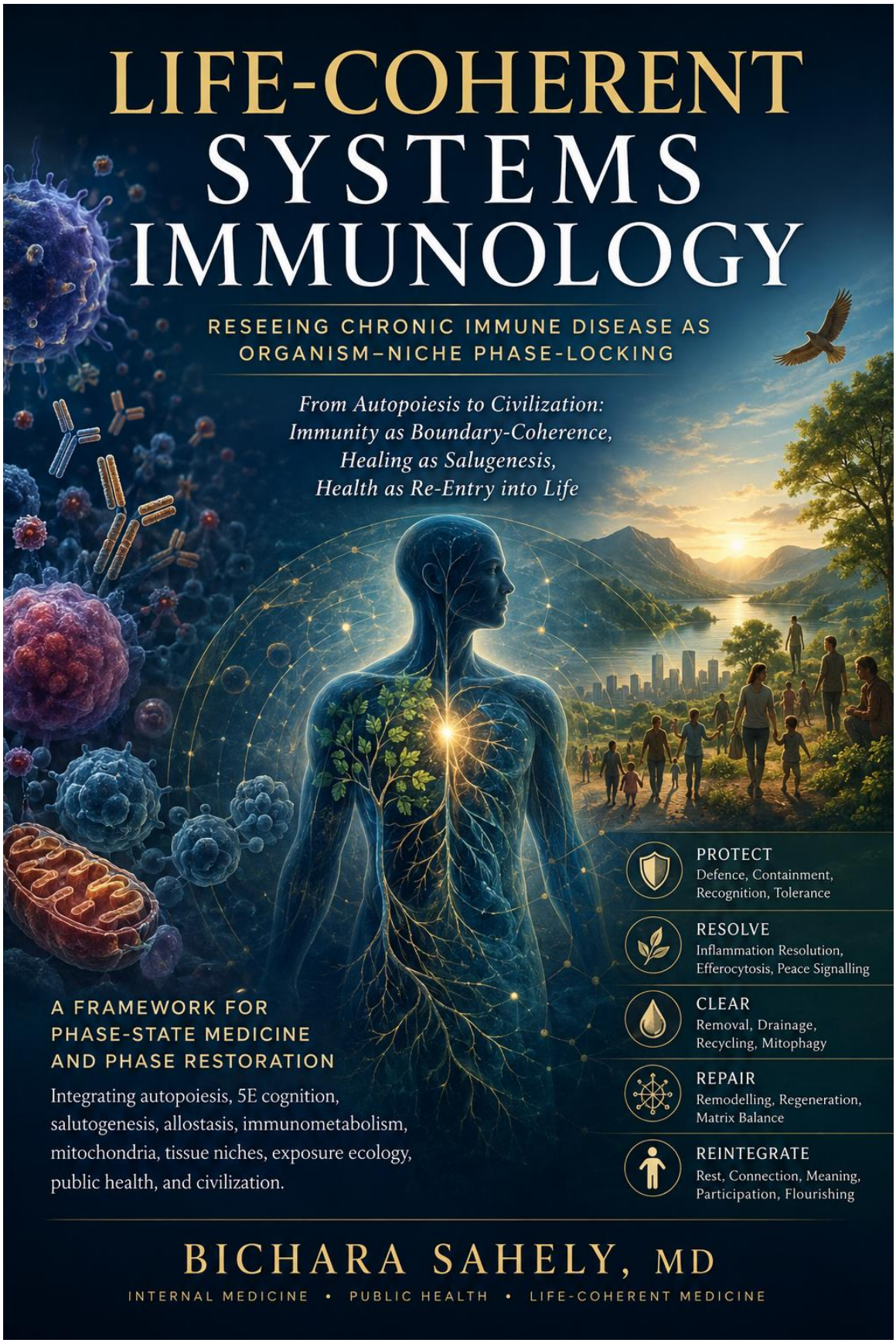
LIFE-COHERENT
SYSTEMS
IMMUNOLOGY
RESEEING CHRONIC IMMUNE DISEASE AS ORGANISM–NICHE PHASE-LOCKING
From Autopoiesis to Civilization:
Immunity as Boundary-Coherence,
Healing as Salugenesis,
Health as Re-Entry into Life
PROTECT
Defence, Containment, Recognition, Tolerance
RESOLVE
Inflammation Resolution, Efferocytosis, Peace Signalling
CLEAR
Removal, Drainage, Recycling, Mitophagy
REPAIR
Remodelling, Regeneration, Matrix Balance
REINTEGRATE
Rest, Connection, Meaning, Participation, Flourishing
A FRAMEWORK FOR PHASE-STATE MEDICINE AND PHASE RESTORATION
Integrating autopoiesis, 5E cognition, salutogenesis, allostasis, immunometabolism, mitochondria, tissue niches, exposure ecology, public health, and civilization.
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INTERNAL MEDICINE • PUBLIC HEALTH • LIFE-COHERENT MEDICINE

Life-Coherent Systems Immunology

Reseeing Chronic Immune Disease as Organism–Niche Phase-Locking

From Autopoiesis to Civilization: Immunity as Boundary-Coherence, Healing as Salugenesis, Health as Re-Entry into Life

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Internal Medicine · Public Health · Life-Coherent Medicine

Academic synthesis / theoretical framework paper
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Abstract

Immune-mediated disease is commonly described through observer-made categories such as autoimmunity, autoinflammation, allergy, infection, immunodeficiency, fibrosis, chronic inflammation, and post-infectious illness. These distinctions are clinically necessary, yet they do not fully describe what the living organism is doing. This paper proposes a life-coherent systems immunology in which immunity is reframed not primarily as a war against non-self, but as the organism's living boundary-coherence process: an embodied, embedded, enactive, extended, and evaluative way of conserving identity while remaining open to a changing world.

The central claim is that many chronic immune-mediated diseases can be understood as maladaptive organism–niche phase-locks. In health, the organism moves through adaptive immune-metabolic phases: surveillance, boundary sensing, danger detection, defence, containment, resolution, clearance, repair, memory, and re-entry into ordinary health-cycle participation. In chronic disease, one or more of these phases becomes persistent, recurrent, or self-sustaining. Defence does not resolve, clearance does not complete, repair does not reintegrate, memory does not update, or conservation does not release. Disease becomes unfinished living: unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration.

The framework integrates autopoiesis, organism–niche unity, 5E cognition, salutogenesis, salugenesis, allostasis, immune resilience, immunometabolism, mitochondrial biology, trained immunity, virome and mobile genetic elements, tissue-niche regulation, resolution biology, clearance systems, exposure ecology, public health, and civilizational coherence. Molecular sensors, inflammasomes, cGAS–STING, complement, transcriptional regulons, metabolic intermediates, mitochondrial danger signals, cell danger responses, microbial ecologies, fibroblast memory, tissue mechanics, drainage pathways, and neuroimmune systems are interpreted as phase-setting processes within the organism's attempt to conserve coherence under perturbation.

Clinically, the paper proposes diagnosis as phase-state reasoning. The task is to name the disease, but also to identify the regulatory lock: recognition/misrecognition, danger/inflammasome activation, nucleic-acid/interferon tone, viral/mobile-element boundary disturbance, barrier-type 2 inflammation, mechano-microbial enthesis/IL-17 activation, immune-complex vascular injury, trained innate readiness, immunodeficiency-dysregulation, resolution/clearance failure, repair-overbuild/fibrosis, or neuroimmune/allostatic pain-fatigue conservation. Treatment is reframed as phase restoration: suppression where damage must be prevented, resolution where inflammation must complete, clearance where danger material remains, repair where structure must be restored, and reintegration where health-cycle participation has been lost.

At the public health and civilizational levels, the rising burden of immune-mediated disease is interpreted as a possible signal of increasing organism–niche incoherence. Polluted air, unsafe housing, disrupted microbiomes, ultra-processed food systems, sleep disruption, toxic exposures, chronic psychosocial threat, climate instability, fragmented care, and reduced access to health-

generating conditions may repeatedly interrupt healing-cycle completion. Public health is therefore reframed as protection of health-cycle conditions at population scale, and civilization as life-coherent only when its institutions protect the conditions under which organisms can complete adaptive cycles.

Life-coherent systems immunology does not replace conventional diagnosis or evidence-based treatment. It offers a deeper clinical grammar for seeing chronic immune disease as a living process rather than a static label. Its purpose is to help clinicians, researchers, patients, and public health systems understand how immune processes become locked — and what conditions, signals, relationships, and care may allow life to move again.

Keywords

autopoiesis, organism–niche unity, systems immunology, life-coherent medicine, boundary-coherence, 5E cognition, salutogenesis, salugenesis, allostasis, immune resilience, phase-state medicine, phase restoration, chronic immune disease, autoimmunity, autoinflammation, allergy, immunometabolism, mitochondria, cell danger response, trained immunity, virome, resolution biology, clearance, tissue niches, exposome, public health, civilizational coherence

Executive Summary

Life-Coherent Systems Immunology proposes an organism-centered framework for understanding chronic immune-mediated disease. It begins from a clinical concern: modern immunology has generated powerful disease categories and molecular explanations, yet many chronic immune conditions remain difficult to understand through diagnostic labels alone. Terms such as autoimmunity, autoinflammation, allergy, chronic inflammation, fibrosis, immunodeficiency, and post-infectious illness describe important patterns, but they do not always explain how the living organism became stuck in those patterns.

The paper reframes immunity as the organism's living boundary-coherence process. Immunity is not primarily a war against non-self. It is the way a living organism conserves its identity while remaining open to nourishment, microbes, air, relation, repair, learning, and participation. The immune system must defend without becoming permanently defended, tolerate without becoming vulnerable, repair without overbuilding, remember without fixation, and return to ordinary life after perturbation.

The central concept is **maladaptive organism–niche phase-locking**. In health, the organism moves through adaptive phases: surveillance, boundary sensing, danger detection, defence, containment, resolution, clearance, repair, memory, and re-entry into the health cycle. In chronic disease, one or more of these phases becomes locked. Inflammation persists after its work should be complete. Debris, immune complexes, damaged mitochondria, mucus, crystals, toxins, matrix fragments, or biofilms remain uncleared. Repair becomes fibrosis. Memory becomes hypervigilance. Fatigue and pain become persistent conservation states. The organism cannot re-enter ordinary rhythms of sleep, movement, nourishment, relation, and participation.

The framework integrates several bodies of knowledge. Autopoiesis and organism–niche unity provide the living-systems foundation. 5E cognition reframes immunity as embodied, embedded, enactive, extended, and evaluative sense-making. Salutogenesis explains the coherence, resources, and meaning needed for health. Salugenesis describes the biological generation of healing. Allostasis and allostatic load explain how adaptation becomes costly when recovery is incomplete. Immunometabolism and mitochondrial biology show how energy, redox state, chromatin, and danger signalling shape immune phases. Tissue-niche science explains why diseases take specific forms in the airway, gut, skin, synovium, enthesis, vessel, kidney, lung interstitium, bone marrow, and nervous system.

Clinically, the paper proposes that diagnosis should become **phase-state reasoning**. Physicians should still name the disease according to established clinical standards, but they should also ask what regulatory lock is dominant. Is the patient locked in recognition and misrecognition, innate danger sensing, interferon alarm, viral boundary disturbance, type 2 barrier inflammation, mechano-inflammatory enthesitis, immune-complex vascular injury, trained innate readiness, immune deficiency with dysregulation, failed clearance, fibrosis, or neuroimmune pain-fatigue conservation? This second layer of reasoning helps identify what transition has failed and what kind of treatment may be needed next.

Treatment is reframed as **phase restoration**. Suppression is necessary when immune activity is destructive. Resolution is needed when inflammation cannot complete. Clearance is required when danger material remains. Repair is needed when tissue integrity has been lost. Reintegration is needed when the organism cannot return to ordinary health-cycle participation. The aim is not to force the organism back to normal, but to create the conditions under which the next coherent movement becomes possible.

The public health implications are equally important. Bodies do not heal in abstraction. They heal in air, housing, food systems, microbial ecologies, work rhythms, social relations, climate conditions, and care systems. Polluted air, unsafe housing, disrupted sleep, ultra-processed food systems, toxic exposures, chronic psychosocial threat, climate instability, and fragmented care may repeatedly interrupt healing-cycle completion. Public health is therefore reframed as the protection of health-cycle conditions at population scale.

At the civilizational level, chronic immune disease becomes a signal of organism–niche incoherence. A civilization is life-coherent when its institutions protect the conditions under which organisms can complete adaptive cycles. It becomes pathogenic when it normalizes chronic perturbation and then medicalizes the resulting phase-locks. The paper therefore connects clinical immunology to a wider question: what kind of world allows living beings to defend, resolve, clear, repair, reintegrate, and flourish?

The framework remains deliberately humble. It does not replace conventional diagnosis, urgent treatment, disease-specific mechanisms, or evidence-based medicine. It does not claim that all chronic disease is immune disease, that all immune disease has one cause, or that exposure, mitochondria, microbiome, stress, virome, or civilization explains everything. Its contribution is a deeper clinical grammar: a way of seeing chronic immune disease as unfinished living, where the task of medicine is to understand the lock, support the next adaptive transition, and help life move again.

Author Note

This paper is part of a broader life-coherent medicine and systems-health project seeking to reconnect clinical practice, biology, ecology, public health, and civilizational design around the conditions that allow living beings to conserve coherence, repair injury, and participate meaningfully in the world.

The framework is offered as an integrative clinical and theoretical grammar, not as a replacement for established diagnostic categories, validated disease classifications, or evidence-based treatment. Its purpose is to help clinicians, researchers, and public health thinkers see immune-mediated disease as a dynamic organism–niche process rather than only as a set of isolated immune pathways or categorical disorders.

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Epigraph

The organism does not name itself autoimmune, autoinflammatory, allergic, fibrotic, or phase-locked. It lives, responds, conserves, compensates, closes, opens, clears, repairs, remembers, and changes structure while conserving the organization that makes it a living unity.

Prefatory Note

This paper begins from a simple clinical concern: many patients with chronic immune-mediated illness do not appear to be suffering from one isolated malfunction. They appear to be living within unfinished biological processes. Defence does not fully resolve. Clearance does not complete. Repair becomes excessive or misdirected. Memory becomes hypervigilant. The organism remains caught between protection and participation.

Modern immunology has produced extraordinary knowledge of cells, cytokines, receptors, pathways, and disease categories. Yet clinical experience often reveals something that pathway diagrams alone cannot fully capture: the patient is not merely a site of immune activity, but a living unity trying to conserve coherence under conditions of perturbation. Disease appears not only as molecular error, but as a failed transition in the organism's effort to return to ordinary living.

The aim of this paper is therefore not to discard conventional immunology, but to re-see it. Autoimmunity, autoinflammation, allergy, infection, immunodeficiency, fibrosis, chronic inflammation, and post-infectious illness remain clinically necessary distinctions. But they may describe where the organism has arrived more clearly than how it became locked there. A deeper clinical grammar is needed: one that can follow the organism's movement through danger sensing, defence, containment, resolution, clearance, repair, memory, adaptation, and reintegration.

