the artificial transfer of "fully charged" microbial sentinel cells during the birth process. In turn, these charged cells could be either purified or, to allow for any as yet unknown co-factors, delivered as a complex mixture as for the post-birth FMT process described above.

In practise, the situation is complicated by the need to find healthy donors, bearing in mind that the "health" systems of most of the world actually track disease, and are based on the assumption that disease is something externally imposed on a genetically healthy state. In other words, "health" is more akin to the traditional peoples reported by Burkitt [7], capable of bearing healthy children. While their modern-day equivalents include the Tsimane, they have been studied for more than ten years [51] and will have been exposed to the problems of antibiotics, delivery of babies by C-section, and the unquantifiable levels of "exposome" pollution that are inseparable from modern life [68]. Similarly, although ethical animal experiments could be performed before human studies, an example of different laboratory animal microbiomes affecting the result of gene-based experiments was presented earlier [38]. Until we know more about this very new situation, it seems necessary to work with wild animals wherever practicable. One possibility may be to work with the semi-wild animals of the Amboseli Baboon research project [83] or, alternatively, wild boar may swallow ingestible sensors [40]. Bird and other non-mammal eggs may provide information about evolutionary pathways. In particular, pigeons produce so-called crop milk, from both sexes [84] and, like human breast milk [85], such "milk" includes bifidobacteria. Rather than these agents actually occupying the intestine, however, their primary role could be to stimulate the immune system of the young [32]. It is important to note that any information obtained from traditional peoples should be compensated for, possibly by the methods evolved for ethnobotanical knowledge of medicinal plants as cancer therapies [86].

9. Summarising the Hypothesis

It will be apparent that the acceptance of the existence of an microeukaryote microbiome transferring immune system information from mother to child casts a new light on the concept of inheritance. Although such concepts have been reviewed in our recent e-book "Dysbiosis of the Evolved Intestinal Microbiome: Lessons for the Health of Future Generations" [32] it is worth restating some of the key points here:

1. Microeukaryote Microbial Sentinel Cells. The first key point is that sentinel cells, such as dendritic cells [42], as well as being part of our innate immune system, should also have an evolved counterpart in the intestinal microbiome of the vertebrates (i.e., microbial sentinel cells).
2. Faecal Inoculation. The essence of this hypothesis is that microbial sentinel cells should transfer up-to-date information from mother to offspring (live birth or egg) about the microbial environment into which it has just been born. At the moment it is not clear if specific bacteria (or mobile genetic elements) also need to be

transferred along with the microeukaryote microbial sentinel cells themselves. Of course, the most obvious way to disrupt this process is by C-section delivery under sterile conditions. Although studies have been performed to elucidate the effects of C-section [39], the outcome is complicated by the presence of pre-existing dysbiosis. Similarly, as discussed above (see Section 3) maternal colectomy ensures that any children are effectively germ-free [35]. To my knowledge, the effect on the health of such children has not been studied.

3. Microbiome Handshaking. The key point here is that the microbial sentinel cells mentioned above should interact with the gut wall of the offspring, effectively calibrating its immune system to recognise antigens (harmful or otherwise) associated with the microbiome of the mother. By analogy with a similar exchange of information between two electronic devices, we term this process "biological handshaking" and consider it to be analogous to the borrowed concept of computer viruses. A failure here has disastrous consequences and is probably the best way to understand autoimmune diseases such as Bostock's hay fever. Likewise, this phenomenon may explain the observed increase of cancer diagnoses in younger patients, if there is an inability of the "uncalibrated" immune system to deal effectively with precancerous lesions in this group.
4. Mobile Genetic Elements. The so-called "good bacteria" are considered to be associated with health, but the nature of this association has never been made completely clear [19]. Interestingly, as stated above, Carl Woese was developing the concept of the Darwinian threshold, in which microbes update their skills by the uptake of mobile genetic elements [45]. Indeed, bearing in mind the earlier discussion on the role of bacteriophage viruses (see Section 2), it is possible that the direct focus on the bacteria themselves may be misplaced.
5. Dysbiosis. In this scheme, dysbiosis represents the failure of the handshaking process, with concomitant brain-gut-immune system communication problems as the new-born grows to adulthood. Equally, although bacteria can be uploaded from the environment, once microbial sentinel cells are lost they cannot be replaced naturally, implying that dysbiosis passes from mother to child down the maternal line. Indeed, this is probably the most succinct way to understand the epidemiology associated with the dysregulation of immune system, brain, and gut.

