

The Microbiota, New Central Dogma of Biology Relationship between Microbiota and State of Health of Living Beings

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Abstract

Few other scientific disciplines have met with as much success in the biomedical field as Microbiomics.

The foundations of Microbiomics follow the research of Pasteur, Koch and other famous microbiologists who studied the pathogenic power of bacteria, until more recent authors also demonstrated the beneficial role that many bacteria present in the intestinal flora have.

It is up to Isaac Kendall, the definition of microbiota, which is the complex of microbes present in the intestine, and to have recognized its alteration, called dysbiosis, the cause of the most widespread diseases, furthermore he also described its role in other biological activities and on the immune system.

Since then, a large group of authors have engaged in a real competition in order to search for the most unlikely pathogenetic connections between dysbiosis and many pathologies for which no certain cause has not been demonstrated yet.

Thus an inexhaustible source of etiological hypotheses has fictitiously and randomly replaced our ignorance about the certain causes of diseases that affect humans.

In this article We are going to criticize firmly this improper use of scientific investigations conducted with the use of Microbiomics, highlighting the obvious contradictions of the results obtained and the close business connections with pharmaceutical and food multinationals.

Keywords: Microbiome, Microbiota, Axes Gut-organs, Metagenomic, Faecal microbiota transplantation, Microbiome Market

Introduction

“Better a sincere declaration of humility in recognizing one's limits, than an ostentatious assertion of scientific truths yet to be demonstrated.”

Anonymous

Since Microbiomics made its appearance in the biomedical field it has become the central dogma of biology - a re-edition of the historic DNA-Protein dogma of Watson and Crick - with which we can explain the origin of all diseases known today.

The new discipline has overcome the doubts and uncertainties that underline the arduous path of biomedical research, and has claimed to have solved all mysteries and revealed the causes of any disease.

It has thus become a useful and convenient viaticum that guides us into the dark meanders of biological mechanisms.

Since its discovery everything has become clear about the origin of pathologies, from cancer, which affects any system, to cardiovascular diseases, Alzheimer's, Autism, etc., we finally know everything and we have the solution at

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hand to be able to eradicate them. There is no disease for which the causes and solutions are not known, thanks to the microbiota.

The ostentatious certainty of the conclusions with which Microbiomics has subjugated the scientific world is unlikely.

It has overshadowed and surpassed all traditional biomedical theories and the acquisitions we have arrived at after centuries of experimental and clinical study and research.

The truth revealed by Microbiomics has relieved us of the burden of further investigating phenomena relating to health and disease.

But is it really true?

Let's examine facts and documents.

Birth of Microbiomics, When Bacteria Dictate the Law

Since Arthur Isaac Kendall: (May 7, 1877-June 20, 1959) [1], discovered the intestinal microbiota and hypothesized its fundamental role in digestive function, in various metabolic functions and in the interaction with the immune system, a flourishing literature on the subject began.

In order to date there are millions of articles, studies and research already published, focused on the connections between the intestinal microbiota and well-being or disease and on the close connection between the brain microbiota, known as the Gut-Brain Axis, its influence on the most diverse biological activities, and its fundamental role for health Fig.1, [2].

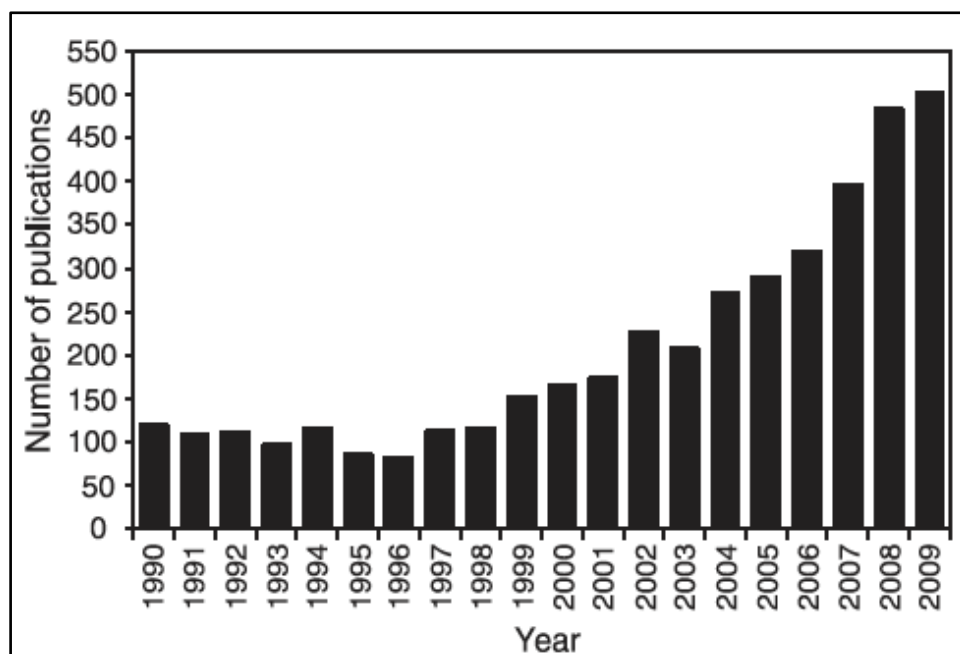


Figure1. Number of publications related to the intestinal microbiota in the last two decades, per year.