Life-coherent systems immunology is offered as such a grammar. It asks what immune disease looks like when viewed not only from the observer's categories, but from the organism's side: as embodied, embedded, enactive, extended, and evaluative boundary-coherence. It asks what healing requires when disease is not simply inflammation to suppress, but unfinished living that must be helped to move again.

Part I. Re-Seeing Immunity

1. Introduction: Why Immune Disease Requires a Deeper Clinical Grammar

Immune-mediated disease is often described through categories made by observers: autoimmune, autoinflammatory, allergic, infectious, immunodeficient, fibrotic, chronic inflammatory, or post-infectious. These categories are clinically necessary. They allow physicians to recognize patterns, communicate diagnoses, stratify risk, select therapies, conduct research, and organize care. Without such distinctions, clinical medicine would lose much of its practical power.

Modern immunology's major classificatory distinctions have been shaped by the development of self/non-self recognition, innate/adaptive immunity, pattern-recognition theory, danger-based models, and tissue-contextual accounts of inflammation (Janeway, 1989; Matzinger, 2002; Medzhitov, 2008; Medzhitov & Janeway, 1997).

Yet these categories can also obscure the living process by which an organism conserves itself, responds to perturbation, repairs injury, remembers danger, and attempts to re-enter ordinary living. A patient with rheumatoid arthritis is not only "autoimmune." A patient with asthma is not only "allergic." A patient with long COVID, chronic fatigue, post-infectious dysautonomia, inflammatory bowel disease, psoriasis, lupus, interstitial lung disease, chronic sinusitis, fibromyalgia, or environmentally triggered illness is not merely the bearer of a diagnostic label. Each is a living organism whose immune, metabolic, neural, microbial, mitochondrial, vascular, connective-tissue, and ecological relations have entered a particular pattern of constraint.

The problem is not that current diagnostic categories are wrong. It is that they often describe where the patient has arrived rather than how the living organism became locked there.

Modern immunology has achieved extraordinary explanatory depth. It has identified cells, cytokines, receptors, transcription factors, inflammasomes, complement pathways, pattern-recognition systems, antigen-presentation mechanisms, immune checkpoints, immunometabolic switches, tissue-resident memory programs, and molecular signatures of inflammation and tolerance. These advances have transformed clinical care. Targeted biologic therapies, small-molecule inhibitors, immune checkpoint modulation, vaccination, antimicrobial treatment, transplantation immunology, and increasingly precise diagnostics are among the great accomplishments of modern medicine.

These advances reflect the extraordinary explanatory power of molecular and cellular immunology, especially in defining immune recognition, inflammatory signalling, complement activation, immune-cell differentiation, metabolic reprogramming, and targeted immune modulation (Buck et al., 2017; Janeway, 1989; Medzhitov & Janeway, 1997; O'Neill et al., 2016; Ricklin et al., 2010).

But the conceptual grammar of immune disease remains fragmented. Autoimmunity is often framed as misrecognition of self. Autoinflammation is framed as excessive innate immune

activation. Allergy is framed as maladaptive type 2 immunity. Fibrosis is framed as excessive repair. Chronic inflammation is framed as persistent activation. Immunodeficiency is framed as impaired defence. Post-infectious illness is framed through persistence, dysregulation, or sequelae. These framings are useful, but they remain partial. They do not yet fully answer a deeper clinical question: what is the organism trying, failing, or no longer able to complete?

This question becomes especially important once immunity is understood not only as defence against foreignness, but as a context-sensitive process shaped by danger, tissue damage, microbial relations, metabolism, resolution, and repair (Belkaid & Hand, 2014; Hooper et al., 2012; Matzinger, 2002; Medzhitov, 2008; Serhan & Savill, 2005).

A life-coherent systems immunology begins from this question.

The organism-centered orientation developed here draws on autopoietic biology, embodied/enactive cognition, salutogenesis, allostasis, and cell danger response biology as complementary ways of understanding living systems under perturbation (Antonovsky, 1979, 1987; Maturana & Varela, 1980, 1987; McEwen, 1998; Naviaux, 2014; Varela et al., 1991).

It does not begin by asking only which pathway is overactive, which antibody is present, which cytokine is elevated, or which diagnostic box is most appropriate. It asks how the organism is conserving coherence under conditions of perturbation. It asks what kind of boundary process is occurring. It asks whether the organism is defending, containing, clearing, repairing, remembering, adapting, withdrawing, overbuilding, shutting down, or attempting to re-enter ordinary participation. It asks what phase of living has become unfinished.

This shift matters because immune activity is not an isolated molecular event. It is always embodied in a whole organism. It occurs in tissues with histories. It is shaped by barriers, nerves, vessels, hormones, mitochondria, metabolism, microbiota, viromes, extracellular matrix, sleep, food, air, housing, social relations, trauma, work, climate, pollution, and care. The immune system is not sealed inside the anatomical body as a self-contained defence machine. It is a living regulatory process through which the organism negotiates its boundary with the world.

This framing extends autopoietic and enactive accounts of living systems, in which organisms conserve identity through ongoing structural coupling with their worlds rather than by passively receiving environmental instructions (Di Paolo et al., 2018; Maturana & Varela, 1980, 1987; Varela et al., 1991).

From this perspective, immunity is not primarily a war against the outside. Nor is it only a self/non-self discrimination system. It is the organism’s living boundary-coherence process: a way of conserving autopoietic identity while remaining open to exchange, nourishment, learning, symbiosis, reproduction, repair, and participation. The immune system must close enough to protect life and open enough to allow life to continue. It must distinguish danger from nourishment, threat from signal, symbiont from pathogen, debris from self, injury from invasion, memory from fixation, and repair from overgrowth.

The organism therefore faces a fundamental immune problem: how to remain itself without becoming closed to the world.

This formulation preserves the insights of self/non-self and danger models while widening them through organism–niche reasoning: immune recognition is not only about foreignness or damage, but about maintaining viable participation across changing internal and external conditions (Janeway, 1989; Matzinger, 2002; Medzhitov, 2008; Pradeu, 2012).

Too little boundary protection leads to infection, invasion, permeability, immune collapse, or uncontrolled injury. Too much boundary protection leads to hypervigilance, allergy, autoimmunity, chronic inflammation, fibrosis, pain, fatigue, and loss of participation. Health is not preservation alone and not openness alone. It is coherent movement between protection and participation.

This paper proposes that many chronic immune-mediated diseases can be understood as maladaptive organism–niche phase-locks. A phase-lock is not a thing inside the patient. It is an observer distinction for a living pattern in which the organism becomes caught in a regulatory state that was originally adaptive, partially adaptive, or compensatory, but which now prevents the next necessary transition. Defence does not resolve. Clearance does not complete. Repair does not reintegrate. Memory does not remain flexible. The organism remains suspended in unfinished biological work.

In this sense, chronic immune disease is often less like a simple error and more like an interrupted cycle.

The language of interrupted cycles is consistent with allostatic and cell danger response models, in which adaptive state changes become pathological when they persist, fail to resolve, or cannot transition back into ordinary function (McEwen, 1998; McEwen & Stellar, 1993; Naviaux, 2014, 2020; Sterling & Eyer, 1988).

An organism detects perturbation. It shifts from ordinary health-cycle participation into a healing-cycle response. It senses danger, allocates energy, mobilizes inflammation, contains damage, clears debris, remodels tissue, updates memory, restores function, and returns to ordinary living. But when perturbations are recurrent, exposures remain unresolved, clearance is impaired, allostatic load is excessive, tissue niches become self-sustaining, or regulatory margins collapse, the healing cycle may not complete. The organism remains caught in defence, containment, inflammation, repair, shutdown, or hypervigilance. Disease then appears as the persistence of a phase that should have been transitional.

This interpretation also aligns with resolution biology, which emphasizes that inflammation does not simply fade passively but must be actively terminated through coordinated pro-resolving, clearance, and repair processes (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

This is why the language of “phase-locking” is clinically helpful. It does not reduce disease to a single molecule, single exposure, single immune cell, single pathogen, or single psychosocial factor. It allows multiple mechanisms to be integrated into one dynamic grammar.

Autoantibodies, inflammasomes, interferons, mitochondrial danger signals, trained immunity, tissue-resident memory, dysbiosis, viral persistence, environmental exposure, impaired lymphatic drainage, allostatic burden, fibrosis, and neuroimmune sensitization can all be understood as contributors to regulatory lock-in. They differ mechanistically, but they may share a common dynamic form: the organism cannot complete the transition from perturbation back into coherent participation.

Diverse mechanisms can therefore be read as contributors to regulatory lock-in, including trained immunity, mitochondrial danger signalling, inflammasome activation, interferon responses, dysbiosis, impaired clearance, fibrosis, and neuroimmune sensitization (Chen et al., 2016; Netea et al., 2016; Schroder & Tschopp, 2010; West & Shadel, 2017; Wynn & Ramalingam, 2012).

This framework is not meant to replace established immunology. It depends on it. Nor is it meant to dissolve diagnostic categories into vague holism. The aim is instead to place diagnostic categories within a wider organism-centered grammar. A disease name remains important, but it may not be enough. The clinician must also ask: What phase is this organism in? What transition has failed? What tissue niche sustains the lock? What exposures keep the process unfinished? What memories have become overactive? What forms of clearance, resolution, repair, or reintegration are blocked? What conditions would allow life to move again?

These questions are not merely theoretical. They affect clinical judgment.

If a patient is in active destructive inflammation, suppression may be necessary. If inflammation is unresolved rather than simply excessive, resolution biology becomes relevant. If debris, toxins, immune complexes, damaged mitochondria, crystals, biofilms, or matrix fragments remain uncleared, clearance becomes central. If tissue has entered an over-repair state, fibrosis and remodelling must be addressed. If the nervous system has become locked in pain, fatigue, threat vigilance, or autonomic instability, neuroimmune regulation and allostatic load become part of the immune picture. If the patient's housing, air, food, sleep, social safety, or ecological conditions repeatedly perturb the organism, treatment cannot be confined to pharmacology alone.

The framework therefore moves from disease category to living process, from pathway to phase, from mechanism to organism–niche relation, and from suppression alone to phase restoration.

This is also why the framework must be salutogenic and salugenic. Salutogenesis asks about the conditions, resources, meanings, and coherence fields that allow health to be generated and sustained. Salugenesis asks about the biological processes by which healing is generated and completed. Both are needed.

Antonovsky's salutogenic model shifts attention from disease causation alone toward coherence, meaning, and generalized resistance resources, while Naviaux's cell danger response framework helps explain how cellular healing programs may remain incomplete under persistent perturbation (Antonovsky, 1979, 1987; Naviaux, 2014, 2020).

Health is not merely the absence of disease, and healing is not merely the silencing of symptoms. Health is the organism's ongoing participation in coherent cycles of nourishment, activity,

relation, repair, sleep, learning, adaptation, and meaning. Healing is the successful completion of transitions that allow return to those cycles.

When immune disease becomes chronic, both health and healing are disrupted. The patient is not only inflamed. The patient may have lost the conditions under which inflammatory work can complete. The organism may no longer be able to afford the transition back to ordinary living.

The implications are clinical, public health, and civilizational. At the clinical level, life-coherent systems immunology invites phase-state reasoning. At the public health level, it asks whether modern environments protect or undermine the conditions required for immune coherence: clean air, safe housing, healthy food, microbial diversity, sleep, movement, social safety, ecological stability, meaningful participation, and timely care. At the civilizational level, it raises a larger question: what happens when whole societies normalize chronic perturbation and then medicalize the biological consequences?

This broader move is consistent with social-determinants, exposome, air-quality, climate-health, and environmental-health frameworks that understand health as shaped by cumulative organism–environment relations rather than by clinical factors alone (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Rappaport & Smith, 2010; Wild, 2005; World Health Organization, 2021).

The rising burden of immune-mediated, allergic, metabolic-inflammatory, post-infectious, fibrotic, and chronic inflammatory conditions may be understood, at least in part, as an epidemiological signal of organism–niche incoherence. This does not imply a single-cause theory. It does not deny genetics, infections, diagnostic improvements, medical advances, or disease-specific mechanisms. Rather, it asks whether multiple rising disease patterns may share a broader background: bodies increasingly exposed to recurrent perturbation while losing the margins, rhythms, relationships, and environments needed to complete adaptive cycles.

This paper unfolds that possibility carefully. It begins with observer humility, because any framework can become another form of closure if it forgets that its categories are distinctions made by observers. It then re-sees immunity from the organism's side as a living boundary-coherence process. It interprets immune activity as embodied, embedded, enactive, extended, and evaluative cognition. It then develops the logic of preservation, development, coherence, salutogenesis, health cycles, healing cycles, allostasis, immune resilience, and phase-locking. Only after this conceptual ground is established does the paper descend into molecular, cellular, mitochondrial, viral, microbial, and tissue mechanisms. It then returns to disease expression, exposure ecology, epidemiology, clinical translation, biomarkers, treatment, public health, and civilizational implications.

The goal is not final explanation. It is better clinical seeing.

A life-coherent systems immunology does not claim that every immune disease has one root cause, that inflammation is always bad, that modern immunology is reductionist in any simple sense, or that social and ecological conditions replace molecular mechanisms. It claims instead

that immune disease can be more faithfully understood when mechanisms are situated within the organism's attempt to conserve coherence under changing conditions.

The immune system is not merely defence. It is not merely self/non-self recognition. It is not merely inflammation. It is not merely molecular signalling. It is a living process of boundary coherence.

When that process moves flexibly, the organism can protect itself and participate in the world. When it locks, life narrows. The task of medicine is not only to name the lock, but to help the organism find the next possible movement.

2. Observer Humility: Distinctions as Instruments, Not Possessions

Every clinical framework begins with an act of distinction. A physician distinguishes fever from normal temperature, inflammation from quiescence, infection from sterile injury, autoimmunity from autoinflammation, allergy from intolerance, fibrosis from repair, remission from relapse, and disease from health. These distinctions are indispensable. Without them, medicine could not diagnose, communicate, study, treat, or teach.

The need for distinction is not in question; the epistemic issue is whether clinical distinctions remain flexible instruments of inquiry or become reified descriptions of the living process itself (Maturana, 1988; Maturana & Varela, 1980).

Yet every distinction is also an act of observation. It is made from a standpoint, for a purpose, within a history of concepts, instruments, measurements, institutions, and clinical needs. The organism itself does not begin with our categories. It does not name itself autoimmune, autoinflammatory, allergic, fibrotic, immunodeficient, inflamed, resilient, salugenic, or phase-locked. It lives. It responds. It conserves. It compensates. It opens and closes. It clears, repairs, remembers, adapts, withdraws, and changes structure while conserving the organization that makes it a living unity.

This recognition is not a rejection of scientific realism. It is a discipline of humility. Clinical categories are not arbitrary, but neither are they identical with the living process itself. They are instruments that help observers coordinate action.

Maturana's account of objectivity and observation is especially relevant here: explanations arise within the domain of distinctions made by observers, and their validity depends on the coherence of operations within a community of inquiry rather than on access to an observer-independent view from nowhere (Maturana, 1988).

Their value lies in what they allow us to see, what they allow us to do, and whether they help life recover coherence.

