gastrointestinal disorders

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Review

Microbiome–Gut Dissociation in the Neonate: Obesity and Coeliac Disease as Examples of Microbiome Function Deficiency Disorder

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Abstract: The purpose of this article is to provide a direction for translational research based on an analysis of the nature of complex, immune-related conditions such as obesity and coeliac disease. In essence, it seems that the prevalence of these non-communicable diseases is related to the degradation of the microbiome during the industrialisation of society, and that their nature can be used to infer the functions of the "pre-industrial" microbiome. Based on this analysis, the key point is the necessity for the fully functioning microbiome, acting alongside the parental genetic inheritance of the child, to be in place immediately after birth. In our view, this is achieved by the seemingly accidental process of *maternal microbial inheritance* during normal birth. Note, however, that this is not possible if the microbiome of the mother is itself degraded following previous problems. Under these conditions the health of a child may be affected from the moment of birth, although, with the exception of atopic diseases, such as eczema and food allergy, the consequences may not become apparent until late childhood or as an adult. In this way, this *microbiome function deficiency hypothesis* incorporates the epidemiological observations of David Strachan and David Barker in that their onset can be traced to early childhood. Coeliac disease has been chosen as an illustrative example of a multifactorial disorder due to the fact that, in addition to a series of immune system manifestations and a potential problem with food absorption, there is also a significant psychological component. Finally, it is worth noting that an ingestible sensor calibrated to the detection of interkingdom communication molecules (semiochemicals) within the intestine may offer a practical way of assessment and, perhaps, amelioration of at least some of the consequences of non-communicable disease.

Keywords: cancer; celiac disease; energy compensation; gut–brain axis; heavy metal pollution; ingestible sensor; maternal microbial inheritance; microbial sentinel cells; non-communicable disease; semiochemicals; weight set-point theory; translational research

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1. Introduction: Obesity and the Puzzle of Non-Communicable Disease

While it is clear that the growth in incidence and severity of obesity is linked to both food and exercise, the difficulties associated with human studies means that further progress is beset by a lack of adequate evidence. Although quantitative techniques, such as experiments involving doubly labelled water, allow some factors to be better understood [1], the science is still far from settled and, while scientists debate, the problem is increasing across the world [2].

Although they come in various guises, as outlined in a 2015 review by Casazza, the two primary assumptions underlying obesity research are that people eat too much (sometimes described as hyperphagia) and/or do too little [3]. However, although not mentioned in this review, there is invariably an unrecognised third major assumption; that the energy lost through faeces is, and always has been, negligible. Although this may be true nowadays,

it has not always been the case and, perhaps, the most direct way to understand obesity is that the output of energy by the faecal route has become negligible across most of the world in recent decades [4]. Significantly, there are three basic forms of non-communicable disease, of which obesity is only the most visible. The symptoms of immune system problems are often obvious only to the sufferer, while the third manifestation, poor mental health, may actually be invisible to the affected individuals themselves. Recently, we have found a way to connect all three forms of non-communicable disease in modern industrialised societies by reference to the degradation of the long-established intestinal microbiome under the influence of toxic heavy metal ions [5]. Furthermore, the damage to the microbiome has been passed on down through the generations by the seemingly accidental process of *maternal microbial inheritance*. Accordingly, the normal mutualistic interaction with the parental genetic inheritance of the child has been lost [4]. Although this situation has been termed *dysbiosis,* it has also been noted that this expression is too general to be useful [6]. Likewise, Brüssow bemoans the fact that the field is driven more by methods than by hypotheses but, although he does not stress the point, his review, nevertheless, emphasises the exclusive focus on the bacterial microbiome, affording no mention of microeukaryotes [7]. Our interpretation of the findings of Brüssow is that there are no unambiguous cases of specific bacteria associated with a fully functioning microbiome [4]. Furthermore, to be clear, in this work we use the term dysbiosis as a convenient shorthand for *microbiome function deficiency disease* [4]. Equally, while the term "microbiota" can be used to mean the microbes themselves, usually bacteria, the term microbiome has been used to include their genes. In this work, we employ these two terms interchangeably, but only to smooth the flow of discussion by avoiding repetition. Unicellular eukaryotes are present in the enclosed intestinal microbiome and are assumed to have a significant role, albeit not precisely defined as yet [5].

The term *epigenetics* was first coined by Waddington in 1942 to describe the temporary changes in gene expression needed during the translation of a given genotype into its equivalent adult phenotype [8]. Eventually, attention focused on the heritability of epigenetic instructions associated with "paternal effects" [9], while the whole concept of epigenetic inheritance or "missing heritability" [10] has been questioned on the grounds of inadequate evidence [11]. In principle, the notion of maternal microbial inheritance could supply an alternative method of transmission of epigenetic information if, as has been suggested, the microbes transferred to the neonate could crosstalk with the epigenome [12]. In light of that possibility, we have previously suggested [4] that the mutualistic body/microbiome combination represents an assembly capable of undergoing evolutionary changes both above and below what has been called the Darwinian Threshold [13], referring to the dominance of horizontal gene transfer, and conforming, at least approximately, to the principles of the holobiont [14,15] (however, note the "helpful or hollow" cautions of Moran and Sloan [16]). If so, the likelihood is that this holobiont-like assembly has co-evolved with the Vertebrata across the Ediacaran–Cambrian boundary [5]. Note that our scheme relies on the presence of microeukaryotes to give the microbiota greater capability than might be expected from bacteria alone. Interestingly, such unicellular eukaryotes have already been referred to as the "missing link" in studies of the intestinal microbiome [17].

Two non-microbiome explanations for obesity are mentioned here for the sake of completeness. Firstly, the carbohydrate-insulin model suggests that a high-glycaemic-load diet itself drives unspecified hormonal changes that encourage a "positive energy balance" lifestyle. Definitive tests of this new hypothesis are anticipated [18]. Secondly, it has been argued that the increase in the ratio of omega-6 over omega-3 has led to obesity via a change in eicosanoid metabolites and hyperactivity of the cannabinoid system [19]. To our knowledge, however, it has not been demonstrated that this can produce the range of non-communicable diseases that are commonly observed in affected human and domesticated animal populations. In contrast, one of the features of non-communicable disease is its parallel with both the industrialisation of society and the concomitant reduction in faecal

energy excretion [4]; we believe that this makes a microbiome-based explanation inherently more likely.

Of course, the failure of the microbiome might, in principle, allow a connection with a number of other non-communicable diseases. It is the purpose of this article to propose an outline mechanism to illustrate the nature of these connections. Although we chose coeliac disease as an example of such diseases, the same mechanism also applies to the increasing incidence of cancer in the modern world.

