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Review Article

A Shift in Classical Concepts Regarding Pathophysiology, Driven by a Realistic Perception of the Pathogenesis of Allergic Reactions

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Abstract

This review proposes assessing the animal organism, its state of life, health, and response to external factors from the perspective of ontological constructivism, attempting to analyze the best-known, and thus accessible, components of the biological life process. The evolution of responses is examined in a sequence of stages termed by the author "natural lavage with mucosal secretions," "pre-inflammation," and then aseptic inflammation and antigen-dependent inflammation. Emphasis is placed on the fact that the immune system is a unified structure that interacts with antigens of both infectious and non-infectious origins according to a single algorithm. This supports the pathophysiological concept of inflammation as a typical, universal response of the body to exposure to a phlogogen of any origin, thereby substantiating the assertion that allergy is a particular manifestation of inflammation as a syndrome. A critical assessment is given to the current understanding of allergy pathogenesis, which distorts the cause-and-effect relationships in the sequence of processes that form the disease picture. A proposal has been put forward to consider biochemical reactions occurring on mucous membranes and skin within the microbiome's environment as neutralizing the antigenic properties of external protein structures through enzymatic breakdown into low-molecular-weight products. These products, upon penetrating the internal environment, lose their ability to trigger an inflammatory response involving the immune system. The duality of inflammation, in which localized and generalized forms are combined, is considered as a morphologically justified manifestation of opposing protective and destructive effects on the microorganism.

Keywords

Ontological Constructivism, Phylogeny Inflammation, Co-occurrence of Allergy and Inflammation. Selective Fermentopathy, Inflammation Dualism

1. Introduction

Claiming reliability in the assessment of research results conducted at the applied level necessarily presupposes the use of the postulates of ontological naturalism in analytical work. At their foundation lies a holistic perception of all that exists — the surrounding reality in its full scope — along with systematization as a representation of the world as a community of interacting components. In nature, there are no isolated entities in any way disconnected from surrounding phenomena and objects, or

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generated independently of such processes. Everything is permeated by regularities that unite the surrounding world into a structured system.

It should be emphasized that medicine is a branch of the natural sciences, which justifies considering events of the surrounding reality as manifesting themselves to the same extent within this applied field of study.

Having declared as its topic a philosophical assessment of such a phenomenon as inflammation, it becomes necessary to compare the visibly observable manifestations of the body's response to external influences with the fundamental expressions of the essence of the surrounding nature.

The essence of environmental reality is inherently rational, as evidenced by evolutionary optimization characterized by universality, uniformity, and typicality of expression — by the manifestation of a single consequence across the widest variety of initiating causes — bringing to perfection the responsive reaction to localized damaging external influences. This is reflected in the defining formulation of inflammation as a pathophysiological process.

Universalism arises from the rationality of nature, shaped by the transformations of living organisms throughout the evolutionary process. In nature, there is nothing superfluous and nothing deficient. Rationalism elevates optimization to an absolute value. Any object or phenomenon of the surrounding reality has its own place and significance within the structure, interconnected by regularities into the wholeness of the surrounding world, thereby determining its precise position within an ontologized construction.

Every object and/or related phenomenon identified by a researcher should be perceived as an element of a composite architectonics, a composition fulfilling the role assigned to it by nature; its exclusion leads to chaotization and entropy. To designate something discovered in nature outside of a system, without its assigned place, is possible only within the narrow outlook of a researcher who does not require an assessment of surrounding reality in its complete state. To ascribe harmful properties to a studied phenomenon with one-sided characteristics is possible exclusively within the framework of subjective expression.

The currently established practice of evaluating research results in the overwhelming majority of cases follows a simplified, one-step approach.

As a clear confirmation of this prevailing interpretation, modern allergology defines the nature of allergy as a disorder, a deviation from the norm, a defect of immune system function, thereby designating specific IgE as a morphological object isolated and torn from the structure of responsive reactivity to the presence of an external agent with immunogenic properties. This contradicts the established essence of being and thus determines the inadequacy of the existing paradigm of allergology.

2. Stages of Formation of the Inflammatory Response in the Evolutionary Process

All normal and pathophysiological processes of a living organism exist in unity, proceeding in their specific manifestations one from another and forming an integral complex of reactive responses. This defines inflammation as part of active counteraction within a broader framework than that preserved in the modern, scholastically fixed canon.

For the attentive observer, it is not difficult to arrange well-known, physiologically grounded phenomena into a ranked sequence, demonstrating a direct dependence on increasing functional complexity as the number of arising tasks grows.

With full clarity, such a construction begins with a phenomenon that may be acceptably designated as the "natural lavage by mucosal secretion." It should be noted that nasal mucus is produced continuously, moving in a directed manner into the oropharyngeal cavity, where salivary gland secretion is likewise constant. The accumulated total volume is reflexively swallowed at intervals regulated by the autonomic nervous system. It must be acknowledged that a continuously operating secretory process is energetically highly demanding, which is characteristic of the functioning of the most primitively organized structures.

As for regulatory mechanisms, despite the undeniable participation of the autonomic nervous system, the constancy of secretion cannot be explained solely by reflexes inherent to neural activity. Do the goblet cells of the nasopharyngeal epithelium and the salivary glands perceive the constantly circulating airflow during respiration as a physiologically irritating environmental stimulus? The properties of mucosal secretion ensure adhesion of microorganisms — both those permanently residing in the parietal region of the nasopharynx and those entering with inhaled air. Ordinary logic provides grounds to assume that the strongly acidic environment of the stomach phylogenetically arose as a means of disinfecting microorganisms delivered together with the volume of mucosal mucus. The contrast with the alkaline environment of the duodenum complements what was initiated in the stomach. It is important to note that the enzymes of the stomach and duodenum evidently participate in the breakdown of the protein structures of microorganisms.

Of further interest is a phenomenon that may tentatively be designated as "pre-inflammation." Exposure of the mucous membranes of the upper respiratory tract to air cooled below 0 ℃ causes catarrhal phenomena — *lacrimatio, rhinorrhoea, hyperaemia, oedema* — and in the case of prolonged exposure manifests as *dolorōsus, ustio, pyrosis* — typical symptoms of an inflammatory reaction. Upon cessation of the physical factor (subzero air temperature), the inflammatory symptomatology resolves without any artificial therapeutic intervention. It should be emphasized that signs of alteration are not observed in this case, as they are morphologically absent.