The danger in medicine is not distinction itself. The danger is possession by distinction: the moment when a useful category hardens into an assumed reality, when the diagnosis becomes the patient, when the pathway becomes the disease, when the biomarker becomes the truth, or when the observer forgets that the living organism exceeds every map drawn around it.

This is especially important in immunology because the field is rich with powerful distinctions. "Self" and "non-self," "innate" and "adaptive," "tolerance" and "immunity," "danger" and "homeostasis," "pro-inflammatory" and "anti-inflammatory," "Th1," "Th2," "Th17," "Treg," "autoimmune," "autoinflammatory," "allergic," "fibrotic," "resolving," and "chronic" are all immensely useful. They organize experiments, guide diagnoses, structure therapies, and allow shared inquiry. But they are not the organism's own language. They are observer-made handles on a living process.

The history of immunology illustrates this point clearly: self/non-self recognition, pattern recognition, danger theory, and newer accounts of immune identity each make different aspects of the living process visible while obscuring others (Janeway, 1989; Matzinger, 2002; Medzhitov & Janeway, 1997; Pradeu, 2012).

Nelson Vaz's observer-dependent immunology sharpens this caution from within immunology itself: terms such as antigen, antibody, specificity, defence, and immune response are not simply the organism's own categories, but distinctions coordinated within the observer's explanatory language, experimental practices, and expectations (Vaz, 2022).

The same must be said of the framework proposed in this paper. Terms such as *life-coherent systems immunology*, *organism–niche phase-locking*, *boundary-coherence*, *salugenesis*, *health-cycle re-entry*, and *phase-state medicine* are also distinctions. They are not final truths. They are not new possessions to replace old possessions. They are proposed instruments for seeing chronic immune disease more dynamically, more relationally, and more faithfully from the side of the living organism.

In this sense, life-coherent systems immunology should itself be treated as an enactive and clinical distinction: a way of coordinating perception and action, not a final description of the organism's essence (Di Paolo et al., 2018; Maturana & Varela, 1980; Varela et al., 1991).

The purpose of the framework is therefore not to claim superior closure. It is to generate more life-conserving clinical seeing.

A diagnosis such as lupus, rheumatoid arthritis, asthma, inflammatory bowel disease, psoriasis, vasculitis, long COVID, chronic sinusitis, interstitial lung disease, or common variable immunodeficiency names something real and clinically consequential. But it does not exhaust the patient's biological situation. The diagnosis may tell us which pattern has become recognizable to medicine. It may not yet tell us which healing transition failed, which tissue niche sustains the process, which regulatory memories remain active, which exposures continue to perturb, which clearance pathways are blocked, or which health-cycle conditions have been lost.

Observer humility asks medicine to hold both truths together. The category matters. The organism exceeds the category.

This distinction is consistent with organismic and enactive approaches in which living systems are understood through their histories of structural coupling, not only through external descriptions imposed by observers (Maturana & Varela, 1980, 1987; Varela et al., 1991).

This matters ethically as well as scientifically. When a diagnosis becomes too possessive, the patient can disappear behind the disease label. A person becomes "a lupus patient," "a rheumatoid," "a difficult autoimmune case," "a chronic fatigue patient," "a fibromyalgia patient," or "an allergic phenotype." Such labels may assist clinical coordination, but they can also narrow attention. They can make the patient's living history, niche, suffering, adaptive attempts, exposures, meanings, and possibilities less visible.

The same risk appears at the molecular level. A patient can disappear behind an elevated cytokine, a positive antibody, a genetic variant, a transcriptional signature, a mitochondrial marker, or a microbiome profile. The result is not necessarily reductionism in the crude sense. Often it is something subtler: the replacement of the living process by the measurable fragment.

Measurement is necessary. But measurement must remain answerable to life.

Biomarkers, molecular signatures, and disease classifications are indispensable for clinical care, but their meaning depends on context, timing, tissue state, and the organism's larger regulatory condition (Buck et al., 2017; Medzhitov, 2008; O'Neill et al., 2016).

The organism is not a collection of test results. It is a living unity whose structure changes through its history of coupling with the world. A laboratory marker, imaging finding, histological pattern, molecular pathway, or diagnostic criterion becomes clinically meaningful only when it is interpreted within the organism's attempt to conserve coherence under actual conditions of living.

This is why the framework developed here begins with observer humility before it introduces organism-centered immune coherence. Without humility, any integrative framework can become another closed system. It can begin by criticizing reductionism and end by imposing its own totalizing language. It can replace one rigid map with another. It can claim to see the whole while forgetting that "the whole" is also a distinction made by an observer.

This reflexive caution follows directly from autopoietic and enactive epistemology: any account of living systems must include awareness of the observer's role in bringing forth the domain being described (Maturana, 1988; Maturana & Varela, 1980; Varela et al., 1991).

The proper stance is different. The clinician, researcher, or theorist should ask: What does this distinction make visible? What does it obscure? What actions does it invite? What harms might follow if we mistake it for the organism itself? Does it help us reduce suffering, protect life, restore coherence, and keep inquiry open?

A life-coherent framework must therefore be reflexive. It must apply its own principle to itself. If immune disease is described as maladaptive phase-locking, that description must remain an instrument, not an identity. No patient is "a phase-lock." No organism lives inside a taxonomy. The term is useful only if it helps clinicians follow the living process more carefully: to see when defence cannot resolve, when clearance cannot complete, when repair has become overbuilt, when memory has become hypervigilant, when the tissue niche has become self-sustaining, or when the organism cannot re-enter ordinary rhythms of life.

The framework also requires humility before uncertainty. Chronic immune-mediated diseases are not all the same kind of process. Some are driven primarily by genetic defects. Some are shaped by infections. Some arise through autoantibody-mediated mechanisms. Some involve barrier disruption, dysbiosis, type 2 immunity, immune complexes, interferon activation, inflammasome dysregulation, metabolic stress, mitochondrial dysfunction, fibrosis, impaired clearance, environmental exposures, neuroimmune sensitization, or combinations of these. Some disease

processes are well understood. Others remain poorly mapped. Some patients improve dramatically with targeted suppression. Others require repair, rehabilitation, exposure removal, metabolic support, antimicrobial treatment, sleep restoration, psychological safety, social support, or environmental change.

Observer humility prevents a unifying framework from becoming a single-cause theory.

The claim is not that all immune disease is caused by one process. The claim is that many immune-mediated diseases can be better understood when their diverse mechanisms are interpreted as regulatory patterns within the organism's attempt to conserve coherence. This is a grammar of relation, not a replacement for mechanism. It invites molecular precision and organismal context to belong together.

Such humility is also important when discussing contested domains. Conditions such as chronic inflammatory response syndrome, post-infectious syndromes, environmentally linked illness, mold-related illness, long COVID, chronic fatigue syndromes, dysautonomia, mast-cell activation syndromes, and complex multi-system inflammatory states require careful language. Patients may suffer profoundly. Mechanisms may be real but incompletely characterized. Evidence may be uneven. Clinical experience may run ahead of consensus. Consensus may lag behind patient reality. In such terrain, medicine must avoid both dismissal and overclaiming.

This caution is particularly important in environmentally linked and post-infectious illness, where patient suffering may be substantial while mechanisms, diagnostic criteria, and treatment evidence remain uneven or contested (Bush et al., 2006; Institute of Medicine, 2004; Naviaux, 2020; World Health Organization Regional Office for Europe, 2009).

Observer humility offers a way through this difficulty. It allows clinicians to say: something is happening, the patient's suffering is real, current categories may be incomplete, mechanisms require careful investigation, and proposed distinctions must remain open to revision. This is not weakness. It is scientific and clinical maturity.

The organism-centered approach also changes how we understand "error." In conventional language, immune disease is often described as immune error: the immune system attacks self, overreacts to harmless substances, fails to clear infection, overbuilds scar, or remains inflamed without reason. Sometimes this language is appropriate. But from the organism's side, what appears as error to the observer may have begun as adaptation under constraint. Hypervigilance may have begun as defence. Fibrosis may have begun as repair. Fatigue may have begun as energy conservation. Fever may have begun as host defence. Pain may have begun as protection. Avoidance may have begun as survival. Inflammation may have begun as a necessary transition.

The pathology lies not only in the response itself, but in its persistence, misplacement, excess, insufficiency, or failure to transition.

This interpretation is supported by allostatic theory, resolution biology, and cell danger response biology, all of which emphasize that adaptive responses become harmful when they are

excessive, prolonged, poorly terminated, or unable to return to baseline participation (McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005; Sterling & Eyer, 1988).

This distinction is clinically important because it shifts the question from blame to history. Instead of asking only, "Why is the immune system wrong?" we ask, "Under what conditions did this response become necessary, and why can it not now complete, resolve, or reintegrate?" The organism is not treated as irrational machinery. It is approached as a living unity whose current pattern may be intelligible when viewed in relation to its history, structure, exposures, tissue niches, developmental pathways, and present constraints.

This stance does not romanticize disease. Maladaptive immune activity can destroy tissue, disable lives, and kill. Severe inflammation must be treated. Autoimmune attack must be controlled. Infection must be addressed. Fibrosis must be prevented where possible. Immunodeficiency must be recognized. The point is not to soften pathology into metaphor. The point is to understand pathology as a failed or locked biological process rather than as a mere defect detached from the organism's living context.

Observer humility also alters the meaning of treatment. If categories are instruments, then interventions are perturbations introduced into a living system. A drug does not simply "fix" a pathway in isolation. It perturbs an organism that responds according to its structure, history, and current state. The same biologic agent, corticosteroid, antimicrobial, dietary change, environmental intervention, rehabilitation program, sleep restoration, or psychosocial support may have different effects depending on the organism's phase-state, tissue niche, allostatic load, metabolic reserve, microbial ecology, and relational context.

Clinical care itself is structural coupling. The consultation, the diagnosis, the explanation, the medication, the monitoring, the relationship, the reassurance, the warning, the referral, the follow-up, and the shared plan all become part of the patient's organism–niche field. Care can reduce threat, increase coherence, clarify meaning, mobilize resources, and open a path to the next adaptive transition. It can also create fear, confusion, dependency, stigma, overmedicalization, or mistrust. Medicine is not outside the system it observes. It enters the patient's world as part of the niche.

In autopoietic terms, clinical care becomes part of the organism's structural coupling with its environment; in salutogenic terms, it can either strengthen or weaken comprehensibility, manageability, and meaning (Antonovsky, 1987; Maturana & Varela, 1980).

This is why the observer must be ethically accountable. The categories we use do not merely describe. They coordinate action. They shape what is reimbursed, researched, treated, dismissed, legitimized, or ignored. They influence whether patients are believed, whether environmental conditions are investigated, whether social determinants are considered, whether symptoms are psychologized, whether biology is overmedicalized, and whether public health responsibilities are recognized.

To distinguish is to participate.

A life-coherent systems immunology therefore asks medicine to use distinctions lightly but responsibly. Lightly, because no category should be mistaken for the living organism. Responsibly, because distinctions carry consequences. They can liberate or constrain care. They can open inquiry or close it. They can help life move again or trap it inside explanatory rigidity.

The methodological commitment of this paper can therefore be stated plainly: the distinctions proposed here are clinical and scientific instruments, not ontological possessions. They are offered to improve perception, deepen inquiry, guide action, and support healing. They must remain revisable in light of patient experience, biological evidence, clinical outcomes, and ethical reflection.

The organism does not belong to our framework. Our framework must remain answerable to the organism.

3. From Observer-Centered Immunology to Organism-Centered Immune Coherence

Once observer humility is established, immunology can be re-seen from a different starting point. Instead of beginning with the observer's categories — autoimmune, autoinflammatory, allergic, infectious, fibrotic, immunodeficient, chronic inflammatory — we can begin with the living organism itself.

The organism is not a passive object upon which immune events occur. It is an autopoietic unity: a living system that continuously produces and conserves the organization that makes it a living being. It maintains itself through ongoing exchange with its niche, yet it does not dissolve into that niche. It remains open to matter, energy, signals, relations, and perturbations while conserving the boundary conditions that allow it to remain itself.

This formulation follows Maturana and Varela's account of autopoiesis, in which living systems continuously produce and conserve the organization that constitutes them as living unities (Maturana & Varela, 1980, 1987).

This is the fundamental tension of living immunity: the organism must remain open enough to live and closed enough to conserve itself.

Enactive approaches to cognition extend this biological insight by showing that living systems enact meaningful worlds through their own embodied organization and histories of coupling (Di Paolo et al., 2018; Varela et al., 1991).

The immune system participates directly in this tension. It is not merely a defensive apparatus added to the organism. Nor is it only a molecular surveillance system for detecting foreignness. It is part of the organism's ongoing conservation of identity through changing relations with the world. It helps determine what may enter, what must be excluded, what can be tolerated, what must be cleared, what should be repaired, what must be remembered, and when ordinary participation can resume.

This broader understanding incorporates but exceeds classical self/non-self and danger models by treating immune activity as a process of relational regulation, tissue interpretation, and organismic viability (Janeway, 1989; Matzinger, 2002; Medzhitov, 2008; Pradeu, 2012).

Vaz and Varela's early organism-centered immunology anticipated this shift by challenging antigen-centered defensive models and proposing that immune phenomena be understood through a conservative, self-referential network of organismic interactions rather than through a simple self/non-self warfare logic (Vaz & Varela, 1978).

From this view, immunity is the organism's living boundary-coherence process.

Boundary does not mean a rigid wall. A living boundary is selective, dynamic, intelligent, and historically formed. Skin, mucosa, gut epithelium, vascular endothelium, placenta, lung

interface, blood-brain barrier, lymphatics, extracellular matrix, microbiome, antibodies, complement, innate immune sensors, T cells, B cells, macrophages, dendritic cells, mast cells, fibroblasts, nerves, mitochondria, and metabolic pathways all participate in boundary regulation. The boundary is not located in one place. It is enacted across the organism.

Barrier tissues, complement systems, microbiota, immune cells, mitochondria, lymphatics, and tissue-resident regulatory circuits all participate in this distributed boundary process (Belkaid & Hand, 2014; Hooper et al., 2012; Ricklin et al., 2010; West & Shadel, 2017).

Coherence does not mean stillness or uniformity. It means adaptive fit among processes that must move together without collapsing into chaos or rigid fixation. Immune coherence requires the coordination of defence, tolerance, metabolism, repair, clearance, memory, tissue function, microbial ecology, neural regulation, and organismal behaviour. It is not the absence of immune activity. It is the capacity of immune activity to arise, transform, complete its work, and reintegrate into the larger rhythms of living.

This view brings allostasis, immune resilience, and resolution biology into relation: immune health is not static inactivity, but flexible state-transition capacity under changing demands (McEwen, 1998; Serhan & Savill, 2005; Sterling & Eyer, 1988).

This shift from observer-centered immunology to organism-centered immune coherence changes the meaning of immune disease. In an observer-centered frame, disease is often defined by the category to which it belongs: lupus as autoimmunity, gout as autoinflammation, asthma as allergy, sepsis as dysregulated infection response, fibrosis as excessive repair, immunodeficiency as failed defence. In an organism-centered frame, these categories remain useful, but they are placed within a deeper question: how has the organism's boundary-coherence process become constrained?