The attention of researchers for the new interpretative tool, based on the microbiota, has grown exponentially, and has offered a fruitful resource for clinical investigations, prospective studies, meta-analyses, etc. in which to drawing inspiration.

Unknown Microbiome.

The microbiota is considered the set of different microorganisms from which it is

formed, it includes viruses, bacteria, fungi, yeasts, etc. and is widespread in every part of the body with different and specific microbial colonies, and presents a wide individual variability and a range of microbiological spectra, which change throughout life and in different pathological, environmental and nutritional conditions, etc. Fig.2.

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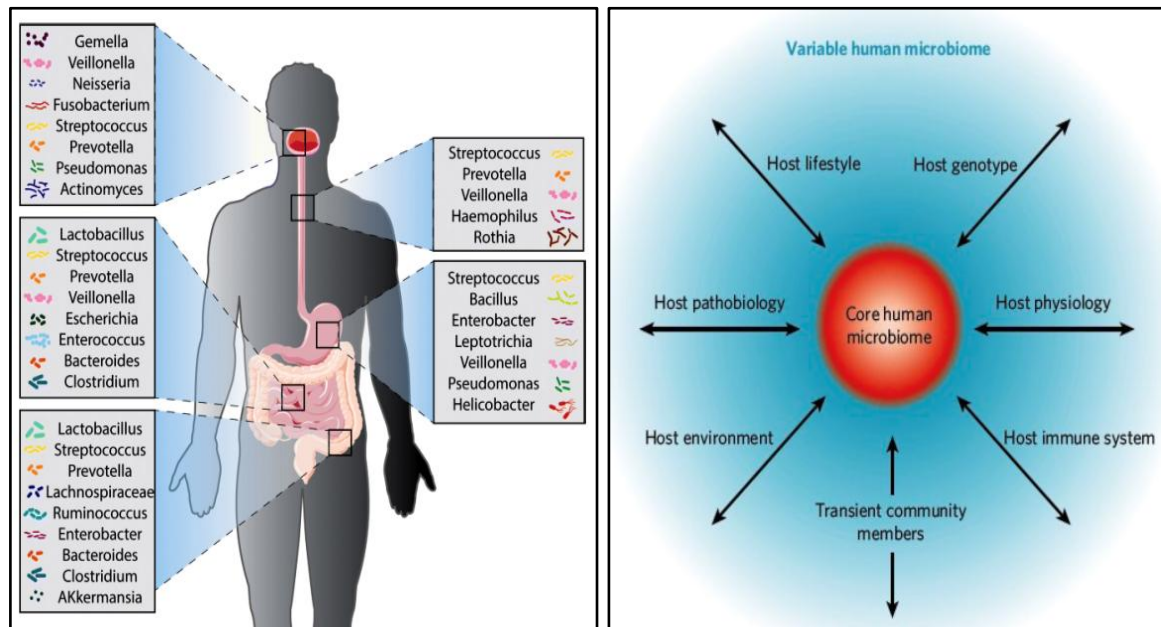


Figure2-From. Peter J. Turnbaugh et al; The Human Microbiome Project, NATURE Vol 449|18 October 2007, The concept of a core human microbiome.

The widespread diffusion of studies on the microbiota has given rise to a new discipline, Microbiomics, and has also favored the birth of international research organizations including the Human Microbiome Project: Human Microbiome Project :[https://commonfund.nih.gov/\[3-7\]](https://commonfund.nih.gov/[3-7]).

This great research work has provided the explanation of the already known and hypothesized effects of the intestinal bacterial flora in digestion, in various metabolic functions and in the interaction with the body's immune defenses.

As mentioned before, the most numerous investigations have studied the surprising correlations between the altered composition of the intestinal bacterial flora, known as intestinal dysbiosis, and the multiple organic and mental pathologies that afflict humans.

According to the new paradigm, there is no organic or mental pathology that does not have a causal link with intestinal dysbiosis , and even more surprising is the fact that the list of pathologies increases every day [8-17].

For its investigations, Microbiomics has equipped itself with a powerful tool, Metagenomics, which explains all pathologies with the genetic examination of the bacterial colonies that live in our intestine. Thanks to this tool, he archived and erased with one stroke of the sponge centuries of research on Pathology, Physiology, Genetics, Microbiology, Biochemistry, Immunology, etc.