2. The Role of the Microbiome in Training the Immune System

Perhaps the clearest early indication of modern non-communicable disease was reported by the well-regarded Dr John Bostock in 1819 [20]. He described a mysterious set of symptoms, starting when he was only eight years old, which plagued him for a few weeks every summer. He called this disease *catarrhus aestivus*, and we now know it as seasonal allergic rhinitis, or hay fever. In the early half of the 19th century knowledge of disease in general was expanding rapidly, but this one seemed to be unique. Over the next nine years he discovered a total of twenty-eight cases, and he was sufficiently thorough to ensure that they belonged only to the very highest ranks of society, often royalty [21]. Compare this with the worrying increase in hay fever and asthma described by David Strachan in the late 20th century [22], concerns that were repeated only a few years later [23].

While Strachan mentioned the idea that microbial exposure somehow "trains" the immune system of the child to differentiate the various antigens found in its environment [22], an idea which was later followed up by Rook and his team, no definitive evidence of an *external* training entity was observed [24]. Nevertheless, low diversity of the intestinal microbiome is known to be associated with poor health outcomes [25] and we have suggested that it has its greatest effect on the new-born [4]. This process, presumably relying on an *internal* training system passed on by maternal microbial inheritance, would help to account for the epidemiology of such diseases as food allergy [26] and the so-called "atopic march" as the sequence of disease unfolds [27]. Of course, autoimmune conditions such as coeliac disease may also start in the child [28], alongside the closely related type 1 diabetes [29], and these diseases are also found in domesticated animals [30].

It is now known that the bacterial microbiome can empower the immune system by the production of vitamins and short-chain fatty acids (SFCAs) [31], and it is feasible that the low diversity of the modern microbiome may produce the observed symptoms by somehow nullifying this effect. However, we have recently suggested that as yet unknown microeukaryotes may represent a form of *microbial sentinel cell*, with the ability to pass antigens directly from the mother to the neonate [4]. This may well be analogous to dendritic cells [32] and both may have descended from an evolutionary precursor [5]. The basic principle is outlined in Figure 1, which illustrates the idea that the single most important function of the microbiome is to calibrate the initially naïve immune system of the neonate against the antigenic environment of the mother. This educational role for the microbiota has already been recognised in both the innate [33] and adaptive aspects of the immune system [34].

In conclusion, although it cannot be said to be proven as yet, it seems to be feasible that the intact, functioning microbiome prevents immune system problems in the neonate and, presumably, in the adult also. In turn, it is part of the responsibility of the adult to keep the microbiota well supplied with adequate amounts of nutrition in order that the mother can give her child the best possible chance of independent life. This relies on the formation of an efficient gut–brain axis [4].

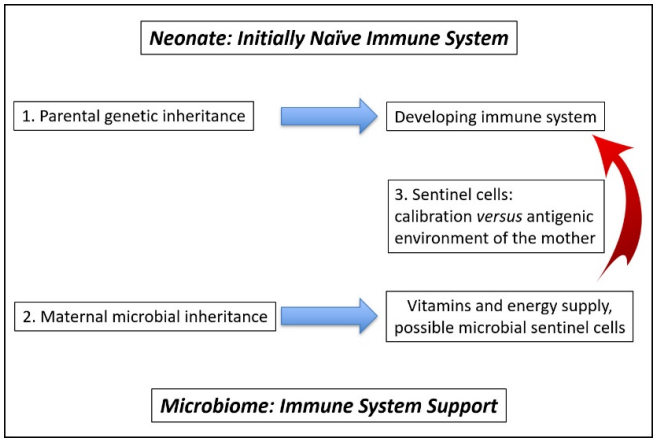

Figure 1. The Role of the Foetal Microbiome in Immune System Education. **Box 1**. The foetus develops according to its parental genetic inheritance, but initially with a naïve immune system. **Box 2**. The microbiome of the neonate is provided by its microbial inheritance from the mother. **Box 3**. The microbiome of the mother contains factors which help to educate the immune system, avoiding conditions such as hay fever or coeliac disease.

3. The Microbiota–Gut–Brain Axis as an Explanation of Obesity

Unfortunately, the epidemiology of other forms of non-communicable disease are not as clear-cut as hay fever, as conditions tend to present themselves differently in each individual. An article published in the New England Journal of Medicine in 2012 covered the changing nature of disease over the previous 200 years, documenting the steady shift of the cause of death from infectious to non-communicable conditions, such as coronary heart disease [35]. Of course, this period covered the establishment of the Germ Theory of Disease and the development of antiseptics and antibiotics, alongside the industrialisation of society. Significantly, at the date of this work, 2012, there was a degree of understanding of the value of intestinal microbiota, however, this phrase was not mentioned in this article [35].

The potential for an apparently leisure-induced epidemic of obesity was recognised as far back as 1912, in an editorial carrying the evocative title "The Automobile Knee" [35]. Interestingly, of course, the gain of abdominal fat shows up most clearly in previously wasp-waisted women, while in men, the subtler change from muscle to fat is not so readily apparent. Accordingly, one of the earliest and most comprehensive of the popular diet books was based on the personal experience of the author, Dr Lulu Hunt Peters, and was written specifically for women. It was first published in 1918 with the title "Diet and Health: With Key to the Calories" and is still available [36].

Significantly, although the range and extent of non-communicable disease has indeed increased substantially throughout the 20th century, it did so across the generations, so slowly that, essentially, people did not notice. Accordingly, when a Western-educated surgeon, Denis Burkitt, found himself operating amongst the traditional societies of Africa during the middle of the 20th century, he was very surprised to find that the majority of what he termed the diseases of "Modern Western Civilization" were essentially absent from people living in these societies [37]. Recognising an environmental cause, he focused on what he knew; that the levels of dietary fibre in Western-style diets were significantly lower than in the majority of the African societies that he studied [37]. Importantly, however, he noted that the Maasai (Masai in his day) consumed a more Western-like diet based largely on grain, dairy, and other animal products, *and yet remained free from disease*. Lacking knowledge of the microbiome, he frankly admitted that he was unable to explain the immune system problems of what he called "Modern Western Civilization". Finally, as was normal for the times, he simply failed to mention any problems of mental health whatsoever [37].

Quoting a personal communication about references in art and literature, Burkitt reported his belief that obesity was rare before the late 18th century [37]. Significantly, perhaps, this was

about the same time that Bostock was describing his hay fever [20], lending some credence to the concept that they both have the same cause [4]. Needless to say, these Burkitt-like afflictions, including obesity, are no longer restricted to the "leisured classes" of earlier times and, moreover, are increasingly apparent in childhood. At this point, it is worth emphasising the observations of the epidemiologist David Barker; that the roots of adult disease can be traced to early life, not only heart and circulatory disease, but seemly, also schizophrenia [38]. Although normally termed the "fetal origins hypothesis", our work stresses the infant rather than the foetal aspects [4]. While the evidence is not considered totally secure, and there is no universally-recognised mechanism in which early life can affect the adult, nevertheless, many epidemiological factors are in favour of his hypothesis [39,40]. In this context, a comparative study of English ten-year-olds of both sexes, has shown worrying trends, even across the short time-period from 1998 to 2014. Worryingly, although there were increases in girth, height, and weight, meaning that their average body mass index remained the same, *their strength decreased* [41]. A similar effect was recently reported among Slovenian children [42].

