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Inflammation: a highly conserved, Janus-like phenomenon—a gastroenterologist' perspective

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Introduction

Inflammation, a conserved reaction [1] with dual (Janus-like) roles in defense and organogenesis [2], is being intensively re-appraised.

Morphogenesis and biology of inflammation

At target level, reddening, temperature increase, swelling, pain, and loss of function are classic hallmarks going along with inflammation. Essentially, **these changes** are mediated by: increase of vascular permeability with fluid passage (oedema); concentration of immune inflammatory cells; concentration of blood, stasis, tissue ischemia and damage, hypoxia, the latter being the key to the biochemical events [3]. This is reflected in a number of systemic responses: constitution of a hypermetabolic state with some 30% increase of energy demand [4]; arrest of “routine” tissue economy in favour of a “war” economy, resulting in anaemia with tissue iron deposition, halt of albumin liver synthesis in favour of release of the acute phase proteins including C reactive protein (C-RP); uncoupling of oxidative phosphorylation with generation of fever; muscle proteolysis [5]. Essentially, these events are mediated by several pleiotropic factors: among the most physiologically important molecules, glucagon [6] which mediates hyperglycaemia and insulin resistance, catecholamines mediating the stress response [7], interleukin (IL)-1 initiating fever [8], IL-6 inciting the liver stress response and acute reactants synthesis [9], **ought to be highlighted**.

Hypoxia, the keystone of inflammation

Under the pressure of hypoxia, several crucial metabolic cell steps undergo dramatic changes that can be divided into three stages [10].

The initial stage, as anticipated, coincides with **the** establishment of tissue hypoxia. In an effort to adjust to this new condition, cell metabolism undergoes a number of changes: oxidative metabolism is only partially delayed; adenosine triphosphate (ATP) is decomposed to adenosine; xanthine dehydrogenase is converted into oxidase. On biochemical grounds, this chain of events may be labelled as “uncoupling of oxidative phosphorylation”; its direct consequence of ATP depletion and energy dispersion in the form of heat, may manifest in the well-known reaction of fever, on clinical grounds. At this point, complexes that play a key role in tissue damage may arise: the reactive oxygen intermediates (ROI), e.g. oxygen atoms with additional unpaired electrons. ROI production

may follow two pathways: 1) Oxygen reaching the cell is not entirely reduced; 2) The neutrophils reaching the inflamed area effect a process of anaerobic glycolysis, and release ROI as by-product.

The arrival of these effectors (the first-line of defense of the immune system) marks the second stage of the inflammatory reaction: the stage is functionally dominated by impairment of energy metabolism and disturbance of oxygen handling.

The third stage, that of repair, is phenotypically and functionally dominated by the return on stage of macrophages bearing the muscarinic receptor of the M2 type, effecting oxidative phosphorylation. In these premises, the maturation of various muscarinic receptors bears a meaning of up-grading or down-grading of inflammatory activity and remains under the umbrella of the sympathetic nervous system (down-grading) or of the parasympathetic nervous system (PSNS) (up-grading on peripheral blood neutrophils, but down grading on cells from inflamed theatres). As a matter of fact, transition to inflammation repair is rarely smooth, with lingering on a stage of chronic activation being marked by persistence of macrophage of the M1 type effecting anaerobic glycolysis.

It seems that in chronic inflammation the body's functions have to cope and adapt with chronic resource shortage, redistribution of energy between energy-storage organs (liver, adipose tissue) and energy-consuming organs (brain, muscles, and immune system). Specifically, an activated immune system in chronic inflammation may impact the nervous system with an oxidative stress and competition for nutrients.

The discussion of these matters takes us now to a clinical level.

Clinics of inflammation (the negative Janus face)

The Central Nervous System (CNS) in oxidative stress (chronic inflammation)

Several basic researchers and clinicians are now relatively confident that an unchecked inflammatory activity may incite severe chronic CNS degeneration such as Alzheimer and/or Parkinson disease in susceptible individuals.

The basis for a competitive clash between CNS and the immune system may be exemplified by the presence on the cells of both systems of the glucose transporter 1 (GLUT1) receptor, the glucose receptor that spares need for insulin to let glucose into cells, witnessing the same competitive avidity for glucose on both tissues [11 ,12].