Microbiomics, focusing only on the microbial component, ignores the numerous factors that influence the pathogenesis of most pathologies and in particular gastrointestinal diseases, and brings everything together and simplifies biomedical research by identifying a single pathogenetic factor as responsible for every evil.

The frantic chase to discover unexplored territories of microbiology has led an innumerable group of researchers to formulate bold hypotheses to identify the pathogenetic potential of the homeostatic imbalance of the microbiota.

The result is an alarming picture of causes and contributory causes of the most varied and unknown pathologies Fig.3.

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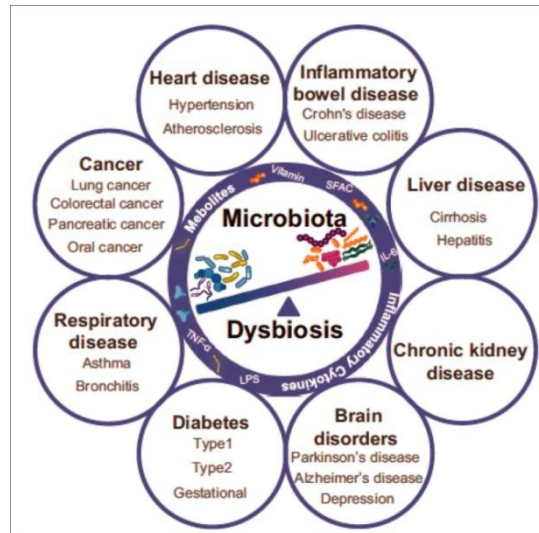


Figure3. Kaijian Hou et al; Microbiota in health and diseases, Signal Transduction and Targeted Therapy (2022) 7:135

The investigation went so far as to recognize a specialization of altered bacterial strains in the organ-specific pathogenesis of many diseases Fig. 4.

Only a few works have raised doubts on the relationship between Dysbiosis and cancer [18].

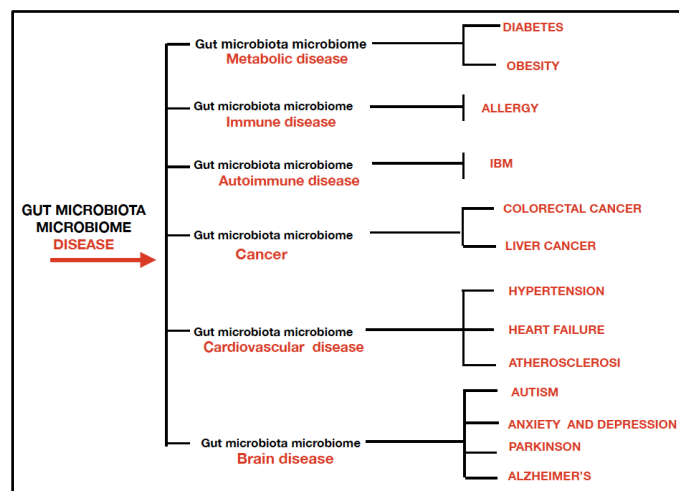


Figure4. Diagram Gut Microbiota and Disease

A partial and summary list can be found in the following articles, in addition to those already cited [19-27].

But what is disconcerting, and casts a sinister light on the consistency of many works, is that other articles claim that the same bacteria can prevent and even cure the diseases for which they are responsible. These are generally probiotics [28].

Once the direct connection between intestinal dysbiosis and pathologies was defined, the research further explored and focused attention on the close link between the intestine and the brain which led to the identification of a privileged route of

anatomical-functional communication between the two organs, it is what has been called *the gut-brain axis*.

And it revealed the synergistic activity of the intestine-brain axis in the determinism of the same pathologies previously attributed exclusively to the dysbiosis of the intestinal microbiota.

The result was an inseparable union between the two systems so as to define them as a single anatomical-physiopathological entity, which led to an infinite series of pathogenetic hypotheses and publications [29-38].

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Following the prolific scientific trend of the gut-brain axis, other gut-organ connections have been explored, resulting in the discovery and description of a widespread network of axes, heart-brain,

lung-brain, epidermis-brain, and so on. Via, which have in common the presence of a resident microbiome and are all dependent on the central gut-brain axis [39-42], Fig. 5.