The first sign that the intestinal microbiota may have an effect on behaviour came when researchers found that specially raised germ-free mice exhibited fearless behaviour, effectively an emotional deficit, a situation that was only partly repaired by providing the missing microbes at a later stage of development [43]. In addition, although the skin is also a microbe-rich environment, the gut microbiota seem to have a major effect on the emotional response to acne, for example, in what has been described as a gut–brain–skin axis [44]. More recently, the microbiota–gut–brain axis has been recognised as a part of the problem of obesity, but the exact details of the connection are, as yet, unclear [45].

A potential solution to this dilemma has been described by Sudo, who reported finding biogenic amines behaving as interkingdom signalling molecules [46]. These molecules, *semiochemicals*, are specific chemicals released by one species with the aim of modifying the behaviour of a different species. It is possible that bodily hormones and microbial semiochemicals are actually the same compounds but produced in different circumstances, with the overall aim of stimulating the formation of a mixed neural/chemical signalling system. As examples, it is suggested that ubiquitous amines such as dopamine, serotonin, and histamine are involved in the microbiota–gut–brain axis [46]. It is important to note that such signalling molecules may act on the gut wall, initiating further actions, without necessarily exiting the gut in order to directly influence the rest of the body or brain. Such a process would be underway from the moment of birth and is summarised in Figure 2. Of course, a failure to establish a secure gut–brain connection in the neonate could have consequences for the subsequent development of the brain, perhaps explaining the epidemiological observations of Barker described above [38]. The role of the microbiota–gut–brain axis in mental health will be dealt with in a later article.

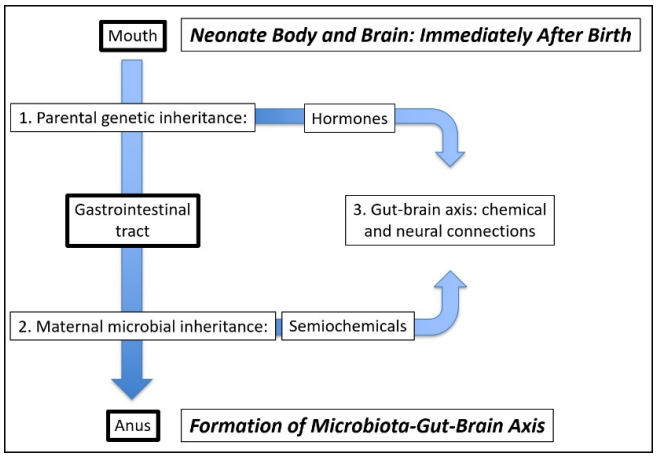

Figure 2. The Role of the Foetal Microbiome in Connecting Microbiota, Gut, and Brain. **Box 1**. The foetal gastrointestinal tract (dark border) develops according to its parental genetic inheritance. At the

same time, hormones are produced by the endocrine system. **Box 2**. The microbiome of the neonate is provided by its microbial inheritance from the mother. At the same time, semiochemicals are produced, acting as interkingdom signalling molecules. **Box 3**. The combined action of hormones and semiochemicals creates and maintains channels of neural and chemical communication between microbiota, gut, and brain.

4. The Mutualistic Microbiome

At its most basic, mutualism between two partners implies two complementary actions, each helping the other. We have suggested that the primary purpose of the microbiome is to calibrate the immune system of the neonate against the microbial environment of the mother, thereby helping the young animal, and its microbiome, to an independent existence as quickly as possible [47]. A failure of this system, while requiring significant pharmaceutical intervention in humans, would ultimately be fatal in the wild. The *quid pro quo* for such immune system assistance requires the microbiome to be fed with a portion of the food of the animal. A failure of this nutrient-sharing function ultimately leads to the full range of these microbiome-related non-communicable diseases, as follows:

4.1. Calibration of Neonate Immune System

As illustrated above (Figure 1), we have previously suggested that the functioning microbiome of the mother will pick up antigens corresponding to its environment, possibly via the intermediary of so-far hypothetical microbial sentinel cells and will pass them on to the neonate by the apparently accidental process of maternal microbial inheritance [5]. In this way, information about her environment becomes available to be taken up by the neonate. In the absence of this "calibration", the neonate immune system will be prone to overreact, for example, when faced with unknown but suspicious antigens, such as those contained within pollen, or possibly after viral infection. This form of microbiome deficiency disease expresses itself as a propensity for the later development of atopic or autoimmune disease. The timing will vary with the extent of microbiome damage, the genetic inheritance of the individual, and the nature of the provocation [48]. This deficit probably also accounts for the rise in the incidence of cancer in the modern world, at least in part [49]. Granted that the uncalibrated immune system has difficulty in distinguishing harmless from harmful, self from non-self, its inability to eliminate precancerous cells would not be surprising. It is interesting to note, for example, that a suitably diverse microbiome can be transferred to a pancreatic tumour and, thereby, slow its growth [50]. Similarly, it seems reasonable to suppose that an increase in circulating nutrition would contribute to accelerating the growth of a tumour and, presumably, its virulence.

4.2. Nutrient-Sharing Function

Granted that the ability to pass microbiota-related immune system information on to the offspring must remain intact at least until the reproductive life of the animal has passed, it follows that the microbiome must receive its share of the nutrition taken in by that animal. Equally, as each partner of the body/microbiome combination relies on one another for survival, they must develop a responsive method of communication enabling an equitable division of the available nutrition, as illustrated by the development of the microbiota–gut–brain axis in Figure 2. Events such as famine or illness will require the body to temporarily receive a greater share of the available nutrition, while the microbiome, in turn, may become dormant until the danger passes [4]. Pregnancy, by contrast, will require a more proactive response, as the microbiome undergoes a rearrangement ready to pass on to the neonate [51].

4.3. Gut Motility

The scheme of Figure 3a illustrates this idea of the partition of nutrition. While the line on the left represents the gastrointestinal tract, the method of communication is the balance of hormone versus semiochemical production in the centre of the diagram. According to this scheme, partition is achieved by virtue of the adjustment of gut motility

and peristalsis (box centre-left). A more rapid flow allows a greater portion of the nutrition to be handled by fermentation [4], albeit that this passes some nutrition back to the body in the form of short-chain fatty acids [31]. In principle, therefore, the outflow of energy can be represented by three waste streams: carbon dioxide is emitted after metabolism (box top right) and solid waste can theoretically be split into an undigested part of food e.g., cellulose (box bottom left), and microbial overgrowth (box bottom right). It is our view, that this scheme, while allowing the accumulation of safely stored fat, nevertheless, avoids the consequences of excessive, unsafe fat accumulation and obesity. It follows that the roots of obesity lie in the disruption of this hormone versus semiochemical balance, i.e., in gut–microbiome disconnection [4].