Switching to a purely clinical ground, one may pinpoint that immune activity (inflammation) can negatively affect nervous processes in at least four specific pathways, of which two are driven by infectious/inflammatory processes originating in the enteric system.

1) Inflammation-induced vasculitis can bear specific consequences: Parsonage-Turner syndrome (amyotrophic neuritis) [13] and Cogan syndrome (sensorineural hearing loss) [14] are two examples often shown in co-morbidity with inflammatory bowel disease (IBD). Interestingly, initial reports are suggesting that physical exercise can downgrade inflammation in IBD, and can synergize with official drugs, possibly sparing expensive/toxic immune suppressors

2) According to appealing modern hypotheses, certain forms of Parkinson's disease could derive from periodontitis [15]. On this line of thinking, inflammatory mediators deriving from inflamed teeth tissues would cause phenotypic changes of microglia (ramification loss and acquisition of ameboid structure) [16]. Such primed cells would then be prone to respond to subsequent inflammation hits, thus originating full-blown Parkinson's. In this case, studies on the effects of body exercise have already come of age: not only the progression of neurological degeneration can be delayed [17], but also non-motor symptoms like depression can respond to muscle training [18]

3) As alluded to above, activated immune cells may behave as competitors of neural cells, causing diversion of glucose stream and CNS starvation at the basis of cerebral shrinking

4) Alpha-synuclein is a prion-like nerve cell protein that can accumulate within the enteric nervous system (ENS) [19]. Behaving as a chemoattractant for neutrophils and monocytes, it rises promptly in response to a number of infections with tropism for the ENS: influenza strains [20], chickenpox [21], and JC virus [22]. With a likely meaning of preventing ascending infection, in these cases alpha-synuclein is transported cranially to higher brain stem structures (Fig.1).

Fig.1

This physiologic defense process can however turn out to be harmful: individuals with repeated enteric infections stimulating protein synthesis, may accumulate protein in the mid brain and develop a Parkinson like syndrome [23]. Interestingly, vagotomised patients lacking this route of protein transport seem to be protected from developing Parkinson's disease [24]. Another related research pathway stems from the observation of an increased mucosal permeability in Parkinson's disease patients. A set of animal experiments, inspired by this observation, was meant to use aged 344 Fischer rats that spontaneously accumulate alpha-synuclein within their ENS [25]. Challenged with an invasive *Escherichia coli* strain that facilitates bacterial attachment, these rats were found to accumulate synuclein in gut plexuses, hippocampus, and striatum, posing the basis for Parkinson's disease development [26]. It is exciting to note that in this vision Parkinson's disease and IBD would stem from the shared step of an undue exposure of sub-mucosal reactive tissue to antigenic irritants: in IBD, activation of Gut-Associated Lymphoid Tissue (GALT) induces mucosal damage under the phenotypes of either ulcerative colitis (UC) or Crohn's disease (CD); in Parkinson's disease, exposure of ENS causes overproduction of synuclein. Noteworthy, recent acknowledgment of the multifactorial pathogenesis of Parkinson's disease has advised a few authors to name it "syndrome" [27]; in a similar mind frame, a few years ago we proposed to use the term "syndrome" for the IBDs [28].

Non-pharmacologic check of immune inflammatory disease

The basic immunologic data delineated above have suggested that clinical immune-mediated disease may arise if fuelled by underlying poorly checked chronic inflammation. Research in the last decades has gathered together a number of inflammatory disorders (including the CNS affections alluded to above) falling under this category. The list is variegated and refers to metabolic disease (diabetes, obesity, fatty liver), rheumatic disease, IBD. The results of a well conducted work in 2015 [29] have clearly implicated that the natural history and need for drugs in these diseases can be favourably influenced by regular physical exercise; the mediator of such an effect has been identified as being the protein lactoferrin (LTF), as released upon muscle exercise. We now briefly cover the question of how physical exercise must be dosed to be therapeutic, then we move on to report on LTF, its mode of release, and mechanism of action, utilizing molecular/cellular and macroscopic (gut) keys of interpretation.