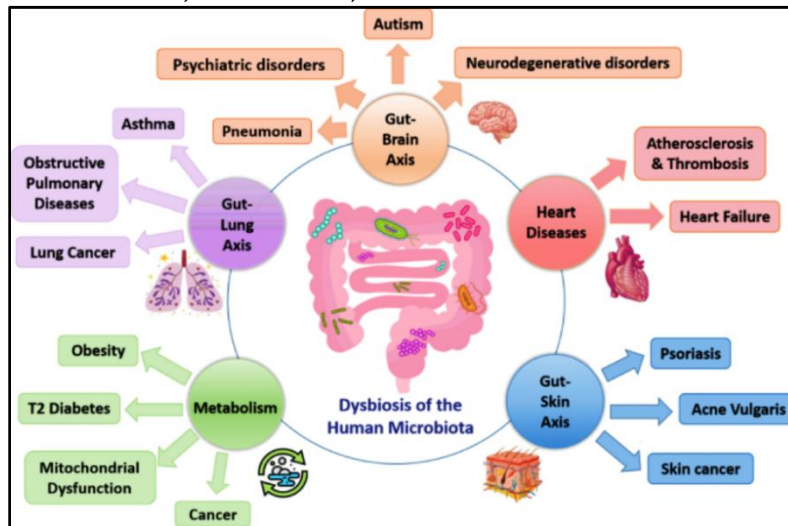


Figure5. Schematic representation of the correlations Intestine with other organs

In this way, a dense network of microbiological interactions and communications has been built which spreads fundamental physiological and pathophysiological messages through the vascular system.

It is singular that this microbiological network is super imposable

on the already known neuronal communication network that connects the brain and autonomic nervous system Fi. 6, and uses the neurotransmitter system whose dysfunctions (*Autonomic Nervous System Dysfunction*) have clinical relevance [43-47].

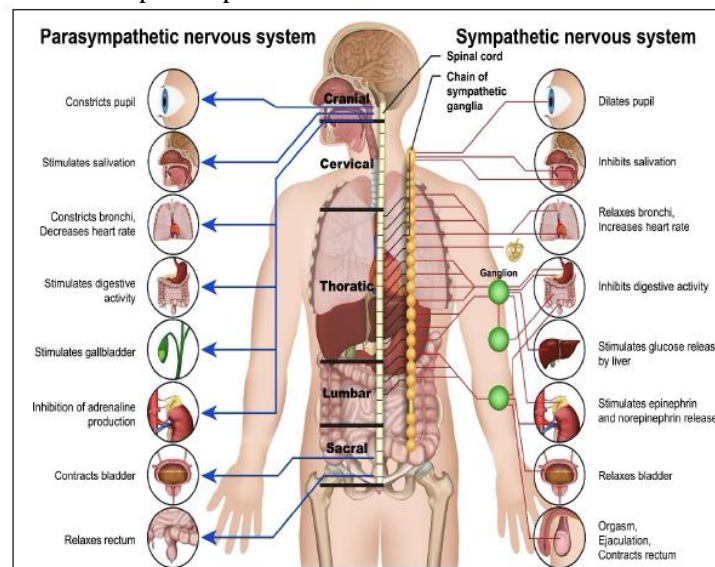


Figure6. Autonomic Nervous System

In such circumstances, deriving the contribution of intestinal dysbiosis or autonomic nervous system dysfunctions to the pathologies listed, Fig.4, becomes a difficult task.

Before tackling the critical examination of the postulates that underlie the Microbiomics concept, let's summarize the key concepts that inspire it, we have extrapolated them from the article already cited [7]:

1. Human beings, throughout their entire life cycle, from birth to death, are accompanied by the presence of intestinal microbes. Environmental factors, lifestyle, age and other factors can influence intestinal microbiota balance and their impact on human health. Intestinal microbes play a primary role in the development of various types of diseases.
2. Depending on the regions where it is located, the microbiota can be classified into intestinal, oral, respiratory, and skin microbiota. Microbial communities are in symbiosis with the host, contributing to homeostasis and regulating immune function. However, dysbiosis of the microbiota can lead to dysregulation of bodily functions and full-blown diseases. A large body of evidence demonstrated, more than a decade ago, that intestinal microbial alteration is a key factor in the pathogenesis of many local and systemic disorders.
3. Normal flora is the site of many physiological functions such as enhancing host immunity, participating in nutrient absorption, and protecting the body against pathogenic microorganisms. Numerous researches have shown a bidirectional interaction between gut microbiota and many organs within the human body such as the lungs, brain and skin.
4. The future of medicine is strongly linked to the quality of our microbiota. Targeting microbiota dysbiosis will be a huge challenge for the future.
5. At the same time we must introduce clinical approaches that use the microbiota for the treatment of diseases, or its remodulation with the use of bacterial strains selected with fecal microbial transplantation.

In order to understand the key concepts and the rationale which inspires the conception of the Microbiome and its postulated biological function, it is necessary to recall and clarify some elementary concepts of intestinal microbiology and physiology.

The Resident Microbiome and its Variations

The Microbiome is a complex system that includes numerous microorganisms, billions of billions of individuals, diversified and including prokaryotic organisms (without a nucleus, such as viruses and bacteria) and eukaryotes (provided with a nucleus and internal organelles, such as yeasts, protozoa, and multicellular organisms), which reside in different sites of the organism that hosts them.

The microbiota is widespread in all living animal and plant species, it shares the environment with the species that host it, and follows their evolution.

If we restrict the investigation to animal species only, we will find that each animal organism has its own specific microbiota, which phylogenetically follows all the evolutionary variations of the host.

