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Individual's Adaptive Processes: Rephrasing in Terms of Inflammation

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Abstract

Inflammation, one among the evolutionary driving forces, is now acknowledged under two subheadings, depending on whether the individual immune system has been educated under the pressure of nature's physiologic stressors, or under man-made artificial drifts. In the former case, the reaction is demarcated and self-resolving, at the expense of possible host death. In the latter, the evolution is chronic, sparing subject's life at the expense of chronic multi-organ inflammatory disease. There is now evidence that this disorder is reaching epidemics-like proportions. Adaptation with immunologic down grading and tolerance may be the way to individual's survival. We analyze the literature that in our own arbitrary opinion supports this view, including a final proof-of concept based on human volunteer data elaboration.

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Premises and working rationale

The key that we are proposing to best decode the following paragraph is: Early Life Adversity (ELA).

The interaction between the individual and the outer world has consistently been considered as problematic. As the working hypothesis, two possibilities can be conjectured: a clash-based encounter, which ideally must identify a winner for the clash to be terminated [A], and an adaptive one, [B] whereby the two opposing parties are modulated in the birth of a previously unnamed third-party entity. We got indeed interested and surprised when, reading through a recent review [1] reassessing the issue of emotion regulation we noted that the authors had used label A to indicate emotion dysregulation, vs label B, denoting cognitive change (cognitive reappraisal as preferred by others), to identify option B, denoting substantial coincidence between our methods. At the risk of oversimplification, the adaptive solution (just an example) may be identified in the life cycle of a non-cytopathic virus which leaves the infected cell undestroyed, yet with newly synthesized antigens (shared) on both the cell wall and the viral capsid.

The French-American philosopher and scientist René Dubos (1901-1982), studied the interplay between the individual and the surrounding, and theorized an advantage for the adaptive behavior, after which common sense would expect a reduction of war side-effects and a progressing society, rather than a regressing one.

Recently, revisiting Dubos' aphorisms, biased by our immunological education, we were tempted to interpret Dubos' words in an immunological language, simply asking: is it feasible to see a second immunological meaning dimming below Dubos's philosophic narration, and propose that the adaptive phenomena said to be advantageous can be renamed in the immunological term "tolerance" which likewise is said to be advantageous in the opinion of many immunologists?

In the narrative review text that follows, we arbitrarily chose to discuss a few typical cases of immunological tolerance to verify whether they are so common in nature, as to remind of the macroscopic adaptive phenomena propelled by Dubos.

The states of health or disease are the expressions of the success or failure, experienced by the organism, in its efforts to respond adaptively to environmental challenges (1965)

Background

The inflammatory process. Inflammation is a primordial and highly conserved process.[2] Its main steps – vasodilation, blood stasis, edema, cell influx are all clearly finalized to restrain and disarm the invader. The details of these events can roughly be ranked with the order of magnitude at which they are hosted. Traditional scholastic teaching assigns to inflammation the classic attributes of redness, increased heat, swelling, pain, and function loss, all implying the underlying changes that follow. At tissue level, we see vasodilation, fluid extravasation, blood cell influx, and eventual tissue damage. It is the subcellular compartment that hosts the crucial changes. Stasis-induced hypoxia can trigger two crucial events: it drives M1-type macrophages to switch on anaerobic glycolysis with ensuing impairment of the mitochondrial respiratory chain, reduction of ATP formation and increase in the energy debt; furthermore, it enhances T-cell cytotoxic potential. An Imperfect functioning of the respiratory chain causes defectively reduced oxygen and formation of ROS (reactive oxygen species), a factor of major cell damage. Finally, the release of two cytokines (among many others) can cause the inflammation to become systemic. IL-6 causes the liver acute-phase-response, and IL-1beta acts at the hypothalamus level: protein catabolism and fever are the mostly ready consequences, being at the basis of the bodily deterioration of inflamed individuals.

It must be pointed out that with the above words we wanted to describe classic inflammation as well known by the physicians of the past centuries. Today's era has witnessed the epidemic appearance of a creeping, sneaky form of fever.