Dosing of physical activity as antidote or pre-emptive measure against inflammatory disorder or malignancy

Common sense and empiricism have long suggested the beneficial effects of physical exercise for a variety of illness conditions. The further guess was that a relatively low activity level could be as effective, or even more appropriate than extreme exercise, as verified in a number of studies. One of these, issued in 2017 [30], included a group of breast cancer patients, prescribed a 150 min of exercise per week, according to general physical activity guidelines. The authors looked at both the behaviour of known breast cancer risk factors (sex hormones, insulin, inflammatory markers), along with the measure of the variations of a few anti-cancer markers, i.e. catecholamines and myokines. They found that the former had undergone adaptation to long-term training; the latter instead, were induced acutely upon any exercise bout. Based on these findings, the authors propose the existence of a sort of a synergy between the transiently increased exercise factors, and the effects of regular exercise, with the “acute” anti-cancer components mediating the positive effects of the “regular” ones.

The next question was about the mechanisms of the anti-inflammatory/anti-cancer effects of catecholamines and comprised 47 healthy volunteers subjected to a 20-min moderate (65-70% VO₂ peak) exercise [31]. Looking at the effects of the elevated epinephrine levels in the subjects (mediated by the beta-2 adrenergic receptors) it was found that this epinephrine release did suppress tumour necrosis factor in monocytes, an efficient inflammation marker.

Perhaps an exhaustive answer to the dosing question has been provided by a paper published in 2016, which examined 174 articles [32]. This systematic review and meta-analysis utilized the measure named MET, i.e. the per-minute oxygen need of an inactive organism. It was found that a baseline MET of 600 (yielding a minimal 2% diabetes reduction risk) can yield a 19% reduction risk for MET 3600. The key point in the paper was that the curve tended to plateau for extreme values (i.e. the gain of diabetes risk was no higher than 0.6% if MET raised from 9000 to 12000).

Interestingly, this validates numerically the premise in this paragraph that affordable levels of physical performance are sufficient to achieve tangible anti-inflammatory and anti-neoplastic effects.

Cellular pathophysiology of LTF in the context of inflammation

A MEDLINE search, using lactoferrin/inflammation as key-words, yielded 207 reviews; as the basis for this chapter we chose one recent publication issued in Nov 2017 [33] insofar as contextualizing LTF on the ground of inflammation (the main theme of this review); the references in this paper were further manually elaborated.

1) Background

LTF is an 80 KDa monomeric single polypeptide chain of 692 amino acids; the structure is organized in two homologous lobes: The N and C lobes, each binding a single ferric ion Fe^{+++} . This glycoprotein can be found in secretions (chiefly maternal milk and colostrum) or in neutrophil granules

2) Actions and Mechanisms

2a. LTF is a pleiotropic protein, its actions depending on a mix of inherent characteristics (e.g. affinity for bacteria lipopolysaccharides) and a specific iron-binding capacity.

2b. The cumulative result of this combination may be seen as the coexistent capacity to trigger defense mechanisms (for example bacterial killing due to iron chelation) and to terminate potentially harmful inflammatory states, for example by inactivating free lipopolysaccharides (LPS), thus depriving the toll-like receptor (TLR) chain of the fuel to sustain the inflammatory cascade. Notably, therefore, with LTF we have the warrior and the peace-maker on the same molecule.

3) Points of attack of LTF into an inflammatory chain

Monocytes/Macrophages do usually gather where cell debris and fragmented nucleic acids concentrate (so-called DAMPS) or danger signals. LTF can interact with cellular receptors that sense these danger signals, triggering this chain of events: (a) interaction with TLR, suppressing inflammatory chain; (b) LTF can reduce release of chemoattractants (IL-8), interacting with CD14 accessory molecules; (c) inactivating LPS, LTF sets the stage for termination of the inflammatory state