The cutting of onion bulbs is accompanied by *rhinorrhoea*, *hyperaemia*, *oedema*, and with prolonged exposure by *dolorōsus, ustio, pyrosis* — typical symptoms of an inflammatory reaction. The cause lies in the caustic volatile chemical substances contained in the cells of this plant: 1-propenyl-L-cysteine sulfoxide (PRENCSO), a cysteine derivative, and the enzymes alliinase and LFS (lachrymatory-factor synthase). When the integrity of onion cells and their vacuoles is disrupted, PRENCSO is converted under the action of alliinase into 1-propenesulfenic acid, which in turn, with the help of LFS, is transformed into the volatile lachrymatory factor 1-sulfinylpropane. Upon contact with the mucous membrane of the eyes, it stimulates nociceptors, thereby causing *lacrimatio* [1, 2]. Cessation of exposure to such a chemical factor acting on nociceptors leads to normalization of the affected individual's condition without the use of therapeutic agents. In this case as well, signs of alteration are not observed, as they are morphologically absent.

The rapidity with which inflammatory symptoms manifest in the described cases indicates the neural, reflex nature of the response. It should be noted that the reactive response acquires a discrete character, in contrast to the continuously operating process of lavage by mucosal secretion. It is characterized by the construction of a universal mechanism involving ligand-affinity receptors of effector cells, which shifts the process into an energy-efficient mode. Evidently, there are insufficient grounds to recognize the described environmental factors as phlogogens; nevertheless, the reactive response to their impact coincides with the manifestations of classical inflammation.

Further, as an example requiring obligatory evaluation, one should consider a condition that quite evidently occupies an intermediate, borderline position, dividing — and thereby demarcating — normal and pathological physiology. Clinicians designate this condition as a disease, assigning to the nosological form rosacea (acne rosacea) the ICD-10 code L71. However, in its debut stage — defined as erythematous-telangiectatic, livid flushing erythema — one can observe identity with the phenomena of the preceding rank, namely "pre-inflammation." The same autonomic nervous system reflex activity is present, without signs of alteration, and with a ligand-dependent activation mechanism.

With a high degree of probability, hypersympathicotonia takes place; the search for its cause should be undertaken by a neurologist in consultation with infectious disease specialists and endocrinologists. Persistence of HIV, HSV, or CMV undoubtedly affects the autonomic nervous system; increased tone of the sympathetic component may also result from dysfunction of endocrine organs such as the thyroid gland, pancreas, or adrenal glands. Such assumptions may not be confirmed in a specific patient, which necessitates the search for and identification of a phlogogen of external or internal localization whose impact on the reactive structures of the macroorganism manifests through indirect or direct characteristics of inflammation.

Without understanding or elucidating the mechanism of what is occurring, the clinician does not contemplate the possibility of controlling the developing inflammatory process by eliminating the primary etiological triggering factors, thereby aggravating the patient's condition and allowing the formation of a papulopustular form with pronounced inflammatory symptoms.

One should also not forget such nosological forms as urticaria: L50.2 (caused by exposure to low or high temperature), L50.3 (dermatographic urticaria), L50.4 (vibratory urticaria), and L50.6 (contact urticaria). Evidently, by grouping these together with L50.0 (allergic urticaria), the authors of ICD-10 demonstrate a unified understanding of the inflammatory nature of these conditions.

Within this section it is also appropriate to include the nosological entity "pseudo allergy" (ICD-10 code T78.4 — allergy, unspecified). The entire diversity of causes of this type of inflammation is united by one characteristic: the immune system does not participate in forming the macroorganism's response to the impact of the phlogogen.

Next in the considered ranked order appears a group of conditions characterized by signs of alteration as a consequence of exposure to phlogogens of physical and/or chemical nature. Classical textbook examples — such as injury from electric current or from strong acids and alkalis causing damage to integumentary tissues — remain scholastic illustrations. Of particular interest is pneumoconiosis, with formation of a fibrous capsule around a phlogogen of physical nature lacking antigenic properties, thereby manifesting the result of the inflammatory reaction as an isolator between the phlogogen and the tissues of the macroorganism.

It is important to emphasize that the immune system does not participate in the complex of cellular and humoral manifestations of this type of inflammation. Despite the diversity of phlogogens — silicon dioxide, coal dust, asbestos, talc, kaolin, metals, cotton dust, sugar cane dust — the inflammatory reaction in pneumoconiosis is typical; its universalism consists in the formation of a fibrous capsule that localizes the phlogogen and thereby terminates its damaging effect on lung tissue. Notably, the proliferative component of the inflammatory process predominates in this example. At the focal, local level, its productivity as a protective factor is evident. With relatively low quantitative dust exposure, such a form of inflammatory process results in a beneficial state.

There is no doubt that alteration leading to disruption of the integrity of integumentary tissues under the influence of a phlogogen of physical or chemical nature creates the possibility of infection, thereby involving the immune system in the developing complex of inflammatory reactions. Since, within the same time interval, the processes of inflammation formation in response to a physical and/or chemical phlogogen are supplemented by a phlogogen of infectious nature possessing antigenic characteristics, these processes proceed simultaneously, blurring the boundary between aseptic inflammation without participation of the immune system and the re-

sponse to pathogen invasion with its inevitable immune involvement. Clinicians, however, tend to perceive such a combination as a single process. This entrenched misconception affects the objective assessment of the developing pathological condition and subsequently leads to incorrect and erroneous therapeutic recommendations.

All of the above-described reactive responses of the macroorganism cannot be divided into separate types, since the foundation of their manifestations lies in evolutionary transformation, becoming more complex with the emergence of more advanced forms of animal life. Nature has not abandoned any mechanism, preserving them in humans as representatives of the currently most developed biological organism, manifesting this accumulated evolutionary heritage in the clinical symptomatology of inflammation with immune participation.

The triviality of the dogma that the immune system reacts exclusively to biological structures bearing antigenic characteristics is mitigated by the fact that such interaction is possible only within the internal environment of the macroorganism. The relevance of this clarification is associated with a fairly widespread representation in publications whose authors report the detection of antibodies of various classes in the lumen of the intestine, the respiratory tract, or on the apical surface of epithelial cells. At the same time, experimental results confirming such findings are lacking. This paradox may be explained by the fact that processes occurring at the boundary between the external and internal environments — specifically, the penetration of substrates and their degradation products from the external environment into the internal milieu — are not presented in objective description, thereby allowing for creative exposition of personal viewpoints.