Inflammatory patterns over time. Laboratory data of patients followed since the last century have accumulated to delineate the picture of a variant chronic inflammation that in some world areas has assumed the features of an epidemic-like disorder. Such "inflammacitizens" [3] typically present with chronic fatigue often taking the features of organ pathology, classifiable under rheumatic criteria; their inflammation often lacks the "cardinal signs", only manifesting with an excess of circulating C-reactive protein, and/or elevated sedimentation rate (ESR). Intriguingly, recent leaps forward, widening the

field of observation, have unveiled notes of this blunted inflammation in sufferers from disorders that present as unrelated to an inflammatory condition: we allude specifically to neurological disease and depression. Strongly suggesting a causal relationship, often these inflammatory clues show a deviation from normal that readily correlates with the severity degree of the underlying neurologic involvement, thus rendering unlikely a simple bystander role [4].

A General Bias to Tolerance Prevails in Nature: a Reappraisal

The ultimate goal of tissue defense is a highly conserved one in nature; it can be achieved following two main ways. The "classic" destruction of the offender; or, alternatively, pursuing tissue protection with neutral or positive effects on pathogen fitness (referred to as points A and B, on age 1 above). This pathway can further be dissected into mechanisms and goals [4]

Health-promoting effects from host cell compartment

A1 A role for *amphiregulin*: [5] EGF receptor ligand, regulates tissue damage in viral infection, chiefly*lung pathology*. Produced mainly by innate lymphoid cells under the influence of IL-33, it can also PAG 5: num be released by T-regs.

Quenching inflammation, whilst promoting tissue repair (fibrosis), amphiregulin carries this double action encased in its name. The recent outbreak of the SARS-CoV-2 pandemic [6] has dramatically redirected the investigators' and caretakers' attention towards the double-sword action of amphiregulin. [this concise paragraph is duly inserted for updating reasons, but details are indulged on exclusively to the extent they further justify the inclusion of this peculiar factor into the relevant list]. Indeed, a fraction of all COVID patients do succumb to lung failure [7], seemingly in connection to an unchecked hyper-inflammation translated into a "cytokine storm."[8] On this premise, the peculiar action of amphiregulin may be anticipated to play a relevant role. On this line, the available data, though complex to interpret, seem coherent in indicating dramatic gender differences: the fact that men are most likely to run a lesser inflamed flu (though not free from mixed complications) [9], is mirrored by men's capacity to release more amphiregulin on flu[10]. One of the leading themes in this paper, namely the superiority of smart tolerance over unleashed inflammation, is duly illustrated by these findings.

Ansun BioPharma has finally moved to action and has designed a few anti-COVID trials. DAS181 consists of a recombinant sialidase domain that removes sialic acid, fused with an amphiregulin sequence that binds glycosaminoglycans on airway epithelial cells. Because viruses use sialic acid as a receptor for infecting epithelial cells, Ansun BioPharma thinks DAS181 can block SARS-CoV-2 entry and prevent infection and spread. (www. AnsunBiopharma.com) last consulted……

Ansun BioPharma's U.S. trial will enroll 20 patients with severe COVID-19 pneumonia.

On the same line, *pro-resolving lipid mediators* support tolerance mechanisms by promoting de-*novo generation of FOX-P3 expressing T-regs.*

A2. *Microbial associated molecular patterns* (MAMPs) can resolve immunopathology through tissue repair functions.

Inflammasomes play a significant role: IL-18 dependent *caspase* activation, on which epithelial repair depends. The role of intestinal inflammasomes is peculiar: inflame and protect at the same time.

Organismal metabolism and immune cross-talk.

B1. Role of anorexia: inflammation-induced anorexia can be positive or detrimental.[11] Tendentially, anorexia can limit pathology and be positive for the host promoting tolerance in 2 animal models: fruit-fly and Salmonella. In a simplified chain: INFECTION -♢INFLAMMATORY RESPONSE-♢Production of ROS-♢Neural damage -♢ROS damaging action is blocked by the ketone bodies originated by anorexia. In this context, hyperglycemia can also be protective. In these models, the pathogen may take advantage from limiting its noxious potential, favoring survival and pathogen spread. [12]

B2. The case of muscle wasting (sarcopenia) Generally, inflammation-induced muscle wasting is considered a damage limiting host survival. In these premises, microbiome driven inflammation limits muscle wasting favoring disease tolerance. [13]

T-cell exhaustion and disease tolerance

The process of T-cell exhaustion may include three steps:

Loss of proliferative capacity

Loss of cytotoxic potential

Increase of apoptotic death

In general, these processes are finalized to promote disease tolerance in graft versus host (GVH) and autoimmunity. Of note, hypoxia can favor T-cell cytotoxic activity; DNA methylation can induce T-cell exhaustion.