The organism-centered question is not simply, "What is wrong with the immune system?" It is, "What is the organism doing, under what conditions, with what history, in what tissue niche, and why can this process not complete its adaptive transition?"

This question is especially important because the niche does not instruct the organism. The world does not write commands into a passive body. Rather, the niche perturbs a structurally determined living unity, and the organism responds according to its organization, history, and present structure. The same exposure, infection, trauma, pollutant, food antigen, microbial signal, medication, stressor, or social condition may have different biological meanings in different organisms because each organism has a different history of structural coupling.

The body does not respond to "the environment" in general. It responds from its own structure to particular perturbations encountered within a lived niche.

This is why immune activity is always historical. A flare is not only an event in the present. It may be the reactivation of previous regulatory memory. An allergic reaction is not only a response to an antigen. It may express a barrier history, epithelial state, microbial ecology, developmental exposure pattern, and type 2 immune readiness. Fibrosis is not only excess

collagen deposition. It may be repair that has lost its exit signal. Chronic inflammation is not only persistence of inflammatory molecules. It may be the organism's inability to complete clearance, restore tissue trust, and return to ordinary function.

Organism-centered immunology therefore refuses to isolate the immune system from the living unity in which it participates. There is no immune system in the abstract. There is only immunity as lived by this organism, in this body, in this tissue, with this history, in this niche, under these constraints.

This does not weaken immunology. It deepens it.

The molecular pathways remain real. Pattern-recognition receptors matter. Antigen presentation matters. Inflammasomes matter. Interferons matter. Complement matters. Cytokines matter. Autoantibodies matter. Mitochondrial danger signals matter. Trained immunity, tissue-resident memory, microbiome dynamics, virome interactions, neuroimmune signalling, and metabolic reprogramming all matter. But their meaning changes when they are understood as participants in an organism's boundary-coherence process rather than isolated causal switches.

For example, a cytokine is not simply "pro-inflammatory" or "anti-inflammatory" in a universal sense. Its meaning depends on timing, tissue, concentration, receptor context, metabolic state, developmental history, microbial ecology, and the larger phase of the organism. A molecule that helps contain infection in one context may sustain pathology in another. A repair program that restores integrity after injury may generate fibrosis when it persists. A memory program that protects against recurrence may become hypervigilance when it cannot update.

The same biological process may be protective, transitional, or pathological depending on whether it supports coherent movement through the organism's adaptive cycle.

This context-dependence is a central lesson of modern immunology: cytokines, metabolic programs, and immune-cell states cannot be interpreted apart from timing, tissue, dose, cellular context, and phase of response (Buck et al., 2017; Medzhitov, 2008; O'Neill et al., 2016).

This is the central difference between phase-shifting and phase-locking. In health, immune activity shifts phase in response to changing conditions. Surveillance becomes danger detection. Detection becomes defence. Defence becomes containment. Containment becomes resolution. Resolution becomes clearance. Clearance becomes repair. Repair becomes memory and reintegration. The organism returns to ordinary health-cycle participation.

In chronic disease, one or more of these transitions fail. The organism remains in a phase that should have been temporary. Defence persists after danger has changed. Inflammation persists after containment should have ended. Repair persists after structure should have stabilized. Memory remains active after the context has shifted. Pain and fatigue persist after protection should have relaxed. The living process becomes locked.

This phase-state language draws together allostatic load, cell danger response biology, trained immunity, and resolution failure into a common dynamic grammar of adaptive state changes that

become persistent or maladaptive (McEwen & Stellar, 1993; Naviaux, 2014; Netea et al., 2016; Serhan, 2007).

Organism-centered immune coherence therefore provides a bridge between mechanism and meaning. It allows the clinician to see inflammation not only as molecular activation, but as a biological phase. It allows repair to be understood not only as tissue remodelling, but as an attempt to restore boundary integrity. It allows fatigue to be considered not only as symptom, but as possible energy reallocation, danger response, mitochondrial constraint, autonomic shift, or failed re-entry into ordinary activity. It allows chronic illness to be approached not only as defect, but as unfinished adaptive work.

This does not mean that the organism is always wise in a romantic sense. Organisms can become trapped in destructive loops. Adaptive responses can become maladaptive. Defence can become damage. Repair can become scarring. Memory can become fixation. Tolerance can become permissiveness. Openness can become vulnerability. Closure can become isolation. The organism's structural determination does not guarantee health. It means only that the organism responds according to what it has become.

The clinical task is therefore to understand what the organism has become, how it became so, and what might allow a different movement.

This is where the organism–niche relation becomes essential. Immune disease does not arise inside the body alone. Nor does it arise from the niche alone. It arises through organism–niche coupling. Genes, development, infections, toxins, diet, microbiota, stress, sleep, trauma, climate, housing, work, social safety, medical care, and ecological conditions do not act as isolated causes. They participate in a history of structural coupling through which the organism's immune possibilities are shaped.

A child raised with diverse microbial exposures, safe attachment, clean air, nourishing food, sleep stability, and low toxic burden may develop different regulatory margins from a child exposed to chronic stress, pollution, disrupted microbiota, poor housing, ultra-processed food, recurrent infections, or early-life adversity. An adult recovering from infection in a supportive context with rest, nutrition, care, and low exposure burden may complete a healing cycle that another adult, under chronic stress and environmental load, cannot complete. These are not moral differences. They are organism–niche differences.

The immune system carries these histories.

Vaz and Botelho Andrade's epigenetic immune network supports this historical reading by treating immune organization as a self-referential, organism-centered, and developmentally shaped process rather than as a sequence of externally instructed antigenic reactions (Vaz & Botelho Andrade, 2017).

Such histories may be carried through adaptive immune memory, trained innate immunity, epigenetic regulation, tissue-resident cells, microbial ecology, mitochondrial function, and

stromal or fibroblast programming (Chuong et al., 2016; Netea et al., 2016; Virgin, 2014; Wynn et al., 2013).

It carries them in epigenetic marks, trained innate states, memory lymphocytes, tissue-resident cells, fibroblast programs, microbial communities, mitochondrial capacity, neuroendocrine tone, barrier integrity, vascular function, pain pathways, and behavioural patterns. The organism's past remains present as altered readiness. This is why disease often appears disproportionate to the current trigger. The trigger is only the visible perturbation. The response emerges from the accumulated structure of the organism.

An organism-centered view therefore helps explain why chronic immune disease is often complex without making it vague. Complexity does not mean that "everything causes everything." It means that the present immune state is the result of layered histories that have become biologically embodied. Some layers are genetic. Some are developmental. Some are microbial. Some are metabolic. Some are infectious. Some are toxicological. Some are psychosocial. Some are ecological. Some are iatrogenic. Some are still unknown.

The task is not to collapse these layers into one cause. It is to understand how they converge into a present phase-state.

This is also why the self/non-self metaphor, while historically powerful, is insufficient. The organism does not simply defend self against non-self. It tolerates many forms of non-self: food, commensal microbes, pregnancy, transplanted signals in some contexts, inhaled particles, environmental molecules, and symbiotic relations. It also clears many forms of altered self: apoptotic cells, damaged mitochondria, senescent cells, malignant cells, misfolded proteins, and injured matrix. The immune system is not primarily a border guard checking passports. It is a dynamic coherence process regulating participation, threat, repair, and continuity.

This critique is consistent with post-self/non-self theories of immunity, including danger theory and accounts of immune identity that emphasize context, continuity, and organismic integrity rather than foreignness alone (Matzinger, 2002; Pradeu, 2012).

The danger model improved upon simple self/non-self thinking by emphasizing tissue damage and alarm. Yet even danger is not enough. The organism must not only detect danger. It must evaluate context, allocate energy, mobilize defence, limit collateral damage, clear debris, restore tissue, update memory, and return to participation. Danger sensing is one phase within a larger living cycle.

Pattern recognition and danger sensing help explain immune activation, but resolution biology and cell danger response biology show that activation must be followed by termination, clearance, repair, and return to function (Janeway, 1989; Matzinger, 2002; Naviaux, 2014; Serhan & Savill, 2005).

Similarly, tolerance is not mere non-response. Tolerance is active boundary intelligence. It requires the organism to allow what can be allowed without losing coherence. Food tolerance, microbial tolerance, fetal tolerance, tissue tolerance, and self-tolerance are not passive absences

of immunity. They are achievements of regulation. When tolerance fails, the issue is not simply overreaction. It is a disturbance in the organism's ability to remain open without losing itself.

This is why immunity must be understood as both protective and participatory. The immune system protects the organism from invasion, injury, malignancy, and toxic disruption. But it also enables participation in a world full of microbial, nutritional, social, reproductive, ecological, and developmental relations. Without immune tolerance, there is no eating. Without barrier regulation, there is no breathing. Without microbial negotiation, there is no gut ecology. Without repair, there is no growth. Without memory, there is no learning. Without controlled openness, there is no life.

Immune coherence is therefore not achieved by eliminating exposure, suppressing response, maximizing defence, or enforcing purity. It is achieved by maintaining adaptive relations.

This has profound implications for treatment. If immunity is boundary-coherence, then treatment must ask what kind of boundary problem is occurring. Is the boundary too permeable, too reactive, too closed, too damaged, too memory-laden, too poorly cleared, too fibrotic, too energetically constrained, too environmentally perturbed, or too socially unsupported? Is the primary need suppression, tolerance restoration, microbial repair, barrier restoration, clearance, resolution, antifibrotic intervention, mitochondrial support, sleep restoration, exposure reduction, rehabilitation, or renewed participation?

No single therapeutic logic applies to all phase-states. Some patients require strong suppression to prevent irreversible damage. Some require antimicrobial treatment. Some require biologic precision. Some require restoration of barrier integrity. Some require removal from repeated exposure. Some require support for resolution and clearance. Some require rehabilitation after prolonged shutdown. Some require social protection before biological healing is affordable. Many require combinations.

The organism-centered frame does not replace evidence-based treatment. It asks that evidence-based treatment be situated within the organism's phase-state and life context.

This is particularly important in chronic disease, where the therapeutic aim is not always to force the organism back to normal, but to create conditions under which the next adaptive transition becomes possible. The question becomes: What is the minimum sufficient perturbation that allows the system to move without overwhelming it? What intervention reduces damage while preserving capacity? What support expands regulatory margins? What conditions allow the organism to complete unfinished biological work?

This is a medicine of non-forcing precision. It does not mean doing less. It means intervening with respect for the organism's structure, timing, and capacity for transition.

The organism-centered turn also changes public health. If immunity is extended through niche conditions, then immune coherence is not produced by clinics alone. It depends on clean air, safe water, adequate housing, healthy food systems, microbial diversity, toxin reduction, climate stability, sleep-protective rhythms, social safety, meaningful work, equitable care, and ecological

repair. These are not external "social factors" added to biology. They are part of the extended field through which immune regulation becomes possible.

Social-determinants, exposome, climate-health, and environmental-health research support this broader view: bodies are shaped by cumulative material, social, ecological, and institutional conditions (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Rappaport & Smith, 2010; Wild, 2005; World Health Organization, 2021).

A society can therefore become immunologically pathogenic. It can normalize disrupted sleep, polluted air, ultra-processed food, chronic stress, insecure housing, ecological degradation, social isolation, microbial depletion, chemical burden, and climate instability — and then treat the resulting immune phase-locks as individual diseases detached from their niche conditions. This does not mean society causes every immune disease. It means that the organism's immune possibilities are shaped by the world it must live in.

The organism-centered view returns medicine to this larger responsibility without abandoning molecular rigor.

At its deepest level, this shift is metanoic: it asks for a re-seeing. Immunity is not a war machine. It is not a simple identity police. It is not inflammation alone. It is not a collection of pathways floating inside the body. It is the organism's living boundary-coherence process, embodied in tissues, embedded in histories, enacted through response, extended through niche relations, and evaluative of what supports or threatens viability.

To re-see immunity in this way is not to reject conventional immunology. It is to give it a wider home.

That wider home is organism-centered rather than pathway-centered: it preserves molecular precision while situating immune mechanisms within autopoietic identity, embodied cognition, allostatic regulation, tissue context, and organism–niche participation (Maturana & Varela, 1980; McEwen, 1998; Medzhitov, 2008; Varela et al., 1991).

The immune system becomes intelligible as part of the organism's effort to remain alive, coherent, open, and capable of participation. Disease becomes intelligible as a disturbance in that effort. Healing becomes intelligible as restored movement through adaptive phases. Clinical care becomes intelligible as skilled participation in the organism–niche relation.

The organism does not live inside our categories. Our categories must learn to serve the organism's living.

Part II. The Immune System as 5E Organismic Cognition

4. Immune Cognition as Embodied, Embedded, Enactive, Extended, and Evaluative

If cognition is understood not as abstract representation but as living sense-making for viable action, then immunity can be understood as a form of 5E organismic cognition. The immune system does not think in the reflective, linguistic, or symbolic manner of human consciousness. It does not form concepts, deliberate, or represent the world as an observing mind does. Yet it continually participates in biological sense-making. It distinguishes conditions, evaluates perturbations, mobilizes responses, remembers histories, anticipates recurrence, and helps determine what forms of organism–niche participation remain possible.

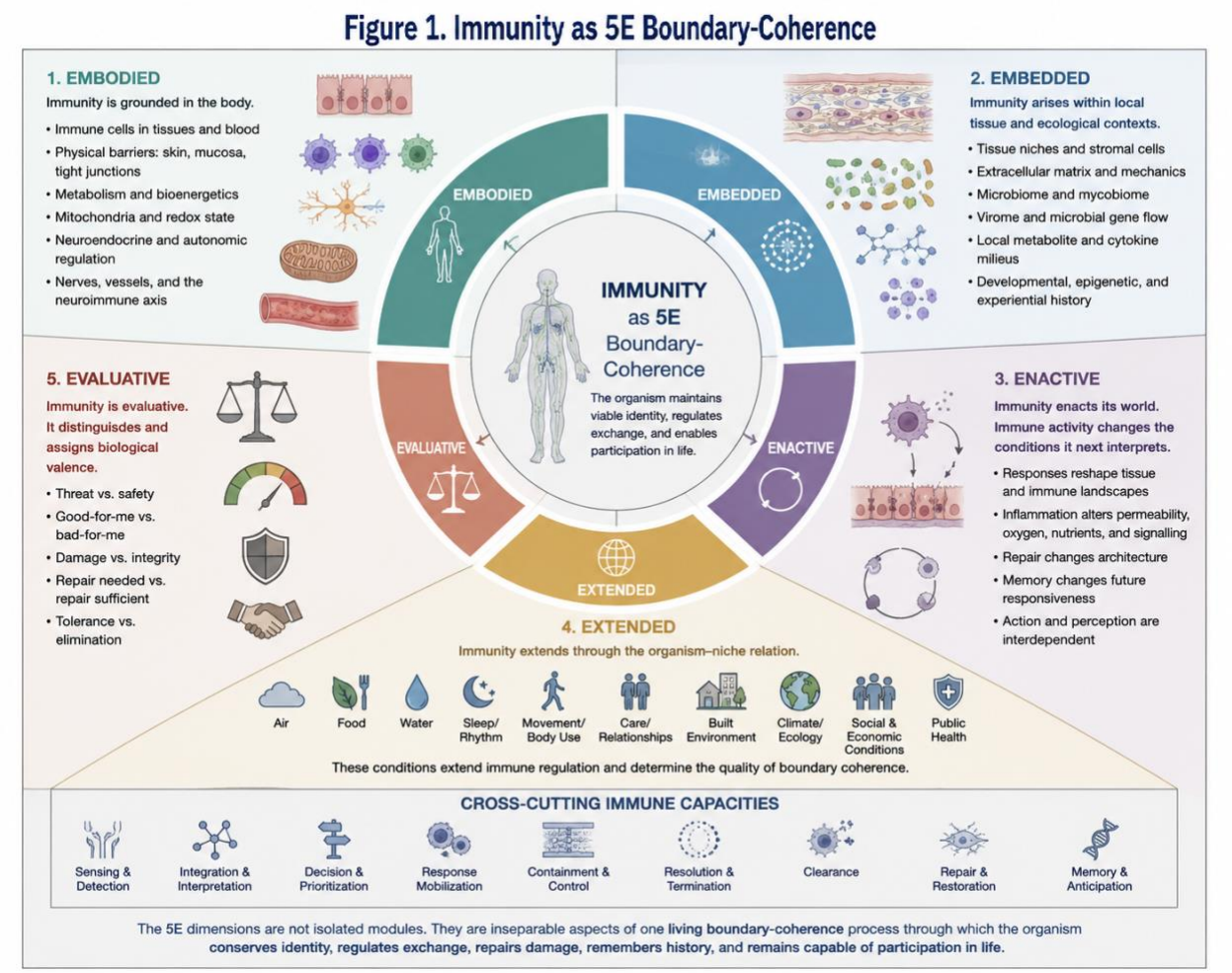
This is cognition in a primordial biological sense: the activity by which a living system brings forth a meaningful world in relation to its own viability.