Thus we talk about microbiota-host **coevolution**, which underlines the continuous adaptation of the host to the environment and of the microbiota to its host.

The property that distinguishes the elementary organisms that form the microbiota in a biologically relevant way is the ability to reproduce with an exponential speed to adapt to the presence or absence of nutrients, the salt concentration, the Ph concentration, the temperature, the conditions of the host, therefore they are in a condition of constant competition and commensalism for mutual dynamic balance.

As environmental conditions and the conditions of the host vary, there is a corresponding variation in the microbiota.

Typical is the diversity of the microbiota found in primates compared to humans and in the variation of the compositions of the microbiota with the age of the host from birth to adulthood and old age.

Equally typical is the variability of the microbiota linked to the pharmacological therapy to which the host is subjected. Antibiotic, antifungal, hormonal, anti-tumor therapy, treatment with energetic purgatives, etc., significantly affect the balance of the microbiome.

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In fact, after each treatment with antibiotics, probiotics are prescribed to restore the altered balance of the resident flora.

The same treatment with probiotics, prebiotics and synbiotics that is proposed to improve intestinal conditions is strongly indicative that the microbiota can be modified.

In addition to the environmental factors outlined, the microbiome can vary based on host conditions. In celiac patients, with Crohn's disease, with Ulcerative Colitis or Irritable Bowel Syndrome, and so on, the structure of the mucous membranes and intestinal secretions, which are respectively the medium and the culture broth of the microbiota, change chronically and drastically, and in these pathologies they determine unfavorable conditions for his survival.

Furthermore, there is the condition of patients undergoing colectomy, in which the removal of part of the intestine produces a drastic reduction with negative consequences for the resident microbiota.

The effect of the host's diet is fundamental in creating the nutritional conditions in which the microbiota can take root and survive [48-49]

In addition to nutrition itself, even more important are the additives that are added to foods in the production chain. The

constant presence of preservatives, emulsifiers, antioxidants, stabilizers etc. in food modifies the normal conditions of the intestinal microenvironment [50-60].

Based on these considerations, it becomes difficult to define and typify a specific microbiome that is stable and to attribute to its effects a determining role for the host's well-being and disease conditions.

Metagenomics and Microbiota Typing

The method adopted for typing bacteria using genetic investigation is a debated and controversial topic.

Genetic typing is decisive in being able to attribute its beneficial or pathogenic effects to a specific microbiota, it is through these tests that the relationships between the genome of a complex of bacteria and the pathogenetic action assigned to them are established [61-62], Fig. 6.

Genetic testing is performed using the 16S Ribosomal RNA (rRNA) sequencing technique.

The criticisms that have been raised against these methods are very serious and cast an aura of unreliability on the results obtained [63].

Some studies have highlighted the critical issues of the numerous investigations conducted with the study of the microbiota [64-65].

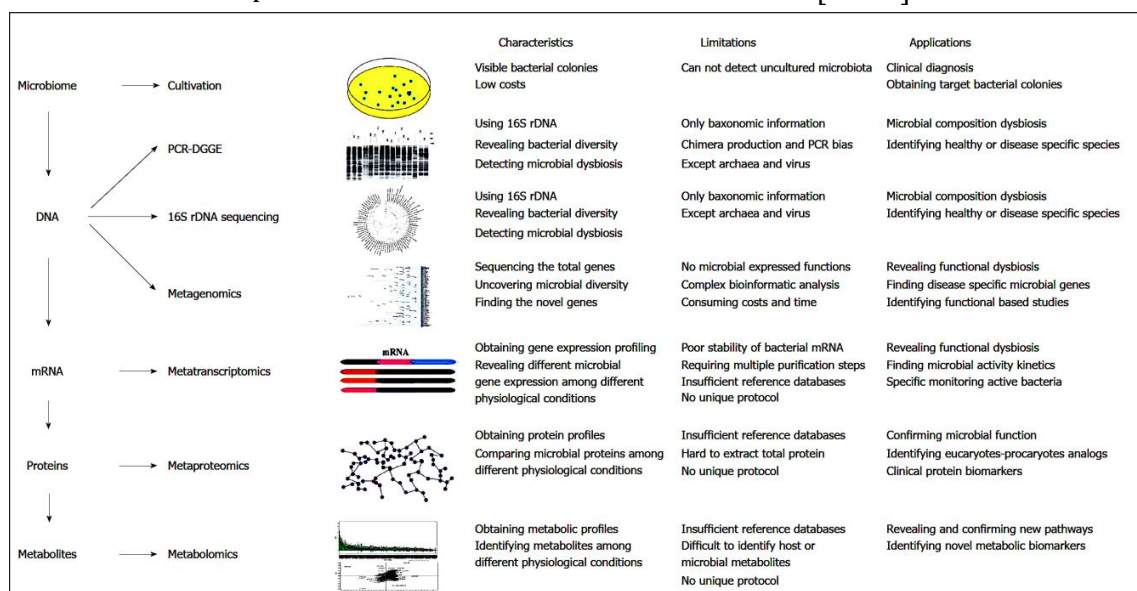


Figure6. Comparison of different gut microbiome study approaches. The characteristics, limitations, and applications of different gut microbiome approaches from cultivation to metabolomics are presented. DGGE: Denaturing gradient gel electrophoresis.

