Review Article

Conflammation: Too Much Conflation in Inflammation? An Attempt to Identify and Resolve the Predominant Contradictions and Anomalies in the Concept of Inflammation

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The use of the word inflammation in recent literature appears to have superseded the classical definition of the word. However, a precise new definition has not yet emerged. As a result, the boundaries of the concept are hazy and it needs to be examined critically whether everything in the semantic basket is indeed "inflammation". Similar to almost all genes, molecules and pathways, inflammation-associated cells and molecules also have a number of other normal physiological functions. Altered expression of these can be associated with functions other than defence. If all these functions are also to be called inflammation, in the entire life ranging from embryo implantation to death, the body can be said to be always in a state of inflammation. This takes away the need for the concept itself. As a result of the ambiguous definition, inflammation has been blamed for a number of health disorders, but anti-inflammatory treatment has failed to cure or prevent them. In particular, the concept of chronic systemic inflammation is laden with multiple anomalies which might be misleading our understanding of health and medicine. On the foundation of evolutionary logic, a new and clearer perspective of the condition called chronic systemic inflammation can emerge. We discuss the foundations of the new perspective and its relevance to health, disease and medicine.

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Inflammation has become a key term in biomedicine, used extensively in various contexts, but rather loosely and ambiguously. The concept has undergone a number of major transitions in its core definition, working definition, tools for detection, and perceived relevance in medicine. A problem arising because of

the rapid transitions is that the classical definitions are no longer valid, but a precise new definition has not yet emerged clearly and unambiguously. The problem goes beyond semantics and affects the conceptual foundations of physiology, immunology, and medicine. With huge amounts of genetic, molecular, cellular, metabolic, and immunological intricacies coming to light, the field appears to have become lost in details. With the intriguing amount of information, more internal contradictions and conceptual anomalies are accumulating, which need to be addressed seriously. We do not claim to resolve the anomalies in one go, but attempt to point out the critical issues that need to be addressed, starting with the definition, and suggest a possible novel platform based on which a coherent sense can emerge.

I. Historical Context of the Definition of Inflammation

The definition of inflammation has gone through three major phases of transition. The ancient clinical context of inflammation *"Notae vero inflammationis sunt quatuor: rubor et tumor cum calore and dolore"* dates back to the 1st century AD, defining the four cardinal signs of inflammation, namely redness, swelling, fever, and pain, by Aulus Cornelius Celsus. The fifth sign, *functio laesa* or "loss of function," was introduced later. Influentially, *Galen* (3rd cent. A.D.) redefined inflammation (*Phlogosis*) as a reaction of the body against injury. These early ideas were shaped only by the available tools and knowledge of biology and therefore were symptom-based [1][2][3].

Approaching the 19th century, advances in microscopy and cell biology opened the door to the second phase, i.e., the cell-based definitions of inflammation. It was with Elie Metchnikoff (1845-1916) that the view on inflammation shifted to immune cell accumulation and phagocytosis. Neumann (1889) included the healing or restorative component in the definition. Immune cell aggregation was identified as the core of the inflammation process.

The molecular mechanisms of all these functions of the cells were discovered from the middle of the 20th century. Sir Henry Dale in the 1930s primarily reframed inflammation as a process mediated by endogenous active substances (acetylcholine, histamine, catecholamine) formed, synthesised, or released by the body. The field advanced further with more and more molecules being discovered one by one, such as histamine, leukotaxin (chemokines), bradykinin, pyrogenic cytokines, C-reactive protein (CRP), and interleukins [3][4]. As a consequence, the end of the 20th century shifted the focus from cells to molecules. Today, the working definition depends upon showing raised levels of one or a few "inflammatory markers". It is no longer considered necessary to demonstrate cell aggregation, the site of aggregation, phagocytosis, or other cell interactions and their actual relevance to defence and healing. Implicit behind

this working definition is the assumption that the molecules used as inflammatory markers are specific to inflammation alone and always faithfully represent inflammation as defined at the cellular level. Throughout this phase of the transition, the cellular definition of inflammation has not been formally dismantled [3][4]. The use of the word inflammation today often appears to relate to anything that "immune cells" do or any altered expression of the molecules labelled "inflammatory markers". But the 'anything' component of the perception needs a critical look.