4) Inflammatory processes easily leave behind oxygen atoms with additional unpaired electrons (so-called ROS or ROI) (see preceding paragraph on inflammation), with cell oxidative damage potentially deriving. In turn, the cells can rely on an enzyme triad to correct the redox state: superoxide dismutase (SOD) forms hydrogen-peroxide (H_2O_2), and catalase and glutathione peroxidase can convert H_2O_2 into water and molecular oxygen respectively. However, in the presence of ferric ions this detox process is upset, and hydroxyl radicals are allowed to form: if an enhanced microbicidal activity may be considered the positive face of this reaction, this is negatively counteracted by an unleashed lipid peroxidation. The harmful oxidative stress is efficiently terminated by the robust sequestering action of LTF

5) LTF and the progressive damage of mid-brain neurons in Parkinson's disease (see preceding paragraph)
Detectable concentrations of LTF have been shown in the neural bodies of cells resisting the death process of PD, suggesting a role of LTF in the escape mechanisms of these cells. Neuroprotection by LTF was due to its binding to heparin sulphate proteoglycans on the surface of dopaminergic neurons, and subsequently to partial inactivation of focal adhesion kinase (FAK).

Synopsis of the protean effects of LTF, divided in iron independent or dependent mechanisms

A) Iron-independent mechanisms of LTF

Early in the inflammation process

Attenuates nuclear factor (NF)-kB induced gene transcription [34].

Acts as feed-back mediator for acute phase proteins [34].

Interacts with TLRs with down-regulatory effects: Reduction of synthesis of IL-8 [35]; interaction with CD 14 accessory molecules [36]

Late in the inflammation process

Inactivates free LPS [37].

Promotes switch to adaptive immunity [38].

Reduces IL-6 release induced by LPS (upon surgery) [39].

Restricts development of systemic inflammatory response syndrome (SIRS) [40].

B) Iron-dependent mechanisms of LTF

Bacteriostatic effects due to iron chelation [41].

Oxidative burst attenuated by iron sequestration [42].

ROS (ROI) production reduced by iron chelation [42].

Lipid peroxidation reduced [43].

We believe the data reported above can be interpreted in the following way. The action of LTF concentrates on two opposite but cooperating pivots. At one extreme there is a primary defense role, witnessed by the obvious presence of LTF in colostrum and milk (8 mg/g and 4 mg/g respectively); at the other extreme we note the specific ability of LTF to terminate an immune-inflammatory response, for example by inactivating the LPS

reactivity. In the ultimate analysis, LTF can be considered a particular acute phase protein, belonging to the family of Alarmins [44], peculiar proteins released from neutrophils upon infection, capable to further alter immune reactivity.

These data on the role of LTF in the pathophysiology of inflammation at the cellular level can now introduce a final note on LTF in the macroscopic context of gut and its relationship with CNS function and pathology, insofar as remaining the core of this review.

LTF down-regulates T helper (Th)1 lymphocyte circuits, and favours growth of the regulatory *Bifidobacterium* strains [45]; in a model of gut inflammation triggered by *adherent-invasive Escherichia coli*, LTF was found to inhibit tumor necrosis factor (TNF), IL6, and IL8 responses in cultured colonic biopsies [46]. Gathered together, these findings supported the role of LTF as a pluripotent factor capable to lead the immune response to rest, downgrading the deleteriously competitive power of the immune system. It has been anticipated that LTF might be the main factor that permits the normal growth of the newborn CNS; in its absence, the newborn's immune system would be stimulated to the point of making CNS shrink for glucose starvation [47]. The recent determination of cognitive impairment in obese children (obesity is now deemed a pro-inflammatory condition) speaks in favour of the above statements [48].

It is believed that our ancestors could have been prone to extinction if forced to exclusively respond to the outer world with their inflammatory mechanisms: inflammation would have kept their CNS from evolution, and, in addition, would have limited reproductive capacities [49]. It is believed that instead they were saved by their physical exercise: frequent changes of gathering places in search for food, running to avoid wild animal encounter, plant climbing to escape flooding. Such an abundant exercise, particularly of upper limbs, was responsible for the release of a wealth of regulatory myokines from the stimulated muscles (IL6, IL8, IL15) which in turn direct LTF release from immune cells including neutrophils [50]. The muscles are now labelled by many as the forgotten immunological organs [51].