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Wang WL, Xu SY, Ren ZG, Tao L, Jiang JW, Zheng SS. Application of metagenomics in the human gut microbiome. *World J Gastroenterol* 2015; 21(3): 803-814

An aspect of no less importance is that many clinical works do not indicate the duration of effectiveness obtained with the replacement treatment with the modification of the microbiota [66-68].

But the criticisms don't end there.

The concept of the uniqueness of individuals has never been emphasized enough.

Among the eight billion people who populate our planet, no two individuals are exactly alike in terms of their biological characteristics, not even two identical twins share the same phenotype from a morphologically functional point of view, much less the same microbiota.

Therefore, when we talk about the microbiota representative of a general physiological or pathological condition we make a gross mistake, we can only state that a certain microbial population is present in the average of the individuals tested.

The same concept of individual uniqueness obviously applies to all biomedical fields.

It is no coincidence that today personalized medicine is increasingly supported.

The Representation of the Organ-Microbiota Axes

We have already mentioned the thriving literature that is developing on this topic.

After having identified the gut-brain axis, microbiota cartographers have described other axes that associate the function of the gut microbiota with that of other organs and vice versa Fig. 5.

So far, three main axes have been identified so far:

Gut brain axis;

Gut Lung Axis;

Gut Skin Axis

Each of the axes described is the means that involves a specific organ in the pathogenetic activity of the intestine to produce the typical harmful manifestations.

This interpretation calls into question other organ-specific etiopathogenetic factors in addition to those evoked in the first version in which the responsibility was relegated to the intestinal microbiota alone.

This change of perspective goes beyond the concept of the dysfunction of a single organ, even as important as the intestine, and requires the contribution of other factors in the determinism of all the pathologies that affect the human race.

It is an aberrant and anti-scientific vision, extremely reductive and simplifying the multiple and complex phenomena that determine the state of well-being and illness.

Identifying a single cause, even if it is produced by different entities, as the basis of all pathologies is the equivalent of the biblical attribution of original sin to Adam as the primary and sole cause of all human suffering.

To summarize the criticisms of the microbiome approach, we report some sentences taken from the Publications Office of the European Union:

"It should be underlined that to date research on the intestinal microbiota is very focused on bacteria. Very few studies have examined the viral component (or virome) and eukaryotes such as protozoa, yeast and fungi, or even bacteriophages.

Microorganisms in the gut not only aid in the digestion of food, but are also, perhaps more importantly, involved in establishing the immune system response, defense against pathogens, the endocrine system, and even mental health. They are already present before birth and influence human health.

The composition is determined and varies greatly depending on diet, but also lifestyle, age, genetics, disease, use of antibiotics, etc. they're important. Dietary changes can account for up to 57% of changes in the gut microbiota, while genes account for no more than 12%.

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We still lack a lot in terms of mechanistic understanding of how microbes contribute to disease onset. Many animal studies have been conducted, while limited data are available regarding human studies. A major challenge is the variation in the normal functional human microbiome, but also the use of different techniques to assess dysbiosis in humans which could lead to the generation of different results."

From: Knowledge Health and Consumer Safety, *The Human Gut Microbiota: Overview and analysis of the current scientific knowledge and possible impact on healthcare and well-being*, EUR 29240 EN, Publications Office of the European Union, Luxembourg, 2018, ISBN 978-92-79-86471-1, doi 10.2760/17381, PUBSY No. 112042

Splitting of Investigations

The observations reported in the text highlight a crucial aspect of the entire approach to investigations on the Microbiota, and it is their "**bacteriocentric**" vision, which examines only the component of the microbiota, neglecting all the other aspects that contribute to the clinical effects observed.

In truth, this procedure is very widespread in research; in the description of phenomena, particular, micrometric aspects isolated from the context are privileged, therefore the result is a sectoral and fragmented vision of the events as a whole.

Except then to transfer the observed results and extrapolate them to the entire process. It is the Down Up procedure that is widely followed when the phenomena to be examined are very complex, with their subdivision into individual micrometric phases, only isolated aspects are captured, so it is believed that the entire procedure can be reconstructed in its overall logic.

Despite its limitations, such a method is understandable when the individual aspects are correlated and interdependent, as in the case of metabolic processes, where each step determines the next and the interruption of a phase blocks the entire process.

But they are absolutely not acceptable when the effects observed are

not downstream of the previous steps, or are completely disconnected from each other, as in the case of the procedures described by Microbiomics .