II. Burden of History, Burden of Simplicity, and the Perception Bias

We know today that almost no gene, protein, or pathway has a single function. Typically, in physiology, a gene or molecule is first discovered in a certain context, gets a name, and builds an "image" in that specific context. Later, many other functions of the same entity are discovered, but still, in the popular image, we continue to perceive the entity in its first discovered context. This is a burden of history that might create a bias in our perception. For example, insulin was discovered in the context of diabetes and glucose regulation. We know today that apart from glucose regulation, insulin has a wide range of functions spanning stem cell maintenance, tissue homeostasis, protein metabolism, angiogenesis, sex, reproduction, memory, and behavioural decisions [5][6][7][8]. But if there is a change in plasma insulin levels, we almost invariably relate it to glucose, insulin resistance, and diabetes in some way or another. Even in the context of glucose regulation, it is clear now that the role of insulin is not as it was perceived classically [9][10]. But rather than acknowledging the more complex and evidence-based picture, diabetes medicine continues to go by the oversimplistic classically perceived role. We continue to perceive the systems as modular, although they are shown to work as networks [10]. Thus, both the burden of history and the burden of simplicity shape our perception of a cell, gene, molecule, or pathway. Many more examples illustrate the phenomenon.

Classically understood as a "bone formation marker", osteocalcin is now known to be involved in multiple functions in the body, such as metabolism, reproduction, and brain function. It enhances adiponectin release from adipose tissue and improves glucose tolerance and energy metabolism in muscle. It also supports exercise adaptation by promoting glucose and fatty acid utilisation, influences male fertility by boosting testosterone production in Leydig cells, and regulates brain development and cognition through effects on neurotransmitter synthesis and hippocampal growth [10][11][12][13]. Still, the primary perception of osteocalcin is in the context of bone health.

Similarly, “adipose tissue” is a multi-functional endocrine organ that secretes leptin, adiponectin, and resistin, stores energy, regulates glucose homeostasis, and controls lipid metabolism and steroid hormone conversion. The tissue also plays a role in adipokines that influence appetite, insulin sensitivity, blood pressure, and inter-organ communication. In essence, adipose tissue is far more than a fat-storage organ; it is a complex, hormonally active tissue that integrates metabolic, immune, vascular, structural, and behavioural signals across the entire organism. But in our perception, the “primary” function of adipose tissue still remains the storage of excess energy [14][15].

First known by the observation that it inhibits macrophage migration and hence named Macrophage Migration Inhibitory Factor (MIF), the molecule is now known to have diverse pro-inflammatory and anti-inflammatory functions. Several studies have demonstrated that MIF has pro-inflammatory roles; for example, it maintains macrophage priming through TLR4 upregulation and acts as a critical autocrine/paracrine regulator of macrophage activation through TLR4 [16], sustains MAPK signalling while overriding glucocorticoid suppression [17], activates the NLRP3 inflammasome [18], drives chemokine release through CD74 receptor engagement [19], induces TNF production in monocytes and macrophages [20], and enhances NFκB-dependent antimicrobial responses [21]. It was also found that MIF deficiency results in reduced expression of inflammatory mediators like IL-1β, CCL2, and MMPs, and increased production of anti-inflammatory cytokines such as IL-10 in the lesion area, suggesting that MIF can induce anti-inflammatory effects as well [22]. Furthermore, studies have shown MIF to have neuroprotective effects by inducing expression of BDNF. Similarly, MIF has been found to upregulate serotonin, THP2, and BDNF in vitro as well as during exercise [23]. MIF was found to be released in the ischaemic heart; it stimulates AMPK, a master energy-sensing enzyme that increases cellular ATP production and limits energy consumption [24]. Given the span of functions of MIF, the name is a complete misnomer, but it still continues to be used and inevitably shapes the perspectives of a person entering the field.

Although Heat Shock Proteins (HSPs) were first known for the intracellular chaperone functions of protein homeostasis, protein folding and refolding, aiding in the removal of defective proteins, cell signalling transduction, cell cycle, and apoptosis regulation, they also serve as danger signal molecules to alert the immune cells to recognise the existence of damaged cells [25][26].

These diverse examples demonstrate how cells and molecules are often named in the context of their discovery, which often continues to be perceived as their “primary” function. This burden of history and

burden of simplicity has haunted the field of immunology too. We see that the cells perceived as “immune cells” have many other functions not directly related to injury and infection. Similarly, molecules primarily discovered in the context of immune function are shown to have other normal physiological functions too. But we are biased in our perception, and we continue to see them as “immune cells” and “inflammatory markers”. If we see any change in the population and behaviour of cells or expression and standing levels of the molecules, we immediately call it inflammation without considering the possibility that it might be in some other context too. Therefore, we need to look carefully at alternative functions of these cells and molecules and decide whether they always reflect inflammation as perceived today. The functions of immune cells not directly related to innate immunity are worth highlighting, as they are an important part of a system that works as a network, not as modular mechanisms [27][28].

