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PERSPECTIVE

The human gut microbiota is neither an organ nor a commensal

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The recent explosive increase in the number of works on gut microbiota has been accompanied by the spread of rather vague or improper definitions, chosen more for common use than for experimental evidence. Among them are those defining the human gut microbiota as an organ of our body or as a commensal. But, is the human gut microbiota an organ or a commensal? Here, we address this issue to spearhead a reflection on the real roles of the human gut microbiota in our life. Actually, the misuse of the vocabulary used to describe the properties and functions of the gut microbiota may generate confusion and cause misunderstandings both in the scientific community and among the general public.

Keywords: commensal; diet; gut microbiota; holobiont; human health; metabolism; organ; symbiosis

The human body is colonized by a very large number of microorganisms (bacteria, virus, fungi, archaea). They are at least as many as the human cells [1], and live with us, on our tissues or inside some of them, primarily in the gut [2]. The collective names for them are 'microbiota' or 'microbiome; [3]. Until 2010, the role of the human microbiota in the different compartments of the body was largely unknown and neglected, and any involvement of gut microbiota in chronic neuroinflammatory diseases as multiple sclerosis (MS) was considered purely speculative. In 2011, Berer *et al.* [4] showed that experimental autoimmune encephalomyelitis (EAE), the animal model of MS, can be triggered in mice by injecting the antigen MOG, the myelin oligodendrocyte glycoprotein, but only in the presence of the 'commensal' gut microbiota. The autoimmune processes leading to EAE were indeed driven by activated T cells and related anti-MOG antibodies, but the microbiota was essential in triggering inflammation and the activation of T cells. Both MOG and commensal microbiota were found to cooperate in developing the experimental disease. These results confirmed the previous work of Ochoa-Reparaz *et al.* [5], where it was shown that the reduction with antibiotics of gut 'commensal' bacteria can impair the development of EAE.

Since then, in just a few years, things have changed a lot. As reported in https://pubmed.ncbi.nlm.nih.gov/, from 2010 to 2020 there has been an exponential growth in the number of papers published on gut microbiota, for a total of over 32 000 papers, but with only 466 in 2010 compared to 7747 in 2019. This growing interest in the human microbiota is also due to important research projects, such as the Human Microbiome Project-1 and Human Microbiome Project-2 [6], and the corresponding European Microbiome Support project [7]. These projects have made it possible to characterize microbial communities from

Abbreviations
ANS, autonomic nervous system; BAs, bile acids; EAE, experimental autoimmune encephalomyelitis; HPA, hypothalamic–pituitary–adrenal; LPS, lipopolysaccharide; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NT, neurotransmitters; SCFAs: short-chain fatty acids; TMAO, trimethylamine N-oxide.

different compartments of our body and to investigate host–microbiome interplay and microbial inter-relationships.

The human gut microbiota is now recognized as an important partner of the host, as it is believed to affect not only the functions of the intestine, but also those of all other organs, including the brain.

The purpose of this review is to critically reconsider what the microbiota represents for us, through the re-evaluation of two of its attributes—'organ' and 'commensal'—which are becoming commonplace, but whose use may be improper, redundant or even restrictive, and alter our vision about the meaning of the presence of the gut microbiota for our life. The misuse of these terms, among others such as 'eubiosis' and 'dysbiosis', may cause misunderstanding both in the scientific community and among the general public. Even the term 'Mediterranean diet' is vague, if there is no precise reference. Instead, we need to have clear definitions, based on scientific evidence, to properly communicate our research on the microbiota.

Is the human gut microbiota an organ of our body?

Since it is so integrated into our being at all levels, many researchers tend to describe the human gut microbiota as an additional organ of our body [8–14]. Some of them have called it an 'organ-like collection of microbes', 'microbial organ', 'microbial system', or 'metabolic organ' [8]. Very recently, the term 'meta-organism' has been used to indicate the close relationship between the human gut microbiota and the brain [14].