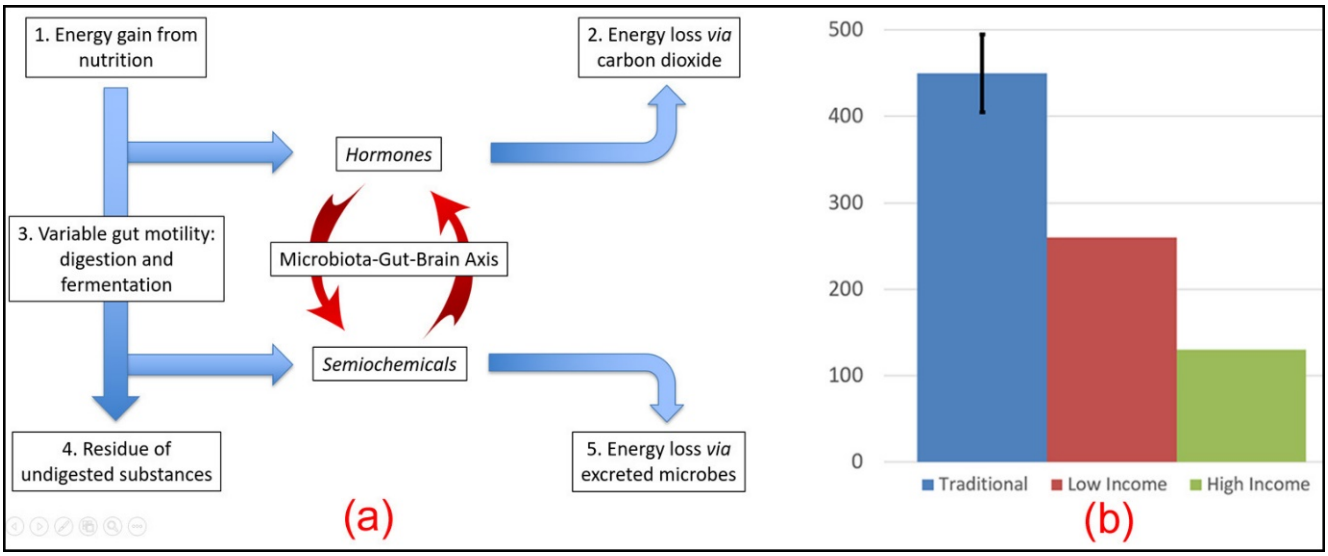

Figure 3. (**a**) The Role of the Adult Microbiota–Gut–Brain Axis in the Partition of Nutrition. **Box 1**. Energy is gained by nutrition. As this system is common across the Vertebrata, in principle, it accommodates all diets from extreme carnivore to herbivore. **Box 2**. The output of carbon dioxide represents the product of metabolism. Many studies are concerned with measuring carbon dioxide output, for example, using double-labelled water [1]. **Box 3**. The balance of hormones and semiochemicals operating through an intact microbiota–gu–brain axis controls gut motility and peristalsis through the gastrointestinal tract. Under normal conditions, a significant amount of nutrition reaches the microbiota, allowing their growth, while at the same time the products of fermentation, short-chain fatty acids, are returned to the body. **Box 4**. Faecal output includes a significant amount of indigestible material, for example, cellulose, in addition to sloughed-off cells from the gastrointestinal tract. **Box 5**. Faecal output contains a significant proportion of intestinal microbes. However, energy output by this route is not currently measured. (**b**) Faecal Weight v. Population Lifestyle as a Measure of Likely Pollution. Traditional. Refers to people pursuing their lifestyle unaffected by the modern world, with negligible heavy metal pollution. As reported by Denis Burkitt, their average untreated faecal output amounted to 400–500 g/day [37]. Low/high income. Refers to people categorised by the Human Development Index according to the method of Rose et al. [52]. Their untreated faecal mass amounted to approximately 260 g and 130 g, respectively, in agreement with Burkitt's figure of "less than" 150 g/day for people living in what he describes as Modern Western Civilization [37]. Although Rose et al. refer to different fibre intake of these populations [52], it is likely that this also corresponds to an increasing level of pollution within different societies.

4.4. Faecal Energy Excretion

The indefatigable Denis Burkitt left us with a description of the lifestyle of the traditional peoples that he studied, not only their diseases and food type, but also their faecal output. Specifically, he described them as producing from 400–500 g of untreated faecal matter per day and compared this with the average offering of people living in Western

civilisation of "less than" 150 g [37]. In contrast, it is reported that, on average, people from the richer countries produce only approximately 130 g of untreated matter per day, while those from lower-income countries dispose of a more respectable 260 g per person per day, the difference being put down to dietary fibre consumption [52]. The decline in faecal weight with the increasing wealth of society is illustrated in Figure 3b. Interestingly, the composition of modern-day faeces is between 25 and 50% bacterial biomass [53], while Jeroen Raes and co-workers have reported that the greater the diversity of these faecal bacteria, the shorter the intestinal transit time, i.e., the higher the gut motility [54]. Unfortunately, as there will be variable proportions of water, the actual level of faecal energy excretion currently remains unquantified.

5. Dysbiosis: Microbiome Function Deficiency Disease

Modern non-communicable disease is best looked at as if it were a series of systems going wrong, but with the patient complaining of only one or two conditions at any given time [48]. In this way, for example, autoimmune disease is often found to overlap with mental health conditions, such as depression [55]. While it is often considered that one causes the other, the possibility remains that they are both due to an underlying dysbiosis, i.e., that the relationship is not causal [48]. Equally, whether or not it is perceived as a problem, being overweight is a common accompaniment to all non-communicable diseases, as is a degree of difficulty with defecation, whether or not it amounts to actual constipation [56]. In certain circumstances, including some sufferers of coeliac disease, a poorly-functioning intestine can seemingly keep the weight under control, simply because the food is not being absorbed. The current situation is outlined in Figure 4, in which microbiome–gut disconnection prevents any residual semiochemical output of the microbiome from acting so as to speed up the gut. In support of this hypothesis, it is found that a relatively high microbial diversity in the intestine is associated with a shorter transit time [54], possibly indicative of a stronger gut–brain axis. Conversely, in this hypothesis, a longer transit time effectively forces greater levels of nutrition into the body, and it is possible that such microbiome–gut disconnection cannot be fully repaired in the adult. Accordingly, as body mass increases, a new equilibrium position is reached in which the greater energy expenditure and, hence, carbon dioxide generation, brought about by movement of the heavier body, balances the reduced energy excretion due to lower faecal output [4]. This explanation for dysbiosis also helps account for a number of puzzling observations that have occasioned much debate recently, as set out in the following sections.