It should be noted that the immune system, with respect to antigenic structures, is equilibrated and balanced through mutual interactions. A deeper evaluation of these established relationships undoubtedly reveals the fundamental question of immunology: why, in the course of phylogenesis, did humans develop an immune system with such a complex structure, multicomponent instrumentation, and high degree of specificity to counteract a sequence of merely ten amino acids assembled into an epitope — structures that, in morphological assessment, may appear insignificant fragments of proteins? Evidently, antigenic structures possess such destructive potential that phylogenesis led to the formation of a distinct system — the immune system — whose essence lies in confronting what might otherwise seem morphologically trivial structures.

A reasonable answer may be sought in the quantitative diversity of epitope constructions, which renders comparable the precisely regulated totality of reactive responses and the complex mechanism of the immune system to the multitude of opposing antigenic elements. However, the truth may lie in another dimension.

Epitopes must be considered as ligands capable of forming a bond with a complementary part of a substrate molecule of the macroorganism. The consequence of such binding is a redistribution of the substrate's energy balance, which leads to tissue and organ destruction, functional obstruction of life-support systems, and ultimately to the disintegration of the macroorganism. If this assumption corresponds to reality, then the modern allergological practice of applying the "only correct, pathogenetically substantiated" allergen-specific immunotherapy (ASIT) — in which preventing allergen penetration into the internal environment is not set as a task — may be detrimental to the patient.

It should be noted that the entire spectrum of xenobiotics, comprising millions of compounds, can be divided into two distinct groups: those possessing antigenic properties and all others. Upon penetrating the internal environment, a xenobiotic must overcome the mucosal and cutaneous barriers, as well as histohematogenous barriers; it must then undergo enzymatic degradation — primarily in the liver — enabling breakdown products to be excreted or sequestered in tissues. The harmfulness of a non-antigenic xenobiotic is strictly dose-dependent, creating a distinct paradox that allows a wide range of such substances to be utilized as medicinal agents. One should recall Salvarsan (arsphenamine), developed by Paul Ehrlich; strychnine, the principal alkaloid of *Strychnos nux-vomica*; the glycosides of *Digitalis grandiflora* (gitoxin and digitoxin); and atropine, an alkaloid found in *Atropa belladonna*. The therapeutic properties of these substances are governed by their concentration within the organism's internal environment; exceeding this threshold leads to severe complications, including fatal outcomes.

Addressing the evolution of the immune system, it should be noted that authors of reviews evaluating developments across a million-year timescale often consider it sufficient to confine their analyses exclusively to forms of reactive response toward infectious agents. Yet there is no reason to doubt that nutrition and respiration, as obligatory elements of the existence of a living organism, inevitably entail contact with structures referred to in modern terminology as "allergens." Oncological and autoimmune processes are not phenomena limited to modern times. Such a truncated approach to interpreting events at the systemic level renders conclusions limited, impoverished, and distorting objective reality — clearly demonstrating sectoral thinking devoid of an understanding of ontological constructivism. By excluding non-infectious antigen-allergen structures from evaluative analysis, one loses comprehension of the unified functioning of the immune system as an integral mechanism in relation to the entire diversity of epitopes.

3. The Crisis of the Modern Paradigm of Allergology

3.1. Substitution of Cause-and-Effect Relationships in Modern Allergology

Modern allergology is in a theoretical crisis, the foundational thesis of which remains sIgE mediation. Thus, the cause

of allergy has been formulated. Within such an interpretation, sIgE occupies a central, primary, determining role, raising a philosophical question regarding causal relationshipsIt should be noted that the ideas about the essence of external and the sequence of manifestations of particular events.

It should be recalled that in the 1920s, *O. Prausnitz* and *H. Küstner* proposed the existence of a certain factor capable of transferring allergy from a diseased individual to a healthy one [3]. In the 1960s, K. Ishizaka isolated an immunoglobulin which, at the initiative of the WHO, received the unified designation IgE [4].

With full clarity, contemporary allergology may be recognized as "factor-based," with priority in shaping the concept of the nature of allergy belonging to *Otto Prausnitz* and *Heinz Küstner*.

The sequence of cause-and-effect relationships chosen by allergologists has served as the foundation for the formation of Allergology as an independent medical discipline, with principles distinct from those of General Immunology and specific to itself. It is quite plausible that this explains the conservatism in views on the pathogenesis of allergy that has persisted for more than a century.

Having defined sIgE as the cause, Factor-Based Allergology insists on recognizing it as a defect, a deviation from the norm, an error in the functioning of the immune system. In doing so, Allergology enters into dispute with Nature itself, accusing it of forming reactions to external influences that are allegedly intrinsically harmful to the macroorganism. Being absolutely confident in its correctness, this dispute does not remain within theoretical polemics: Factor-Based Allergology imposes its own solution upon Nature, reformatting and transforming the natural maturation of the humoral component of the immune response. As its instrumentarium, it resolutely advocates allergen-specific immunotherapy (ASIT), a form of targeted therapy using monoclonal antibodies against sIgE.

The concept of Factor-Based Allergology asserts and defines the moment of clinical manifestation of allergy symptoms as a consequence of the initiation of sIgE induction. The absence of sIgE in a patient's past history is used as an argument for allergological health. Such an assertion allows for the presence of an allergen within the internal environment without clinical manifestations.

3.2. The Importance of Processes Occurring at the Boundary of the External and Internal Environment

It should be noted that Factor-Based Allergology holds rather limited notions regarding the essence of the external and internal environments and the boundary between them. A considerable number of allergology specialists are convinced that a food bolus entering the esophagus is already within the internal environment, and that a portion of air penetrating the alveolar tree is likewise within the internal environment. However, the fundamental disciplines of medicine — anatomy and histology — refute such notions.

In reality, biochemical processes of degradation of high-molecular substrates into low-molecular products, occurring within the habitat of the microbiome on the apical surfaces of epithelial cells of mucous membranes and skin, constitute the barrier that an antigen must overcome to enter the internal environment. It should be emphasized that not the morphological structures of the integumentary tissues of the macroorganism — which would need to be destroyed as a necessary condition for penetration into the internal environment — but rather the complete proteolysis of protein structures into low-molecular peptides serves as the guarantee of allergological health.