Interest in the effects of diet composition on local and systemic inflammation has lingered behind for some time. In the last decade, the attention of investigators was necessarily re-directed towards studying the reasons for the erratic response of IBD to the various anti-TNF antagonists, and one of the main questions asked whether simultaneous treatment of the patient with biologic drugs and a special diet could improve effectiveness. Most of the studies were drawn in CD [52]. Two main designs were used: 1) Investigation of the effects of

superimposing an elemental diet; 2) Study of the effects of diet modification in the course of treatment, using a Food Frequency Questionnaire (FFQ). A few messages could be retrieved from these studies. The adding of an elemental diet yielded mixed results; the FFQ suggested that abandonment of a high-fibre diet in favour of red meat, processed meat, and salty and elaborated food during treatment could tip the balance to intestinal inflammation.

In this chain of events, the prime mover is the shortage of fibre, which boosts growth of mucin-degrading strains, such as the various *Ruminococci* that are found abundant in UC; degradation of mucus would then make available sulphate for degradation by noxious bacteria such as *Bilephila Wadsworthi*, capable to induce gut membrane ulceration. Large breaches in the mucus shield would allow antigenic luminal contents to be intercepted by TLR sensors, which, responding to bacterial antigenic motifs, can activate the pro-inflammatory chain down to TNF- α production with local and systemic inflammation [52].

Another team of investigators conducting a behavioural neurology study evaluating whether the diet constituents identified above as pro-inflammatory could mediate the intellectual decline. In a large cohort of middle-aged men and women [53], they found that a pro-inflammatory dietary pattern at two measurement occasions five years apart predicted faster mental decline on a ten-year follow-up. This is again a hint that the enteric system may convey some negative signals towards the CNS (Table 1).

Table 1

Last but not least, the role of pro biotics as inflammatory modulators is being under an increasing attention.

Microbiome and inflammation

According to their role in the host, intestinal microbiota can be divided into three categories [54]. The first category contains the physiologic bacteria that are symbiotic with the host. They attach to the deep mucosal epithelial cells, and most are anaerobic bacteria. These bacteria represent the dominant microbiota of the intestine (e.g., *Bifidobacterium*, *Bacteroides*, and *Peptococcus*) and play a key role in nutrition and immune regulation. The second category contains conditional pathogens that inhabit the host. They are mainly facultative aerobic bacteria and intestinal nondominant bacteria (e.g., *Enterococcus* and *Enterobacter*). These organisms are

harmless when intestinal microecological balance is maintained but can be harmful to humans under certain conditions. The third category contains mostly pathogens (e.g., *Proteus* and *Pseudomonas*). When microecology is in balance, long-term colonization of pathogens is rare, and the number of these organisms is small and non-pathogenic. If changes in the enteral and external environments lead to a decline of intestinal-dominant microbiota, then intestinal microbiota imbalance will occur, with pathogens or conditional pathogens increasing to the point of causing diseases [55].

Human commensal bacteria, such as *Bifidobacterium*, can synthesize and supply vitamins such as vitamin K and the water-soluble B vitamins. The phyla Firmicutes and Bacteroidetes produce short-chain fatty acids (SCFAs) from resistant starch or indigestible carbohydrates (dietary fibre) through collaboration with species specialized in oligosaccharide fermentation (e.g., *Bifidobacteria*). SCFAs are major anions in the colon, mainly as acetate, propionate, and butyrate. Butyrate is a primary energy source for colonic epithelial cells [56].

The gut microbiota plays a fundamental role in the development of the host's immune system. The host immune system, in turn, shapes the structure and function of the gut microbiota [57].

An unfavourable alteration of the composition and function of the gut microbiota is known as dysbiosis, which alters host–microbiota interaction and the host immune system. There is growing evidence that dysbiosis of the gut microbiota is associated with human diseases, such as IBD, irritable bowel syndrome, allergy, asthma, metabolic syndrome, and cardiovascular diseases.

The relationship between microbiome and inflammation seems to be dual (Janus-like) too.