III. The Non-Defensive Functions of Immune Cells

Although macrophages are perceived primarily in the context of immunology, their functions are diverse and start right from embryonic life, where infection and injury stimuli are almost non-existent or taken care of by the maternal immune system. Macrophages are critical in embryo implantation. Abnormal macrophage distribution, number, or polarisation is linked to recurrent implantation failure (RIF) [29]. The placental macrophages of foetal origin, called “Hofbauer cells”, play a key role in angiogenesis, vasculogenesis, and placental mesenchyme development [30]. Interestingly, the signals involved in the developmental and re-modelling functions are IL-8 and MMP-9, which are also recognised as pro-inflammatory signals.

In adult life, macrophages play an essential role in maintaining tissue balance by clearing dead cells, apoptotic cells, and cellular debris, which helps preserve tissue integrity. This includes efferocytosis, which is the removal of effete/senescent cells before they trigger more damage. Although this role has parallels with the phagocytosis role in inflammation, it is a part of normal physiology, not triggered by any infection or injury challenge. Furthermore, macrophages play an active role in lipid metabolism and adipose tissue regulation; regulation of ECM and collagen synthesis; angiogenesis; iron homeostasis in the liver; and growth factor expression [31][32].

The name Natural Killer cells is a glaring example of the burden of history. The non-destructive functions of NK cells can be traced to reproduction, pregnancy and foetal development. NK cells play a crucial role in facilitating endometrial tissue remodelling, supporting vascular function, and contributing to

placental formation. The uterine NK cells, like endometrial NK (eNK) cells and decidual NK (dNK) cells, act as regulators of placentation. They are primarily involved at the maternal-foetal interface in driving angiogenesis on the maternal side and vasculogenesis on the foetal side. The dNK cells regulate uterine spiral artery development, and control the oxygen supply at the maternal-foetal interface as well as ensure a good maternal-foetal blood supply [33]. The uterine NK cells secrete osteoglycin that regulates collagen fibril structure and contributes to foetal heart and tissue development [34]. Improper functioning of dNK cells at the maternal-foetal interface leads to placental dysfunction [35][36][37].

B cells are found to be abundant, especially during embryonic brain development. They are directly linked to developing-brain processes and are known to support oligodendrogenesis and myelination. Additionally, B cells are involved in remyelination by producing natural antibodies (nAbs) against unidentified myelin antigens [38][39][40][41][42][43]. T cells are involved in complex brain processes including spatial learning, memory, emotional behaviour and stress responsiveness [44].

Given the span of functions of these cells, calling them “immune cells” appears to be a burden of history. If their role in embryonic development had been discovered first, we might have called them developmental cells and said that they also contribute to immune function as a secondary role.

IV. Non-Defensive Functions of the So-Called Inflammatory Markers

Similarly, what we call inflammatory markers today also have a set of different functions. It is hence unfair to assume that an altered or elevated level of inflammatory markers is directly linked to inflammation. Exercise, for example, triggers high levels of IL-6, but this is not accompanied by elevated IL-1β or TNF-α (the canonical pro-inflammatory cytokines). Instead, exercise-induced IL-6 stimulates anti-inflammatory molecules like IL-10 and IL-1ra. Here, IL-6 leads muscle to utilise fatty acids and promotes a shift from catabolic, glucagon-dependent pathways to anabolic, insulin-dependent pathways, helping glucose absorption by muscle and contributing to recovery. Thus, IL-6 plays an important role in metabolic regulation in the muscle tissue. It stimulates lipolysis and releases energy sources into the bloodstream. It also stimulates insulin secretion and insulin sensitivity. It induces proteolysis in muscle, making amino acids available for protein synthesis. Similar to leptin, IL-6 functions as an indicator of energetic status. Higher levels signal that more energy is available and can be allocated to maintenance functions such as tissue repair. In adipose tissue, IL-6 production may indicate that when stored energy

is available it is allocated to somatic maintenance, which is called “adaptive metabolic allocation”, that has nothing to do with inflammation [45]. Furthermore, IL-6 contributes to appetite suppression and delayed gastric emptying, thereby attenuating postprandial glycemia. Beyond metabolic regulation, IL-6 plays critical roles in skeletal muscle hypertrophy and bone remodelling [46].