Innocuous antigens, immunity, and disease tolerance

In certain contexts, the mechanisms that promote tolerance to oral antigens (Ags) (for example) can also induce disease tolerance mechanisms. On this ground, T-regs are again crucial, given that T-regs can also be alerted by repeated Ag administration.

Specific Take-Home Messages From These Premises

The paper summarized above conveys a few messages that help understand clinical and immunologic evidence. The concept of “immunological resistance” as a highly conserved inflammatory machinery bound to destroy the pathogen may no longer fit the whole scene. Pathogen handling is now rather intended as managed by traditional resistance and by “disease tolerance” mechanisms in different proportions according to the case. Disease tolerance is conceived as a sophisticated mechanism connected to host immune down-regulation and instauration of adaptive phenomena recalling

Dubos adaptive strategies that are the topic of this paper. The tolerant host, rather than simply pointing to pathogen destruction, tries to get acquainted with it, for example with some biochemical specificities, seeking advantage from them and, most importantly, limiting tissue damage enhanced by inflammation. The paper cites a few examples of this circuitry: infection–dependent anorexia may factor in detoxifying ROS; elaboration of inflammation through certain inflammasomes may favor tissue repair mechanisms; some lipid mediators may behave as pro-inflammatory, but also, as regulatory elements by raising T-reg populations. In this intellectual construction, the concept of tolerance may come close to approach adaptation pathways, thus ***merging immune and behavioral*** concepts. As the clinical support to these concepts, we cite three examples including the post-prandial syndrome, and two cases whereby physical exercise and adoption of a non-Western diet are proposed as anti-inflammatory strategies. In the final proof-of-concept, acquaintance with non-conventional basic lifestyle, is discussed to promote rearrangement of the immune tissue configuration. All-in-all, we are caring to underscore in a gentle yet straight-forward style, that nowadays Nature is consistently warning about an active down- handling of natural events all around us. Obviously, any action from human beings should now be held up until notice, bearing in mind the (so far) endless and sterile debates over the alleged “world heating up”-

The Role of Physical Exercise [1]

On an individual basis, the benefit of physical exercise (PA) is understood by common sense, and our ancestors were familiar with the aphorism that a healthy mind does nicely fit a healthy body. In the last decades, such popular wisdom has consistently become the object of intense studies, and the results have now come of age. While clinical reviews have reached the notable feat of documenting over 20 pathologic conditions (including malignancies) that may gain advantage from body exercise, a recent systematic study has faced the issue from a more basic approach. The results can be presented as three distinct points [13].

POINT 1. PA antagonizes glucose intolerance; reduces blood lipids and LDL cholesterol; restores endothelial dysfunction. The data are said to underlie clinical facts: reduction of thrombotic events, and regulation of blood pressure. As the clinical pay-back of such positive premises, regular PA is expected to reduce cardiovascular (CV) risk equally or better than conventional drugs.

POINT 2. Background knowledge: sympathetic tone is increased in aging tissues, leading to restriction of leg blood flow, increase of arterial BP, and large artery hypertrophy. Furthermore, increased sympathetic tone causes a diminution of peripheral blood flow, and an increased metabolic syndrome with glucose intolerance, and an irregular heart rate linked with more likely sudden death.

POINT 3. Beginning 2001, so-called polypills[14] were designed and launched onto the cardiovascular market and tested for their capacity to antagonize CV risk. Typically, a polypill is reported to contain therapeutic doses of statins, diuretics, beta-blockers, ACE inhibitors, and aspirin. Data released in 2003 showed that an 88% reduction of CVD, and an 80% diminution of strokes could be achieved by a polypill. In comparison trials, results achieved by PA were comparable with an advantage for PA on LDL cholesterol levels. Though these data are still under scrutiny, the obvious advantage of PA

over a polypill is the absence of drug induced toxicity. Similarly obvious disadvantages of PA are its feasibility in cardiac and severely ill rheumatic subjects. Questo paragraph 14 (dato per interessare le poly.pills e cade bene, a me sembra si posizioni altrettanto bene in quanto precede il tema di(Physical exercise)

The Role of Physical Exercise [15]

The mechanism underlying the therapeutic (anti-inflammatory) action of PA was studied in depth by us.