The immune system is therefore not only defensive. It is interpretive, but not in a mentalistic sense. It interprets through molecular binding, cellular activation, metabolic reprogramming, tissue signalling, barrier regulation, inflammatory amplification, resolution, clearance, repair, and memory. It does not "know" in the way a person knows. It knows by changing state. It knows by altering permeability, temperature, pain, fatigue, appetite, mucus, swelling, antibody production, cytokine profiles, complement activity, mitochondrial function, tissue remodelling, and behaviour.

Immune cognition is therefore not located in a central immune mind. It is distributed across the organism. It is embodied, embedded, enactive, extended, and evaluative. These five dimensions help reframe immunity as living boundary-coherence rather than as a simple defence apparatus or self/non-self recognition system. They also help explain why chronic immune disease cannot be adequately understood by molecular pathways alone, even though molecular pathways remain indispensable.

The 5E frame allows us to see immune activity as a whole-organism process of sense-making under constraint.

This organismic understanding of cognition draws on enactive and embodied accounts of living systems, together with Peil Kauffman's affective-evaluative account of an enacted or 5E mind, in which sense-making is not detached representation but the activity by which organisms conserve viability through embodied engagement with their worlds (Di Paolo et al., 2018; Maturana & Varela, 1980, 1987; Peil Kauffman, 2017, 2020a, 2020b; Varela et al., 1991).



Caption. Immunity is represented as a distributed, organism-centered process of boundary-coherence. It is **embodied** in tissues, barriers, metabolism, mitochondria, nerves, vessels, and body-state change; **embedded** in tissue niches, stromal cells, microbiomes, matrix, mechanics, and local ecologies; **enactive** because immune action changes the field the organism next interprets; **extended** through air, food, water, housing, sleep, movement, care, climate, public health, and social conditions; and **evaluative** because immune activity distinguishes threat from safety, damage from integrity, tolerance from elimination, and repair need from repair sufficiency. Together, these five dimensions frame immunity as living sense-making for viable action rather than as a simple defence apparatus.

4.1 Embodied Immunity

Immune cognition is first embodied. The immune system does not operate apart from the body. It is the body sensing, responding, protecting, clearing, repairing, and remembering through its own tissues and states. Immunity is distributed through barriers, blood, lymph, bone marrow, spleen, gut, skin, lung, liver, kidney, synovium, enthesis, brain, nerves, vessels, fascia, adipose tissue, mitochondria, microbiota, and extracellular matrix.

This distributed view is consistent with systems immunology, immunometabolism, microbiome research, mitochondrial immune signalling, and tissue-resident accounts of immune regulation (Belkaid & Hand, 2014; Buck et al., 2017; Hooper et al., 2012; O'Neill et al., 2016; West & Shadel, 2017).

To say that immunity is embodied is to say that the organism knows perturbation through body-state change. Fever, fatigue, pain, swelling, stiffness, itch, mucus production, cough, diarrhoea, nausea, anorexia, malaise, sleepiness, tenderness, warmth, redness, and altered energy are not incidental accompaniments of immune activity. They are part of the organism's immune cognition. They are ways in which the body reorganizes itself around threat, injury, repair, or conservation.

A fever is not merely an elevated temperature. It is a coordinated organismal shift in thermal regulation, metabolism, immune activation, microbial constraint, and behavioural withdrawal. Fatigue is not merely a subjective complaint. In many immune states, it may represent energy reallocation, inflammatory signalling, mitochondrial constraint, autonomic shift, sickness behaviour, or the body's attempt to reduce expenditure while repair or defence is underway. Pain is not only an alarm. It may become a protective boundary signal, a movement regulator, a memory of injury, or, when locked, a persistent neuroimmune phase-state.

Immune activation is therefore expressed through coordinated organismal state changes, including metabolic reallocation, sickness behaviour, sleep alteration, neuroimmune signalling, mitochondrial stress, and allostatic adjustment (Besedovsky et al., 2012; McEwen, 1998; Naviaux, 2014; Picard et al., 2018).

Embodied immunity therefore refuses to treat symptoms as noise. Symptoms are not always transparent. They can mislead, persist, amplify, or become maladaptive. Yet they are still expressions of the living body's regulatory state. They are signals of how the organism is currently conserving, defending, withdrawing, repairing, or failing to reintegrate.

This matters clinically because immune disease is often lived first as bodily disruption before it is named by diagnosis. The patient may feel exhaustion before laboratory inflammation is recognized. They may feel stiffness before synovitis is confirmed. They may feel air hunger before airway inflammation is mapped. They may experience brain fog before neuroimmune mechanisms are understood. They may feel poisoned, inflamed, swollen, reactive, hypersensitive, or fragile before medicine can classify the process.

Embodied immunity asks the clinician to listen to the body's pattern without reducing it either to subjective report alone or to measurable biomarkers alone. The lived body and the measured body must be brought into relation.

In chronic immune disease, embodied cognition can become locked. The body may remain in a state of defence when the original danger has passed. It may remain fatigued because energy allocation cannot normalize. It may remain painful because neuroimmune circuits continue to protect against movement, contact, or exertion. It may remain inflamed because tissues continue to generate danger signals. It may remain reactive because barriers, mast cells, sensory nerves, or

epithelial surfaces have become hyperresponsive. The organism's embodied sense-making becomes narrowed around threat.

Healing, then, is not only the normalization of a laboratory marker. It is the restoration of embodied participation: movement, sleep, appetite, warmth, strength, clarity, touch, breath, digestion, relation, and ordinary rhythm.

This emphasis on restored participation aligns with salutogenic reasoning, in which health is understood not merely as the absence of pathology but as coherence, manageability, meaning, and the recovery of life-supporting capacities (Antonovsky, 1979, 1987).

4.2 Embedded Immunity

Immune cognition is also embedded. Immune meaning is always tissue-specific, context-specific, and history-specific. A molecule does not have the same biological significance everywhere. The same cytokine, antigen, microbial metabolite, mechanical stress, immune complex, or danger signal may mean different things in the gut, skin, airway, synovium, kidney, vessel, enthesis, lung interstitium, or brain.

The immune system is embedded in tissue worlds.

Tissue-specific immunity is now central to understanding why the same immune mediator, cell state, microbial signal, or repair program can have different meanings in different anatomical and ecological contexts (Belkaid & Hand, 2014; Galli et al., 2011; Hooper et al., 2012; Wynn et al., 2013).

The gut is not simply a tube exposed to antigens. It is a dense ecological interface where food, microbes, mucus, epithelium, immune cells, metabolites, nerves, bile acids, hormones, and vascular flows participate in tolerance and defence. The skin is not merely a surface. It is a sensory, microbial, immunological, thermal, and social boundary. The airway is not only a conduit for air. It is an interface with particles, allergens, viruses, pollutants, humidity, microbiota, epithelial alarms, smooth muscle, and breath. The synovium is not merely a joint lining. It is a mechanically active, vascular, immune, fibroblast-rich niche. The enthesis is not only a tendon insertion. It is a site where mechanical force, microbial history, IL-17 biology, and tissue stress may converge. The brain is not immune-privileged in any simple sense. It is immunologically regulated through microglia, barriers, glymphatic clearance, meningeal immunity, vascular signals, and systemic inflammation.

Discoveries of meningeal lymphatics, glymphatic clearance, and neuroimmune communication have further weakened simple notions of central nervous system immune isolation (Aspelund et al., 2015; Louveau et al., 2015; Xie et al., 2013).

The same signal means different things in different tissue niches because immunity is embedded in local histories and local demands.

This embeddedness explains why immune diseases have preferred anatomical patterns. Psoriasis affects skin and nails. Asthma affects airways. Inflammatory bowel disease affects the gut. Rheumatoid arthritis favours synovium. Spondyloarthritis often involves entheses and axial structures. Lupus may involve skin, joints, kidney, blood, vessels, and brain. Vasculitis takes form through vessel size and tissue perfusion. Fibrotic lung disease is shaped by alveolar and interstitial repair niches. These patterns are not random. They reflect the specific ways tissues participate in immune regulation.

The tissue is therefore not merely the target of immune disease. It is part of the regulatory circuit that gives disease its form.

This is especially evident in diseases shaped by stromal cells, macrophages, fibroblasts, epithelial barriers, endothelial regulation, tissue-resident memory, matrix remodelling, and local microbial ecologies (Galli et al., 2011; Wynn et al., 2013; Wynn & Ramalingam, 2012).

Embedded immunity also means that the organism's niche is not external background. The niche enters immune regulation through food, microbes, toxins, air, allergens, occupational exposures, infections, temperature, humidity, housing, stress, sleep, social threat, caregiving, antibiotics, medications, climate, and culture. These are not vague contextual factors. They are part of the perturbation field within which immune meaning is generated.

A pollen grain in one organism may be ignored; in another it becomes an allergic trigger. A food protein in one gut may be tolerated; in another it becomes inflammatory. A viral infection in one person may resolve; in another it may trigger persistent dysregulation. A pollutant exposure in one airway may be buffered; in another it may amplify epithelial alarm. The difference lies not only in the external object, but in the organism–niche history through which that object becomes biologically meaningful.

Embedded immunity therefore undermines simplistic cause-effect thinking. The question is not only, "What exposure caused this disease?" It is also, "What organism–tissue–niche configuration allowed this exposure to become a persistent perturbation?"

Clinical reasoning must therefore be ecological without becoming vague. It must ask where the disease is located, what tissue logic is active, what niche relations sustain it, and how the local immune world can be changed. A gut disorder may require microbial, dietary, epithelial, metabolic, inflammatory, and psychosocial interpretation. An airway disorder may require attention to allergens, pollutants, viral history, epithelial integrity, smooth muscle, mast cells, and housing conditions. A joint disorder may require attention to synovial inflammation, mechanical load, systemic immune memory, metabolic state, and rehabilitation.

Embedded immunity reminds us that there is no generic immune response. There are only immune responses in places.

Tissue context is central because inflammatory signals, immune cells, stromal cells, microbial communities, and repair programs acquire different meanings in different anatomical and

ecological niches (Belkaid & Hand, 2014; Galli et al., 2011; Wynn et al., 2013; Wynn & Ramalingam, 2012).

4.3 Enactive Immunity

Immune cognition is enactive. The immune system does not merely detect a pre-given world. It changes the world it senses. Immune perception and immune action are inseparable. Inflammation, mucus, antibodies, complement, fever, coagulation, fibrosis, pain, fatigue, tissue remodelling, microbial shifts, and behavioural withdrawal all transform the organism–niche field. The immune system brings forth the next immune world the organism must interpret.

This formulation follows enactive biology: living systems do not merely register pre-given environments, but participate in generating the conditions to which they must next adapt (Di Paolo et al., 2018; Maturana & Varela, 1980; Varela et al., 1991).

This is crucial. An immune response does not simply answer a perturbation; it creates new conditions. Neutrophil activation clears microbes but can damage tissue. Complement opsonizes and lyses but can amplify inflammation. Antibodies neutralize pathogens but can form immune complexes. Mucus traps particles but can obstruct airways. Fibrosis stabilizes injury but can stiffen organs. Pain protects damaged tissue but can restrict movement and participation. Fatigue conserves energy but can lead to deconditioning if prolonged. Inflammation recruits repair but can produce new danger signals if unresolved.

The immune system therefore participates in a recursive loop: it senses, acts, changes the field, then senses the changed field.

Such recursive loops are central to chronic inflammatory persistence, where damage signals, altered tissue mechanics, microbial shifts, immune memory, metabolic changes, and repair programs may reinforce one another over time (Netea et al., 2016; Serhan & Savill, 2005; Wynn et al., 2013; Wynn & Ramalingam, 2012).

In health, this loop remains adaptive. The organism detects perturbation, mobilizes defence, limits spread, clears debris, repairs tissue, updates memory, and returns to ordinary participation. Each action changes the next condition, but the sequence remains coherent. The immune response is transitional.

In chronic disease, the loop can become self-sustaining. Inflammation generates damage. Damage generates danger signals. Danger signals sustain inflammation. Fibroblasts remodel tissue. Remodelling changes mechanics. Altered mechanics sustain immune activation. Microbial dysbiosis changes metabolites. Altered metabolites reshape immune tone. Pain reduces movement. Reduced movement impairs circulation, lymphatic flow, and metabolic resilience. Fatigue reduces activity. Reduced activity alters sleep, mood, muscle, mitochondria, and social participation. What began as response becomes niche.

This is enactive phase-locking.

The organism is no longer merely responding to the original perturbation. It is responding to the world produced by its own unfinished response.

This helps explain why chronic immune disease may persist after the initiating trigger is gone. The infection has cleared, but interferon tone, mitochondrial stress, tissue damage, autonomic dysfunction, or immune memory remains. The injury has healed structurally, but pain circuits and inflammatory priming persist. The allergen is intermittent, but epithelial and mast-cell readiness remains heightened. The exposure has ended, but tissue remodelling, trained immunity, or neuroimmune sensitization continues. The organism now lives in a world partly brought forth by its prior responses.

This helps connect enactive organismic theory with biological mechanisms such as trained immunity, cell danger response persistence, mitochondrial stress signalling, and tissue remodelling (Naviaux, 2014, 2020; Netea et al., 2016; West & Shadel, 2017; Wynn & Ramalingam, 2012).

This does not mean the disease is imaginary or self-created in a psychological sense. It means the organism is enactively involved in the continuation of its own biological field. Living systems do not merely react to environments. They participate in generating the conditions to which they must next adapt.