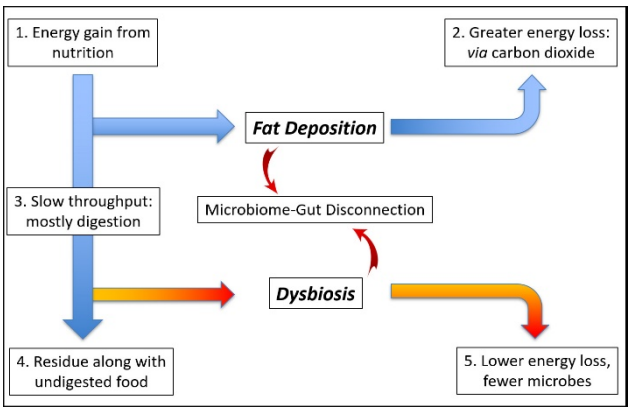

Figure 4. Microbiome–Gut Disconnection Stemming from the Neonate. **Box 1**. Energy is gained by nutrition. As suggested by Burkitt, populations subject to dysbiosis are likely to benefit from lower-energy foods containing a greater proportion of dietary fibre [37]. **Box 2**. The output of carbon dioxide represents the product of increased metabolism commensurate with the greater weight of a body carrying extra stored fat [4]. The increase in energy used by metabolism effectively balances the decrease in energy lost by excretion (**Box 5**). **Box 3**. In the absence of a functioning microbiome, ineffective semiochemicals

means that gut motility decreases. Accordingly, most food is digested, with relatively little reaching the microbiome. Extra fat is stored in the body, until the gain in weight compensates for the lack of excretion, as described for **Box 2** [4]. **Box 4**. Faecal output includes indigestible material, along with sloughed-off cells from the digestive tract. Certain non-communicable conditions, such as coeliac disease, may lead to undigested food passing through, limiting the absorption of nutrition and giving a slim and healthy appearance to the sufferer [28]. **Box 5**. Faecal output contains a significant proportion of intestinal microbes. To our knowledge, energy output by this route has not been measured but is likely to be significantly reduced for heavily polluted populations, as illustrated by Figure 3b [37,52].

5.1. Energy Homeostasis

Set-point theory holds that body weight, similar to temperature and water content, is physiologically regulated through the hypothalamus, albeit, according to a 1997 review by Keesey, "shifting over a lifespan in conjunction with naturally occurring but still unspecified physiological changes" [57]. In a sense, this is the opposite of Barker's epidemiological findings on what he called the "infant and fetal origins of adult disease" [38], as Keesey maintains that it is the shift of these set-points during adult life that accounts for obesity. This position has been stated in an Endocrine Society Scientific Statement of 2017, while not mentioning the microbiome at all, unless it is encompassed within the catch-all term "environment" [58]. In a similar fashion, the situation has recently been described as "broken energy homeostasis", again with no microbial involvement recognised [59]. In a more recent article, Berthoud suggests that " ... the current obesogenic environment impinges mainly on a critical pathway linking hypothalamic areas with the motivational and reward systems to produce uncompensated hyperphagia" [60]. It is worth noting, however, that there is little ground for the existence of such widespread hyperphagia, instead coming into the category of a "common belief in obesity research", as described by Casazza [3]. Alongside these deliberations, we have the slow realisation that gut microbiota exert control over important aspects of metabolism including, for example, the hypothalamic–pituitary–adrenal axis, and that the microbiome can, therefore, be considered to be an endocrine organ in its own right [61]. Although the wording may differ, all the above quoted authors agree that (again quoting Berthoud) " ... despite significant progress in defining this complex neural circuitry, many questions remain" [60].

5.2. A Sliding Set-Point?

The fact that faecal weight has decreased alongside the industrialisation of society affords the opportunity to resolve this sliding set-point dilemma. While the hormones that provide control over aspects of behaviour are located in the brain, the microbiome is a parallel system outside of the control of the brain. Accordingly, we suggest that there are two ways in which weight control can become compromised.

1. There is no feedback from fat stores to the brain;
2. Such feedback is limited to designated areas where fat may be stored, such as subcutaneously, while any overspill, such as visceral fat, goes unrecognized.

Making the reasonable assumption that microbiome symbiosis has evolved alongside the vertebrates themselves [5], the first point seems to be feasible if a failure of the faecal energy excretion system had never been subject to evolutionary pressure. The second point is similar, in that fat outside the anticipated storage areas had never required an evolved response. Overall, the situation is analogous to navigation by a process called dead reckoning, in which knowledge of wind, tide, and currents (equivalent to a hormone-based feedback system) enables a skilled navigator (the brain) to calculate their position (the set-point). This "dead reckoning analogy" leads to the mistaken hormonal defence of a sliding set-point due to the unexpected failure of the microbiome. In this way, Keesey's set-point hypothesis [57] can agree with Barker's infant and fetal origins hypothesis [38] if the source of the problem lies in the maternal microbial inheritance of a dysfunctional microbiome [4].

5.3. Energy Compensation

In principle, excess food energy could be "burnt off" by exercise but, in reality, these aims are undermined by a poorly-understood compensation process in which total energy expenditure is held within defined limits by a currently unknown mechanism [62]. A recent study using respirometry and doubly labelled water confirmed that increases in exercise-activity energy expenditure are accompanied by a significant reduction in basal energy expenditure [63].

5.4. Body Temperature

Of course, what we call exercise is but a small proportion of our overall activity energy expenditure, known as non-exercise activity thermogenesis (NEAT) [64]. Interestingly, NEAT appears to decrease with the wealth and levels of industrialisation of a given society, and, although the mechanisms of the control of energy expenditure are not entirely clear, they are likely to be related to the functioning of the hypothalamus, including temperature control [64]. Interestingly, the suspected reduction in body temperature from 37 °C to 36.6 °C since the middle of the 19th century has recently been confirmed by studies of the records of United States service personnel [65]. It is possible that this represents both the beginning of the industrialisation of the United States of America, and also the beginning of their obesity crisis.

6. The Cause of Microbiome Function Deficiency Disease

6.1. Modern Foods

As the primary visible symptom is weight gain, suspicion naturally falls on the changing nature of our food. Feeding experiments were undertaken in which mice containing a human-type microbiome were only offered food low in microbiota-accessible carbohydrates across several generations. Eventually, these mice were found to have reduced bacterial diversity [66]. Interestingly, it is worth noting that laboratory-grown animals may be missing relevant microbes in the first place, a point that was brought home more clearly when two populations of genetically identical mice raised by different suppliers gave different results in a human disease model. As their microbiomes were found to differ, this suggests a wider problem with animal models for human disease [67]. Bearing in mind that bacterial fermentation of dietary fibre is associated with the production of short-chain fatty acids, known to have benefits for the prevention of diseases related to immune system disturbance in humans [68], these observations led to the current interest in supplementation via so-called prebiotics and probiotics, which were found to be especially helpful for pre-term infants [69]. However, there are suggestions that the probiotic concept is not the whole story. As an example, although bifidobacteria have been identified as a valuable bacterial genus associated with good health [70], they do not seem to be present in the microbiome of the Hadza, people considered to be relatively free from non-communicable disease [71]. Alongside this, many taxa of bacteria fall below the limits of detection on a seasonal basis, including types that are essentially never found in non-traditional, industrialised societies [72]. In addition, as stated above, Burkitt mentioned the steppe-dwelling, cattle-rearing Maasai peoples as being free from non-communicable disease, even though their diet was much more akin to the modern diet of grain and animal products [37]. In summary, it seems that an exclusively diet-based rationale cannot be the whole story.

