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Review Article

The intestinal microbiota: Towards a multifactorial integrative model. Eubiosis and dysbiosis in morbid physical and psychological conditions

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Abstract

The human intestinal microbiota is considered "an organ within an organ", partially shrouded in mystery, as the issue related to the bacterial component but less the viral component and the other microorganisms present has been thoroughly investigated. To date, research has focused attention on the bacterial component and on the correlations between intestinal dysbiosis and the onset or worsening of dozens of physical and psychological pathological conditions, as well as integrative therapies to re-establish eubiosis, linked to targeted prebiotics and probiotics; however, the scientific community has not yet focused on the exact distribution of all the microorganisms that are part of the microbiota and the complete mapping of the microbiome, as well as the development of a protocol of specific therapies to be implemented (integrative or with monoclonal antibodies) to facilitate the reconstructive processes of natural eubiosis. If therefore, knowing the Microbiome (and the Microbiota) is important from a neuroimmunological point of view, on the other hand, it is essential to deepen the correlations with the onset of some physical and psychological pathologies; in particular, focusing the studies on the already well-known "microbiota-intestine-brain" axis would help to demonstrate whether the onset of psychopathological conditions are a contributing cause of dysbiosis or (more likely) dysbiosis causes an altered production of serotonin, dopamine, GABA and noradrenaline, capable of generating or worsening directly related psychopathologies, such as anxiety, depression, mood disorders, schizophrenia, psychotic and personality disorders. On the other hand, it is known that psychiatric drug therapies do not cure the morbid condition but aim to stabilize the patient who becomes dependent on it, and then witness a rapid worsening in the event of drug suspension or interruption. If we then wanted to search for an objective to investigate, the writer proposes to focus on the hypothesis according to which intervening on intestinal dysbiosis could decrease or eliminate the neurobiochemical cause at the base of many psychic disorders, such as anxiety, depression, bipolar and psychotic disorders, decreasing or eliminating the necessarily prescribed drug therapy.

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Introduction

The term "intestinal microbiota" refers to the set of symbiotic microorganisms (bacteria, viruses, fungi and protozoa) found in the human digestive tract, and is made up of different ecological niches that host a population made up of a plurality of species and from many strains; from the term "microbiota" we distinguish the term "microbiome" which is used to refer to the totality of the genetic patrimony that the microbiota can express. It is no coincidence that the "microbiota" is considered a real "organ within the organ" as it performs functions that we would otherwise not be able to perform, including the ability to assimilate indigestible components of our diet, such as plant polysaccharides [1].

The intestinal mucosa, after the respiratory one, represents the largest surface of our organism: a real defence organ that acts as a barrier against immunogenic or harmful factors

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present in the intestinal lumen [2]. And we live in fact with many different species of bacteria; in particular, in humans, there are up to a thousand different species of microorganisms (of which four hundred are just bacteria). However, the types of bacteria are different depending on the portion of the gastrointestinal tract taken into consideration, as Helicobacter Pylori prevails in the stomach, while in the intestine (from ileus to colon) the bacterial species are much greater and variable [3]. Among the components of the human microbiota are listed those that cause fermentation (80%) such as Lactobacillus and Bifidobacteria, and those that cause the putrefaction of the remains (20%) such as Escherichia, Bacteroides, Eubacteria and Clostridium. Many are useful and harmless as constituents of the equilibrium human microbiota of eubiosis, but taken individually they can be dangerous or even fatal. Generally, these bacteria are divided into: a) commensal or physiological, which belong to the organism; b) pathogens, which cause disease); c) probiotics, which affect the host by improving the intestinal microbial balance. Equally important in terms of Microbiota are the prebiotics, i.e. non-digestible food ingredients that in the large intestine stimulate the growth / metabolic activity of a limited number of microbial groups, important for the proper functioning of the organism and the symbiotics which are a combination of probiotics and prebiotics [4-6].

In the twentieth century, Elia Metchnikoff, the father of probiotics, had already hypothesized that the presence of bacteria in the intestine could somehow positively influence human health and longevity. He was convinced that the bacterial flora was responsible for the production of toxins and the control of auto-intoxication: this stemmed from an epidemiological observation of the longevity of the Balkan populations who consumed large quantities of yoghurt (rich in probiotic elements) [7] In the common imagination, however, the term "bacteria" evokes something negative, harmful to health, from which one should stay away; in fact, few know that the body of an adult individual hosts something like 100,000 billion bacteria, a number greater than the number of cells that make up the organism and even greater than the number of human beings that have appeared on Earth to date [8].