Clinically, enactive immunity shifts treatment from linear correction to loop interruption and phase transition. The clinician asks: What self-sustaining loop is now active? Does inflammation generate damage that sustains inflammation? Does fibrosis change tissue mechanics in ways that sustain immune activation? Does dysbiosis maintain barrier alarm? Does pain restrict movement and thereby impair repair? Does sleep disruption amplify immune reactivity? Does fear or uncertainty sustain autonomic threat? Does treatment itself create new perturbations?

The therapeutic task becomes the careful alteration of the loop so that the organism can move to the next phase. Sometimes this requires suppression. Sometimes clearance. Sometimes repair. Sometimes exposure removal. Sometimes microbial restoration. Sometimes graded rehabilitation. Sometimes sleep protection. Sometimes social safety. Often it requires multiple coordinated changes.

Enactive immunity also brings responsibility to medical intervention. Every treatment changes the organism–niche field. Antibiotics may save life but alter microbiota. Steroids may suppress inflammation but affect metabolism, infection risk, mood, bone, and repair. Biologics may prevent tissue destruction but alter immune readiness. Surgery may remove damaged tissue but create new repair demands. Reassurance may reduce threat; dismissal may amplify it. A diagnosis may organize care; it may also become a feared identity.

Medicine acts inside the system it treats.

Clinical care can therefore be understood as a perturbation within the organism–niche relation, capable of altering comprehensibility, manageability, meaning, threat physiology, treatment

adherence, and the conditions under which recovery becomes possible (Antonovsky, 1987; Maturana & Varela, 1980).

This does not mean intervention should be avoided. It means intervention should be phase-aware, context-aware, and ethically aware. The question is not whether to act, but how to act in ways that help the organism complete adaptive transitions rather than deepen lock-in.

4.4 Extended Immunity

Immune cognition is extended. The immune system is not confined to the anatomical body. Its regulation extends through the conditions that make coherent organism–niche participation possible. Food systems, air quality, water, housing, microbial ecologies, workplaces, schools, climate, public health infrastructure, antibiotics, vaccines, sanitation, social relationships, caregiving, economic security, sleep rhythms, cultural practices, and medical systems all participate in shaping immune regulation.

This extended view is supported by exposome, social-determinants, environmental-health, and climate-health frameworks, all of which show that biological regulation is shaped by cumulative material, social, ecological, and institutional conditions (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Rappaport & Smith, 2010; Wild, 2005).

This does not mean that immunity is metaphorically social or ecological. It means that immune function depends materially on conditions beyond the skin.

The gut immune system depends on food quality, fibre, microbial exposure, antibiotic history, agricultural practices, food processing, contaminants, and stress physiology. Airway immunity depends on air pollution, allergens, dampness, mould, viral circulation, housing ventilation, occupational exposure, smoking, climate, and urban design. Skin immunity depends on barrier care, temperature, humidity, microbes, chemicals, sunlight, work conditions, and social contact. Neuroimmune regulation depends on sleep, safety, trauma, loneliness, sensory load, movement, and meaning. Mitochondrial immune capacity depends on nutrition, toxins, infection history, circadian rhythms, activity, and metabolic health.

The immune system is therefore extended through the niche conditions that support or undermine regulation.

Air quality, dampness and mould, food systems, microbial exposures, chemical burden, sleep disruption, and climate instability are not external additions to immune biology; they are part of the organism's regulatory field (Institute of Medicine, 2004; World Health Organization, 2021; World Health Organization Regional Office for Europe, 2009).

This has major implications for clinical medicine. If a patient's asthma is worsened by damp housing, treatment cannot be fully coherent if it addresses only airway smooth muscle and inflammation. If inflammatory bowel disease is shaped by food systems, stress, microbiome disruption, and access to care, then medication alone may be necessary but incomplete. If

chronic inflammation is amplified by sleep deprivation, shift work, poverty, pollution, or social threat, then the immune system is being perturbed through extended conditions. If recurrent infection reflects housing crowding, nutrition, occupational exposure, or inadequate public health infrastructure, then immune vulnerability is partly socially organized.

This does not reduce biology to society. It restores biology to its real conditions.

Extended immunity also clarifies why public health is not separate from immunology. Clean water, sanitation, vaccination, air quality, safe housing, nutrition, occupational protection, toxin regulation, maternal-child health, antibiotic stewardship, and climate adaptation are immune interventions at population scale. They shape exposure, resilience, microbial ecology, inflammatory burden, developmental programming, and healing-cycle completion.

Public health protects the conditions under which immune coherence becomes possible.

Public health can therefore be read as immune prevention at population scale: reducing avoidable perturbation, increasing resistance resources, supporting microbial and environmental conditions, and protecting the capacity for healing-cycle completion (Commission on Social Determinants of Health, 2008; World Health Organization, 2021; World Health Organization Regional Office for Europe, 2009).

The extended view also changes the meaning of responsibility. Chronic immune disease should not be framed as a personal failure to regulate, tolerate, eat correctly, think positively, or manage stress. The organism regulates within the niche it is given. A person cannot individually breathe clean air if the air is polluted. They cannot sleep safely if housing is insecure. They cannot restore microbial diversity if food systems are degraded and antibiotics are misused. They cannot reduce allostatic load if social life continually threatens dignity, security, or survival. They cannot complete healing cycles if work, poverty, violence, displacement, or ecological instability continually re-injure them.

Life-coherent medicine therefore must avoid patient blame. It must recognize that many immune phase-locks are sustained by conditions no individual can fully control.

At the same time, extended immunity does not deny personal agency. Patients can often make meaningful changes in sleep, food, movement, exposure awareness, relational boundaries, pacing, stress regulation, treatment adherence, and care-seeking. But such agency is real only when supported by conditions. The goal is not to moralize lifestyle. The goal is to identify which organism–niche relations can be changed, at what scale, by whom, and with what support.

Extended immunity therefore links clinical care to public health and civilizational design. A society that disrupts sleep, pollutes air, degrades food, destabilizes climate, increases toxic burden, fragments communities, accelerates stress, and then sells individual solutions to immune dysfunction is not life-coherent. It is producing anti-salugenic conditions and medicalizing the consequences.

This is not an argument against medicine. It is an argument for medicine to remember the world.

The point is not to replace clinical medicine with social explanation, but to situate clinical intervention within the broader organism–environment relations through which disease risk, recovery capacity, and health inequities are produced (Marmot et al., 2008; Rappaport & Smith, 2010; Wild, 2005).

4.5 Emotive and Evaluative Immunity

Immune cognition is finally evaluative. The immune system continually participates in biological valuation. It distinguishes what supports viability, what threatens it, what can be tolerated, what must be cleared, what must be repaired, what should be remembered, and what should be ignored. This evaluation is not conscious emotion, reflective judgment, or moral appraisal. It is biological valence: the organism's living distinction between conditions that conserve coherence and conditions that endanger it.

This distinction resonates with enactive and affective accounts of cognition in which valuation, salience, interoception, emotional sentience, and organismic need are fundamental to living sense-making rather than late additions to cognition (Barrett et al., 2016; Di Paolo et al., 2018; Peil Kauffman, 2015, 2017, 2020a, 2020b; Varela et al., 1991).

The immune system is evaluative because life itself is not indifferent. A living organism must prefer, in the most basic biological sense, some conditions over others. Oxygen matters. Nutrients matter. Barrier integrity matters. Microbial balance matters. Temperature matters. Tissue continuity matters. Energy matters. Reproduction, repair, rest, movement, relation, and future viability matter. The immune system participates in this field of mattering.

A pathogen is not simply a foreign object. It is evaluated in relation to threat, location, dose, virulence, tissue damage, immune memory, and organismal state. A commensal microbe is not simply non-self. It may be tolerated, cultivated, constrained, or attacked depending on context. Food is not merely antigenic material. It must be tolerated and metabolized. Apoptotic cells must be cleared quietly. Necrotic cells may provoke alarm. Damaged mitochondria may signal danger. Extracellular ATP may indicate injury. Double-stranded DNA in the wrong compartment may indicate viral infection or cellular rupture. Mechanical strain may indicate tissue stress. Pollutants may alter barrier meaning. Social threat may change inflammatory tone.

Immune evaluation is therefore relational. Nothing means the same thing everywhere.

This relational interpretation extends danger and immune-identity theories by emphasizing that immune meaning depends on context, compartment, tissue state, damage, memory, microbial relation, and organismal viability (Matzinger, 2002; Medzhitov, 2008; Pradeu, 2012).

This evaluative dimension helps overcome a limitation of purely mechanistic descriptions. Mechanisms describe how signals are transduced, pathways activated, cells differentiated, and responses executed. Evaluation asks how those signals acquire biological significance for the organism. Why is this microbe tolerated here but attacked there? Why does this antigen become harmless in one context and allergenic in another? Why does this injury resolve in one patient

and become fibrotic in another? Why does this infection clear in one organism and leave persistent dysregulation in another?

The answer lies not in the object alone, but in the organism's evaluative state.

Evaluative immunity is closely related to the organism's preservation and development. Preservation requires boundary protection, defence, containment, clearance, and memory. Development requires openness, tolerance, symbiosis, learning, growth, reproduction, repair, and participation. Coherence requires flexible movement between these attractors. The immune system must continually evaluate whether to close or open, attack or tolerate, inflame or resolve, remember or forget, scar or regenerate, conserve energy or expend it.

Chronic immune disease may therefore be understood as evaluative fixation. The organism continues to evaluate the world through danger when danger has changed. It evaluates food, pollen, microbes, tissue antigens, mechanical stress, chemicals, or internal debris as threats in ways that narrow participation. Or it fails to evaluate genuine threats adequately, leading to infection, malignancy, or unresolved injury. Or it evaluates repair as still necessary after repair has become overbuilt. Or it evaluates activity as unsafe after the initiating insult has passed.

In such states, immune meaning becomes locked.

This is where biological evaluation intersects with lived experience. A patient with chronic immune disease may feel unsafe in their own body. They may experience foods as threats, exertion as danger, environments as hostile, infections as catastrophic, sensations as warning signals, and ordinary life as physiologically expensive. These experiences are not "merely psychological." They may reflect a body whose evaluative systems — immune, neural, endocrine, metabolic, mitochondrial, and interoceptive — have become organized around threat. Subjective experience and immune regulation are not identical, but they are coupled.

This coupling can be understood through allostasis, interoception, neuroimmune signalling, sleep-immune regulation, and mitochondrial stress biology, all of which link bodily state, perceived threat, energy regulation, and immune tone (Barrett et al., 2016; Besedovsky et al., 2012; McEwen, 1998; Picard et al., 2018).

This coupling is clinically important. A patient's fear may amplify immune and autonomic reactivity. But the fear may also be a response to real biological instability. Dismissing the experience as anxiety may deepen threat. Treating every sensation as objective danger may deepen fixation. The clinical task is to help restore trustworthy distinctions: what is dangerous, what is safe enough, what can be attempted, what must be avoided, what needs treatment, what needs time, and what can gradually re-enter ordinary life.

Evaluative immunity therefore supports a medicine of careful reorientation. The organism must be helped to re-evaluate. Not through persuasion alone, but through changed conditions, reduced exposures, controlled inflammation, restored sleep, improved clearance, repaired barriers, safer movement, reliable care, microbial and metabolic support, meaningful explanation, and gradual re-entry into life.

The immune system cannot be argued out of a phase-lock. It must be given conditions under which a new biological evaluation becomes possible.

This is the deep significance of a 5E immune framework. Embodied immunity reminds us that immune cognition is lived through body-state change. Embedded immunity reminds us that immune meaning arises in tissue and niche contexts. Enactive immunity reminds us that immune action creates the next world the organism must interpret. Extended immunity reminds us that immune regulation depends on conditions beyond the body. Evaluative immunity reminds us that immune activity is organized around biological mattering.

Together, these dimensions reframe immunity as organismic sense-making for viable action.

The 5E framing therefore gives molecular immunology a wider interpretive home: immune pathways become the embodied, embedded, enactive, extended, and evaluative means by which the organism conserves coherence under changing conditions (Di Paolo et al., 2018; Maturana & Varela, 1980; Peil Kauffman, 2015, 2017, 2020a, 2020b; Varela et al., 1991).

This reframing does not replace molecular immunology. It gives molecular immunology a richer interpretive field. Pattern-recognition receptors, cytokines, complement, inflammasomes, interferons, T cells, B cells, macrophages, mast cells, fibroblasts, mitochondria, microbiota, and epigenetic states are not less important in a 5E framework. They are more meaningfully situated. They become the embodied, embedded, enactive, extended, and evaluative means by which the organism conserves coherence.

The immune system is therefore not an internal police force, not a battlefield, and not a simple classification machine. It is a living participant in the organism's ongoing answer to the question: under these conditions, how can life continue?

5. Preservation, Development, and Coherence: The Attractor Logic of Immune Life

If immunity is a form of embodied, embedded, enactive, extended, and evaluative organismic cognition, then its deepest logic cannot be reduced to defence alone. Defence is essential, but it is not the whole of immune life. The organism must protect itself, but it must also remain open to nourishment, relation, growth, microbial partnership, reproduction, repair, learning, and participation. It must preserve itself without closing against the very world that sustains it.

Immune life therefore moves within a dynamic field of three attractors: preservation, development, and coherence.

This triadic framing draws on organismic, enactive, and affective accounts of living systems in which self-preservation, development, and coherence are not separate functions but interdependent tendencies of viable life (Di Paolo et al., 2018; Maturana & Varela, 1980; Peil Kauffman, 2015, 2017, 2020b; Varela et al., 1991).

Preservation is the organism's need to conserve boundary integrity, protect its living organization, defend against invasion, contain damage, clear danger, and remember what has threatened viability. Without preservation, the organism becomes vulnerable to infection, toxicity, injury, malignant transformation, uncontrolled permeability, and collapse. Preservation is the immune logic of defence, containment, vigilance, and survival.

Development is the organism's need to remain open to the world in ways that allow growth, learning, symbiosis, tolerance, reproduction, repair, and adaptation. Without development, the organism becomes rigid, hypervigilant, overprotected, isolated, inflamed, allergic, fibrotic, and unable to participate. Development is the immune logic of openness, tolerance, plasticity, mutualism, and transformation.

Coherence is the living capacity to move flexibly between preservation and development without becoming trapped in either. It is not a compromise in the weak sense. It is the higher-order coordination that allows the organism to protect itself when protection is needed, open when openness is possible, repair when repair is required, remember without fixation, tolerate without collapse, and return to ordinary living after perturbation.

Immune health is not preservation alone and not openness alone. It is coherent movement between protection and participation.

This view parallels allostatic and salutogenic models of health, where health depends not on static balance but on flexible adaptive movement, coherence, and sufficient resources for meaningful participation (Antonovsky, 1979, 1987; McEwen, 1998; Sterling & Eyer, 1988).

This attractor logic helps explain why immune disease often appears paradoxical. The same organism may be hyperreactive in one domain and vulnerable in another. A patient may have

allergic inflammation and recurrent infections. Another may show autoimmune activity and impaired viral control. Another may have chronic inflammation and poor repair. Another may have fibrosis and fragility. These are not contradictions when immunity is understood as a dynamic field rather than a single linear function. The organism may be locked into preservation in one tissue, underdeveloped in tolerance elsewhere, depleted in resilience, and unable to coordinate transitions across levels.