10. Can We Find Microeukaryote Sentinel Cells?

Needless to say, this is a very new interpretation of the nature and extent of non-communicable disease. Probably the most direct and helpful way to accrue evidence for this mechanism is to identify these hypothetical microeukaryote microbial sentinel cells themselves. Three steps are likely to be involved:

1. Candidate Eukaryotes. While the faecal microbiome represents a good source of bacteria, there is no reason to suppose that microbial sentinel cells should be present in a waste product. Indeed, it is possible that such cells are only generated in the latter stages of pregnancy, perhaps after the embryo is nearly complete. Equally, transfer to the baby will probably be quite random, implying a relatively large number of such cells with a correspondingly high chance of picking some up by swabbing at an early stage. The "sting in the tail", however, is that such cells would only be expected if the mother herself does not suffer from non-communicable disease, even if not yet diagnosed (see discussion in Section 5).
2. Identification of Microbial Sentinel Cells. While such swabs will pick up a large number of eukaryotic cells, identifying the key cells may be more difficult. While passive behaviour (waiting to be swallowed) is possible, they may be actively programmed to follow a chemical scent to mouth or, perhaps, to the anus. Of course, active movement would make identification easier.
3. The Transmission of Health. The full hypothesis states that such cells have evolved [32], and their analogues should therefore be found in all representatives of the Vertebrata. Of course, we have already seen problems of bacterial composition in animals raised within two different laboratories [38] and it could be that microbial sentinel cells cannot be recovered under these circumstances. Essentially the same unreliability arguments apply to pet [46] or farmed [47] animals. Interestingly, Burkitt himself made the point that such diseases are "rare or unknown in undomesticated animals" [7].

In summary, although there are practical and ethical objections, the promise of a future free from non-communicable disease should make the detection of microbial sentinel cells an objective worth pursuing.

11. Can We Reverse Existing Disease?

The essence of this hypothesis is that health (in the sense of freedom from non-communicable disease) can only be guaranteed if brain and body are fully coordinated from birth [32]. In turn, the implication is that autoimmune disease, for example, starts when the brain can no longer control the body's response to an irritant—

as if a portion of the immune system is under local control and over-reacts when faced with seemingly local problems. Similarly, we have previously suggested that weight gain follows from a slowdown in the rate of peristalsis as the brain loses communication with the gut following the developmental failure of the gut-brain axis after birth [32].

Parkinsonism is another example of a non-communicable disease that involves both motor disturbance and, it seems, the immune system. When dopamine-based motor control regimens were less successful, attention turned to electrode-delivered deep brain stimulation [80]. More recently, however, less invasive transcranial technologies have proved promising, using either magnetic, direct- or alternating-current. Significantly, at least some of these techniques have been shown to influence the immune system and thereby mediate clinical improvements [87]. Combining these successes with the reported "psycho-neuro-endocrine-immunological basis of the placebo effect" [77] and there may be new ways to control a range of non-communicable diseases.

It is important to note, however, that at this stage both "prevention" (Section 10) and "amelioration" (this section) should be pursued independently. Even if the microbial sentinel cell hypothesis does not stand up to scrutiny, the overall idea of immune-gut-brain communication appears to stand on its own merits.

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D.S. confirm that I was the sole contributor to this article. The author has read and agreed to the published version of the manuscript.

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