The gut microbiota as a component of the holobiont with its host

A more extensive vision of the relationship between our organism and the gut microbiota is the controversial concept of the 'holobiont', that is, the biologic symbiosis between the host as a whole and his/her gut microbiota, seen as the collective contribution of the eukaryotic and prokaryotic counterparts in a multicellular organism [15–20]. This concept, which attributes to the human gut microbiota a role that far exceeds that of the organ of the body, needs further evaluation, as not all animals need a microbiome [21]. Moreover, to make a decision whether the concept of the holobiont is reasonable or not, we have to overcome some points that may be against this concept: (a) The composition of the gut microbiota is probably the result of a process involving ecological, and not host, filtering [16], but the holobiont theory infers that host genetics contributes to microbiome composition [18]; (b) the composition of the microbiota is fluctuant and, as we will see later, with a double face, favorable or detrimental to the host; (c) the gut microbiota is not 'a proper part of the host' as it is largely interchangeable and shared among different hosts [19–20]; and (d) the components of a holobiont must respond to ecological changes as a unit, and evolve as a hologenome, what is difficult to achieve for the whole microbiota together with its host [17].

The gut microbiota as a complex entity interacting with other organs of the host

The microbiota interacts mainly with the organs involved in the digestion of food (gut), its transformation after absorption (liver), and its storage (adipose tissue). The question is as follows: Does the microbiota interact with them like an organ?

At present, it seems not quite right to attribute the functions of an organ to a community of microbes, the human gut microbiota, whose number exceeds, even if only slightly [1], that of its host cells and whose functions, moreover, are mostly independent of the will of the host. As a matter of fact, there are several aspects of the microbiota that do not correspond to the classic vision of an organ in our body.

On the other hand, the intestinal microbiota cannot be considered simply as a foreign environmental factor, because it is so linked to the host in a complete mutualistic relationship, at the endocrine, neural, immune, and metabolic levels, and apparently so important for the health of the host. Thousands of years of evolution have led to the possibility of symbiosis between two entities, which, however, remain different. So it can be affirmed that the microbiota is foreign to us but that at the same time it is part of us, in its diversity.

Interaction with the gut and the role of the gut microbiota in food digestion

The most important contribution by the gut microbiota to the host is that in favor of his intestine, as it ensures optimal gut functionality in digestion, energy harvest, mucosal immunity, integrity of the intestinal barrier, defense from pathogens, production of vitamins, neurotransmitters (NT), and potentially bioactive compounds, which are useful molecules for the host, such as the short-chain fatty acids (SCFAs) [8,22–27] (Fig. 1).

As regards its relationship with the intestine, the microbiota presents itself primarily as a catabolic