Preservation, development, and coherence are therefore not separate compartments. They are dynamic tendencies within the living organism.

5.1 Preservation: Boundary, Defence, Containment, and Memory

Preservation is the most familiar face of immunity. It includes the organism's capacity to detect danger, defend against pathogens, contain injury, neutralize toxins, clear damaged cells, prevent malignant expansion, and remember prior threats. Preservation is indispensable. Without it, life is exposed.

Classical and modern immunology have rightly emphasized this protective dimension through innate recognition, pathogen defence, complement activation, inflammatory signalling, immune memory, and antimicrobial response (Janeway, 1989; Medzhitov & Janeway, 1997; Ricklin et al., 2010).

The immune system must know how to close.

It must close barriers against invasion. It must activate inflammation when tissues are injured. It must recruit neutrophils, macrophages, complement, antibodies, cytotoxic cells, fever, coagulation, and antimicrobial programs when threat exceeds tolerance. It must prevent microbes from crossing from tolerated niches into sterile compartments. It must recognize altered self when cells become infected, stressed, senescent, or malignant. It must generate memory so that future threats can be met more rapidly.

In acute illness, preservation may dominate appropriately. Fever, fatigue, anorexia, pain, swelling, and withdrawal can all serve preservation. The organism reallocates energy away from ordinary activity toward defence and repair. It narrows participation to protect integrity. It changes appetite, movement, sleep, and social behaviour. It temporarily becomes less open so that life can continue.

Acute preservation involves coordinated immune, metabolic, behavioural, and allostatic shifts that can be adaptive when they are proportionate and time-limited (McEwen, 1998; Naviaux, 2014; Sterling & Eyer, 1988).

This is not pathology. It is adaptive closure.

Pathology begins when preservation cannot relax, update, or hand over to resolution, clearance, repair, and reintegration. Defence that should be transitional becomes chronic. Vigilance that should protect becomes hypervigilance. Memory that should guide becomes fixation.

Containment that should limit damage becomes isolation of damaged tissue. Repair that should restore becomes fibrosis. The organism remains in a posture of threat.

Many immune diseases can be interpreted as preservation locks. Autoimmunity may involve a defensive or clearance process that has lost tolerance for certain self-structures. Autoinflammation may involve innate danger systems that remain overactive. Allergy may involve barrier and type 2 immune programs that evaluate ordinary environmental exposures as threats. Fibrosis may involve repair programs that continue to preserve boundary integrity by overbuilding tissue. Chronic pain and fatigue may involve neuroimmune preservation states that continue to restrict activity long after the initiating danger has changed.

Preservation locks may involve danger signalling, trained innate memory, unresolved inflammation, mitochondrial DAMPs, fibrotic repair, and immune recognition patterns that remain active beyond their adaptive window (Matzinger, 2002; Naviaux, 2014; Netea et al., 2016; West & Shadel, 2017; Wynn & Ramalingam, 2012).

In each case, the problem is not that preservation is wrong. The problem is that preservation has become disproportionate, misplaced, persistent, or unable to transition.

A life-coherent clinical grammar therefore asks: What is the organism preserving? What threat does this response imply? What history made this preservation strategy necessary? What damage is it now causing? What would allow preservation to soften without abandoning safety?

These questions matter because aggressive suppression of preservation can be harmful when genuine danger remains. Conversely, failure to interrupt excessive preservation can lead to irreversible damage. The clinical art lies in discerning whether the organism still needs defence, whether defence has become self-sustaining, and what transition is now possible.

5.2 Development: Openness, Tolerance, Symbiosis, Growth, and Repair

Development is the less visible but equally essential dimension of immune life. The organism must not only defend; it must learn how to live with what is not itself. It must tolerate food, cultivate microbial partners, permit pregnancy, allow tissue growth, support repair, adapt to changing environments, and participate in relational worlds.

The immune system must know how to open.

Food tolerance is an immune achievement. The gut must encounter vast quantities of foreign proteins without reacting destructively. Microbial tolerance is an immune achievement. The organism must live with bacteria, fungi, viruses, and phages that contribute to digestion, immune education, barrier function, and metabolic signalling. Tissue tolerance is an immune achievement. The organism must limit collateral damage during infection and inflammation. Developmental tolerance is an immune achievement. The infant immune system must learn the world without treating everything new as danger.

Tolerance is actively constructed through barrier tissues, regulatory immune circuits, microbial ecology, mucosal education, and developmental immune calibration rather than through mere absence of response (Belkaid & Hand, 2014; Hooper et al., 2012; Medzhitov, 2008).

Repair is also developmental. After injury, the organism must not simply close the wound. It must rebuild a livable tissue architecture. It must coordinate inflammation, proliferation, matrix deposition, vascular change, epithelial restoration, nerve adaptation, and functional reintegration. Repair is not merely the end of defence. It is a developmental process by which the organism recovers the possibility of participation.

Repair requires coordination among inflammation, macrophage state, fibroblast activity, extracellular matrix remodelling, angiogenesis, epithelial restoration, and resolution pathways (Fullerton & Gilroy, 2016; Serhan & Savill, 2005; Wynn et al., 2013; Wynn & Ramalingam, 2012).

Development therefore involves openness with discernment. It is not passive permissiveness. The organism does not simply allow everything. It learns which relations can be included without loss of coherence. Tolerance is active boundary intelligence.

Disease can arise when developmental openness is insufficient, excessive, or disorganized.

When openness is insufficient, the organism becomes hyperreactive. It treats food, pollen, commensals, tissue antigens, innocuous particles, or ordinary mechanical stimuli as threats. Allergic disease, some autoimmune patterns, inflammatory bowel disease, and certain barrier disorders may reflect failures of developmental tolerance. The organism cannot remain open without mobilizing defence.

When openness is excessive or poorly bounded, the organism may become vulnerable. Barrier permeability, chronic infection, dysbiosis, immune exhaustion, immunodeficiency, impaired tumour surveillance, or unresolved biofilm states may reflect failure of adequate preservation within development. The organism remains too open, too permissive, or too unable to contain.

When repair is disorganized, development itself becomes pathological. Fibrosis, hypertrophic scarring, airway remodelling, strictures, adhesions, vascular remodelling, and chronic tissue stiffness may be interpreted as failed developmental reintegration. The organism builds, but it does not restore coherence.

This shows why development cannot be separated from preservation. Too much openness without protection threatens survival. Too much protection without openness prevents life. Development requires preservation, and preservation must eventually serve development.

This interdependence reflects the larger organismic requirement that living systems remain open enough to develop while conserving the boundaries that make continued life possible (Maturana & Varela, 1980, 1987; Varela et al., 1991).

A life-coherent clinical grammar therefore asks: What form of openness has been lost? What form of tolerance has failed? What relation has become impossible? What repair has not completed? What developmental pathway has been blocked? What conditions would allow the organism to reopen safely?

In practice, this may involve restoring barrier integrity, supporting microbial ecology, reducing unnecessary exposures, improving nutrition, protecting sleep, treating infection, reducing inflammation, rehabilitating movement, re-establishing trust in bodily signals, or changing social and environmental conditions. Development is not a vague ideal. It is enacted through concrete biological and niche conditions.

5.3 Coherence: Flexible Movement Between Protection and Participation

Coherence is the organism's capacity to move between preservation and development in a timely, proportionate, and context-sensitive way. It is the dynamic coordination that allows immune life to remain neither rigidly defended nor dangerously open.

Coherence means that surveillance can become defence when danger appears. Defence can become containment when spread is limited. Containment can become resolution when threat decreases. Resolution can become clearance when inflammatory work is done. Clearance can become repair when debris is removed. Repair can become memory when learning is needed. Memory can become readiness without becoming fixation. The organism can then re-enter ordinary health-cycle participation.

Coherence is therefore rhythmic. It depends on timing.

This temporal emphasis is central to allostasis, resolution biology, and cell danger response theory: a response that is adaptive in one phase can become pathological if it persists beyond its proper window (McEwen, 1998; Naviaux, 2014; Serhan, 2007; Sterling & Eyer, 1988).

A response that is healthy for hours may be damaging for months. A cytokine that is protective during acute infection may become pathological when chronically expressed. A fibrotic response that stabilizes a wound may disable an organ when persistent. A fatigue response that conserves energy during acute illness may become disabling when locked. A fear response that protects after injury may become constricting when it prevents all re-engagement.

Disease often arises not from the existence of a response, but from its failure to change phase.

Chronic inflammation, fibrosis, trained immunity, mitochondrial danger signalling, and persistent sickness or conservation states can all be interpreted as examples of adaptive programs that fail to transition appropriately (Naviaux, 2014, 2020; Netea et al., 2016; West & Shadel, 2017; Wynn & Ramalingam, 2012).

This is why immune health cannot be defined simply as low inflammation. Inflammation may be necessary. Nor can it be defined as maximal immune strength. A maximally aggressive immune

system would be destructive. Nor can it be defined as tolerance alone. Excessive tolerance can permit infection or malignancy. Immune health is the capacity for appropriate phase-shifting.

This view integrates classical defence, tolerance, allostasis, and resolution biology into a single dynamic understanding of immune health as flexible regulatory capacity rather than maximal activation, minimal inflammation, or passive tolerance (Antonovsky, 1987; Janeway, 1989; McEwen, 1998; Serhan & Savill, 2005).

The organism must be able to change its mind biologically.

Coherence also requires scale integration. Molecular, cellular, tissue, organ-system, behavioural, relational, and ecological processes must not work against one another. A patient may receive a biologic agent that improves inflammatory markers while poor sleep, unsafe housing, persistent exposure, metabolic overload, and social stress continue to erode regulatory capacity. Another may adopt lifestyle changes while untreated destructive inflammation continues to damage tissue. Another may receive excellent pharmacological suppression but no rehabilitation, leaving the organism unable to re-enter movement and participation.

Coherence requires that interventions align with the organism's phase-state and life conditions.

This is the basis of phase restoration. The clinician asks not only what is elevated, suppressed, positive, negative, inflamed, or deficient. The clinician asks what transition is needed now. Does the organism need defence? Does it need suppression of destructive defence? Does it need resolution? Does it need clearance? Does it need repair? Does it need rehabilitation? Does it need exposure removal? Does it need microbial reconstitution? Does it need sleep? Does it need social safety? Does it need time?

The answer may change over the course of illness. A patient in an acute flare may need strong anti-inflammatory therapy. The same patient later may need clearance, repair, conditioning, sleep restoration, and re-entry into meaningful life. A patient with infection may need antimicrobial defence first, then resolution and microbiome repair later. A patient with fibrosis may need inflammation control, antifibrotic strategy, mechanical rehabilitation, and prevention of further injury. A patient with post-infectious dysregulation may need pacing, autonomic support, mitochondrial recovery, immune monitoring, and gradual reintegration rather than forced exertion.

Coherence is not one intervention. It is the right sequence.

Phase restoration therefore requires therapeutic timing: suppression, antimicrobial defence, resolution, clearance, repair, rehabilitation, sleep restoration, exposure reduction, and social support may each be necessary at different moments in the organism's recovery trajectory (Antonovsky, 1987; McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005).

5.4 Pathological Lock-In of the Attractors

Each attractor has healthy and pathological expressions.

The same biological tendency can therefore support life in one context and restrict it in another, depending on timing, tissue state, intensity, regulatory resources, and the organism's capacity to transition (Peil Kauffman, 2015; McEwen, 1998; Naviaux, 2014).

Preservation is healthy when it protects boundary integrity, contains danger, clears threat, and preserves life. It becomes pathological when it hardens into chronic inflammation, allergy, autoimmunity, fibrosis, hypervigilance, pain, fatigue, or excessive closure.

Development is healthy when it supports tolerance, symbiosis, learning, repair, growth, and openness. It becomes pathological when openness becomes excessive permeability, infection susceptibility, dysregulated expansion, tumour permissiveness, maladaptive remodelling, or failure to contain.

Coherence is healthy when the organism moves flexibly between protection and participation. It becomes pathological when phase transitions fail and the organism becomes locked in unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration.

This is the central phase-locking claim of the manuscript: pathology is often not the mere presence of defence, openness, or repair, but their persistence, misplacement, excess, insufficiency, or failure to complete adaptive transition (Fullerton & Gilroy, 2016; McEwen & Stellar, 1993; Naviaux, 2014; Serhan, 2007).

This can be summarized as follows:

Attractor	Healthy immune expression	Pathological lock-in
Self-preservation	Defence, containment, clearance, boundary protection, threat memory	Chronic inflammation, allergy, autoimmunity, fibrosis, hypervigilance, pain-fatigue restriction
Self-development	Tolerance, symbiosis, learning, growth, repair, openness	Excessive permeability, infection susceptibility, dysregulated expansion, failed containment, disorganized repair
Coherence	Flexible movement between protection and participation	Maladaptive phase-locking, failed resolution, failed clearance, failed re-entry into health-cycle participation

This table is not a taxonomy of diseases. It is an orientation device. It helps the clinician ask what kind of immune logic is currently dominant and whether that logic is adaptive, insufficient, excessive, or locked.

A patient with severe infection may need stronger preservation. A patient with uncontrolled autoimmunity may need preservation to be restrained. A patient with food intolerance, dysbiosis, or barrier reactivity may need developmental tolerance restored. A patient with fibrosis may need repair redirected. A patient with chronic post-infectious fatigue may need help exiting conservation mode and safely re-entering activity. A patient with recurrent flares may need investigation of the conditions that keep triggering preservation before development can stabilize.

The point is not to force patients into three boxes. The point is to see immune life as movement within a field.

5.5 Clinical Meaning of the Attractor Logic

The attractor logic helps medicine avoid two common errors.

The first error is overdefensive medicine. In this mode, disease is interpreted primarily as threat, and treatment becomes suppression, elimination, control, or attack. This approach is sometimes necessary and lifesaving. But if generalized, it can obscure tolerance, repair, resilience, meaning, and niche conditions. The immune system becomes a problem to control rather than a living process to understand and guide.

The second error is overdevelopmental medicine. In this mode, disease is interpreted primarily as blocked growth, stress, lifestyle imbalance, trauma, toxicity, or loss of harmony, while destructive inflammation, infection, immune deficiency, malignancy, or tissue damage may be underestimated. This can lead to undertreatment, delayed diagnosis, or patient blame.

Life-coherent systems immunology requires both protection and participation. It respects the necessity of decisive biomedical intervention while also recognizing that suppression alone may not restore health. It values lifestyle, environment, relationship, and meaning while refusing to reduce disease to personal behaviour or vague imbalance. It seeks a clinically disciplined middle path: phase-aware, mechanism-informed, organism-centered care.

This middle path preserves biomedical precision while widening clinical attention to the organism's regulatory state, resistance resources, tissue context, and conditions for restored participation (Antonovsky, 1987; McEwen, 1998; Medzhitov, 2008; Naviaux, 2014).