6.2. Antibiotics and Antiseptics

Of course, because antibiotics are specifically designed to interfere with microbial growth, they have a profound effect on the constitution of the bacterial microbiome [73]. Alongside this, unicellular eukaryotes such as *Blastocystis* may also be affected by antibiotics [74]; however, as the vermiform appendix has been implicated as a reservoir of intestinal biodiversity, the use of antibiotics may not lead to the actual extinction of any of the various classes of microbial constituents except, perhaps, after appendectomy [75]. Equally, of course, as the use of antiseptics made surgery safer, they have contributed to

the significant increase in the delivery of babies by caesarean section, along with a belated recognition of the effect of this procedure on the microbiome [76]. It is important to note, however, that it only requires a small number of viable microbes to populate the neonate intestine, especially when supported by the constituents of breast milk [77] and, in addition, the role of the breast milk microbiome itself has not yet been clearly defined [78]. On the whole, the evidence is that the establishment of the microbiome is delayed, rather than altered, by a C-section mode of delivery [79]. Nevertheless, it is important to note that the timing of the microbiome function may well be more significant than its eventual composition, as illustrated by the relationship between C-section birth under sterile conditions and the development of obesity [80]. In the light of these observations and bearing in mind the fact that Dr John Bostock developed his hay fever before the advent of formal antiseptics and antibiotics, it seems that these antimicrobial agents cannot be the whole story.

6.3. Heavy Metal Pollution

In a recent publication [5], we suggested that the properly-functioning intestinal microbiome owes its flexibility and diversity to a phage-induced viral shunt mechanism, as first described in the upper layers of the sea [81], and more recently in the soil [82]. Likewise, in our opinion, the epidemiology of hay fever, and similar immune system diseases, is best predicted by the effect of heavy metal ions within the intestine inhibiting this viral shunt mechanism and constricting the viability of the microbiome as a whole. More specifically, we have suggested the presence of hypothetical precursors of dendritic cells [32], which we have termed *microbial sentinel cells* [5]. With their antigen-seeking ability, such cells may be expected to be specifically inhibited by heavy metal ions. Indeed, it is possible that such cells may no longer be found in heavily polluted populations. As noted above, it is already obvious that microeukaryotes have long been neglected in microbiome-related studies, in spite of their likely importance [17].

In summary, bearing in mind the early onset of Bostock's hay fever, it seems likely that his problem arose in his mother, probably due to the heavy metal-based cosmetics applied by the more well-off members of society in the 18th century and earlier [83]. As industrialisation got underway during the 19th and 20th centuries, so the proportion of people affected by pollution increased, considering that the addition of lead to petrol only ceased in most of the world at the turn of the 21st century [84]. Indeed, lead deposited in major cities has continued to be observed long after this time [85]. Meanwhile, the levels of other toxic metals are increasing [86] and their effects on animals further down the food chain are belatedly being considered [87].

7. Burkitt's "Diseases of the Western World"

Denis Burkitt was a surgeon trained in modern Western-based medicine and, in an article first published in 1958, described a form of infectious carcinoma in African children that now bears his name: Burkitt's lymphoma [88]. In later talks and articles, however, he told of his surprise at the realisation that many of the skills he had been taught at the prestigious School of Medicine in Edinburgh were of no use amongst those people of Africa still following their traditional modes of life. In essence, the corresponding diseases simply did not exist in those communities. While mentioning several such diseases, he specified eighteen that were restricted to people living in what he called the Westernized world [37]. These conditions are set out in alphabetical order in Table 1, labelled according to their primary relevance to our microbiome function deficiency hypothesis:

Table 1. Selected Westernized dietary fibre-related diseases specified by Burkitt, and their characterisation into the primary cause according to the microbiome function deficiency hypothesis.

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 **

* Primarily immune system disorder. ** Primarily failure of the microbiota–gut–brain axis, but with three related manifestations: 1. Malabsorption of nutrition due to reduced gut motility and, 2. Increased abdominal pressure on defecation and, 3. Although unrecognised by Burkitt, poor mental health.

7.1. Immune System Disorders

While Burkitt, lacking knowledge of the microbiome, could not understand how a shortage of dietary fibre could lead to problems with the immune system, the discovery that the production of short-chain fatty acids by the microbiota affects certain components of that system has allowed a reappraisal of his hypothesis [68]. Nevertheless, while noting that it may not be necessary, it remains possible that immune system deficiencies are due to the absence of microbial sentinel cells caused by prior poisoning [5]. Although Burkitt assigned the increase in tumours of the large bowel to a lack of dietary fibre, more recent studies have cast doubt on the exact nature of this relationship [89] and we, therefore, assign tumour incidence primarily to a malfunctioning immune system. Equally, while there is suspicion that multiple sclerosis is caused by the Epstein–Barr virus, it is clear that there are other factors involved [90]. It is likely that the answer will eventually be found in a combination of genetic and microbial inheritances, alongside any provocation caused by the virus [48].

7.1.1. Malabsorption of Nutrition

Obesity is the most outwardly visible of the three basic types of non-communicable disease, in which absorbed nutrition is converted into fat for storage and for onward synthesis to, for example, cholesterol. While an attempt has been made to understand the development of type 2 diabetes in the absence of microbial involvement as a personal fat threshold [91], further attempts have tried to engage with the bacterial microbiome as a predicted glycaemic response [92], however, the methodology and conclusions of the latter have been challenged [93].

7.1.2. Abdominal Pressure

Although Burkitt laid the blame for many or all of these diseases on the lack of fibre in the diet, we assign a degraded gut–brain axis to causing the problem by inhibiting peristalsis. In human society, unrestricted defecation carries an unacceptable social cost and, therefore, requires the conditions to be appropriate before any action takes place. Accordingly, some sort of signal should pass from the brain to the gut initiating the necessary movements. In the absence of such a signal, force will be required to complete the act of defecation and it is this that causes the increase in abdominal pressure. While the concept of constipation is actually difficult to define, perhaps the only way it can be recognised in an individual is when a detectable change in bowel habit takes place [56]. Nevertheless, it is reasonable to imagine that extra fibre in the diet would indeed improve gut motility, although it would not constitute an actual cure as such. Finally, although Burkitt considered thrombosis and embolism to be in the general category of "common venous disorder" [37], we consider that increased abdominal pressure on defecation may contribute by temporarily slowing blood flow.

7.1.3. Mental Health

When considering Burkitt and his contemporaries, it is important to note that the psychological sciences were not considered worthy of serious medical attention. Even when Sigmund Freud, the founder of psychoanalysis, had achieved a measure of respectability [94], its teachings were still far from being fully accepted. For example, although the expression "gut feelings" has been used since time immemorial, it is only recently that the connection between intuition and depression is beginning to be investigated [95]. It is likely that the section of the brain responsible for interpreting these "gut feelings" will atrophy in the absence of adequate input from the microbiome–gut interface. Unfortunately, we have little idea as to the prevalence of poor mental health in either the traditional African or the Westernized communities that Burkitt observed.