Anatomophysiological notes and pathological profiles

The intestine is a portion of the digestive system between the pylorus and the anal orifice. From the anatomical point of view, it is divided into two sections, the small intestine (or small intestine) and the large intestine (or large intestine). The small intestine begins with the pyloric valve, which separates it from the stomach, and ends with the ileocecal valve, which connects it with the large intestine. About 7 meters long and with an average diameter of 4 cm, it can be divided into three sections: duodenum, jejunum and ileum. The first represents the segment most involved in digestive processes, while the second and third are involved in the nutrient absorption process (90%). The internal surface of this tract of the digestive tract is raised to form folds, which in turn have numerous and thin protrusions called villi: this anatomical peculiarity has the purpose of increasing the contact surface, to optimize the digestive processes and the 'absorption. Each villus is covered with cells whose membrane, facing the internal lumen, has thin protrusions called microvilli (brush border): the conformation of these cells (enterocytes) has the purpose of further increasing the digestive and absorbing capacity of the intestine. At the base of each villus, there are small dimples called crypts; as well as the villi, the crypts are also covered with cells which, however, unlike those covering the protruding part, are still immature. Enterocytes live only a few days and as they age these cells detach from the villus and pass into the intestinal lumen to be eliminated with the faeces; the cell population renewal process is continuous and the cleaved enterocytes are promptly replaced by new cells that migrate from the crypts. As they rise from the crypt towards the top, the enterocytes mature, age and, upon reaching their apex, flake off. The phenomenon of cell migration causes the enterocyte population to be completely replaced by new cells every 3-5 days, to continuously renew and maintain a high digestive and absorbing efficiency of the intestine. A dense network of capillaries flows into each villus, essential for the transfer of nutrients from the intestinal lumen to the bloodstream. Unlike water, mineral salts, carbohydrates and amino acids, lipids do not enter the blood directly but, crossing the enterocyte, flow into a blind-bottomed lymphatic vessel in the centre of the villus; vitamins, on the other hand, deserve a separate discussion since some of them, by their lipid nature, follow the lymphatic pathway common to fats, while the others, being water-soluble, are absorbed directly by the blood capillaries. In the small intestine the digestion of food is thus completed, already started in the mouth for starch and in the stomach for proteins. The large intestine, on the other hand, with a length of about 2 meters, that is four times shorter than that of the small intestine and a larger diameter, extends from the ileocecal valve to the anus and can be divided into six portions: cecum, ascending colon, transverse colon, descending colon, sigma and rectum; at this level, the accumulation of residues from the digestive process and their expulsion to the outside through the faeces takes place. The absorbent capacity of the large intestine is however important since, especially in the colon, there is a considerable absorption of water and electrolytes. The longer the digestive products remain in the large intestine, the greater will be the reabsorption of water and salts. This phenomenon becomes evident in case of diarrhoea (loss of salts and water) or constipation (particularly hard, compact and dehydrated stools). Vitamins are also absorbed in the large intestine, not so much those introduced with food (already absorbed in the small intestine), but above all those produced by the billions of symbiotic bacteria that populate the colon. These microorganisms synthesize in particular vitamin K and some vitamins of group B. The large intestine also acts as a "deposit" for the faeces, thanks to a much larger diameter than that of the small intestine. As mentioned previously, the colon also has the property of concentrating digestion residues and, ultimately, of promoting their expulsion. By absorbing water and increasing faecal mass, dietary fibre and the supplements that contain it stimulate intestinal motility, facilitating evacuation. When they are not supported by an abundant intake of liquids, the laxative effects of the fiber are instead modest. The duration of digestion, however, is related to the

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quantity and quality of the food ingested. The faeces, excreted outside through the anus, are mainly made up of water (75%), bacteria, fats (since their digestion is more complicated than that of other nutrients), inorganic substances (minerals and in particular calcium, iron, zinc), proteins, undigested material (especially fiber) and desquamated enterocytes [9].

The bacteria present in the gastrointestinal lumen differ in type and location. At the level of the esophagus, we find bacterial species such as Prevotella, Streptococcus and Veillonella; in the stomach, an organ involved in the secretion of hydrochloric acid in which the pH is highly acidic (pH≈2), are home to bacteria including Helicobacter, Proteobacteria, Bacteroidetes, Actinobacteria and Fusobacteria; at the level of jejunum and ileus, where the digestion and absorption of monosaccharides, amino acids and fatty acids takes place, there are Enterococci and Lactobacilli, while in the ileum and colon (at the level of which the absorption of bile acids occurs) there is a myriad of bacteria, including Ruminococcus, Staphylococcus, Streptococcus, Peptococcus, Escherichia, Eubacterium, Clostridium and many others [10].