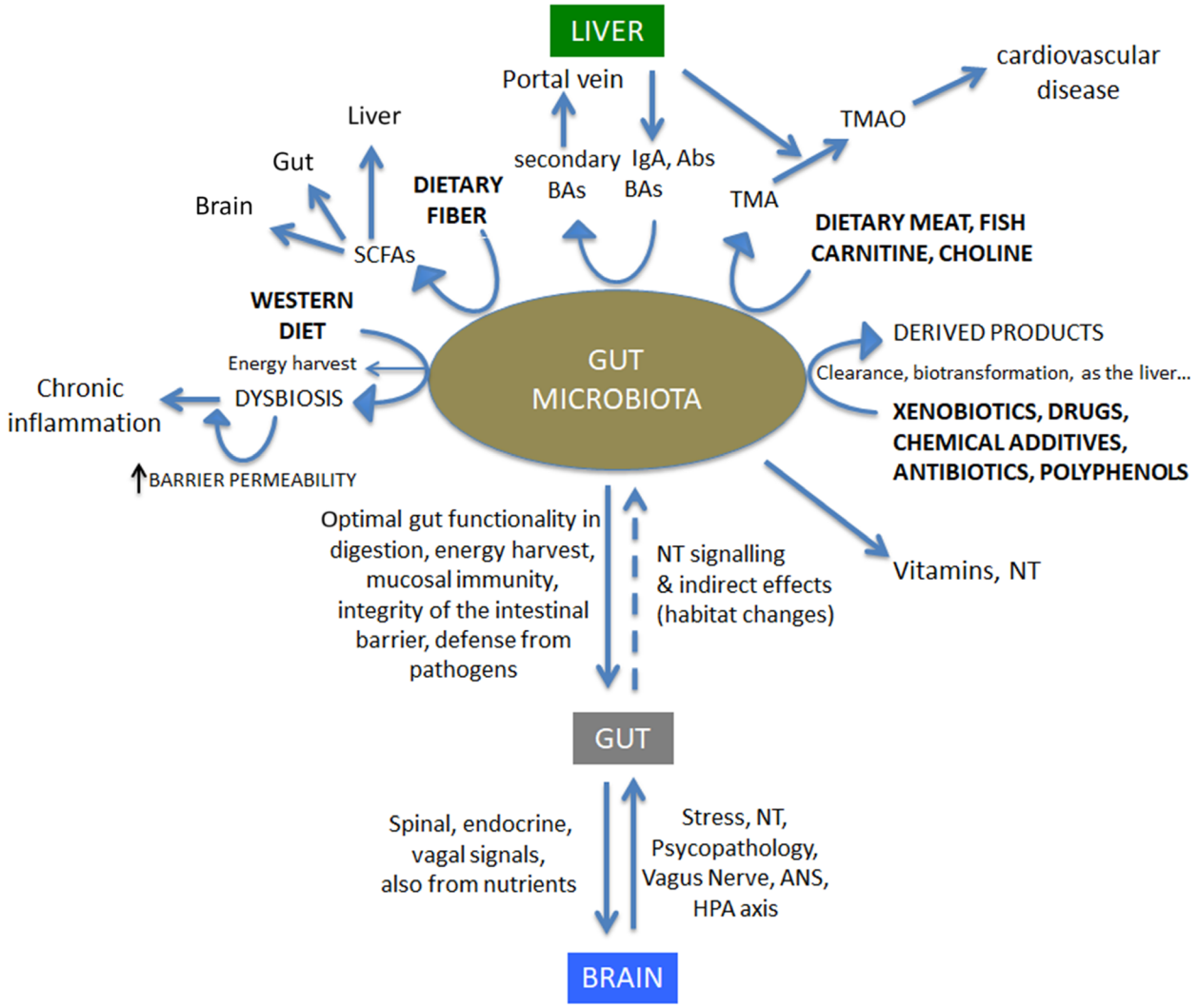

Fig. 1. The gut microbiota as a complex entity interacting with other organs of the host. See text for further details (ANS: autonomic nervous system (sympathetic and parasympathetic/vagal efferents); HPA: hypothalamus–pituitary–adrenal axis; BAs: bile acids; NT: neurotransmitters; TMAO: Trimethylamine N-oxide; SCFAs: short-chain fatty acids).

system that takes care of the habitat in which it operates and defends it from new colonizations. The microbiota is so closely correlated with intestinal functions that the most frequent risk to avoid is to confuse the microbiota with the intestine. Instead, it is better to see for the microbiota a distinct, albeit complementary, role different from that of the intestine.

Accordingly, if we really want to highlight the strong relationship between the microbiota and the intestine, we could say that the gut and gut microbiota together form a '*microbial-assisted digestive system*'.

In support of this definition, it would be sufficient to recall that the human gut microbiota helps in the digestion of what we cannot digest (fiber), and in harvesting the excess energy taken from the environment in form of food (Fig. 1). In other words, the human gut microbiota seems to have an important buffering role in food digestion.

The relationship of the gut microbiota with the liver, and its role in the clearance and transformation of foreign molecules

The role of gut microbiota in the energy metabolism of the host and biotransformation of foreign substances has been well described in previous works [28–32].