CRP, another commonly used inflammatory marker, also has other normal functions. CRP exists in two isoforms. In its monomeric form (mCRP) it acts as a chemoattractant and is generated at the site of injury, which is at the core of classical inflammation. CRP in its pentameric form (pCRP) is involved in wound healing, clearance of damaged cells, and tissue regeneration, which can be considered a legitimate part of inflammation. However, tissue repair and maintenance is also a normal process that continues in the absence of any injury or infection trigger, and it is suggested that pCRP is produced for this purpose even without inflammation. In 2018, Giudice et al. [45] argued that moderately elevated levels of IL-6 and CRP can occur in the complete absence of inflammation and tend to have anti-inflammatory effects.

V. Need to Ask a Fundamental Question

Does an elevated level of an inflammation-associated molecule necessarily reflect elevated inflammation?

To understand how inflammation works, it is important to understand the principle behind how immune cells aggregate at the site of injury. Here, the gradient is the key. The chemoattractants act as signalling molecules that form concentration differences in the body. The concentration differences lead to the formation of gradients. The strength of such a gradient depends upon the level of the chemoattractant molecules at the site of injury (local level) and the basal systemic level. The gradient allows the immune cells to migrate to the appropriate location. When the basal levels rise, the gradient weakens. Therefore, it is likely that higher levels of some of the inflammatory markers tend to decrease rather than increase the inflammatory response. It might be misleading, therefore, to assume that a higher level of a molecule involved in cell migration response always indicates a higher inflammatory response [47].

Innate immunity is a spatiotemporal process. Cells migrate based on different signals. The relative concentrations of molecules at different locations may be more important than the absolute ones. The same molecule may have different effects based upon where it is secreted, what its relative levels are at different locations, which other signals accompany it, and which cells and receptors it interacts with. The

downstream pathways of cell surface receptors and soluble receptor molecules can be very different [48][49][50][51].

Therefore, inferring anything from the raised levels of one or a few molecules can be misleading. For the same reason, classifying molecules into pro- versus anti-inflammatory is too simple to be true and useful. Many molecules have been claimed as both pro- and anti-inflammatory in different contexts. Further, the repeated failure of anti-inflammatory treatments to prevent the disorders believed to result from chronic systemic inflammation, in spite of reducing the marker levels [52][53][54][55][56][57] necessitates fundamental rethinking of inflammation and its associated pathophysiology.

VI. Potential Absurdities/Anomalies That Need Critical Re-Examination

Systemic inflammation: Systemic inflammation is characterised by heightened levels of inflammatory mediators, like cytokines, chemokines, and acute-phase proteins like CRP. It is said to be a whole-body inflammation response. The cellular process of inflammation comprises the aggregation of immune cells. Aggregation is a locale-specific process, and it is absurd to say that they aggregate everywhere. Clearly, the concept of systemic inflammation is not compatible with the classical cell aggregation-based definition. If the working definition of systemic inflammation is based on one or a few markers, it can be misleading, as argued earlier. If it is about the activation of immune mechanisms, one would expect that with systemic inflammation, the system would be ready to launch a quicker response to injury/infection, leading to rapid recovery. But in contrast, in disorders like diabetes characterised by systemic inflammation, wound healing is typically delayed or impaired [58][59] and the frequency and severity of cutaneous infections are higher [60][61].

Inflammaging: With age, the level of systemic inflammation is said to go up, and that is assumed to be central to the age-related changes in body functions and health, a phenomenon called inflammaging. A serious problem with this argument is that the association between ageing and inflammatory markers is not consistent across human communities. The data behind inflammaging comes mainly from Western, Educated, Industrialised, Rich, and Democratic (WEIRD) societies. However, only 11% of the world's population lives in these societies. Hence, WEIRD societies are not necessarily a good model for studying inflammation. Different societies, like the Filipino and Shuar communities, showed lower levels of ageing-associated CRP than WEIRD societies. McDade [62] suggests that different communities show a

distinctly different pattern; hence, one should not assume that inflammation increases with age, and concepts such as “inflammaging” must be used carefully.

Is this inflammation? Without any explicit definition, the word inflammation is being used for anything that the so-called “immune cells” do. For example, the role that macrophages play in embryo implantation has also been called inflammation [29][32][63]. The ambiguity as to whether the response of these cells to defence-related triggers is to be called inflammation or anything that these cells do will be called inflammation needs to be resolved first. In the case of the latter, even embryonic development, metabolism, and normal tissue homeostasis will have to be called inflammation. This means that right from zygote formation to death, the body is in a continuous state of inflammation. This makes terms like the “inflammatory response” meaningless. If the behaviour of these cells above normal is to be called inflammation, the distinction between normal and danger-triggered responses needs to be clarified first.