It must be acknowledged that the space extending from the oropharynx to the rectal cavity, from the nasopharynx to the alveoli, all cavities of the urogenital organs, and the cranial sinuses constitute the external environment. This means that processes occurring on the mucous membranes of these organs and systems — including digestion and gas exchange — take place outside the internal environment of the macroorganism, rendering immune reactions in this location impossible. Such a representation allows the legitimate conclusion that human nutrition is external, similar to that of prokaryotes inhabiting the intestinal mucosa.

Nevertheless, the notion that swallowing a food bolus or inhaling deeply is sufficient for an allergen to interact with components of the immune system remains remarkably persistent. Another group of allergologists, who rightly believe that an allergen must overcome the barrier of mucous membranes and skin, consider the destruction or damage of epithelial integrity — even if only local — as a necessary condition for such penetration.

At the same time, the need to explain the preservation of nasopharyngeal epithelial integrity in respiratory allergy to molecular components of grass or tree pollen does not arise.

Thus, allergology ignores what occurs within the spatiotemporal interval between the contact of a biologically derived external substrate with the barrier structures of the macroorganism and the fact of its presence within the internal environment — i.e., in the intercellular space of the epithelial submucosal layer. Quite often, authors either do not consider it necessary to articulate their position or designate the highly complex set of processes unfolding at the boundary between the external and internal environments by the single term "absorption."

It should be noted that absorption implies the movement of a substance, in any aggregate state, from an area of higher atmospheric pressure to an area where atmospheric pressure is lower relative to the substance's location. Such conditions are not created by nature in the human organism (an infant, during breastfeeding, creates negative pressure in the oral cavity, thereby ensuring suction of milk).

For modern allergology specialists, it has become justified to regard their notion of the constant presence of an allergen

within the internal environment as valid, which distorts objective reality by introducing the concept of a "beneficial allergen," disregarding the fact that this phrase constitutes an oxymoron. The desire to preserve the legitimacy and authority of the thesis regarding the primary role of sIgE in the formation of the allergic reaction has made it necessary to introduce into clinical practice the theory of "acquired immune tolerance," intended to link the manifestation of clinical allergy symptoms exclusively with the induction of sIgE.

Allergologists attribute to the macroorganism, among other properties, the capacity for non-reactivity to allergens, employing a purely declarative argumentation that reduces to describing a state of constant contact between the immune system and allergens in which no allergic reaction occurs.

It must be acknowledged that this theory represents an adaptation [5] of conclusions drawn by *R. Medawar* and colleagues [6] in experiments on the induction of tolerance in a recipient — specifically, a mouse embryo — to tissues from an adult donor mouse. Such theoretical adaptation contains a substantial flaw, since allergological tolerance, according to allergologists, arises in the postnatal period during the lifetime of the born child, whose immune system has already had time to form, and does so without the use of massive immunosuppression, which is the basis of modern transplantology. This contrasts with the protocol of R. Medawar's experiment, in which immunization with adult donor tissue inoculum was performed prenatally in a mouse embryo recipient; after successful birth, a transplanted skin graft from the adult donor was not rejected for a prolonged period.

3.3. Place of Infectious Allergens in the Classification

The absence of objective substantiation at the fundamental level is complemented by applied-level narratives. Modern allergology does not deny the induction of sIgE to antigens of infectious nature. Thus, the authors of the publication "Types of Exogenous Allergens" [7] distinguish a section titled "Infectious Allergens," which includes:

1) bacteria of tuberculosis, brucellosis, tularemia, toxoplasmosis, leprosy; the bacterium of syphilis; streptococci, staphylococci, pneumococci; enterobacteria, etc.;
2) fungi: dermatophytes; the genus *Candida* (*C. albicans, C. krusei, C. tropicalis, C. pseudotropicalis*); cryptococci, histoplasma, blastomycetes, coccidioides; mold fungi;
3) viruses: herpes, influenza, parainfluenza, hepatitis B.

Furthermore, staphylococcal enterotoxin A, classified as allergen o72, and enterotoxin B (o73), are included in a rather heterogeneous group designated by the letter "o" [8, 9].

In the conceptual document *Molecular Allergology User's Guide*, published by the European Academy of Allergy and Clinical Immunology (2016), section B08 "Role of Microbial Allergens in Atopic Dermatitis" states that 14 immunogenic allergens produced by three species of *Malassezia* — *M. furfur, M. sympodialis*, and *M. globosa* — have currently been characterized. Thirteen allergens, all produced by *M. furfur* or *M. sympodialis*, are listed in the official allergen nomenclature of the International Union of Immunological Societies (IUIS; http://www.allergen.org).

In section B07 "Allergic Bronchopulmonary Aspergillosis (ABPA)," *Reto Crameri* writes that *Aspergillus fumigatus* (*A. fumigatus*) is a ubiquitous mold, constantly present both indoors and outdoors, acting simultaneously as a primary and opportunistic microorganism associated with many pathological conditions and as a major source of allergens. It contains 23 cloned allergens officially approved by the WHO/IUIS Allergen Nomenclature Sub-Committee, and more than 80 putative IgE-binding proteins have been described. *A. fumigatus* represents the most complex allergen source described to date.

Departing slightly from the main topic, it should be noted that a patient's condition associated with exposure to allergens of *Aspergillus fumigatus*, as well as *Dermatophagoides pteronyssinus* (d1) and *Dermatophagoides farinae* (d2), is primarily a sanitary and hygienic problem related to the patient's living environment. The use of detergents and disinfectants in areas of high humidity, along with frequent and regular laundering of bedding, is sufficient to prevent the aforementioned problems.

From the standpoint of General Immunology, in which the immune system is evaluated as a single, unified structure opposing antigens of any nature and forming a response according to a common algorithm, a contradiction arises in the position of modern allergology. By employing the concept of "acquired immune tolerance," modern allergology attributes dual characteristics to the immune system. In interaction with "classical" allergens, the immune system allegedly acquires tolerance. At the same time, there are no grounds for discussing the formation of tolerance to antigens of infectious origin. This artificially created paradox forces the clinician to decide at their discretion whether a given disease has an allergological basis or represents a classical infectious process. This choice determines a diametrically opposite therapeutic strategy — either to prescribe immune-transforming ASIT with accompanying immunosuppression, or to implement specific stimulation of the immune system combined with antimicrobial therapy.