To have a gut microbiota, it means to have available a great collection of exclusive enzymes, different from

those of the host, although similar in their functions. Thus, besides to be a catabolic system as mentioned above for its additional and complementary role in digestion, the gut microbiota may be seen as a community of cells capable to cooperate in many metabolic reactions needed for the biotransformation of foreign molecule that we cannot metabolize easily enough, such as drugs, xenobiotics, polyphenols, antibiotics, and chemical food additives. To understand the metabolic importance of gut microbiota, it is enough to know that there are maybe 3000 cytochrome P450 enzymes in gut bacteria, while the correspondent CYP450 in humans are only 57 [33].

The availability of such a large number of microbial enzymes capable of modify molecules already in the intestine, before reaching the liver, is of great importance, even if it creates problems in taking oral medications. Indeed, the presence of human gut microbiota should be taken into account during therapeutic intervention, as the microbiota can metabolize drugs and as therapy itself may affect both the metabolic activity of the gut microbiota and its composition [30].

On the other hand, the fact that the microbiota performs useful functions for the intestine and liver is not surprising, considering that both are digestive organs and that both, the hepatocytes and the intestinal epithelium have in common the same developmental origin from the ventral foregut endoderm.

The relationship between liver and gut microbiota is two-way and very simple, very different from that with gut: The liver influences the population of microbiota by release of bile acids (BAs) and IgA antibodies, while the microbiota returns to the liver the secondary BAs [34] (Fig. 1). The rest of the work related to liver activity is done by the microbiota in the intestine and serves to transform or neutralize non-nutrient molecules.

However, as we will see, the gut microbiota can be involved in our chronic inflammatory diseases, even those of the liver, so closely connected to the intestine through the portal vein, but studies on the liver–microbiota relationship in pathology are still to be clarified. What is known is that in the above-mentioned pathologies, the microbiota population changes from a state favorable to our organism (eubiosis) to another (dysbiosis), which is deleterious.

The gut microbiota as a 'beneficial' or a 'deleterious' microbial 'organ'

Gut eubiosis and gut dysbiosis

If we want to consider the microbiota as an organ, we must take into account the fact that, unlike real host organs, the microbiota can exist in two different conditions.

The first condition, called eubiosis, is characterized by a high biodiversity, a harmonic intermicrobial condition and mutualistic relationship between the microbiota and the host. In particular, as already mentioned, a eubiotic gut microbiota ensures the optimal functionality of the intestine, which means the gut microbiota takes care of its habitat. Eubiosis has an anti-inflammatory nature and is favorable for human health.

The second condition, called dysbiosis, is the one in which biodiversity is strongly reduced and the microbial action becomes progressively pro-inflammatory and detrimental for human health. The terms eubiosis and dysbiosis are used very frequently, but it should be clear also in this case that they are vague and ambiguous definitions which have in no way a rigorous scientific basis but are rather focused on associations as it is the case for dysbiosis, which is frequently associated with terms such as microbial imbalance, loss of biodiversity, and loss of homeostasis [35,36]. As an example, a recent definition of dysbiosis is the following: 'A narrow definition of dysbiosis is as a stable microbial community state that functionally contributes to the aetiology, diagnosis or treatment of a disease' [37].

In effect, what we know so far is that the condition we call dysbiosis is very often associated with a disease or even a state of malaise, even psychic or behavioral, of the host. All in all the definitions are vague [36].

What's harmful in dysbiosis?

What is more deleterious for the host about the shift from eubiosis to dysbiosis? Surely, on the one hand it is the decrease in microbes capable of digesting fiber and consequently the decrease in the supportive role of SCFAs and the loss of biodiversity. On the other hand, in dysbiosis, the toxic factors to be considered could be the increase in bile acid derivatives, harmful for some beneficial bacteria, and trimethylamine N-oxide (TMAO) [38,39], deleterious for the host, as it has been associated with cardiovascular diseases, inflammation, and cancer. But this may not even be enough. It is therefore necessary to discover what else about the dysbiotic state of the microbiota may be more deleterious for our health.