The cause-effect confusion: Macrophages play a role in lipid metabolism and the formation and maintenance of adipose tissue [31]. Thus, there is an association between adipose tissue and macrophages. Does this mean that adipose tissue “causes” inflammation? It is necessary to look at this and many other associations critically for cause-effect relationships so as to avoid misinterpretations.

The good-bad connotation: Almost throughout the literature on chronic inflammation, the word is used with a negative connotation. Is inflammation always bad? If so, how did it survive the selective forces during evolution? The evolutionary underpinnings of physiology and pathophysiology are yet very superficially understood. Everything that we theorise in this field needs to withstand robust evolutionary analysis. Evolutionary medicine is no longer a speculative field; it is rapidly becoming a robust, testable, and applicable foundation of all our understanding of physiology and medicine [64]. If any mechanism of the body is harmful to itself, the question of why it remained evolutionarily stable needs to be addressed critically and systematically. Any evolutionary hypothesis needs to be backed by sound evolutionary principles, make differential testable predictions, and contribute novel insights to our understanding of health and disease [64]. Handwaving arguments are no longer acceptable in evolutionary medicine. The immune system being highly complex, insights into its evolution have started emerging only recently [65].

VII. An Evolutionary Interpretation of "Chronic Systemic Inflammation"

One of the principles of evolutionary medicine is the mismatch hypothesis [6]. The mechanisms of our body evolved for a set of ecological challenges faced by our ancestors and are optimised for it. But today's lifestyle is substantially different from what we evolved for. It is possible that a system that was adaptive in one context can turn maladaptive in a mismatched context. Mainstream evolutionary medicine has discussed a limited range of mismatches, such as the dietary mismatch and the fight-or-flight response. There are more mismatches whose potential effects have not been appreciated so far. Understanding evolutionary mismatch has two distinct components: the first one being why and under what context the system evolved, and the second, what kind of mismatch makes it maladaptive and how.

During human evolution, a unique change was the loss of fur, which changed the nature of innate immune challenges for the skin. In mammals, two distinct systems are involved in recruiting immune cells to the cutaneous and subcutaneous tissues, involving two distinct chemokine groups. The first one is dedicated to homeostatic dynamics of immune cells which maintains a healthy population of immune cells in the absence of injury. The second is the response specifically triggered by injury, infection, pain or malignancy [66].

It is important to note that much of the homeostatic immune cell dynamics of the skin in mammals specifically involves the vasculature of hair follicles [67][68][69][70][71][72]. There is a strong association of immune cells with hair follicles starting from the morphogenesis stage itself [71][72]. During human evolution, fur was lost. The density of hair follicles reduced substantially, and this is expected to have affected the normal homeostatic immune cell dynamics in the skin. After losing fur, compensatory or alternative mechanisms independent of hair follicles should have evolved. But simultaneously after losing fur, the frequency of immune stimulation of skin by pricks, bruises, friction, insect bites, heat, UV exposure and other minor injuries would have increased considerably. This is in contrast to the other mammalian species to lose fur, namely the naked mole rat, which spends most of its life in burrows with little exposure to many of the above stimuli.

We suggest here that when both types of pathways are almost always active, some redundancy is created, due to which the evolution of alternative baseline homeostatic pathways may have remained subnormal in humans. Injury-stimulated pathways are likely to have played a major role in the immune cell

dynamics of human skin owing to the high frequency of minor injuries after losing fur. Although not yet carefully examined at a mechanistic level, this hypothesis is strengthened by the observed differences in humans versus other mammals in the signalling pathways of immune cell extravasation in the subcutaneous tissue. In humans, the altered association of immune mechanisms with hair follicles, suppression of CCL2-CCR2, CCXL8/IL-8 [73], altered E-Selectin and P-Selectin signalling [74][75], absence of Siglec-5 [76], altered STING and iNOS signalling [77], altered mast cell behaviour and evidence of selection on pro-inflammatory alleles [78] together strengthen our hypothesis, although a much more careful contextual analysis and interpretation of these pathways is required. Since there exist several differences in the details of immune mechanisms across species [79][80][81], segregating the alterations specifically induced by the loss of fur in humans is difficult to mark out at this stage, and careful primary work would be needed to examine this possibility.

Assuming that human skin immune dynamics has evolved differently from other mammals, it is possible to visualise the lifestyle-related changes of modern humans. In today's urban lifestyle, we live in an all-time cushioned environment, and the frequency of minor injuries has come down dramatically. This is bound to alter the behaviour of immune cells considerably. If injury stimuli are reduced and the baseline homeostatic extravasation has evolved to work sub-normally, there would be a reduced flow of immune cells from blood to skin with a modern lifestyle.