We essentially pinpoint that human voluntary muscles are our forgotten immunologic organs[16]. Muscle exercise leads to protean effects on so-called *Myokines* with dramatic increase or decrease effects:

Myostatin effects growth inhibition of muscle: exercise antagonizes myostatin, thus favoring muscle hypertrophy and adiposity reduction.

PA enhances IL-6, causing leptin-like activity leading to glucose uptake and lipid oxidation; careful attention should be paid to avoid missing particular conditions: e.g., in physiological conditions, IL-6 may inhibit pro-inflammatory cytokines in an intriguing (contradictory) neuronal cell protection role well-known in the list of this protean cytokine. [17] Again on the same line, it must be stressed that so far so forth, anarchic T/B clones were shown to control the potential to fully arouse a diabetogenic pancreatitis. And, to feed up a seminal discussion to sustain next seminal meetings over the world, it seems to fall appropriate to assertively reiterate the propensity of IL-8 to promote angiogenesis. [18]

Final Common Pathway of PA and Myokine Release

The final action of PA is mediated by the release of LACTOFERRIN (LTF) at blood cell level.

LTF is an 80-kDa monomeric protein. Its anti-inflammatory action is mediated by an interaction with monocytes/macrophages. LTF interacts with Toll-like receptors; reduces release of the chemoattractant IL-8; inactivates LPS, favoring termination of the inflammatory chain.

Seen from the GI Tract, Inflammation presents its Multifaceted Peculiarity

It has recently been realized that the functional position of the GI tract as a barrier organ can equally lead to consider inflammation as a “physiological phenomenon” or as a potentially harmful chain reaction that requires to be restrained.

A1. So-called post prandial syndrome. [19] We ought to Dror (repeatedly cited by ourselves recently and colleagues the intriguing demonstration that the act of feeding is based on an inflammatory response. Released from the digestion products, Lypo-polysaccharides can activate omental macrophages to release IL-1 beta. Rich in surface IL-1 receptors, the pancreatic Langerhans cells would then concentrate IL-1 beta, effecting an IL-1 dependent insulin secretion. These events make a unique confirmation of the double action of the GI tract, whereby feeding and immunological response are

unseparated.

A2. Diet-driven inflammatory responses. If the post prandial syndrome can well be considered as a repetitive yet self-limited inflammatory para-physiologic event, diet dependent inflammations may be by definition durable, and, as potentially harmful, require control.

A3. Food availability changes and increase of inflammogenic potential. One may consider as the turning point the switch to agriculture and livestock farming some 10,000 years ago. Before these changes variety was imposed by seasons and/or migratory patterns; thereafter, human diet composition began to be influenced by:

Glycemic load, Fatty Acid composition; Total Fiber Content. These changes were too quick to be addressed by genetic responses: microbiome changes got involved

A second turning coincided to the advent of industry food following World War 2. Relevant changes were: introduction of chemicals to improve conservation and palatability; also, the presence of refined cereals, sugar, cheese, butter, and coffee increased. In addition, industry impacted the quality of farmed animal feed, and the proportion of unsaturated fatty acids in the products for consumers

Nowadays, the complex of these changes has led to the definition of the Westernized Style Diet (WSD), said to contain the problematic (inflammogenic) factors:

Simple refined carbohydrates

Saturated fats

Red Meat

Dairy products and industry foods

Studies say that WSD, “rich in caloric dense foods”,[20] is at the basis of obesity and hypertension, and may promote intestinal inflammation through microbiota alteration. If these alterations coincide with excessive imbalance between harmful and protective species, dysbiosis may develop, leading to loss of tolerance. In inflammatory bowel disease (IBD), a representative example, we have the reduction of species variability, whilst pro-inflammatory components do rise consistently.

Thus, in the two instances of the post prandial syndrome, inflammation is dealt with either as a paraphysiologic event, or a prevalently harmful reaction to be converted by tolerance biased forces.