The human intestinal microbiota [11] therefore represents a real organ that has the purpose of protecting the well-being of our organism, under different profiles. The main bacterial populations that can be grown in the faeces of the newborn between 0-3 days of life include enterobacteria (including E. Coli), bifidobacteria, lactobacilli and streptococci-staphylococci (the latter temporarily dominant). The intestinal microbiota of the newborn, composed of only a few bacterial genera in the first days of life, then develops strongly and rapidly depending on the environment and the possible intake of antibiotics, to further vary and stabilize later. Its functions are also influenced by numerous factors, such as age, diet, immunocompetence, intestinal pH, transit time in the small intestine and colon, the interaction between the various constituents of the flora itself and, finally, the availability of fermentable dietary substrates. In adulthood, the distribution of the microbiota in the gastrointestinal tract is as follows: in the Duodenum we find Streptococcus, Lactococcus and Staphylococcus; in the Digiunto we find Lactobacillus, Streptococcus, Enterococcus and yeasts; in the ileum, we find segmented filamentous bacteria, Enterobacteriaceae, Bacteroides and Clostridium; in the Colon, we find Bacteroides, Clostridium, Lachnospiraceae, Proteobacteria, Actinobacteria, Prevotellaceae, TM7, Fusobacteria and Verrucomicrobium. With ageing, on the other hand, there is a significant variation in its composition, with an increase in Bacteroides, Escherichia Coli, Streptococcus, Clostridia, Lactobacilli and a decrease in Bifidobacterium, taking into account the important interactions between the diet, the intestinal microbiota, the use of drugs and gastro-intestinal transit that can modify this natural eubiosis, interfering with the different functions it performs, including: a) "Metabolic" (such as the fermentation of non-digestible dietary residues, the production of short-chain fatty acids "SCFA", the fermentation of sugars and the production of substances with antibiotic activity such as bacteriocins, lactocidins, acidolins, and others, and again the anaerobic metabolism of peptides and proteins, the synthesis of vitamins of group B and K, the absorption of calcium, magnesium and iron ions and the metabolism of primary bile acids). b) "Trophic" (control of the proliferation and differentiation of epithelial cells); "Protective" (barrier effect against pathogenic germs). c) "Immunological" (involvement in the development of systemic and local immunity).

To live, the intestinal bacterial flora derives the energy necessary for its sustenance from the digestion of dietary fiber and other products (especially sugars) that are indigestible to humans. Short-chain fatty acids (or SCFAs) are formed from bacterial degradation of the fiber, in particular, butyric acid and propionic acid, also absorbed at the level of the large intestine. Fatty acids, fundamental components of lipids, are molecules made up of a chain of carbon atoms, called an aliphatic chain, with only one carboxylic group (-COOH) at one end. The aliphatic chain that constitutes them tends to be linear and only in rare cases occurs in a branched or cyclic form. The length of this chain (up to 6 carbon atoms in the SCFA) is extremely important, as it influences the physicochemical characteristics of the fatty acid: as it elongates, the solubility in water decreases and consequently increases the fusion point. SCFAs are volatile molecules with high water solubility and are absorbed as such in the colon and conveyed to the liver via the portal vein. The production of short-chain fatty acids, most of which are absorbed by the intestine allowing the body to use undigested nutrients in the upper part of the digestive tract, is the most important physiological process mediated by the intestinal microbiota. However, it is difficult to establish the influence of the composition of the diet on the production of SCFAs in the human intestine, being the only method of determination represented by the dosage in the faeces, significantly affected by their rapid absorption by the colonic mucosa. Various data have been obtained by subjecting humans to a diet with different fiber content: it has been seen that a diet rich in fiber causes excretion of SCFA about 3 times higher than a diet lacking or poor in fiber. The percentage of individual SCFAs can also vary, as it can be influenced by the type of fiber. Our body can use these fatty acids for energy. For this reason, it is incorrect to say that fiber is calorie-free, without specifying that its modest caloric intake is compensated by the loss of nutrients linked to its chelating and laxative properties. In addition to being a source of energy, short-chain fatty acids also have bioactive properties, as they can have various effects on metabolism. Butyric acid (4 carbon atoms), produced by the bacterial flora that populates the large intestine, appears to have a protective effect against colon cancer; acetate (2 carbon atoms) and propionate (3 carbon atoms) are metabolized respectively by peripheral tissues (muscles) and by the liver and have the function of modulating the metabolism of glucose and cholesterol, while butyrate is an important source of energy for the colon epithelium. The effect of butyrate and propionate on the contractions of the colon that favour the aboral progression of the contents with a regulatory effect on the evacuation, could lead to believe that a deficiency of SCFA represents one of the pathogenetic mechanisms of constipation and would also explain the regularizing effect of the alvo of some fibers, especially the soluble ones that do not increase the fecal mass. The formation of SCFA, especially propionate

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and butyrate, also contributes to the defence mechanisms of the intestinal wall and butyrate is considered as the primary nutrient for epithelial cells and is the preferred substrate of colonocytes [10,12-14].

Intestinal homeostasis

Intestinal homeostasis (or eubiosis), is "the natural tendency to achieve relative stability, both of the internal and behavioural chemical-physical properties, which unites all living organisms, for which this dynamic regime must be maintained over time, even to varying external conditions, through precise self-regulating mechanisms". The purpose of the intestinal microbiota is to maintain this balance, as it regulates the integrity of the epithelium, the motility of the intestine (peristalsis) and the formation of the immune system (innate and adaptive immune responses). The immune system, in maintaining intestinal homeostasis, is called into question by the presence of good and bad luminal bacteria, food antigens, for which it is continuously stimulated. Intestinal tissue has many immune cells compared to other tissues. The intestinal immune system must counteract pathogens and must coexist with the resident gut microbiota. This tolerance is mediated by multiple factors, including the composition of the intestinal microbiota itself, the intestinal epithelium, stromal cells and innate and adaptive intestinal immune cells. Among the mechanisms involved in intestinal tolerance are those that minimize the exposure and immune recognition of intestinal microflora and those that mitigate immune responses through intracellular and intercellular mechanisms. Exposure of the intestinal mucosa to the microbiota is minimized by several defense mechanisms: intestinal mucus produced by goblet cells, production of antibacterial peptides (by Paneth cells) and secretion of IgA (produced by B lymphocytes) which limit the penetration of resident bacteria into intestinal tissues [15].