3.4. Genetics Refutes

Accepting ontological constructivism as the normative framework for evaluating the phenomenon under study, it is essential to emphasize the genetic mechanism underlying the diversity of antigen-recognizing fragments of all known antibody isotypes. This phenomenon is associated with numerous random rearrangements of gene groups, sequential deletions, processing, and splicing at both the linear DNA stage and post-transcriptionally. The first to provide convincing evidence that rearrangement of immunoglobulin genes indeed

occurs in the genome of B lymphocytes were *S. Tonegawa* and *N. Hozumi* [10].

It is now generally accepted that immunoglobulin synthesis is encoded by specific genetic segments that are joined together in the genome during lymphocyte development to form a functional gene. This is strikingly manifested in the production of high-affinity specific antibodies. The process of redistribution of gene segments within genomic DNA is called immunoglobulin gene rearrangement. As later established, gene segment rearrangement is characteristic not only of the formation of functional genes encoding antibodies, but also of genes encoding the T-cell receptor.

Of particular relevance in this context are several quotations from the monograph *Lewin's Genes* [11]:

"The mechanisms underlying the formation of immunoglobulins of all isotypes, without exception, are embedded in the process of V(D)J recombination."

"V(D)J recombination proceeds to completion only in T and B cells under the influence of differentiation signals from the external environment."

"The molecular mechanism of V(D)J recombination is identical for all seven immunoglobulin or T-cell receptor loci."

In the content of these quotations, attention should be drawn to the fact that the trigger for the formation of a specific antibody is a differentiation signal originating from the external environment. This means that the phlogogen, with its inherent specific antigenic characteristics, determines the nature of the immune response, taking into account conformational, biochemical, and electrostatic properties, with the formation of high-affinity antibodies as the most effective component of the inflammatory reaction involving the immune system.

An equally important observation is that the mechanism of formation of the molecular structure of immunoglobulins is identical for all isotypes.

As a consequence, randomness in the induction of sIgE — on which modern allergology insists — is not implied. This process leaves no room for assumptions of error or defect in immune system function in the origin of sIgE. Accordingly, the hygiene hypothesis acquires a speculative character.

Noteworthy is the content of the "hygiene hypothesis," presented in 1989 by *D. Strachan*, whose principal thesis describes a collision in which a reduction in microbial load on the immune system leads to hypersensitive reactions, namely allergy. It should be emphasized that the author disregards the basic principles of normal physiology, wherein functional inactivity leads to atrophy of the effector tissue or organ. There is nothing objectionable in publicly expressing one's point of view, even if initially erroneous. The problem lies in the fact that the allergological community reproduces and thereby propagates what may be considered a flawed theory.

Genetic predisposition to allergy is likewise used as an explanatory element in the theory of "factorial" allergology. The principal argument consists of inherited allergic manifestations. By this logic, all viral respiratory diseases should be regarded as genetically predetermined, since relatives along both vertical and horizontal family lines repeatedly experience such infectious diseases.

In maintaining the primacy of sIgE in the formation of the allergic reaction, modern allergology is compelled to generate theories in an attempt to substantiate this assertion.

4. Transformations in Concepts of the Inflammatory Response

4.1. The Significance of Inflammation for the Macroorganism at the Local Level

A significant misconception arising from an erroneous understanding of the causal role of sIgE concerns the place of inflammation within the allergic reaction. The bias consists in viewing allergy and inflammation as distinct, independent states that nonetheless manifest within a single pathogenetic process. In this framework, inflammation, from the standpoint of modern allergology, occupies a subordinate position, arising as a consequence of the developed allergic reaction and acting as a secondary, accompanying phenomenon that aggravates and burdens the patient's condition from the onset of clinical manifestations. This interpretation sequentially and inevitably influences therapeutic tactics, thereby producing a deliberate yet genuinely detrimental impact on the patient's organism.

In modern medicine, the definition of inflammation as an adaptive reaction to the impact of a phlogogen has become fairly entrenched. However, this conclusion cannot be justified, since adaptation implies adjustment, compliance, a bringing of the organism's state into accordance with the initially harmful influence of the phlogogen. Adaptation implies passivity in the interaction with the influencing factor, which nature does not assume for inflammation. On the contrary, active processes are triggered to counteract the agent, leading to *localisatio*, *destructio*, and *eliminare* of the phlogogen. These shifts can be characterized as a systemic state that includes the activity of the homeostatic support systems.

To limit the area affected by the phlogogen, an exudative barrier is formed, achieved through changes in the water-salt balance necessary to create an electrochemical gradient, the ion concentration of which ensures exudation — the movement of water as a solvent for electrolytes — while vascular tone and permeability accompany the required effect. These changes involve the renin-angiotensin-aldosterone system in combination with proteins of the kallikrein-kinin system.

Local micro thrombosis of the vascular network, which prevents the diffuse spread of the phlogogen's effects, is ensured by the coagulation system.

The cytokine network, including chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors, activates effector cells and determines their taxis toward the site

of inflammation.

The effectiveness of the proliferative phase of inflammation is associated with fibroblast activity, ensuring the synthesis of collagen and elastin to repair lost tissue.

The influence of the autonomic nervous system undoubtedly defines the integrative coordination of all participating systems.

4.2. Biochemistry of Processes at the Border

Regarding the pathophysiological postulate of the necessity of primary alteration upon phlogogen exposure, allergy is a vivid example where the penetration of peptides retaining immunogenic properties into the internal environment occurs without damage to the mucosa or skin. Neither the mucosa nor the skin is hermetic; they are permeable to biochemical products, including aqueous solutions of weak electrolytes, such as proteins, which move simultaneously in both directions.

The electrochemical gradient in the "solute-solvent" system is realized through the dualism of diffusion and osmosis. The degree of dissociation, directly dependent on the pH of the medium, determines the rate of weak electrolyte movement under the influence of the dualism of the electromagnetic field, where charges of the same polarity repel and those of opposite polarity attract. The combination of the electromagnetic fields of tight-junction proteins with the electromagnetic fields of allergen proteins determines the ability to overcome the paracellular pathway into the organism's internal environment.

Proteins, as phlogogens designated as allergens, are amphoteric electrolytes in biochemistry. In the formation of tertiary structure, hydrophobic regions are buried inside the molecule, while hydrophilic groups orient toward the surface, facilitating interaction of the protein molecule with water molecules, forming a hydration shell created by the electrostatic attraction of water dipoles to the charged protein particle. There is a close relationship between protein charge and hydration: the more polar amino acids in a protein, the more water molecules are bound, reflecting the protein's solubility in water.