In this respect, there are two points that must be taken into consideration during dysbiosis: (a) the shift to a pro-inflammatory state [35,22,40–41]; and (b) the shift of the composition of the microbiota from obligate to facultative anaerobic bacteria [42].

The shift to a pro-inflammatory dysbiotic condition of the gut microbiota may be a consequence of the effects of a long-term high-fat energy-dense Western diet on the gut microbiota. Persistent gut dysbiosis is associated with intestinal inflammation, increase in the Th 17/Treg ratio and endotoxins such as lipopolysaccharide (LPS). It follows that the intestinal barrier opens and molecules and cells (activated immune cells, antibodies, undigested food, microbes, endotoxins) that were in the lumen come out and go into circulation. The consequence is a low-grade systemic endotoxemia triggering inflammation and metabolic disorders [40].

The shift of the composition of the microbiota from obligate to facultative anaerobic bacteria is another consequence of dietary changes, such as the adoption of an energy-dense Westernized diet. In the case of a persistent energy-rich Western diet, colonocyte metabolism passes from oxidative metabolism, with a high consumption of oxygen, to anabolism with a consequent decrease in oxygen consumption [42]. The lower consumption of oxygen by the colonocytes means a greater availability of oxygen for the microbiota and means another push toward gut dysbiosis. The increase in microbes capable of using oxygen is detrimental for the host, because it means that both the number of competitors for oxygen and the availability of energy for the colonic microbiota are increasing.

To conclude, with regard to the terms eubiosis and dysbiosis, the gut microbiota would be our only organ that can exist in two conditions, one favorable and the other detrimental to the host. The concepts of eubiosis and dysbiosis are useful and widely used, but require more stringent definitions, not just generic associations to health or disease. Actually, there is a strong need to develop a systematic approach for the definition and the management of dysbiosis. A possible hypothesis could be to take levels of cecal or circulating LPS as a possible measure of the degree of dysbiosis. To be tested.

The cooperative and selfish behavior of the gut microbiota

If the gut microbiota is an organ, it must consist of microbes with a marked tendency to cooperate with each other and with the host. Therefore, the basic question is whether the components of the microbiota show cooperative or selfish behavior. The answer to this question is not always the same, but it depends on the condition in which the microbiota is and therefore on its actual population. This may be the reason why very little is known about cooperation and selfishness within the microbial ecosystem in the gut.

In a condition of no stress, the population of the gut microbiota depends on how much we eat, what we eat and therefore on our dietary habits. Thus, returning to the two conditions of eubiosis and dysbiosis, we can affirm that eubiosis is more cooperative or mutualistic, whereas dysbiosis is detrimental to the host [38]. In eubiosis, the preferred food is fiber, which cannot be digested by the host. The complex molecules of fiber require the presence of many enzymes in different species and therefore facilitate cooperation, while in dysbiosis the preferred foodstuffs are those of the westernized diet—saturated fats, simple sugars, and proteins—so there is less need for enzymatic cooperation. Thus, eubiosis is needed in order to have a mutualistic relationship.

Another aspect that determines greater or lesser cooperation is a lack of food. Indeed, if there is a lack of food, there must be more competition between the different microbial species to secure it. In fact, it should be clear that, as we will also see later, the intestinal microbiota is not eating with us at the same table but depends on the remains that arrive in the large intestine, where it is mostly located. The remains can be fibers, which cannot be digested by the host, and are linked to the eubiotic condition of the microbiota, or can be the leftovers of an energy-dense Western diet, mostly linked to a dysbiotic condition. It follows that the microbiota has a cooperative behavior (as it should be for an organ of the body) only in the eubiotic condition, while in the dysbiosis, the cooperative aspect is at least partially lost.

Does the gut microbiota have a structure?