In homeostasis (condition of equilibrium), therefore, the microbiota performs efficiently and effectively; on the contrary, in the hypothesis of "dysbiosis", as a disturbance of the normal homeostatic balance, the intestine loses its natural permeability and the organism becomes ill more easily, first encountering a series of acute and temporary imbalances, such as colitis, diarrhoea, constipation and digestive disorders, up to a whole series (if the dysbiotic cause were to persist or become chronic) of inflammatory bowel diseases (IBD or IBD), including Crohn's disease and ulcerative colitis and in premature babies necrotizing enterocolitis [16-27].

In fact, intestinal epithelial cells, through microbe-associated molecular models (MAMPs), proliferate in the crypts up to the small intestine and release antimicrobial peptides (AMPs). The intestinal epithelium, acting as a real barrier, is formed by several subpopulations of intestinal epithelial cells (IECs) integrated into a single continuous cell layer, divided by tight junctions in apical and basolateral regions. Enterocytes in the small intestine and colonocytes in the large intestine, as well as the specialized Paneth cells in the crypts, sensitize the microbiota to induce the production of AMP. There are goblet cells that secrete mucin, organized in a proteoglycan gel that forms a layer of internal mucus adhering to the intestinal epithelial cells and an external one less reticulated and colonized by the constituents of the microbiota, to limit microbial interaction with the cells epithelial. The inner layer is more impermeable to bacterial colonization or penetration, thanks to its high concentration of bactericidal AMPs, as well as sIgA (secretory immunoglobulin A), which are ferried through the intestinal epithelial cells from their basolateral surface, where they are bound by the polymeric Ig receptor. (pIgR) to the internal mucous layer (heavily colonized by Faecalibacterium prausnitzii, a bacterium with an anti-inflammatory action), where they are then released. Innate lymphoid cells (including LTi) also produce interleukin-22 (IL-22) which stimulates the production of AMP and thus gives integrity to the epithelial barrier: when unregulated effector responses to the microbiota occur, as a result i chronic inflammatory bowel disease (IBD or IBD). In the specific case of chronic intestinal inflammatory diseases, therefore, the mucus layer is altered: it is thinner and less continuous, with reduced concentrations of phosphatidylcholine, as well as the levels of mucin glycosylation; glycans are shorter and generally have a less complex structure, with reduced sulphation levels, causing mucins to be more vulnerable to bacterial enzymatic digestion. Also, the antimicrobial peptides have a positive charge that guarantees their electrostatic adhesion to the mucus, so a lack of negative charges in the mucins reduces the production of antimicrobial peptides; consequently, greater exposure is obtained due to reduced mucosal protection and therefore an altered barrier. In patients with IBD, the first barriers, consisting of antimicrobial peptides, but also the second, consisting of the intestinal epithelium, are missing; the tight junctions are destroyed and the space between the epithelial cells increases, therefore the translocation capacity of the bacteria increases and this leads to the triggering of the chronic relapsing inflammatory process: pro-inflammatory cytokines are released, involved in the alterations of the intestinal barrier, in particular TNF (Tumor Necrosis Factors) and IFN-γ (interferon gamma) are increased in Crohn's disease, while in ulcerative colitis an increase in TNF and IL-13 (interleukin-13) is observed. The last line of defence is represented by the lamina propria; to maintain a condition of homeostasis, the intestine has developed a series of defence mechanisms, both physical (peristalsis, mucus secretion, epithelium) and biological (antibacterial molecules such as defensins, lactoferrin, lysozyme and immune cells): the response integration of these defence systems is reflected in the accumulation of an enormous amount of immune cells located in the Peyer's plaques in the small intestine and the lymphoid follicles in the colon or at the level of the epithelium and lamina propria. For this reason, following a histological examination, the intestinal mucosa appears to be "inflamed" when compared with other mucous tissues and the term "physiological" intestinal inflammation has been coined on this evidence. In this context, macrophages and dendritic cells expose the microbial material and when the activity of CD4 and CD8 (co-receptors belonging to T lymphocytes) is exasperated, T-helper 17 (TH17) lymphocytes come into play. TH17s are induced by TGFβ and interleukin-6 (IL-6) and their maturation is induced by the release of IL-23 by dendride cells (DC) following the phagocytosis of microorganisms that have managed to

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overcome the barrier epithelial. Cytokines released by TH17 lymphocytes (IL-17A and IL-17F) have pro-inflammatory effects by mediating the chemotaxis of neutrophils. Also, TH17 cells produce IL-22 which contributes to epithelial homeostasis and stimulates the secretion of antimicrobial molecules. Acute inflammation is counteracted through CD4 + regulators (TReg) which inhibit the activity of effector T lymphocytes. With the release of cytokines and the reduction of the TReg component, an expansion of CD4 and CD8 follows (they are no longer held in check), so the process becomes chronic. The same issue also related to the implications between intestinal dysbiosis and allergic and histamine-resistant diseases, which have recently been studied to find a solution that takes into account specific immunotherapy in combination with the prescription of probiotics, prebiotics and/or symbiotics [28-33].