8. An Example of Microbiome Function Deficiency: Coeliac Disease

Granted that dysbiosis is due to the maternal microbial inheritance of a malfunctioning microbiome, the propensity for a variety of diseases increases from an early age [48]. Indeed, as noted by Burkitt, often, several apparently different conditions are observed in the same individual [37].

Coeliac disease is an autoimmune reaction which, in the presence of gluten, mainly affects the intestine [28], although it may also be associated with extraintestinal symptoms, such as dermatitis herpetiformis [96]. It shares some genetic features with type 1 diabetes [97] and, similarly, is often found in childhood, although it can develop at any age [98]. An example of coeliac disease has been recognised in the skeleton of a young woman found in a richly decorated first century CE grave in the Italian peninsula and, although a genetic predisposition may be discerned [99], there were significant amounts of lead available in the environment [100]. In turn, there is the possibility of a poor maternal microbial inheritance and consequent dysbiosis.

The incidence of type 2 diabetes in people diagnosed with coeliac disease is about the same as the general population [29], suggesting that the two are independent variables, consistent with our view of a microbiome function deficiency separately affecting both the immune system and the microbiota–gut–brain axis from birth [48]. Interestingly, however, a symptom-free malabsorption of food means that coeliac disease sufferers can appear to be slim and apparently heathy, a fact which probably helps to account for its under-diagnosis within the general population [28]. Finally, coeliac disease is commonly associated with psychological problems but, although the primary symptoms themselves are often reduced with a prolonged gluten-free diet, it is not clear that conditions such as anxiety, depression, and fatigue are likewise reduced [101].

Interestingly, while dietary fibre can normally be considered to be helpful [68], in some people the presence of such foodstuffs can be associated with unacceptable symptoms. These people may be prescribed a FODMAP-excluding diet, i.e., eliminating all fermentable oligo-, di-, and mono-saccharides and polyols [102]. Similarly, uncomfortable symptoms may be ascribed to non-coeliac gluten sensitivity, which also requires an exclusionary diet. Expressions such as "puzzle" [103] and "clinical dilemma" are often applied to these irritable bowel-like conditions [104]. In principle, the concept that everyone in the developed, polluted world suffers from a degree of microbiome function deficiency may help to account for the prevalence of such symptoms, whether or not they are associated with a specific diagnosis [48]. Equally, while the tendency for disease to run in families can be described as "genetic", it may be more a matter of those microbial genes that are transferred by maternal microbial inheritance, rather than the cellular genes themselves. Thus, for the specific instance of coeliac disease, while the HLA-DQ genes have been recognised as necessary for the development of disease, in themselves they are not sufficient. However, rather than being an extra genetic factor [105], it could be that the cause is an environmental influence acting through the microbiome. In a similar fashion, monozygotic twins may have vastly different disease states if their microbial status differs significantly, either at birth via caesarean section or subsequently by antibiotic treatment [48]. In addition,

as stated above, recent observation has illustrated a difference in the outcome of trials involving genetically identical animals raised in two different laboratories. It seemed that the critical difference is due to inflammation [67], raising the question as to whether any laboratory-raised animal model will be adequate without controls in place to guard against the possibility of a deficiency in the animal microbiome itself.

As coeliac disease is directly associated with the intestine, there has been much speculation as to a causative role for intestinal bacteria. Thus, earlier investigations (2008) suggested that a relative shortage of bifidobacteria may be to blame [106], an idea contradicted by the later (2014) observation of the absence of such bacteria in the apparently healthy Hadza [71]. More recently, the interaction of host genetics/epigenetics with the environment and gut microbes in treated versus untreated coeliac disease has been reviewed, noting the role of the host genotype, but without coming to specific conclusions about the precise causes of its various manifestations [107]. Subsequent investigations yielded similarly indecisive results [108], while a search for predictive disease biomarkers has been taken down to the level of individual strains, albeit without specific disease-causing microbes being unambiguously identified [109]. On the whole, therefore, these findings echo the observations of Brüssow, that no specific classes of bacteria have so far been definitively associated with a "healthy" outcome [7]. We note, however, that the above microbiological observations are consistent with our own concept that virtually the whole of Burkitt's "Modern Western Civilization" suffers from a degree of microbiome function deficiency, with the likelihood and timing of actual disease dependent on host genetic vulnerability in combination with external environmental insults [48]. Significantly, as noted above, very few such studies consider a potential role for microeukaryotes in addition to bacteria [17], especially bearing in mind our view that the intact, fully functioning vertebrate microbiome is best considered to be a co-evolved symbiotic microbial community in its own right [5].

9. Microbiome Function Deficiency Disease: Cure, Control, or Prevent?

Attempts have recently been made to understand the microbiome more thoroughly, acknowledging the potential importance of eukaryotes and the concept of dysbiosis but without mentioning the possibility of its degradation by heavy metal poisoning [110]. Although the relative absence of microbiome-based hypotheses were mentioned [7], there is still a need for more methods to be brought to bear [111]. Whether this greater understanding will manage to deliver a cure cannot yet be predicted, however.

Recognising the need for a greater depth of *functional*, rather than *compositional*, understanding, two of us, DS and SJ, have recently suggested the development of an ingestible sensor, a pill-like device bearing a detector and a transmitter, where the detector is calibrated to measure levels of semiochemicals produced in the gut lumen, potentially including dopamine [112]. Using our microbiome function approach, it is worth stating that, following Burkitt's description of the diet of the Maasai [37], the microbiota–gut–brain axis should produce semiochemicals to stimulate gut motility regardless of the type of food consumed. In contrast, in the presence of dysbiosis, with a weaker gut–brain axis and/or less efficient production of semiochemicals, a less readily digested prebiotic-like substance may be required to produce a similar signal from the ingestible sensor. In this way, the development of an effective method of monitoring microbiome function deficiency disease may allow methods of amelioration to be assessed.

In this respect, there are still people living on the fringes of modern civilisation who have not yet suffered the worst effects of such poisoning and, by and large, do not exhibit the symptoms of non-communicable disease. The Tsimane, for example, largely healthy in spite of having a high systemic inflammation, are already engaging with medical teams [113] and may be willing to support further efforts to fully understand the microbiome. Note that adequate compensation could be provided for such assistance using, for example, the "principle of reciprocity" as has been developed for cancer medicines [114].