If the microbiota is an organ, it must have a structure. With regard to its own organization, the gut microbiota does not seem to organize itself like the organs of our body. When it takes on an organized structure, it does so with the strategy of the colonizers and therefore to occupy space and to improve its defense capabilities, not in order to cooperate with the host. Therefore, the human gut microbiota is not something with a well-defined structure on which to rely and work with.

As for the already mentioned eubiotic and dysbiotic conditions, the microbiota can exist in two different states of organization. Indeed, the bacteria usually oscillate between a motile state, with single cell swimming, and a sessile state, with cell forming a chain or sometimes more complex structures [43,44]. Each of

these states offers unique advantages and is more suited to the particular current situation.

In the sessile state, the microbiota first forms microcolonies (small clusters of cells) and then polymicrobial biofilms, not really like an organ [43,44]. Biofilms tend to occupy the mucosal epithelial cells which are not protected by mucus and are therefore liable to direct contact. Microbiota organization in biofilm rather correlates with pathological states, than with a healthy gut, and is intended for its own defense purposes. Indeed, in the sessile state (biofilms), the microbiota appears to be linked to persistent infections and shows an unexpected resistance to antimicrobial agents. In some aspects, microbiota organization recalls that of cancer cells and biofilms appear to be carcinogenic [45].

Additional clues suggesting the human gut microbiota may not be an organ

The human gut microbiota as an outsider companion in our life

The origin of the gut microbiota is environmental [2,46]: For this reason, it is 'seen' by our immune system as a foreign element to be monitored to prevent it from spreading outside the intestine. Definitively, it is what is needed to keep the immune system on alert at all times. It is essential for the onset of inflammatory chronic diseases [4,5], including cancer, and microbial signatures have been found outside the intestine in pathology, thus its contribute beyond the intestinal barrier may be considered deleterious [47].

Being a foreign, unorganized element, the microbiota is not incorporated in our connective tissue and is not innervated, nor does it depend on the nutrients provided by the blood, but depends directly from our intake of food or from the availability of intestinal mucus.

The gut microbiota changes for better or worse in a currently unpredictable way

Each individual gut microbiota is unique and changes its composition continuously over the life of its host. Differently from the host's organs, which are made of a limited number of similar eukaryotic cells, the gut microbiota consists of a huge number of different prokaryotic cells, which are mostly anaerobic in a healthy condition (gut eubiosis), and may become aerobic in an unhealthy condition (gut dysbiosis). This means that, depending on its population, the gut microbiota can be beneficial or detrimental for human health, which is not exactly what we expect from an organ in our body.

Microbial changes are not limited to population: The microbiome is also highly dynamic and changes rapidly. The plasticity of prokaryotic genomes is connected with the ability of bacteria of the same species to adapt to the environment and therefore acquire or lose genetic material through intragenome gene transfer, duplication, or lateral genomic interspecies transfer.

Furthermore, the way the gut microbiota processes information is different from that of human organs. Due to the very high number of microbial cells, the microbiota is able to make a wide range of very variable decisions and to adopt of a great variety of behaviors. Unlike the deterministic processes occurring in the organs of our body, changes in the human gut microbiota can occur on the basis of stochastic processes and therefore are unpredictable [48].

The relationship between the gut microbiota and the host is unbalanced

One consequence of the concept of the microbiota as an organ is to consider its 'bidirectional' relationship with all organs of the human body, including the brain. The relationship with the brain, called the 'gut–microbiota–brain axis' or 'gut–brain axis' [49–55], has been suggested to be involved in the pathogenesis of chronic inflammatory, neurodegenerative, diseases such as Alzheimer's disease, Parkinson's disease, MS, amyotrophic lateral sclerosis, and autism spectrum disorders [40,54].

The correlation of these diseases with intestinal dysbiosis and inflammation and the fact that gut microbiota is essential to trigger inflammation [4,5] suggest a direct, though complementary, role of the dysbiotic microbiota in the onset of neuroinflammatory diseases [40,54]. The opposite direction, from the brain to the microbiota, is different.