The role of probiotics, prebiotics and symbiotics for the survival, efficiency and effectiveness of the Microbiota

The term "probiotic" [34,35] was first introduced in 1965 by veterinarians Lilly and Stillwell; unlike antibiotics, probiotics were defined as factors of microbial origin capable of stimulating the growth of other organisms. The authors, therefore, defined probiotics as those substances which "prolong the logarithmic phase of growth in other microbial species" and which are produced by protozoa capable of promoting the growth of other microorganisms; A few years later, Fuller defines them as "living microorganisms that exert a positive effect on the health of the host with the result of strengthening the intestinal ecosystem" (from substance to microorganism), while Garner and Schaafsma (1998) as "living organisms, consumed in adequate quantities, confer a benefit to the guest "(the need for an" adequate quantity "appears). Today, the concept of probiotic has evolved: in particular, probiotics are useful in areas of the body subject to extensive bacterial colonization, such as the oral cavity, but also in the skin and vagina, where there are specific lactobacilli, the lactobacilli of Doderlein which, similar to those of the intestine, have a protective action against the vaginal environment by reducing the pH. Since 2013, the universally accepted definition is: live and vital microorganisms that confer health benefits on the host when consumed, in adequate quantities, as part of a food or supplement. In practice, probiotics are living microorganisms that can be added to numerous types of products, including foods, drugs and dietary supplements. Lactobacillus and Bifidobacterium species are the most commonly used probiotics, while Saccharomyces cereviasiae yeasts, some E. Coli and some Bacillus species are less frequently used. Probiotics act on the intestinal ecosystem by stimulating immune mechanisms of the mucosa and non-immune mechanisms through antagonism/competition with potential pathogens; it is assumed that these effects are involved in the majority of the observed beneficial effects. Probiotics are therefore bacteria of human origin, resistant to digestive secretions (HCl, bile, bicarbonates), capable of surviving the passage through the GI tract, capable of adhering to intestinal cells, capable of colonizing the lumen of the GI tract, capable of protecting cells from the invasion of pathogens and capable of producing antimicrobial substances, hydrogen peroxide, organic acids and bacteriocins, as well as being able to be antagonists of the carcinogenic and pathogenic flora. The use of probiotics is based on the concept of intervening on the overall intestinal bacterial flora, using a "healthy" microflora, through what has been defined as Microbial Interference Treatment (MIT). The probiotic is able to positively interfere with the health of the host by increasing the intestinal defences with different mechanisms of action, such as:

a) The protection of the mucous barrier, decreasing the adhesion of pathogens to cells and strengthening it by modulation of the cytoskeleton and of the expression of tight junctions proteins, in particular by preventing the redistribution of the occluding protein ZO-1 activated by pathogens, with a mechanism linked to alterations in the secretion of mucus and chlorides.

b) The anti-inflammatory and immune activity on different targets such as epithelial cells (probiotics act on Toll-like receptors TLR-2 and TLR-4), inducing the production of cytokines, able to attenuate the proinflammatory responses induced by pathogens, avoid pro-inflammatory responses to commensal bacteria.

c) The production of enzymes, SCFAs and bacteriocidal agents.

d) The ability to alter the local pH: probiotics can antagonize pathogens by reducing the luminal pH, inhibiting bacterial adhesion and translocation or by producing antibacterial substances and defensins. e) The ability to provide nutrition to colonocytes (SCFA).

e) The ability to restore the balance between "good" and "harmful" bacteria, facilitating the growth of "good" bacteria (Bifidobacterium, Lactobacillus).

f) Promotion of pain control in visceral hyperalgesia.

The term "prebiotic" [35,36] instead derives from "prebiosis", which is the ability of fermentable carbohydrates to cause changes in the intestinal microbiota, favorable to the health of the host. There are various definitions; among the most important:

a) food ingredients that escape digestion in the small intestine and reach the colon, where they stimulate the growth and/or activity of one or a limited number of bacteria, thus improving the health of the host;

b) selectively fermented ingredient that determines specific changes in the composition and/or activity of the intestinal microbiota thus conferring benefits to the health of the host.