In the previous passages we have described numerous situations in which two events are totally unrelated to each other, and are not the consequence of each other, or between which a causal link cannot be demonstrated. Or they are the result of the extreme variability of the supposed causes, in this case dysbiosis .

In order to confirm the lability and inconsistency of the pathogenetic conclusions, there are the presumed coincidences with numerous pathologies about which we know absolutely nothing (Cancer, Alzheimer's, Autism, Schizophrenia, and so on) or for which we have no effective therapeutic measures such as, to remain on the subject, antibiotic resistance. The certain causes of some pathologies are hidden in order to attribute them to dysbiosis (Celiac disease, Diabetes, Atherosclerosis).

By this procedure you can demonstrate everything and the opposite of everything with extreme ease.

The investigations must follow a holistic vision of the phenomena, their fragmentation or isolation from the context invariably distorts the results.

We are going to close the literature review by reporting the repugnant theories of many authors who propose the use of fecal transplantation, **fecal microbiota transplantation (FMT)**, to correct intestinal dysbiosis.

A substantial series of articles supports the use of faecal microbiome extracts which are indicated in various pathologies with effective therapeutic results [69-75].

We must ask ourselves whether the biological characteristics of the strains used remain unchanged during the purification process or whether they do not undergo significant modifications that compromise their supposed therapeutic activity.

For this reason I would like to suggest to these authors to use stool

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extracts directly, to appreciate, in addition to their therapeutic efficacy, also their organoleptic properties.

The Real Causes of the Growing Interest in Microbiomics

In order to understand the real reason about the interest in Microbiomics, and its exponential growth in recent years, we must look up from world literature to the global market that drives this sector.

It is an ultra-billion dollar market that generates staggering figures and involves the major pharmaceutical and food companies that have transformed the demand for well-being into pure business [76-81].

Actually, multinationals have been enslaving research to promote the indiscriminate use of inconsistent and contradictory therapies based on extremely unstable biological systems, the microbiota, strongly conditioned by multiple environmental variables and factors.

This is pure speculation that has paved the way for exponentially growing turnovers that rival those of the pharmaceutical industry. The global prebiotics market in the US was \$6.05 billion and that of probiotics was \$47.6 billion in 2021, Fig.7.

As we look ahead to the next decade, which has been called *'the decade of the microbiome business'*, investors are taking notice of the growing demand and research for these products. Several biotech startups dedicated to microbiome research have emerged (more than 100 R&D companies) in 2021 to leverage and accelerate research in this area. In the last five years, pharmaceutical companies in the field of consumer health have signed agreements worth more than 3 billion dollars to study the microbiome and related drugs in this diagnostic and therapeutic sector (Figure 7).

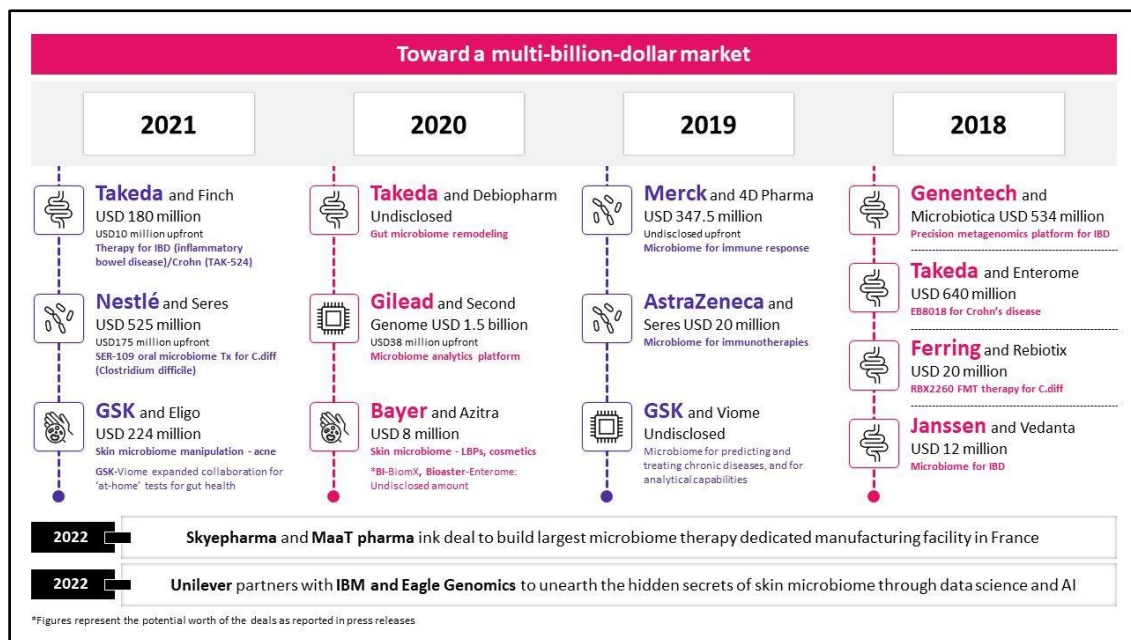


Figure 7. A multi-billion-dollar market

The illustration reveals the deals executed by major pharma and consumer health players with emerging start-ups toward the business and research of human microbiomes. In 2022, Skyepharma and MaaT pharma inked a deal to build the largest microbiome therapy-dedicated manufacturing facility in France, and Unilever partnered with IBM and Eagle Genomics to unearth the hidden secrets of skin microbiome through data science and AI.