In solution, the protein behaves as a colloidal solution with properties of weak electrolytes. The rate of absorption of protein structures into the internal environment directly depends on the degree of dissociation. This is clearly demonstrated by the kinetics of chemical compounds incapable of dissociation in aqueous solutions (non-electrolytes); their molecules are uncharged and freely pass through the mucosal membrane (dichloroethane, carbon tetrachloride, etc.). Conversely, strong acids and bases (sulfuric, hydrochloric, nitric acids, caustic soda, potassium hydroxide) are fully dissociated in any solution, making them impermeable through mucosal barriers. For weak acids and weak bases, the pKa value is critical, determining which fraction of the dissolved substance will be ionized or non-ionized at a given pH. For weak acids, acidic conditions promote conversion to the non-ionized form; for weak bases, low pH values (high proton concentration) promote conversion to the ionized form. The alkaloid strychnine is almost fully ionized in the acidic environment of the stomach and therefore does not cause intoxication when taken orally, and only upon entering the alkaline environment of the duodenum, where the degree of dissociation approaches the isoelectric point, does it pass through the mucosa freely.

The changing pH values at the spatial location of a protein solution at the moment of exposure lead to permanent alterations in the degree of dissociation of protein molecules. The net charge of carboxyl and amino groups continuously shifts from positive to negative and vice versa, passing through the isoelectric state at a specific pH value of the medium. In this state, the net charge of the protein equals zero. The zero charge corresponds to minimal viscosity and maximal resorption through mucosal barriers, which serve as the membrane interface between the external and internal milieus. The pH value is the determining factor for each protein's isoelectric point. For example, the isoelectric states of all twelve isoforms of Bet v 1 fall within the pH range of 4.9-5.9. This implies that by shifting the pH of the nasopharyngeal mucosa toward alkalinity in a patient sensitized to the primary birch pollen component, one could potentially reduce allergen clearance into the internal milieu, thereby preventing seasonal exacerbation of the disease.

Since pH continuously fluctuates, proteins never reside in an isoelectric state for any minimal amount of time. They remain ionized, and their degree of dissociation, expressed by the pKa value, constantly oscillates in response to environmental pH variations. The higher the valency of charges on ionized protein molecules, the higher the viscosity, which reduces their penetrating effect. It must be appreciated that the more complex the three-dimensional structure of a protein — comprising α-helices, β-sheets, domain loops, and branched side chains, each carrying its electrostatic charge — the more external factors must converge at the protein's location at a given moment. This decreases the likelihood of the protein attaining an isoelectric state and, consequently, limits its resorption at that time; however, a moment later, the situation may change, either increasing or further reducing its chances of penetration into the internal milieu.

In addition to environmental pH, exposure of protein molecules to micelles of detergents and other chemical structures with denaturing properties — such as urea, alcohols, and phenols, which are metabolic products of microorganisms — is also significant. The pulmonary surfactant, a classical surfactant lining the alveoli (i.e., at the air-liquid interface), prevents alveolar wall adhesion during respiration by reducing the surface tension of the tissue fluid film covering the alveolar epithelium. Surfactant acts as a classical detergent, participating in the denaturation of proteins that enter the alveoli with the airflow. At present, several hundred detergents are known, divided into two primary classes: ionic and nonionic, depending on the presence or absence of charged groups in the hydrophilic region of their molecules. Protein denaturation increases the degree of dissociation, thereby reducing protein

resorption, but by disrupting the tertiary structure, it renders the protein accessible to proteolytic enzymatic action.

It remains to be mentioned that the paracellular route of penetration into the internal environment passes through channels formed by tight junction proteins, such as claudins, occludin, adhesion proteins, and tricellulin. These proteins, in turn, possess their own electrostatic charge, which inevitably interacts with the electrostatic charge of allergen proteins. This creates a kind of "magnetic lock," which functions depending on the degree of dissociation of protein structures. Taking into account the transcellular transit of metabolites, it stands to reason that paracellular channels provide the primary traffic for weak electrolytes.

The conclusion of the above is that the barrier function is performed not by the morphological structures of the mucous membranes and skin — as the established viewpoint declares — but by the biochemistry of the degradation process, which breaks down high-molecular substrates into low-molecular products, including peptide constructs. During this process, the antigenic properties of allergens are lost.

When evaluating the processes occurring on the mucous membranes and skin, one must take into account the immense diversity (in comparable quantitative terms) of microorganisms. These microbes require and obtain chemical compounds from the external environment, initially in the form of high-molecular substrates. These substrates undergo cleavage on the surfaces of the mucosa and skin, facilitated by exoenzymes produced by the microorganisms that constitute the architectonics of the microbiome. Without accounting for the vital activity of the microbiome — which ensures both microbial anabolism and catabolism — any assessment of events on the mucous membranes and skin becomes a highly simplified scheme that fails to correspond to objective reality [12].

4.3. The Place of IgE in the Structure of the Immune Response

Having rejected the "maximum status" of IgE in the pathogenesis of allergy, we should return to a realistic definition of its place among other humoral factors of the immune system. There is no doubt that its position is ordinary among other immunoglobulins, and its functionality is subject to revision and reassessment. A researcher undertaking this task should note that the penetration of peptide structures into the internal environment occurs without a stage of primary alteration — i.e., without damage to the epithelial cells of the mucosa or skin. This implies the absence of cytokines such as alarmins, which provide chemotaxis for the cellular components of the immune reaction and thereby facilitate the formation of local inflammation.

The analysis should also include a list of immunocompetent cells expressing FcεRI. In addition to the traditionally mentioned mast cells and basophils, in humans, FcεRI is present on monocytes, macrophages, and eosinophils [13-15]; on dendritic cells — specifically a subpopulation known as Langerhans cells [16]. Receptor expression has also been demonstrated on smooth muscle fibers [17], epithelial cells [18], and platelets [19].

Notably, the expression of the FcεRI receptor on fibroblasts is not a universally accepted or standard characteristic of these cells. Although some studies have reported FcεRI expression on fibroblasts, particularly in pathological conditions such as fibrosis, this phenomenon is rare and is not a primary function of fibroblasts.

It should be noted that the aforementioned cells are effector participants in inflammation. By activating these cells, the IgE-FcεRI complex compensates for, replenishes, or replaces the functionality of the absent alarmins when an allergen penetrates the internal environment without disrupting the integrity of epithelial cells, thus participating in the formation of the acute phase of inflammation.