On one side, the number of sulphate-reducing bacteria, such as *Desulfovibrio*, is higher in IBD patients, resulting in the production of hydrogen-sulphate that damages intestinal epithelial cells and induces mucosal inflammation. Diminished colonic butyrogenic bacteria in IBD have been reported in faecal and mucosal samples from patients with IBD and most notably include *Faecalibacterium prausnitzii* and the Roseburia genus, which were also decreased in new-onset CD [58].

On the other side, in case of inflammation, an increase in ambient oxygen levels induced by hyperaemia and increased vascular and mucosal permeability is thought to be one of the mechanisms responsible for the reduction of obligate anaerobes (*Clostridium* groups IV or XIVa), with expansion of aerobes and facultative anaerobes (*Enterobacteriaceae*) [59].

It has been demonstrated that some bacteria, such as *Lactobacillus*, *Bifidobacterium* and *Streptococcus*, have a clinical effect on gastrointestinal inflammation. A large clinical trial was conducted to investigate the efficacy of *Escherichia coli* Nissle 1917, a non-pathogenic strain, on maintaining remission of UC: *Escherichia coli* Nissle

I917 achieved comparable efficacy and safety outcomes to salicylate in the maintenance of remission in UC patients [60]. Studies using VSL#3, a probiotic mixed with 4 Lactobacilli (*Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii subsp.*, *Lactobacillus Bulgaricus*), 3 Bifidobacteria (*Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*) and a Streptococcus (*Streptococcus salivarius subsp. thermophilus*), have yielded the most available evidence of efficacy in IBD patients. A clinical study found that VSL#3 was effective in inducing and in maintaining remission in patients with mild-to-moderately active UC [61].

In addition to bacteria, fungi, viruses, bacteriophages, and archaea that also colonize the gastrointestinal tract are also markedly shifted in IBD [62]. Although the number of fungi in the gut is much lower than that of bacteria (99.1% of the genetic catalogue from the gut lumen being of bacterial origin, whereas fungal DNA accounts for around 0.02% of the entire mucosa-associated microbiota), the volume of a typical fungal cell is much larger than that of a typical bacterium (approximately 100-fold larger). Further, fungi can provide many unique metabolic materials to bacteria. An antibody against fungi (anti-*Saccharomyces cerevisiae* antibody, ASCA) is considered to be a discriminating biomarker for CD [63]. Moreover, the severe form of UC is strongly associated with a polymorphism of the Dectin-1 gene, which encode a receptor that recognizes the β -1,3-linked and β -1,6-linked glucans from fungi [64]. Previous studies have documented that the intestinal fungi can be recognized by the membrane-bound receptors (e.g., lectin receptors, TLR, scavenger receptor family members etc.) of many immunocytes; these receptors further trigger the phagocytosis, respiratory burst, and intracellular signaling pathways, causing the release of multiple pro-inflammatory cytokines following activation by the intestinal fungi [65].

A study utilising epifluorescence microscopy was the first to suggest that there was an increase of bacteriophages in patients with CD compared to controls: the predominant gut viruses identified were double-stranded DNA viruses in the Caudovirales order (including Podoviridae, Siphoviridae and Myoviridae) [66].

At present, the most effective therapy available involving manipulation of the gut microbiome is fecal microbiota transplant (FMT). In FMT, stool from a healthy screened donor is administered to a recipient with the goal of restoring gut microbial diversity toward that of a healthy person. FMT can improve intestinal microecology and the permeability of the intestinal mucosa [67]. It can activate the intestinal humoral immune response to induce the synthesis of immunoglobulin (Ig)A, IgG, and IgM through the TLR pathway, thus protecting the intestinal mucosa. FMT can also reduce the pH value of the intestine and increase the adhesion of bacteria and H₂O₂ to competitively inhibit the adhesion and translocation of pathogens. Finally, FMT can treat

immune disorders by inhibiting the secretion of proinflammatory cytokines and promoting Th1 differentiation, T-cell activity, leukocyte adhesion, and immune-stimulatory factors. FMT can reduce intestinal permeability by increasing the production of SCFAs, thereby reducing the severity of disease. Increased SCFAs production, especially butyrate, which is the main source of energy in colonic epithelial cells, maintains the integrity of the epithelial barrier by reducing intestinal permeability. FMT can also restore the dysbiosis of microbiota.