By our hypothesis, frequent minor injuries are necessary to maintain the normal immune cell population in human skin. The frequent small acute inflammatory responses would be normally accompanied and followed by enhanced lymphatic drainage, removal of immune cells participating in phagocytosis, antioxidant mechanisms, tissue repair and angiogenesis. The healing process involves a set of growth factors, and many growth factor expressions are stimulated by minor injuries. In an injury-free lifestyle, these processes would also be sub-normal. What is more interesting to note is that even the anticipation of injuries stimulates some of these mechanisms [6][82]. Many of the growth factors involved in wound healing are secreted by the salivary glands following behaviours such as aggression [83][84][85][86] that increase the probability of injury. The salivary glands are the appropriate site for expression [82] because animals lick wounds and thereby supply the required growth factors directly.

Against this background, what do we expect to happen with a modern lifestyle that is not only deficient in minor injuries but also in events of anticipation of injuries? The rate of turnover of immune cells is expected to decrease. The extravasation of immune cells will be slower, and so will the lymphatic

drainage. Rapid clearing of chemo-attractants by lymphatic drainage is important for a sharper gradient guiding cell migration. If more of the chemokines diffuse randomly and are not quickly removed by lymphatic drainage, the gradient will be weaker, reducing cell migration further. Since phagocytic activity followed by the clearance of effete cells also goes down, we expect a greater accumulation of senescent cells in the subcutaneous tissue. When senescent cells accumulate, but fresh macrophages are not recruited at a normal rate, it becomes an autocatalytic vicious cycle. Too many senescent cells accumulating and their signals being unable to generate a sharp gradient because of subnormal lymphatic clearance can lead to an accumulation of the signals, which reduces further recruitment rather than enhancing it, leading to the phenomenon of the senescence-associated secretory phenotype (SASP) [87][88][89][90]. The signals given by senescent cells, including interleukins, chemokines, cytokines, proteases, and growth factors that are supposed to facilitate the clearance of senescent cells, are counterproductive because of the inability to form clear gradients. This has been demonstrated in studies showing that a large fraction of multiple cell types in lifestyle-related disorders such as diabetes are senescent [59].

This can simply be the direct result of abnormally infrequent injury stimuli, or it could be because of additional mechanisms. There is likely to be another mechanism evolved to optimise the investment in innate immunity. Investment trade-off is a known principle in evolution. Some trade-off between peripheral and systemic immunity is shown in experimental challenges in invertebrates [91]. The peripheral versus central immunity trade-off is visualised in humans too from an evolutionary perspective [92]. As the modern lifestyle is deficient in peripheral injuries on the one hand, it is likely to be accompanied by more frequent contagious diseases due to crowding. Therefore, disinvesting from peripheral immunity to support systemic immunity is a plausible response of the immune system to a modern lifestyle. A simple way to achieve this is to further weaken the chemoattractant gradient generated from any cutaneous injury. This can be done by increasing the basal levels of some of the chemo-attractants [47]. Since the gradient is due to the difference between local and basal levels of chemo-attractants, increasing basal levels would decrease rather than increase cell migration. This is achieved by the expression of chemokines by central organs such as visceral fat or the kidneys. The raised levels of circulating pCRP may also reduce granulocyte migration [93][94][95][96]. Arguably, this small investment in basal levels of chemo-attractants can save a greater cost of immune cell migration to sites where they are least likely to be needed [47].

The link with obesity and the so-called systemic inflammation is also likely to have evolved for optimising the immune response. Foraging behaviour is optimised by finding the best trade-off between nutritional gains and foraging risk. At the molecular level, this optimisation is brought about by the interplay between leptin (a signal of stored energy) and cocaine- and amphetamine-regulated transcript (CART) (a signal of foraging risk) [97]. When there is enough stored fat, the foraging drive becomes weaker, particularly if foraging is risky. Foraging increases the chances of injury. When foraging becomes unnecessary owing to stored fat, it makes sense to reduce the investment in peripheral innate immunity. When stored energy is minimal, foraging is necessary in spite of the risk, and this is where investing more in peripheral immunity is necessary. It would be most appropriate that the signals for this transition are given by the adipose tissue itself. This transition needs to be sufficiently quick and plastic to be adaptive. However, if fat stores remain high for a long time, as with modern-day obesity, the plasticity may deteriorate [46][98][99].