Prevention of future human disease by modifying the microbiome of children in vulnerable populations may be a possibility. Although faecal transplantation is a procedure

that is normally applied to the intestine of an adult recipient [70], in principle it would be more effective if delivered directly to the head of a vulnerable neonate, i.e., in the absence of a previously established microbiome, thus, replicating the process of maternal microbial inheritance. In addition, while an ingestible sensor may be valuable to determine the status of the maternal microbiome prior to giving birth [112], the procedure variously known as vaginal inoculation, vaginal seeding, or micro-birthing seems to be effective in transferring functioning microbiota to the intestine of the child following its delivery by caesarean section [115], always considering the danger posed by pathogenic microbes [116]. Finally, the observation of antimicrobial resistance is already driving the move toward more specific viral anti-infective agents, which are likely to have less of an impact on the microbiome itself [117], while models have been developed to assess the effect of new oral antibiotics on colonic microbial diversity [118]. Of course, antibiotic prescribing has been at high levels [119], and it could be that moving to injectable formulations would both diminish excessive use, perhaps lessening the development of antimicrobial resistance, and also relieve pressure on the microbiome itself.

10. Summary: Toward a Microbiome Theory of Health

The notion that the failure to transfer a completely functioning microbiome at the moment of birth leads to non-communicable disease is surprisingly effective at understanding the epidemiology of these apparently unconnected diseases. Barker's "fetal and infant origins hypothesis" was first presented in the 1990s and was based on the epidemiology of modern non-communicable disease, but of course without any understanding of the microbiome. Recently, Brüssow, writing in 2019, has pointed out that modern "bacterial" microbiome studies are performed in the absence of a consistent theory as to how the microbiome actually works, a situation which this article attempts to rectify. At its heart, mutualism requires two complementary actions, each helping the other so that the combination may survive. In essence, this article sets out a version of mutualism in which help to the immune system of the host is balanced by the growth of a gut–brain axis in the neonate, as set out in the following six points:

10.1. Immune System

While the body provides a degree of strength and stability, the microbiome retains the flexibility of horizontal gene transfer to engage with the changing microbial threats to the existence of the combined entity. In turn, this accounts for the close association of the microbiome with the immune system (Figure 1). Interestingly, it may be that the relatively high systemic inflammation experienced by the Tsimane is actually the natural state of affairs, representing a *proactive* immune system, while the "hygiene hypothesis" problems noted by Strachan in the population of industrialised nations may suggest an inaccurate, *reactive* immune system. Essentially, the same argument applies to the existence of autoimmune disease, albeit that the onset of such disease in the adult often requires an external trigger, such as a virus. Similar arguments apply to the failure of the immune system to eliminate precancerous cells.

10.2. Microbiota–Gut–Brain Axis

While the microbiome of the adult needs to receive nutrition in order to eventually pass on to the neonate, its relationship with the host is by partition according to need. Accordingly, the microbiota produce interkingdom signalling molecules, semiochemicals, that help to stimulate nerve growth. In turn, hormones produced by the body act as semiochemicals to influence the microbiome (Figure 2). Once established, this communication link is strengthened by continued semiochemical synthesis, thereby partitioning nutrition so as to cope with exigences such as famine or pregnancy (Figure 3a). The failure of semiochemical production by the microbiome, or the failure to establish this communication system in the first place, will have repercussions for the development of the brain during childhood,

perhaps leading to schizophrenia, as noted by Barker. The mental health implications of the loss of the microbiota–gut–brain axis will be covered in a subsequent publication.

10.3. Weight Gain

The loss of semiochemicals in the adult slows peristalsis, reduces gut motility, and leads to a reduction in faecal energy output, as first described by Burkitt (Figure 3b). As a consequence, unless nutrition intake drops, excess energy will be retained as fat, accumulating until a new equilibrium point is reached. As weight increases, there will be an increase in the energy cost of movement, reflected in an increase in carbon dioxide output (Figure 4). While both appetite and metabolic energy expenditure are under the control of hormones, the microbiome does not come under their jurisdiction and, it seems, its failure cannot be compensated for. Accordingly, as weight increases, body temperature drops to compensate for the perceived increase in exercise energy expenditure. Of course, any mechanism that increases circulating nutrition is likely to increase the growth of cancer, with a consequent increase in its rate of detection.

10.4. Antimicrobial Agents

Although, as stated above, a limited diet can lead to the loss of microbial species from the microbiome, nevertheless, it could be that this effect is more likely to show up under laboratory conditions than on a world-wide scale in unrestricted populations. Similarly, neither intermittent antibiotic treatment nor the delivery of babies by caesarean section under sterile conditions are, perhaps, likely to produce the reduction in microbial diversity noted across the industrialised world. In contrast, the distribution of microscopic particles containing heavy metal salts seems to provide a better fit with the observed epidemiology, from the relatively limited exposures of Bostock's day to the widespread contamination of more recent times. It is possible that there is a tipping point beyond which microbes vulnerable to heavy metal poisoning become unviable. As reported by Raes et al., a reduction in microbial diversity is associated with a reduction in gut motility, presumably due to a corresponding reduction in semiochemical output (Figure 4) and, accordingly, the metal particles are retained in what becomes a vicious circle. The key point is that it is the nature of the microbiome that is passed on to the neonate at the time of birth, whether functional or not.

10.5. Snowball Effects and Sentinel Cells

Epidemiology suggests that the greatest effect on the health of an individual follows from an absence of the key microbes immediately after birth. If these microbes are not replenished from the environment during the life of the individual, or if the poisoning continues unabated, then the resultant problems will pass down the generations in a snowball effect. In this context, the microbial sentinel cells that we have posited as antigen-recognition cells cooperating with the immune system of the host (Figure 1) could be classed as vulnerable to poisoning. If so, this may account for the degradation of the immune system and, in turn, may allow the onset of the variety of conditions we are familiar with since Burkitt's day.

10.6. The Prevention of Non-Communicable Disease

It seems that the majority of medical advances in recent years have been in the amelioration of the consequences of non-communicable disease. The analysis presented in this paper suggests that, as the primary damage occurs in the infant, an outright cure for affected adults seems to be unlikely. Nevertheless, the missing microbes, including eukaryotes, should still be present in relatively unpolluted populations. Treatment of the new-born with appropriate microbes immediately after birth may replicate maternal microbial inheritance, at least in part. Animal experiments should be helpful, as would the development of an ingestible sensor to check for the presence of semiochemicals. Once established, further degradation of the microbiome by careful use of antimicrobial

agents and avoidance of heavy metal contamination would be necessary, along with the maintenance of a functioning microbiome after caesarean section.

11. Conclusions

The ultimate aim of any medical research must be to translate its findings into benefits for the patient. Accordingly, the overall tenor of this article has agreed with the findings of Brüssow, that the evidence for the positive involvement of specific classes of bacteria amongst the microbiota is not sufficiently robust to ensure such patient benefits. In agreement with the epidemiological observations of Strachan and Barker, our analysis also suggests that the key semiochemical and immune system information must be in place from the moment of birth, thus, placing the emphasis back on to the maternal microbiota. We can add two further points: (1) that further research should include an investigation into the role of unicellular eukaryotes in the fully functioning microbiome and (2) that an ingestible sensor would be valuable for probing the efficiency of the microbiome itself.

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