Clinics of inflammation (the positive Janus face at the digestive level)

The issue of the digestive tract deserves to be dealt with apart. It constitutes a major surface of exchange between the outer and the inner world; it daily receives huge antigenic loads whereby a subtle immune scrutiny is needed to decide whether tolerate inert antigens, or respond with an efficient, yet potentially harmful reaction, to suspected pathogens. Indeed, the gut carries the biggest antigenic load with the 10^{14} microorganisms of the microbiota [68] (detailed above), and a formidable inflammatory machinery underneath, that is ready to shoot and devastate if aroused by unduly augmented permeability.

The digestive tract is a structured mucosal conduit endowed with a number of specialized segments; it allows the outer world to trespass the body's boundaries to extend from mouth to anus. Together with the lungs, the digestive tract is classified as a barrier organ [69]: the outer world in the lumen (comprising the diet antigenic load, and the overwhelming colon biota) is firmly separated by a tight epithelial wall from an underneath overreactive lymphoid tissue. The molecular structures devoted to antigenic recognition are the nucleotide oligomerization domains (NODs). These are cytosolic receptors belonging to the nucleotide binding oligomerization (NOD-like) receptor family. NODs can detect bacterial peptidoglycans containing intracellular muramyl-dipeptide (MDP). Upon ligand-dependent activation, a chain of immune responses ensue, triggering pro-inflammatory events. Recent studies have highlighted the crucial relationship between the NODs and the microbiome. Constant contact with the abundant antigenic load of the microbiome maintains the digestive mucosa in a state of "paraphysiologic" inflammation. The equilibrium between the host immune responses and the microbiome is maintained by a NOD-dependent surveillance. As the proof of this, acquired NOD malfunction induces dysbiosis, whereas congenital malfunction may precipitate CD [70]. In fact, all the gut immune function is biased to antigenic tolerance: the main immune globulin class that is used by the gut is unable to fix complement, hence it does not sustain prolonged inflammation [71]; intra luminal immune

reactions are prevalently controlled by the prompt T- regulatory (reg) response and by triggering of apoptosis [72] (Table 2).

Table 2

The gut is an immunologically pluripotent site and can exert a dual tolerance/inflammation response according to specific conditions. For example, it has recently been ascertained that a self-limited inflammatory episode can follow the simple introduction of food stuff with the reaction worsening if abundant junk food is ingested [73]. This observation in fact indicates that the gut comprises digestive and immune functions alike. This sort of immune-like food scrutiny is based on the presence of immunological stations in the pericolic fat. This fat tissue, nowadays considered a regularly reactive tissue, consists of lymph nodes whose functioning is fuelled by the surrounding adipose substance: under proper stimuli, leptin and adiponectin may be released to mount a full-blown T- lymphocyte dependent reaction [74].

The IBDs may be thought to originate when tolerance/apoptosis- refractory immune cells take over, with the process being rendered chronic by mixing of environmental (drugs, tobacco, germs) and favourable genetic marker, expressing as inflammatory circuits (IL23/Th17 for example) [75]. The epidemics-like brisk appearance of the IBDs at the end of the 1800's makes it unreasonable to think of a genetic mutation as the cause. Rather, transitioning from rural to metropolitan life, switch from fresh prevalently vegetarian food to elaborated meat recipes, changes of feeding times due to work shift, may have shocked the microbiome, which did not keep pace with the rapid changes [76]. There is an extremely abundant literature summarizing the wealth of knowledge accumulated in a century of studies on IBD [77, 78]; of an utmost interest is the report of recent epidemics-like IBD episodes in countries like Iran, where life and feeding habits have been partially Westernized [79]. **A thorough scrutiny of these issues is provided in a recently published paper [80].**

Discussion

Clinical immunology, rheumatology, and behavioural sciences, to cite just a few among relevant disciplines, are all concord in reckoning that in the Western World a population is growing marked by serological signs of chronic inflammation (circulating IL-6 and C-RP) as well as by clinical features of chronic inflammatory activation, e.g. chronic fatigue, depression, sleep and appetite disturbances. Such people have been labelled