Furthermore, we must not overlook the fact that the expression of the FcεRI receptor by a series of effector cells and the proliferation of B-lymphocytes into plasma cells are described as separate, independent processes, separated both in time and location. This should testify to a possible future interaction between IgE and FcεRI. According to the concept of modern allergology, one must believe that effector cells are prepared in advance, remaining in a state of constant expectation for contact with a randomly occurring IgE molecule — one that is initially "defective" for the macro-organism.

5. Philosophical Assessment of the Inflammatory Response

5.1. The Universe is Dualistic

In response to the degree of destructive impact of an external or internal factor, the inflammatory reaction permits the use of only that functionality which, without excess, is capable of restoring the homeostatic state. A strict sequence in the choice of tools obviously does not exist. However, it is impossible not to notice the increasing constructivism in the sequence of events — from reflexes ensuring constant natural lavage of the mucosa by mucosal secretion, to strictly specific reactions of the immune system. In this process, the inflammatory reaction of the immune response absorbs all phylogenetically accumulated adaptations.

In determining the significance of inflammation among protective reactions, it should be noted that inflammation is essentially a syndrome — i.e., a set of similar symptoms initiated by a very diverse list of causes. The cardinal symptoms of inflammation — *rubor*, *tumor*, *calor*, *dolor*, and *functio laesa* — collectively and necessarily manifest as a result of a phlogogen's influence, regardless of its nature. Such a remark is extremely important in the classification of a condition like allergy.

Defining allergy as a specific case of inflammation requires

an admission of the inadequacy of the term "allergic disease." This fact decisively shatters the entire paradigm of modern allergology and shifts the cause-and-effect relationships of allergy into the format of objective reality. An unexpected yet inevitable conclusion is the need to identify those diseases whose pathogenesis allows for the preservation of the antigenic characteristics of protein structures penetrating the internal environment of the macro-organism. This will certainly be reflected in future editions of the International Classification of Diseases (ICD).

This task is so vast that it will require a fundamental shift in the clinical thinking of specialists, whose competencies should be defined by such integrated disciplines as:

Clinical Microbiology, addressing the multifaceted and most accessible interconnections within the human microbiome.

Clinical Biochemistry of the enzymatic and fermentation processes occurring on the mucous membranes and skin.

Clinical Pathophysiology of inflammation.

Clearly, these disciplines must still be filled with methodological substance and introduced as mandatory subjects within medical educational curricula.

Clearly, these disciplines are yet to be filled with methodological content and introduced as additional subjects in the curricula of educational institutions.

Returning to the philosophical evaluation of phenomena at the ontological level, one should highlight, as a fundamental concept, that physically determined entities exist in a state of equilibrium. Such an equilibrium is possible through the balancing of opposites — a state in which two principles exist inseparably, constituting the unity of any aspect of being. The universe is dualistic; for a natural scientist, regardless of the field of effort, this must be axiomatic.

The dualism of "presence-absence," or "yes-no," should be considered the fundamental and primary construct, which incorporates all existing dualistic structures as derivatives. Spanning everything permeated by human consciousness, this dualism is characteristic of all spheres. In the material world, it is "entropy-extropy." In biological life, the defining pairs are "life-death" and "masculine-feminine principles." In sociology, it is "power-money (material resources)," "production-consumption," and "religious faith-atheism." Universal principles of existence include "good-evil," "truth-falsehood," and "good-bad." When evaluating the human organism from a medico-biological perspective, the states of "health-disease" and "homeostasis-imbalance" are subject to study; at the level of systems and organs, these are "synthesis-cleavage," "constriction-dilation," "osmosis-diffusion," and "electro-magnetism."

At the planning stage of research work, a natural scientist must identify the dualistic pair of the subject of study. This initially ensures the objectivity of the evaluation, leading to effective recommendations as a result of the work performed. Neglecting such requirements will inevitably and predictably lead to a distorted result.

5.2. Inflammation Dualism

A condition such as inflammation is also subject to evaluation from the perspective of dualism. Modern pathophysiology confirms the dualistic nature of inflammation, explaining it by the combination of protective and destructive properties. However, a deeper analysis reveals unassessed characteristics. It should be noted that the structures of each dualism vary. The dualism of "light-darkness," "synthesis-cleavage," and "spasm-relaxation" is determined by cyclicity — the alternation of one component with its opposite. The dualism of "obverse-reverse" and "electromagnetism" exists in a simultaneous state. "Diffusion-osmosis" represents a dualism of linear movements in opposite directions.

The dualism of inflammation is composed of the processes of *localisatio*, *destructio*, and *eliminare* of the phlogogen, which defines the protective orientation of inflammatory functionality. It must be understood that the multi-level, interpenetrating processes of forming a multi-component barrier against a phlogogen are effective locally, at the site of the phlogogen's impact. When natural or artificially organized measures lead to the cessation of the phlogogen's influence, inflammation, having fulfilled its purpose, exhausts itself.

It is fundamentally important to consider that the mechanisms forming pathophysiological processes at the local level remain unchanged during the transition of inflammation into a generalized form caused by the dissemination of a phlogogen, regardless of its nature. Thus, the opposite of the protective competencies of inflammation manifests itself, shifting the response into a state destructive to the macro-organism.

One does not need foresight — mere common attention is sufficient to identify the interconnection between all morphological factors ensuring containment and the formation of a barrier around the phlogogen's impact zone during local inflammation, and the pathological, detrimental states that arise during the development of a generalized form.

Thus, the cytokine system, acting as a trigger for local inflammation, determines the taxis vector of competent morphological structures to the site of phlogogen impact; during generalization, this manifests hypertrophically as a cytokine storm.

An active shift in electrolyte balance, resulting from the energy-intensive antiport of ions by endothelial cells, creates a concentration gradient in the intercellular space due to the hydrolysis of ATP by the sodium-potassium ATPase. This leads to the escape of the liquid part of the blood from the vascular bed, forming an exudative barrier that isolates the location of the phlogogen's impact. During the generalization of the process, the diffuse redistribution of electrolytes in favor of inflammation following phlogogen dissemination leads to the sequestration of a significant volume of the liquid component of circulating blood outside the vascular bed within a short period.