Prebiotics are found naturally in some foods such as onions, garlic, asparagus, chicory, artichokes, oats, beans, soy. Although prebiotics and dietary fibers are often thought to be similar in reality they are not, the components for which a prebiotic effect, in particular, has been reported are non-

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digestible oligosaccharides (NDOs), which contain mixtures of oligomers of various chains length with different degrees of polymerization (DP). These are fructans such as inulin and linear β- (2-1) fructans composed of β-D-fructo-furanosis with linear β- (2-1) bonds. Prebiotics perform numerous beneficial functions for the human body:

a) *Decrease in fecal pH and bifidogenic effect*. Prebiotics stimulate fermentation by specific bacteria in the colon, while dietary fibers may or may not be fermented, depending on their solubility. The acidification of the intestinal contents following fermentation with the production of short-chain fatty acids creates an environment conducive to the growth of symbionts (Bifidobacteria and Lactobacilli acidophili) and hostile to the development of pathogenic microorganisms. Consequently, there is a decrease in toxic metabolites (ammonia, biogenic amines, nitrosamines, secondary bile acids) which, when present in excessive concentrations, cause the mucosa to become inflamed and permeability to be altered, with negative repercussions on the health of the whole organism.

b) *Trophism of the mucosa and cell proliferation*. Short-chain fatty acids, in particular butyric acid, in addition to reducing the proliferation of pathogens and having antiputrefactive properties, are excellent nourishment for the cells of the colon mucosa and help to improve trophism.

c) *Increased bioavailability of minerals*. Prebiotics indirectly facilitate the absorption of water and some minerals in ionized form, in particular Calcium and Magnesium.

d) *Hypocholesterolemic action*. Prebiotics has the ability to reduce plasma cholesterol levels.

Another strategy, aimed at modifying the intestinal microbiota, is represented by the creation of "symbiotics" [37], in which probiotics and prebiotics are used in combination, to exploit the beneficial effects for the host, deriving from the two classes. Symbiotics aim at improving the survival of the probiotic microorganism since the combination makes the fermentable substrate necessary for colonization in the intestine of the microorganism immediately available. The potential combinations that can be obtained between the different bacterial species of probiotics available and the various types of prebiotics are numerous, but there are still few scientific studies available that demonstrate any additive or synergistic activity of the combination.

Dysbiosis and the onset (or aggravation) of extraintestinal, physical and psychological pathologies

In addition to chronic inflammatory diseases [38], directly caused and fueled by the intestinal dysbiotic state, recent studies have shown a direct correlation between dysbiosis and other extra-intestinal pathologies, including diabetes [39], atherosclerosis [40,41], metabolic syndrome [42], autoimmune [43,44] and neurodegenerative [45-47,48] diseases, heart and circulation disorders [49], atopic dermatitis [50], psoriasis [51], asthma [52] and allergies [53] and food intolerances [54].

The intestinal microbiota influences the Central Nervous System through various signalling pathways of the "microbiota-intestine-brain" axis: [55].

1) "*through the regulation of immune activity and the production of inflammatory cytokines*", which can directly affect the brain as they stimulate the HPA (hypothalamus-pituitary-adrenal) axis for the production of CRH (corticotropin-releasing hormone), ACTH (adrenocorticotropic hormone) and cortisol (stress hormone).

2) "*through the mediation of tryptophan metabolism*" which can alter:

a) the downstream production of quinolinic acid (QUIN), which powerfully leads to agony the NMDA receptors, which are found in the main neuronal pathway of the brain (the glutamatergic system). In the extreme scenario of AIDS, quinolinic goes so high that massive toxicity of glutamate is produced (which leads to the death of neurons).

b) the downstream production of kynurenic (KYNA, a product of tryptophan metabolism, which is synthesized and released in the brain through astrocytes, which acts as an antagonist of both nicotine receptors (nAChRs) and glutamates, both of which play a role central in determining neural plasticity as well as in regulating learning and memorization activities).

c) the downstream production of serotonin, a tryptamine, a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system, as well as in enterochromaffin cells in the gastrointestinal tract, mainly involved in the regulation of mood.

3) "*through the production of horn-chain fatty acids (SCFA)*", which even prevent the formation of β-amyloid plaques responsible for Alzheimer's.

4) "*through the production of the neurotransmitters GABA, dopamine, noradrenaline and adrenaline)*" [56-79].

The afferent signalling pathways of the vagus nerve are crucial in mediating the effects of the microbiota on brain function and behaviour; the microbiota influences mammalian brain development and function affecting numerous psychological processes (mood, emotion, social interaction and cognitive function). To date, studies on rodents have been carried out to understand microbiota-brain interactions: emerging data suggest that the microbiota can regulate some aspects of emotional and neuropsychological functions [60].

Irritable bowel syndrome (IBS) is a stress-related disease, therefore it is a disorder of the brain-gut axis, in which gastrointestinal symptoms are accompanied by functional and structural abnormalities of the brain and dysfunction of

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the HPA axis. Therefore, the diversity, stability and metabolic activity of the microbiome is altered: Bacteroidetes decrease and Firmicutes increase. The link between microbiota alterations and IBS (psychiatric co-morbidities, HPA axis dysfunction, loss of cognition) has yet to be established; it is clearer, however, that an altered composition of the microbiota can cause extra-intestinal symptoms in the disorder [61].

The microbiota is also involved in depressive states and dysfunctional anxiety: stress leads to a dysfunction of the HPA axis, an increase in cortisol levels, an increase in the cerebrospinal fluid of CRF (corticotropin releasing factor) and an increase in the level of pro-inflammatory cytokines in plasma. But that's not all: precisely due to the microbiota's ability to regulate the HPA axis and immune activity, its dysbiosis can even interfere with the metabolism of tryptophan, the precious amino acid precursor of serotonin. Not surprisingly, treatment with Bifidobacterium breve 1205 causes a decrease in anxiety-like behaviour in mice, as well as some probiotic strains (B. infantis, L. Rhamnosus and Lactobacillus Helveticus and Bifidobacterium longum cocktail) have direct antidepressant properties. A combination of other probiotics (L. Helveticus and B. Longum) still decreases the production of urinary cortisol in 24 hours, which has a direct action on stress [62-66].