It is indeed well known that the brain communicates with the gut through the sympathetic and parasympathetic/vagal efferents of the autonomic nervous system (ANS) and *via* the hypothalamic–pituitary–adrenal (HPA) axis. Accordingly, the brain can modulate the motility and permeability of the gut as well as its pH, by controlling both the secretion of acids and bicarbonate, the production of mucus, and the mucosal immune response. All the changes induced by the top-down pathways—that is, from the brain to the gut—may affect the gut microbiota as they change its environment. This means that the brain has only indirect

effects on gut microbiota, as the host has control over the environment inhabited by the microbiota and not over the microbiota itself.

Changes in peristalsis may affect the rate at which nutrients pass through the intestine and impaired intestinal transit may influence the gut microbiota. The first can alter the normal functioning of the second, interfere with its rhythms, and therefore disturb peristalsis, the production of acids, enzymes, hormones, and cytokines. Vice versa, diet and intestinal disorders can produce their effects on the central brain and may also be linked to changes in mood.

The human gut microbiota is not a commensal

The other aspect of the microbiota that we want to take into consideration here concerns the use of the term 'commensal', often added to define the microbiota, without there being a real need, and therefore, it is probably redundant or used improperly to indicate what is not harmful [4,56,57]. However, if this is so, more correct definitions would be 'indigenous', 'resident', or 'nonpathogenic' microbiota, instead of 'commensal' microbiota. Even 'mutualistic' would be more appropriate than 'commensal', when defining the gut microbiota as an organ, or as a useful life companion.

Still, the microbiota is also called commensal when it is critical to causing an experimental disease such as EAE [4,5], so it can be difficult to understand why this definition is used in relation to the experimental disease.

Paradoxically, the definition of commensal would be even more correct for the microbiota linked to gut dysbiosis or SIBO ('small intestinal bacterial overgrowth') [58–60], than for the microbiota that has a mutualistic relationship with the host, because in those cases the microbiota has the opportunity to eat the same food as the host.

From a figurative point of view, rather than being a commensal sitting at the table and competing with the host for the dishes, the microbiota acts like somebody on the ground waiting for dietary leftovers. Indeed, the gut microbiota resides mainly in the large intestine, where the undigested food is made available, either because it cannot be digested by the host (fiber), or because there is too much (Western diet), or peristalsis is too rapid.

In the end, since we now know that the gut microbiota really depends on the host diet [61], the term commensal becomes inappropriate especially if it is intended to indicate nonpathogenic microbes. Indeed, things are different: The microbes become commensals in the case of gut dysbiosis, SIBO, and some chronic inflammatory pathologies. In the healthy condition, they eat mostly the host remains.

Discussion

The aim of this work is to stimulate a discussion about the meaning of the existence of human gut microbiota in the human body and calls for caution in using terms that are becoming commonplace to describe the gut microbiota, but for which there is not yet sufficient experimental evidence supporting usage.

This is not the first time that the validity of certain definitions concerning the microbiota has been questioned, for example, the terms microbiome [3] and dysbiosis [35–36], although these refer to the definitions in the literal sense of the term, while here we refer to alleged functions of the microbiota.

This work also aspires to opening new horizons and perspectives in the research on human gut microbiota, which is a very complex entity, so different from our body that it requires study approaches that do not fit into those for the other organs of our body. Further research is needed, before defining the microbiota as an organ and as a commensal.

The current interest in the role of the human gut microbiota in chronic inflammatory diseases is very recent. As mentioned above, until about 10 years ago, the gut microbiota was not considered, except as a rather undesirable foreign entity to be treated, in the eventuality of disorders, with antibiotics, and before that with antibacterials such as the sulfonamides. In even more distant times, purges and enemas were used to prevent the long persistence of putrefactive microbes in the intestine. The general consideration of the gut microbiota was rather negative. It was a 'contaminant'.