Our synthesis necessitates a rethinking of the term systemic inflammation. If the main hallmarks of inflammation—namely, cell migration under a chemoattractant gradient, phagocytosis, facilitated lymphatic turnover, and triggering the follow-up healing cascades—are all impaired or downregulated, calling it inflammation is absurd. What we call chronic systemic inflammation today is not a type of inflammation but actually a deficiency in the normal frequency of acute inflammations. The condition can easily be reversed by reversing the sedentary and injury-free lifestyle. In deficiency diseases, supplementing what was deficient is the best remedy, and no other drug can give comparable relief. Here, a physically active life with more or less normal injury and injury anticipation stimuli is the best remedy. Since the condition is not driven by an inflammation at all, anti-inflammatory treatments will at best show a marginal superficial difference and will not be able to reverse any of the conditions.

Currently, since the popular perception is that chronic inflammation is damaging, the pathology of diabetes, cardiovascular disease, kidney disease and many types of neuronal disorders is said to be caused by chronic inflammation. If we reject the notion that chronic systemic inflammation is inflammation at all, alternative causes for the pathology would have to be sought. This, in fact, is likely to bring more clarity to the pathophysiology of these disorders and lead to more insightful approaches to treatments. We have already said that growth factor expressions are behaviour-responsive and the deficiency of the hunter-gatherer behaviours for which our body is optimised characterises modern lifestyle. Growth factors are expressed by every injury and are important and essential mediators in the healing process as well [100]. The deficiency of the behaviours as well as of frequent minor injuries is bound to alter the

growth factor dynamics. Since growth factors are involved in stem cell maintenance, angiogenesis, neuroprotection and metabolism among other functions, a cascade of changes can follow altered growth factor expression. Growth factors are critical for angiogenesis, revascularisation and endothelial function. Endothelial dysfunction is the underlying cause of multiple disorders [101][102]. The deficiency of a set of behaviours to which our physiology has been optimised is likely to be directly responsible for the pathological changes independent of inflammation [6].

Based on this concept, a set of alternative pathophysiological hypotheses for different lifestyle-related disorders needs to be tested with a differential prediction approach [103]. It is very likely that giving up the chronic inflammation narrative will facilitate research on alternative possibilities of the true pathophysiological mechanisms of lifestyle-related disorders.

Testable predictions of the hypothesis:

If the hypothesis of deficiency of minor injuries and injury-anticipating behaviours is true, we expect a number of outcomes. Some of these testable predictions are already known to be true. It is possible to subject them further to more specific tests.

i. Since the evolution of the human skin immune system has taken a unique path, not shared by any of the laboratory animal models, we expect that no animal models mimic the so-called chronic systemic inflammatory condition in humans very closely and any research using partially resembling models would find only limited translational use, which appears to be true [104][105][106][107][108].
ii. By this hypothesis, diabetics and others affected by lifestyle-related disorders should be much more susceptible to cutaneous infections and non-healing wounds as compared to respiratory and other systemic infections [58][59][60][61].
iii. Impaired wound healing is the most obvious prediction of our hypothesis. In contrast, it is not a straightforward logical prediction of the systemic inflammation hypothesis. If the altered rate of migration of immune cells is a major cause of wound healing problems, enhancing the migration would facilitate wound healing, which has been demonstrated. Exogenous granulocyte-macrophage colony-stimulating factor (GM-CSF) increased the influx of macrophages and neutrophils, followed by an increase in interleukin-6 and monocyte chemoattractant protein-1 production resulting in an increase in neovascularisation and stimulated wound healing [109][110]. In addition, injuries and injury-anticipating behaviours directly trigger a series of growth factors. Growth factors play a role

in M1 to M2 transition as well as other processes in wound healing including neovascularisation, epithelial cell growth and wound closure [111][112][113]. We expect therefore that when the behavioural stimuli are normal, wound healing will be normal. This is testable with an epidemiological approach or a well-designed behavioural clinical trial.

iv. The foraging-related component of our hypothesis expects that adipose tissue is the main organ to initiate the immunity transition. Therefore, obesity and related disorders would be correlated negatively with the mechanisms of peripheral immunity and cutaneous wound healing.

v. Evidence suggests that the lymphatic drainage system is crucial for the clearance of the acute inflammatory response, removal of cytokines, catabolic factors and inflammatory cells from the site of injury/stimulus and other mediators of inflammation in rheumatoid arthritis [114], post-myocardial infarction [115], and even the clearance of lipoproteins from inflamed atherosclerotic tissue [116]. As expected by our hypothesis, lifestyle-related disorders are strongly associated with lymphatic dysfunction, which leads to decreased lymphatic vessel density, decreased collecting lymphatic vessel pumping frequency, decreased lymphatic trafficking of immune cells, increased lymphatic vessel leakiness and changes in the gene expression patterns of lymphatic endothelial cells [117][118].