The fields of use of the microbiota range from therapy, to diagnosis, to prevention, so it is an unlimited market that grows in parallel with the sponsorship of clinical work, Fig.8.

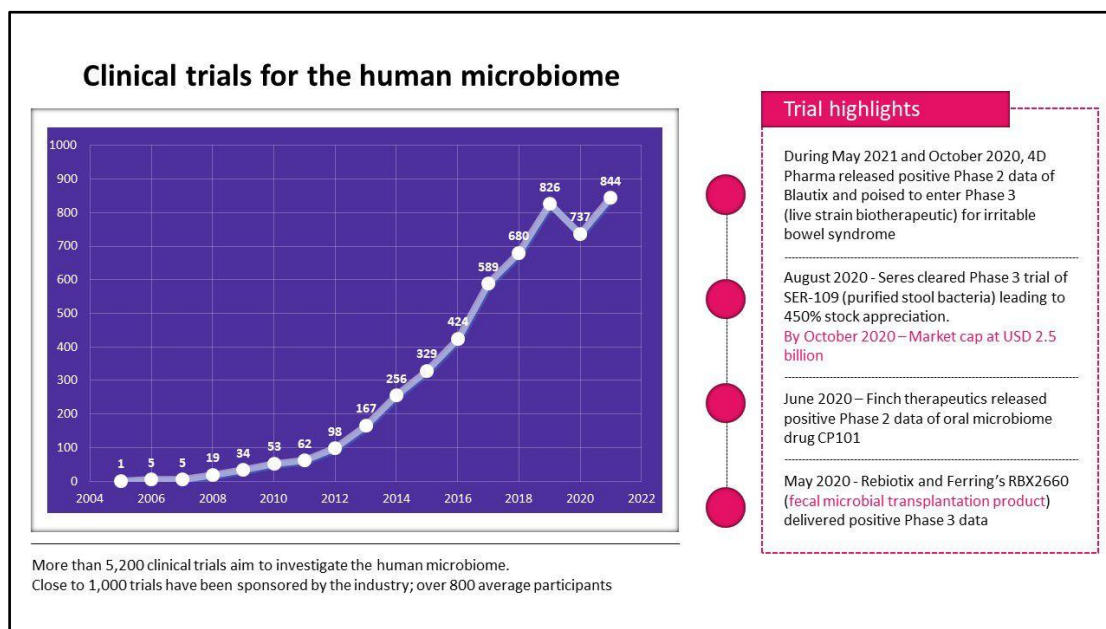


Figure8. Trend of clinical trial registrations concerning microbiome as one of the measurable targets between 2005-2021

illustration showing that over 5,200 trials have been designed to investigate the human microbiome and that close to 1,000 trials have been sponsored by the industry. Trial highlights suggest that during May 2021 and October 2020, 4D Pharma released positive Phase 2 data of Blautix and was poised to enter Phase 3 (live strain biotherapeutic) for irritable bowel syndrome. In June 2020, Finch therapeutics released positive Phase 2 data of oral microbiome drug CP101.

Conclusion

Often, scientific research, faced with the immeasurable complexity of the natural phenomena it must investigate and the limited cognitive capacity with which we are endowed, adopts simplifications and shortcuts, which allow us to enclose in a few postulates and theories, arbitrarily pre-established, an understanding compatible with ours. resources.

The history of epistemology is paved with obscure passages in the explanation of phenomena, in front of which, the most recurrent expression is: "we are not able to give an explanation of such behavior".

Recognizing one's limits is a sign of wisdom and intellectual honesty, because doubt is the basis of knowledge, as Descartes claimed (René Descartes 1596-1650).

For this reason, we are unable to share and accept the dogmatic position of Microbiomics experts, who entrust the fate of our state of health or disease to the

intrinsic, changing and immanent variability of the microbiota.

They have obscured and buried centuries of biomedical research and achievements in doing so.

We prefer to admit my ignorance rather than support inconsistent hypotheses.

However, thanks to the discoveries of microbiomics, according to its supporters, we have the solution to all ills.

We only have one last behavioral defect to correct, it is the unstoppable compulsive tendency of those who want to support the most absurd scientific hypotheses at all costs. But for this reason we have not found yet the suitable microbiota for an effective treatment.

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