Autism (ASD), as a disorder of neurological development (deficit of social interactions, communication and language development) is also related to intestinal dysbiosis: some studies have shown that the use of Bacteroides fragilis repairs the intestinal barrier and normalizes the deficits in communication and anxiety-inducing behaviours. Still, in other studies it was found that patients with ASD have an altered microbial profile, an accentuated inflammatory response and impaired intestinal permeability; in particular, dysbiosis and the consequent alteration of intestinal permeability leads to the diffusion in the bloodstream of a powerful pro-inflammatory endotoxin, called lipopolysaccharide (LPS). This small molecule plays an important role in the modulation of the central nervous system, increasing the activity of areas responsible for the control of emotion such as the amygdala and also stimulates the production of inflammatory cytokines that alter the physiological activity of the brain, modulating the synthesis of neuropeptides. It has been shown that serum LPS levels are significantly higher in autistic patients than in control subjects, supporting a role of the microbiota and, in general, of an alteration of the intestinal barrier in its integrity, in the genesis of ASD [67-78].

Lastly, the same correlations are found between intestinal dysbiosis and epilepsy [79-83], sleep disorders [84,85], as well as in neurodegenerative diseases [86-93], eating disorders [94,95] and obesity [96], as well as psychotic disorders [97-102], bipolarity [103-105] and in personality disorders [106-113].

Also in terms of Covid and correlations with the microbiota, recent studies have shown a direct correlation capable of decreasing the effects of viral infection and protecting the body by increasing the immune response [114-116].

Treatments and therapies

The target of clinical treatment must be "intestinal dysbiosis" [117,118], to promote new homeostasis (eubiosis). In the clinic, four forms of dysbiosis are recognized, each of them with a precise etiopathological and symptomatic mechanism, however, caused by a reduction in the diversity of bacterial species, reduction of beneficial species and/or proliferation (increase) of harmful species:

a) "*putrefactive*", which originate from an increase in the amount of Bacteroids at the expense of Bifidobacteria, is caused by an excessive intake of meat and saturated fats associated with a poor introduction of insoluble vegetable fibers. It mainly affects the large intestine. In addition to poor digestion, abdominal discomfort, postprandial numbness, a sense of general fatigue, there will be constant changes in intestinal functions, mood depression, decreased memory, muscle pain and weakness and changes in sensitivity in the hands and feet.

b) "*fermentative*", which originate from a low acid secretion from the stomach associated with an overproduction of bacteria and yeasts in the stomach and small intestine, often motivated by an intolerance to gluten and carbohydrates. It mainly affects the stomach and small intestine. There will be sensations of bloating, constipation, alternating constipation and diarrhea, associated with a sense of malaise and general fatigue which are classically aggravated by the intake of carbohydrates.

c) "*deficiency*" and "*sensitization*", often difficult to differentiate between them. Both forms are caused and maintained by excessive intake of toxic pollutants, antibiotic therapies and more generally by conditions that cause a decrease in the proportion of probiotic bacteria and an alteration of intestinal motility (which give rise to dysbiosis and inflammation ranging from the syndrome of the irritable bowel up to the development of real inflammatory bowel diseases). These last two conditions have in common that they are caused and maintained by a stressful lifestyle and a diet rich in industrial foods with added chemicals, by the excessive use of antibiotics (taken for pharmacological purposes or indirectly through the ingestion of meat of low quality) and finally, the fact of giving rise to a series of inflammatory changes. These inflammatory states, often of a silent nature (being due more to the production of cytokines and not inflammatory prostaglandins), are now considered causes and contributing causes of generalized inflammatory processes and neurological, cardiopathic, vascular, immunological and endocrinological dysfunctions.

It is therefore essential to proceed with a specific personal and family anamnesis, to identify the acute and chronic causes and symptoms, and then proceed to a targeted and personalized treatment plan that can take into consideration the following hypotheses, also recombined with each other:

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a) A balanced diet, rich in fiber, cereals, fruit, vegetables and liquids (> 2000 ml / dié), not artificial or carbonated, limiting the intake of carbohydrates in the evening, and favouring at least five thousand steps a day or an activity physics every other day for no less than forty-five minutes. Where possible, avoid foods to which an intolerance or allergy has already been shown (following a physical or instrumental examination - RAST test), over-processed foods and the use of synthetic substances such as drugs and cigarettes, as well as alcohol [119,121].