A “Proof of Concept” in Humans

The group of Pruimboom has long studied immunological phenomena from a behavioral approach. In a recent project[21], they followed a volunteer team participating in a fortnight mountain trekking, wherein participants were maintained in basic

life conditions. The working hypothesis was that contemporary mankind run a chronic state of hyperimmunity with generalized inflammation biased towards multiple organs/systems. This deviation would derive from education of the immune system under artificial man-made stimuli. Evolutionary life-threatening stimuli on the other hand, would make physiologic stressors inducing optimal responses with self-resolving capacity. This proof-of-concept, although run in a short time, was shown to reduce the hypermetabolic state and chronic hyperimmunity, favoring distribution of the immune system as though it was turned back to the original driving forces. This proof of concept again showed that immune error was mediated by hyper inflammation, with life-saving adaptation conveyed by a response of tolerisation.

Final Remarks

To the best of our knowledge this particular angle of photographing inflammation has been poorly considered until now. We tried to establish a relationship between a philosophic aphorism (per se evocative and wide and vague at once) and experiences expressed with the rigid language of science. The starting assumption was that the macroscopic phenomena of organism adaptation could be analyzed as encasing the molecular events of immunologic tolerance. On this line, we theorized a parallel between the concepts of adaptation phenomena (used by Dubos) and tolerance (used by us). Saving of clash and damage at different levels are the pay-back of both.

In the extreme synthesis, we are emphasizing o emphasize that life enhancement is based on down-regulating behavioral/molecular compromises, as smart and efficient as they can be. It seems that this holds true for the wide array of examples we discussed, including the dramatically modern case of COVID invasion. Furthermore, a last-minute reinforcement to the above statements is coming from interest mounting on a subtle pathway used by many cell types to down-regulate the expression of autoimmune disorder: alternative splicing. To achieve constrain of excessive autoimmune pathways, cells may defend themselves by alternating synthesis of relevant immune active signals, with unrelated non proinflammatory messages

We like to add that composition of a clash into adaptation or tolerance must necessarily conclude with the creation of a new entity sharing the features of the two initial parties, e.g., an enrichment instead of death.

At this point, a calm word of caution could help us sail to our safe harbor. To this end, we like to point out that a few among the addressees of the …… messages, could indeed wrongly perceive those words as an impulse to gather together things under a reductive sign: leveling down may favor co-habitation; …… but can also take life to dullness!. Unexpectedly, some of those who in a recent past had cried out their readiness to combat all Authority, at factual evidence are forced to regret their inadequacy to manage without a superior guide. Variety has always made the world go round……

The presentation of this paper was implemented a couple of years ago, yet it failed to reach a final venue. Nonetheless, specific research has gone fast, and nowadays we might add a few points to the discussion that were not as manifest at that time.

In fact, the recent studies re-programmed on the topic of immunological down-reading, is now boosting the birth of concepts speaking not of abstract re-phrasing (as suggested above) but rather of curbing a given reaction concretely, for the sake of fine cell immune balance. Today's investigators are [22] ready to utilize the term re-sizing to identify any documented cell-governed restriction of energy exchange, coming to the feat of influencing the cell biochemical phenotype.

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No matter what direction our human eyes may gaze into, the prevalent reply to our trembly inquiries may (at best) get quenched by a patronizing (boring almost discouraging *ritornello): There's hardly a reason to keep raising questions: the desperation for the unavoidable Men's demise at the end, is perhaps far more pervasive than the act of reaching out for Life on beginning. Everything around is gently anesthetizing either our will or struggle; dropping us rusty, torn, and like sleepy pulleys gently rolling, soaked in the delicate oil of resilience. We'd drive an excavator to knock down all curtain and let us grab any thing hindering our hunger from just knowing more…..; but who knows without fear of getting wrong, perhaps revealing at the end only a painful knot tighten around nothing…….*

Surpassed by the unmatched speed of the "Untoward", we are presenting an unripe funeral speech to honor the memory of Doctor Rinaldo Pellicano, often exalted by workmates, relentlessly loved and respected by his splendid family. Rinaldo has passed away last Saturday May 27th in an inescapable chain of lethal events. The loss of Rinaldo is irreplaceable; we can only be consoled in knowing that he rests immortal in the heart and mind of all those who were lucky enough to get to know him.

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