The involvement of the smooth muscle layer of the bron-

chial wall, combined with parasympathomimetic and anticholinesterase activity during the resulting mucosal edema along the bronchial tree, causes sporadic bronchospasm; sustained generalization manifests as bronchiectatic disease or chronic obstructive pulmonary disease (COPD).

Massive exudation is possible into the pleural and pericardial cavities. A neurotropic phlogogen, having overcome the blood-brain barrier, causes cerebral edema. The resulting hypovolemia leads to a decrease in the efficiency of perfusion in all tissues and is the primary cause of shock. The shift in electrolyte balance, along with the reduction in the volume and velocity of blood flow, leads to acute renal failure.

The implementation of the barrier function is associated with a series of events unfolding within the vascular bed in the peripheral zone of the local inflammatory focus. Under the influence of specific cytokines, blood cells — erythrocytes, leukocytes, platelets — and the vascular endothelium express adhesion molecules (selectins, integrins, and the immunoglobulin superfamily). Through the "ligand-effector cell receptor" interaction mechanism, they form cellular aggregations within the vascular lumen, thereby altering blood flow rheology.

After a brief period of vasoconstriction, vasodilation occurs, initially induced by nitric oxide (NO). NO is produced by endothelial NO synthase in response to the stimulation of the endothelium by inflammatory cytokines and bradykinin, which simultaneously increases vascular permeability and thus participates in the development of edema. The trans endothelial migration of white blood cells is facilitated, in particular, by E-selectin and cytokine-induced β2-integrins. A "leukocyte wall" is formed within the inflammatory focus, characterized by a sequential transition from neutrophilic granulocytes to monocytes/macrophages. Against the background of slowed blood flow progressing toward venous stasis, blood coagulation factors are activated, leading to micro thrombosis. This process is intended to maximize the containment of the affecting factor and the resulting decomposition products within the inflammatory focus.

Micro thrombosis [20] in its generalized form — as a consequence of an uncontrolled and competently unmanaged state — affects parenchymal organs, causing infarction of the liver, lungs, kidneys, spleen, and myocardium. A potential clinical oversight during the developing pathological process of Virchow's triad may allow for thrombosis of small branches of the pulmonary arteries or massive pulmonary embolism (PE).

The prevalence of coagulation over fibrinolysis during the inflammatory reaction, especially manifest during generalization, quantitatively depletes the already limited platelet pool. This results in thrombocytopenic petechial rash, clinically observed in both infectious pathologies and allergies. The formation of numerous microthrombi combined with hemorrhages, characteristic of disseminated intravascular coagulation (DIC syndrome), leads to multiple organ failure and coagulation shock.

During the proliferation stage, following neutrophils, monocytes, and macrophages, fibroblasts migrate into the inflammatory focus, stimulated by chemoattractants such as fibroblast growth factors secreted by macrophages. By interacting with fibrin and collagen fibers, fibroblasts form a granulomatous wall along the periphery of the focus, thereby enhancing the isolation of the inflammatory site from unaffected tissues. In the event of generalization, clinical manifestations correspond to the duration of massive phlogogen exposure; in disease classifications, these are grouped into a distinct category — granulomatous diseases.

A distinction is made between infectious granulomas (seen in typhus, typhoid fever, rheumatism, rabies, viral encephalitis, tularemia, brucellosis, tuberculosis, syphilis, and leprosy) and non-infectious granulomas. The latter are encountered in pneumoconiosis, drug-induced reactions (granulomatous hepatitis), and around foreign bodies. It is an established view that both the atherosclerotic plaque [21] and the gouty tophus represent granulomas, were cholesterol and uric acid crystals, respectively, act as the phlogogen during the proliferative stage of inflammation. Wegener's granulomatosis is also included in the list of granulomatous diseases.

Far from having exhausted the various forms of generalized inflammation as a continuation arising from the local process, one must state the primary regularity: the unity of the mechanism triggered by inflammation at the local level scales itself during the generalization of the process, in which clinical manifestations are commensurate with the massiveness and duration of the phlogogen's exposure.

It is reasonable to suggest that acute local inflammation may be regarded as a branch of normal physiology, whereas the generalized form is evaluated through the lens of pathological physiology.

Furthermore, attention should be paid to the specific nature of the dualism of inflammation, which allows for the isolation and independence of local inflammatory forms (e.g., acute rhinitis). The intended outcome of such a form is the realization of a protective function with a favorable resolution for the patient, without transformation into a destructive generalization.

Such isolation is also inherent in certain generalized forms (e.g., anaphylactic shock) that are not preceded by a local stage. The transition from a local to a generalized form, observed in a sufficient number of cases, depends on a set of external factors (specifically, the virulence of the phlogogen in infectious cases or previously established immune tension). This dependency creates the possibility of managing the unfolding inflammatory process through a series of medical interventions.

Manageability of the inflammatory process implies the identification of the phlogogen followed by measures to terminate its influence as a primary and mandatory element of clinical practice. This is followed by the organization of clinical, laboratory, and instrumental studies with maximum informativeness, enabling the monitoring of the localization level and the timely detection of a trend toward generalization.

It remains indisputable that the decision to apply therapeutic agents and the extent of their use rests solely with the clinician.

At the same time, one should trust the completeness of nature's countermeasures against the phlogogen — expressed in *localisatio*, *destructio*, and *eliminare* — which makes it highly probable that a strict recommendation of bed rest and maximal sleep may suffice. Timely detected deviations, primarily in laboratory parameters and homeostatic indices, should be regarded as warranting pharmacological intervention commensurate with the clinical presentation.

6. Conclusion

In conclusion, allergy must be recognized as a specific case of the inflammatory reaction. This realization shifts the contemporary understanding of both the pathogenesis and the therapeutic approach to this pathological state. The impending reform in allergology is destined to reorder the sequence of cause-and-effect interactions as an element of ontological representation, thereby reflecting objective reality.

7. Discussions

It is to be hoped that ASIT (Allergen-Specific Immunotherapy) and targeted therapy in allergology will eventually take their place alongside such treatments as bloodletting — pathogenetically justified several centuries ago — or gastric resection for peptic ulcer disease, which was considered pathogenetically sound only a few decades ago.

Abbreviations

IgE	Immunoglobulin E
ICD	International Statistical Classification of Diseases and Related Health Problems
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
CMV	Cytomegalovirus
DNA	Deoxyribonucleic Acid
V(D)J	Variable, Diversity, Joining

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Conflicts of Interest

The author declares no conflicts of interest.

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