b) Genetic investigation using Next Generation Sequencing (NGS) technology, which allows identifying intestinal microbial communities by analyzing the variable regions V3-V4-V6 of the bacterial 16SrDNA gene. The amplification of DNA by PCR (Polymerase Chain Reaction) starting from a biological sample (after DNA extraction using standard procedures) and the subsequent sequencing in NGS, allow the identification of the bacterial populations present, avoiding the phase of cultivation of the bacteria in the laboratory. After the sequencing phase, the samples are analyzed automatically by dedicated software. The analysis thus allows to detect of the presence of dysbiosis, ie the alteration of the intestinal microbial ecosystem compared to a condition of eubiosis, ie the presence of the correct bacterial flora in the intestine. It also allows you to monitor the effectiveness of treatments implemented to correct dysbiosis[122-125]

c) Investigation of the genetic sequences related to intestinal dysbiosis [126]

d) Use of probiotics, prebiotics and symbiotics [127-130], in addition to lactoferrin [131,132], as food supplements, in the recommended and recommended doses. In particular, lactoferrin intervenes in various physiological mechanisms ranging from bone remodulation, with stimulation of osteoblasts and control of osteoclasts, to wound healing, but the best-known function is its marked antimicrobial activity against many pathogenic species, with direct antifungal, antiparasitic and antiviral, immunomodulating, anti-inflammatory and protective activity of the intestinal mucosa, and synergistic with Bifidobacteria. The antimicrobial effect of lactoferrin then, in detail, is attributable both to the ability of the protein to bind iron and to more direct mechanisms, independent of the chelating activity. In fact, by binding iron, lactoferrin inhibits bacterial growth, which is iron-dependent, while preventing the adhesion of bacteria to the intestinal epithelium, it prevents their proliferation and the formation of pathogenic biofilm.

e) Use of monoclonal antibodies to target specific toll-like receptors (TLRs) expressed on the membrane of dendritic, epithelial and macrophage cells (i.e. all cells where the antigen is present) and reduce chronic inflammation [133,134].

f) Conscious and necessary use, without abuse, of pharmacological therapies, especially in the case of proton pump inhibitors, antibiotics, anti-inflammatories and corticosteroids [135,136]

g) Transplantation of bacterial flora, in chronic and disabling hypotheses, not otherwise treatable. Based on the importance of the microbiota, the practice of fecal transplantation has spread for several years. Faecal transplantation has been especially effective in infection with Clostridium complicate, a bacterium resistant to antibiotics, which causes severe colitis. There are preliminary experiences on the action of microbiota transplantation in lung and urinary infections caused by another antibiotic-resistant bacterium: Kpc, an acronym for carbapenemase-producing Klebsiella pneumoniae, which causes the death of more than 50% of those affected. The studies are still in an experimental phase. To reduce some side effects that transplantation involves, for example, the risk of transmitting harmful microorganisms, medicine is moving towards the use of mixtures of bacteria prepared in the laboratory [137-139].

Concluding remarks

The human intestinal microbiota is still considered "an organ within an organ" partially shrouded in mystery, as if the scientific community has investigated the bacterial component of the intestinal ecosystem, on the other hand little is known about the other symbiontic components, like viruses; only recently has a study [6] demonstrated the presence of about 142,000 non-redundant virus genomes that must be fully understood in their interactional dynamics. To date, research has focused attention on the bacterial component and on the correlations between intestinal dysbiosis and the onset or worsening of dozens of physical and psychological pathological conditions, as well as integrative therapies to re-establish eubiosis, linked to prebiotics and targeted probiotics. In particular, future research, in the writer's opinion, should focus on the following objectives that are not yet fully explained:

a) The exact distribution of all microorganisms that are part of the microbiota and the complete mapping of the microbiome.

b) The development of a protocol of specific therapies to be implemented (integrative or with monoclonal antibodies), having identified the exact dysbiotic condition due to the symptoms, to facilitate the reconstructive processes to return as quickly as possible to natural eubiosis.

c) The analysis of direct correlations between dysbiosis and morbid physical conditions, to be able to prevent the onset of the same or allow for total regression, also thanks to a genetic mapping capable of identifying any constitutive vulnerabilities.

d) The analysis of direct correlations between dysbiosis and psychic morbid conditions, to be able to prevent

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the onset of the same or to allow for total regression. In particular, to focus the studies on the already well-known "microbiota-intestine-brain" axis to be able to demonstrate whether the onset of psychopathological conditions is a contributory cause of dysbiosis or (more likely) dysbiosis that causes an altered production of serotonin, dopamine, GABA and noradrenaline, capable of generating or worsening directly related psychopathologies, such as anxiety, depression, mood disorders, schizophrenia, psychotic and personality disorders. On the other hand, it is known that psychiatric drug therapies do not cure the morbid condition but aim to stabilize the patient who becomes dependent on it, and then witness a rapid worsening in the event of drug suspension or interruption. If we then wanted to search for an objective to investigate, the writer proposes to focus on the hypothesis according to which intervening on intestinal dysbiosis could decrease or eliminate the neurobiochemical cause at the base of many psychic disorders, such as anxiety, depression, bipolar and psychotic disorders, decreasing or eliminating the necessarily prescribed drug therapy.

e) The analysis of direct correlations between dysbiosis and neurodegenerative morbid conditions, as in the case of the production of horn-chain fatty acids (SCFA) which prevent the formation of β-amyloid plaques responsible for Alzheimer's.

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