Nowadays, we are increasingly convinced that the human gut microbiota is important for our health, so important that we have come to think of the gut microbiota as an organ of our body.

Thousands of studies have been published in the last decade. The results obtained in such a short time were so amazing that researchers were induced to attribute to the microbiota roles that are typical of our body, not considering the exceptional nature of the human gut microbiota, which is very different from human cells, also in the view that it is made of trillions of microbes accounting for all kingdoms of life [57].

Therefore, in this review we have briefly argued whether it is correct to consider the microbiota both as an organ of our organism and as a commensal.

A more objective evaluation of roles is necessary in order to avoid points of view that can mislead research, even just working hypotheses.

In our opinion, it would be more appropriate to look at the human gut microbiota as a foreign environmental agent, which has adapted itself to the host and has been accepted by the host over the course of evolution. In our opinion, it could be considered as a kind of sensor of the variations in our relationship with environmental energy, which mainly occurs through the intake of food and the elimination of waste: an interface between our energy and that of the environment, or a buffer system between the food we eat (and therefore the energy we take from the environment) and our energy needs. If our exchange of energy with the environment is, in some way, altered, the first signals of discomfort would come from the gut microbiota and, if gut dysbiosis continues, a spectrum of diseases would open up. This would be much more than the role assigned to an organ.

By assigning the function of an organ to the microbiota, it is claimed that a community of trillions of cells can be controlled in some way by the host itself. This despite the fact that the microbiota is made up of unorganized simple organisms, thus changeable in their functions (independently of the will of the host), and reacting to environmental changes probably by means of stochastic processes. In contrast, animal studies are showing that lack of microbiota or its modifications, besides affecting neurogenesis, myelination, microglia, and the integrity of the blood-brain barrier, influences social behavior and response to stress, and impairs extinction learning [62]. If this is so, then humans are not completely autonomous entities [63], although being well distinct from the microbial world.

More than as an organ, the microbiota may be considered as an ecological community of organisms with a high range of mutualistic or even parasitic interactions between themselves and the host, high frequency of change in their composition and a high capacity for horizontal and vertical gene transfer. It consists of microorganisms that have evolved with us, but are fundamentally foreign to us.

The microbiota is not an organ of our body simply because it is very different from us. It has learned to live with us, but it is different from us. From its point of view, we only provide its habitat and sustenance. Thus, if the microbiota is not an organ functional to the host, could the host not instead be functional to the microbiota?

This intentionally provocative question brings us back to the fundamental question of what the microbiota represents for us.

After all, it may be that the advantages we have from having a eubiotic gut microbiota simply derive from the fact that the presence of the microbiota forces us to always be on the alert, starting with the immune system, and therefore to have our organs in good condition. On the other hand, the microbiota has every interest in assisting the host in order to have the best possible habitat.

At this point, it is possible to hypothesize that, after thousands of years of evolution, some adaptive mechanisms have become common to the host and the microbiota, as they are mutually beneficial, but many other mechanisms have certainly remained independent.

Actually, our world is made up of relationships. Each symbiotic beneficial relationship allows the two interacting parties to exist (acknowledgment) and to foster future mutual existence (evolution of the relationship), but this does not mean that the relationships between the parties must be institutionalized.

For example, it has been reported that the electrically conductive bacteria *geobacter sulfurreducens* form biofilms containing copper sulfide on copper electrodes thus enhancing the flow of electricity [64]. This might improve the performance of fuel cells, but in this case, it is obviously difficult to think that this is a contribution like that of an organ.

To conclude, there is an algebrical expression that gives a good idea of what the collaboration between the gut microbiota (in its eubiotic state) and its host may represent. If A and B are the two entities and we square their sum, $(A + B)^2$, we have as result $A^2 + B^2 + 2AB$. The two entities remain separate, but their collaboration gives a prize, which is 2AB.

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PR and RR conceived and wrote the manuscript.

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