“inflammacitizens” in a relatively recent medical hypothesis dealing with the evolutionary/devolutionary implications of inflammation [81]. This construction first distinguishes acute from chronic inflammation: it is suggested that acute inflammation be construed as a relatively short-lived and aggressively defensive reaction, often resulting in important damage of the targeted tissue; the authors hint that this presentation may be interpreted as a rewind of our life’s origins wherein transition from anoxic to oxygenated metabolic processes proved a turning point [82]; chronic inflammation by contrast, is tentatively presented as an attempt, through the mounting of several inflammatory circuits, to accompany the tissues to modify and get progressively acquainted with the plethora of changes that are being imposed by the life style of Western developed countries [83]. This is a keystone point entering in resonance with data from other disciplines and will be further covered in this text.

Our own discussion of inflammation in the present paper grossly follows this track but extends and implements further pieces of scientific evidence. We too mark the distinction between acute and chronic inflammation and detail the difference on a biochemical basis first, stressing that acute inflammation entails tissue ischemia and anoxia, with specific upset of mitochondrial respiration and establishment of a profoundly negative energy balance.

The chronic inflammation could be an attempt to remodel host’s resilience to the brisk mutation of diet in the Western World. Indeed, we do adopt this hint, and, further strengthening the thesis in the above review, we cite the spread of various forms of gut inflammation over the last century. The whole array of gut inflammation expressions, from the ill-defined features of irritable bowel syndrome (IBS), through microscopic colitis, to the full blown IBD spectrum encompassing the world-known entities of CD and UC, are supposed to be there to react and restrain the microbiome response to the rapidly changed styles, timing, and composition of feeding (see the brief allusion to the NOD function above). Nothing like the pathological observations of the waxing-waning mononuclear cell infiltration of the gut mucosa (so-called physiologic gut inflammation) [84] offers a factual confirmation of the axioms expressed above.

Wrap-up summary

The human digestive tract is the archetype of barrier organs, the anatomic and functional sheaths between the inner and the outer milieu. In the case of the digestive system, a 9-meter conduit is invaded by the antigenic food load several times a day, with the underlying mission to avoid both excessive defense (inflammation) or

detrimental infection. Thus, in the digestive tract feeding and immune response are strictly connected. **Neither clinicians, nor scientists can avoid** interest for this machinery.

Compliance with ethical standards

Informed consent was obtained from all individual participants included in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. Several examples of negative Janus effects (infection or food-borne malfunction) with inflammation trespassing bowel limits.

Mechanism	Clinical consequence	Reference
Food immunogenic response	Post prandial inflammation syndrome	73
Parodontitis	Parkinson-like	15
Enteric nervous system infection	Parkinson-like	23
Reaction to pro-inflammatory food	Intellectual decline	53

This is counter-mirrored by another situation, wherein the indwelling microbes (microbiome) responds to outer world changes.

Table 2. Upsetting the microbiome: local response drives “good” strain selection: a positive Janus effect.

Mechanism	Consequence	Correction
Brisk life style (feeding) change	Upset microbiome to clinical level	Upgrade immune control (NOD function)
Reference 76		Reference 70

In the former case, the outer world breaks in strongly, and the response cannot avoid being detrimental; in the latter, changes are softer, and response can be more tuned to limit damage.

From the data elaborated in this paper, the concept is implemented of inflammation as a multi-organ pervasive noxa, or a resilient response towards evolution: more in- depth study is needed before any anti- inflammatory strategy can be attempted **pretending to adopt** a translational process.

Fig.1 Hypothetical pathway for pathogenic migration of α -synuclein in the gut. The apical surface of enteroendocrine cells (EECs) is exposed to the lumen and thus is in contact with ingested toxins and metabolites produced by gut microbes. The basolateral surface of EECs is in contact with enteric nerves and glia. The toxins uptake by EEC can cause aggregation of α -synuclein inside these cells and this aggregated protein can migrate to enteric nerves, thereby initiating a pathogenic cascade leading to α -synucleinopathies.