vi. If reduced minor injury stimuli are responsible for the altered inflammatory state, increasing such stimuli would reverse the conditions. This is shown to happen by acupuncture and acupressure treatments [119][120][121]. It is well-known that acupuncture and acupressure have substantial anti-inflammatory effects [122]. Some of the studies show that even “sham” acupuncture, i.e., stimulating the skin randomly independent of specific acupoints, is anti-inflammatory, which is compatible with our hypothesis [123][124][125]. If any other behaviour/habit exposes the skin to more frequent injuries, it should reduce the incidence of the disorders believed to be caused by chronic systemic inflammation. Playing with pets, particularly young and subadults, increases minor skin injuries caused by the playful bites and clawing by the animals. This is expected to reduce the incidence of so-called chronic inflammatory disorders, and there is data supporting this expectation [126][127][128][129].

vii. Exercise partially reverses the sedentary lifestyle, but it is also likely to induce the injury anticipation response. Behaviourally enriched exercises or active sports, which mimic many hunter-gatherer behaviours such as chasing and catching something, aiming at something, attacking or defending something, are expected to supplement the injury anticipation responses

and thereby expected to reverse the innate immunity changes. Although there are no specific tests of behaviourally enriched exercises, exercises in general are known to resolve the condition. In obesity-related settings, aerobic exercise was found to decrease peri-lymphatic inflammatory cell accumulation, improve lymphatic function and reverse pathological changes in gene expression in lymphatic endothelial cells, which was independent of weight loss [117]. In the case of diabetic wound healing, exercise significantly increased angiogenesis, inhibited M1 macrophage infiltration and increased M2 macrophage count, which significantly accelerated the wound healing process [130].

viii. The classically perceived role of exercise is that it burns calories and improves the energy balance, thereby reducing fat. The adipose tissue is said to mediate the systemic inflammation [131][132]. An important prediction differentiating this perspective from our perspective is that by our hypothesis, exercise benefits should be seen independent of weight loss. Wherever differentially tested, the advantages of exercise were found to be faster and independent of weight or fat loss [117][130]. Although the adipose tissue is likely to be one of the mediators of the immune transition, there would be mechanisms that work independent of adiposity.

Since, in the lifestyle-associated set of disorders, apart from fractional and inconsistent prevention of complications in some (but not all) of the clinical trials, the success of treatment is extremely limited [133][134][135][136][137][138][139][140], we need to cross-question the prevalent theories. It is likely that the limited effectiveness of treatments is because of a lack of clear perception of the true pathophysiology. Cross-questioning the concept of chronic systemic inflammation is a small part of the bigger picture. Along with that, we should also be open to alternative interpretations that can be tested using a model prediction matrix [141] and testing the predictions eventually.

VIII. Conclusions

At present, there is too much conflation of mutually contradicting ideas in the concept of inflammation. Inflammation needs to be redefined, as it has undergone profound transitions from cell-based to marker-based interpretations. The burden of history and simplicity has led to strong biases in the perception, where the multifunctionality of molecules is underappreciated. The example that macrophages and NK cells are critical in embryonic development and placentation, while B cells contribute to myelination and remyelination in the brain, demonstrates that these cells are not limited to just an “immune” function.

Immune cells and molecules are integral to a wider function of networks and are not merely defence tools. These normal physiological functions of the so-called immune cells and the so-called inflammatory markers should be excluded from the definition of inflammation. An evolutionary perspective suggests that the reliance on molecular markers alone to define inflammation is problematic. It is important to understand that immune cell migration works on the basis of gradients of signal molecules, and their elevated systemic levels may weaken chemotactic gradients, impairing immune cell migration rather than enhancing it. Furthermore, the processes considered harmful today are likely to have been adaptive in ancestral contexts; hence, the underlying ecological and lifestyle factors shape the immune dynamics. A complete rethinking of the concept of “low-grade chronic systemic inflammation” is required, as it is paradoxical to label a condition as inflammation when classical hallmarks of inflammation are impaired or down-regulated.

Loss of fur was a human-specific evolutionary change which brought about a number of changes in cutaneous immune challenges, and the system evolved accordingly. This consideration gives us a new outlook and leads to a novel alternative interpretation of the so-called chronic systemic inflammation, which is not inflammation at all.

Therefore, the word inflammation should only be used in relevant contexts and need not always be associated in the context of elevated levels of one or more markers. The testable predictions and realities match according to the evolutionary perspective. Hence, inflammation must be carefully redefined, recognising its underlying framework that integrates molecular, cellular, and even evolutionary insights.

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