The attractor logic also helps clarify the physician's task. The physician does not simply oppose disease. The physician helps identify the organism's current regulatory attractor, assess whether it remains adaptive, and support movement toward the next coherent phase. Sometimes the physician must strengthen preservation. Sometimes soften it. Sometimes protect development. Sometimes restrain it. Sometimes restore coherence by coordinating multiple levels at once.

This requires humility because the organism may not move according to the clinician's preferred timeline. A system that has been locked for years may not transition rapidly. A patient with low regulatory margins may flare when pushed too hard. A patient with destructive inflammation may deteriorate if treated too gently. A patient with post-infectious dysregulation may relapse with premature exertion. A patient with trauma or dismissal may need trust before adherence is possible. A patient in poverty or unsafe housing may lack the conditions required for biological reintegration.

The attractor logic therefore leads naturally into salutogenesis. If coherence is the flexible movement between preservation and development, then the question becomes: what conditions make coherence possible? What resources allow the organism to understand, manage, and find

meaningful orientation within perturbation? What biological and social supports allow healing cycles to complete?

Immune coherence does not arise from immune mechanisms alone. It requires a field of resistance resources, rhythms, relationships, and meanings that make adaptive movement affordable.

The attractor logic also links directly to salutogenesis: coherence depends on biological mechanisms, but also on resources, intelligibility, manageability, meaningful orientation, and supportive organism–niche conditions (Antonovsky, 1979, 1987; Commission on Social Determinants of Health, 2008).

Preservation protects life. Development opens life. Coherence allows life to continue moving between the two.

Part III. Health, Healing, and Phase-Locking

6. Salutogenesis: Coherence, Meaning, and Resistance Resources

If immunity is organismic sense-making, then immune health cannot be understood only as the absence of inflammatory activation, autoantibodies, infection, tissue damage, or symptoms. It must also be understood as the organism's capacity to remain coherent under changing conditions. This is where salutogenesis becomes essential. Salutogenesis asks not only why people become ill, but how health is generated, sustained, recovered, and renewed in the face of perturbation.

This framing follows Antonovsky's salutogenic model, which shifts attention from disease causation alone toward the conditions, resources, and coherence patterns that allow health to be maintained under stress (Antonovsky, 1979, 1987).

In a life-coherent systems immunology, salutogenesis supplies the coherence-and-resource field within which biological healing becomes possible.

In this sense, salutogenesis complements pathogenesis: it does not replace disease mechanisms, but situates them within the organism-person's capacity to mobilize resistance resources and preserve coherence under demand (Antonovsky, 1987; McEwen, 1998).

This is a crucial shift. Pathogenesis asks how disease arises. Salutogenesis asks how living systems maintain movement toward health despite stress, injury, exposure, infection, loss, uncertainty, and constraint. Both questions are necessary. Without pathogenesis, medicine risks vagueness. Without salutogenesis, medicine risks becoming a science only of damage.

Immune disease requires both.

The immune system is constantly exposed to perturbation. Microbes, food antigens, allergens, toxins, pollutants, mechanical stress, cellular debris, damaged mitochondria, psychological threat, metabolic overload, sleep disruption, thermal stress, injury, medications, and social adversity all alter the organism's regulatory field. The question is not whether perturbation occurs. Perturbation is part of life. The deeper question is whether the organism has sufficient coherence and resources to meet perturbation, complete adaptive responses, and return to ordinary participation.

Salutogenesis begins from this dynamic reality. Health is not a fixed state of perfect equilibrium. It is the capacity to navigate change without losing organismic coherence. In immune terms, this means the capacity to detect danger without becoming chronically vigilant, defend without remaining inflamed, tolerate without collapsing boundaries, repair without overbuilding, remember without fixation, and re-enter ordinary health-cycle rhythms after disruption.

The central salutogenic concept is the sense of coherence. This is not merely optimism, positivity, or psychological resilience in a superficial sense. It refers to the organism-person's

lived capacity to experience life as sufficiently comprehensible, manageable, and meaningful to mobilize resources in the face of stress.

Antonovsky defined sense of coherence through these three core dimensions — comprehensibility, manageability, and meaningfulness — as a central determinant of how persons meet stress and mobilize resistance resources (Antonovsky, 1987).

Comprehensibility means that events can be made intelligible enough to orient action. A patient who understands what is happening in their body, why symptoms fluctuate, what warning signs matter, what treatments are intended to do, and what recovery may realistically require is less likely to be trapped in chaos. In immune disease, uncertainty itself can become an additional perturbation. Unexplained symptoms, contradictory diagnoses, dismissive encounters, unpredictable flares, and fragmented care can amplify threat physiology. Explanation does not cure disease by itself, but it can reduce disorganization and support adaptive participation.

Manageability means that the person has access to resources sufficient to meet the demands placed upon them. These resources may be biological, clinical, psychological, social, economic, environmental, or spiritual. Medication, food, rest, safe housing, clean air, supportive relationships, income, knowledge, transport, laboratory monitoring, specialist care, rehabilitation, sleep, and time are all part of manageability. A treatment plan that is theoretically correct but practically unmanageable is not life-coherent. It may fail not because the patient lacks will, but because the organism-person lacks the resources required to enact it.

Meaningfulness means that the struggle can be connected to values, relationships, identity, purpose, care, or future possibility. Meaningfulness does not romanticize suffering. It does not imply that illness is good, deserved, or spiritually necessary. Rather, it recognizes that human organisms mobilize differently when life still feels worth moving toward. A patient who can connect treatment to caring for a child, returning to work, creating, serving, learning, walking again, sleeping peacefully, or simply reclaiming dignity may have a different field of participation than one who experiences illness as meaningless entrapment.

These three dimensions — comprehensibility, manageability, and meaningfulness — are not external to immune biology. They shape the organism's allostatic field. Confusion, helplessness, and meaning collapse can amplify threat, dysregulate sleep, impair adherence, increase sympathetic tone, worsen inflammation, and narrow behavioural options. Understanding, support, and meaning can reduce unnecessary threat load, improve self-regulation, support treatment engagement, and create conditions in which biological healing becomes more affordable.

This link between lived orientation and biology is consistent with allostatic models in which stress, threat, sleep, neuroendocrine regulation, behaviour, and inflammatory tone are dynamically coupled (Barrett et al., 2016; McEwen, 1998; McEwen & Stellar, 1993).

This does not mean that immune disease is caused by poor attitude or cured by positive thinking. That would be a serious error. Salutogenesis is not patient blame in softer language. It is the recognition that living systems require resources and orientation to heal. A person cannot

meaningfully manage lupus, asthma, inflammatory bowel disease, rheumatoid arthritis, long COVID, chronic sinusitis, vasculitis, or fibrotic lung disease through mindset alone. But neither can the biology of chronic immune disease be fully separated from the conditions under which a person must live, interpret, cope, rest, act, and receive care.

Salutogenesis therefore belongs inside organism-centered immunology because the immune system is not isolated from the lived field of the organism-person.

The concept of resistance resources is especially important. Generalized resistance resources are the broad supports that help organisms and persons meet stress across many situations: adequate nutrition, sleep, social support, stable housing, clean air, education, income security, cultural belonging, physical fitness, emotional regulation, access to care, safe environments, and trustworthy institutions. Specific resistance resources are the targeted supports needed for particular challenges: an inhaler for asthma, insulin for diabetes, biologic therapy for inflammatory disease, antimicrobial treatment for infection, mold remediation for damp housing, pacing strategies after post-viral illness, physical therapy after deconditioning, or renal protection in lupus nephritis.

Antonovsky's generalized resistance resources provide the conceptual foundation for this distinction, while public health and social-determinants frameworks show that such resources are also socially, institutionally, and environmentally distributed (Antonovsky, 1979, 1987; Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

Health emerges when demands and resources remain in workable relation. Disease worsens when demands chronically exceed resources.

This demand-resource imbalance is one pathway by which salutogenic weakness becomes allostatic burden, reducing the organism's capacity to adapt, recover, and return to ordinary participation (McEwen, 1998; McEwen & Stellar, 1993; Sterling & Eyer, 1988).

In immune-mediated illness, this imbalance may become biological. Repeated demands without adequate resources can increase allostatic load, impair sleep, alter metabolism, reduce mitochondrial reserve, disturb barrier function, dysregulate neuroendocrine rhythms, and amplify inflammatory tone. A person exposed to pollution, poor housing, food insecurity, social threat, shift work, trauma, infection, or economic stress may have reduced immune margins. The organism may still attempt to defend, repair, and adapt, but the cost rises. Eventually, adaptive responses become less affordable.

Salutogenesis therefore introduces the idea of immune affordability. Can the organism afford to mount inflammation? Can it afford to resolve it? Can it afford fever, rest, appetite reduction, tissue repair, mitochondrial reprogramming, lymphatic clearance, sleep, and rehabilitation? Can the person afford time off work, medication, safe food, clean housing, follow-up visits, and reduced exposure? A healing cycle that cannot be afforded biologically or socially may remain incomplete.

Immune affordability can be read through allostatic theory: adaptive responses require energy, regulatory capacity, recovery time, and resources, and they become harmful when the cost of adaptation exceeds the organism's margins (McEwen, 1998; Picard et al., 2018; Sterling & Eyer, 1988).

This helps explain why chronic disease often persists not because the organism lacks intelligence, but because the conditions for completion are absent.

A patient with chronic inflammatory disease may receive appropriate immunosuppression, but if sleep remains disrupted, housing remains damp, food remains inflammatory or inadequate, work remains exhausting, stress remains unrelenting, and care remains fragmented, the organism may not regain coherence. Conversely, a patient may improve when medication is combined with rest, explanation, exposure reduction, nutritional support, movement rehabilitation, social safety, and restored rhythm. The difference lies not in "holism" as an ideology, but in whether the total field supports phase transition.

Salutogenesis also clarifies the relationship between stress and immune disease. Stress should not be treated as a vague psychological explanation. Stress is the organism's encounter with demand relative to capacity. It becomes immunologically relevant when it alters neuroendocrine regulation, sleep, metabolism, behaviour, barrier integrity, microbial ecology, inflammation, pain, fatigue, and tissue repair. Chronic stress is not merely a feeling. It is repeated or sustained demand that consumes regulatory margins.

This interpretation is consistent with allostatic-load theory, which treats stress biology as the cumulative physiological cost of repeated adaptation across neuroendocrine, immune, metabolic, cardiovascular, and behavioural systems (McEwen, 1998; McEwen & Stellar, 1993).

This is why allostatic load follows naturally from salutogenesis. The organism survives by adapting, but adaptation has cost. When cost accumulates faster than recovery, immune coherence becomes more fragile. The organism may become more reactive, less tolerant, slower to repair, less able to clear debris, more prone to flare, more vulnerable to infection, or more likely to enter shutdown states.

Allostatic load therefore provides a biological bridge between salutogenic resource insufficiency and immune dysregulation, especially when recovery does not adequately follow repeated adaptation (McEwen, 1998; Sterling & Eyer, 1988).

Salutogenesis therefore does not replace mechanism. It identifies the field in which mechanisms become sustainable or unsustainable.

The concept of meaning also requires special care in immune disease. Meaning is often misunderstood as a psychological overlay added to "real biology." But meaning, in the lived human organism, shapes attention, motivation, autonomic regulation, sleep, social connection, adherence, pain perception, energy allocation, and willingness to engage in difficult care. A patient who understands their disease as a navigable process may participate differently from one who feels abandoned inside an inexplicable body. A patient whose symptoms are believed may

regulate differently from one who is repeatedly dismissed. A patient who can see a pathway toward life may tolerate temporary restrictions better than one who experiences only indefinite loss.

Meaning is not a substitute for treatment. It is part of the organism-person's regulatory ecology.

This has practical clinical implications. The physician's explanation is not merely informational. It can become a salutogenic intervention. To explain immune disease as a pattern of unfinished defence, clearance, repair, or reintegration may help patients understand why symptoms persist, why pacing matters, why suppression may be necessary, why exposure reduction may be relevant, why sleep is not optional, why rehabilitation must be sequenced, and why recovery may require both biomedical and life-context changes. A coherent explanation can reduce fear without minimizing illness.

But explanation must be honest. False certainty is anti-salutogenic. Overpromising recovery, claiming a single root cause, dismissing conventional treatment, exaggerating contested mechanisms, or implying that patients can heal if they simply adopt the correct mindset undermines trust. Salutogenesis requires truthful orientation. The clinician can say: we do not know everything; your suffering is real; these mechanisms may be involved; this is what we can test; this is what we can treat; this is what we can support; this is how we will monitor; this is what would count as improvement; this is where uncertainty remains.

Such honesty can itself restore coherence.

A life-coherent systems immunology also distinguishes salutogenesis from salugenesis. Salutogenesis concerns the generation and maintenance of health at the level of orientation, resources, coherence, and life conditions. Salugenesis concerns the biological generation of healing: the molecular, cellular, tissue, metabolic, mitochondrial, microbial, and organismal processes through which damage is resolved and function restored. The two are inseparable but not identical. A patient may have excellent meaning and support but still require biological treatment. Another may receive excellent biological treatment but lack the life conditions needed for sustained recovery.

Salutogenesis names the coherence-and-resource field of health generation, while cell danger response biology helps clarify how molecular and cellular healing programs may remain incomplete when perturbation, danger signalling, or recovery conditions persist (Antonovsky, 1979, 1987; Naviaux, 2014, 2020).

Salutogenesis provides the field. Salugenesis performs the biological work. Immune coherence requires both.

This distinction protects the framework from reducing healing either to psychosocial meaning alone or to molecular mechanism alone; both organismic resources and biological repair processes are required for durable recovery (Antonovsky, 1987; Naviaux, 2014; Serhan & Savill, 2005).

This distinction prevents two errors. The first is biomedical narrowing, in which disease is treated only at the level of pathways while the patient's coherence field collapses. The second is psychosocial overreach, in which support, meaning, or lifestyle are treated as sufficient while active pathology is undertreated. Life-coherent medicine must refuse both reductions.

The salutogenic question in immune disease can therefore be stated simply: What resources, rhythms, relationships, meanings, treatments, and environmental conditions are needed for this organism to complete the next adaptive transition?

For one patient, the answer may be rapid suppression of destructive inflammation. For another, it may be antimicrobial treatment and drainage. For another, it may be allergen control and barrier restoration. For another, it may be fibrosis prevention and pulmonary rehabilitation. For another, it may be pacing, sleep protection, autonomic stabilization, and careful reconditioning. For another, it may be safe housing, food security, social support, and reduction of toxic exposures. For many, it will be a sequence.

Salutogenesis teaches that healing is rarely produced by one intervention alone. It arises when the organism's demands and resources are brought back into workable relation.

This view also reframes resilience. Immune resilience is not the capacity to endure unlimited stress without consequence. That is a dangerous myth. Resilience is the capacity to absorb perturbation, adapt, recover, learn, and re-enter life without losing coherence. This definition is closer to allostatic and salutogenic resilience than to simple toughness: resilience depends on margins, recovery, resources, and the ability to return after adaptive mobilization (Antonovsky, 1987; McEwen, 1998; Sterling & Eyer, 1988). True resilience requires margins. It requires rest after effort, repair after injury, safety after threat, nourishment after depletion, and support after overload. A society that demands endless resilience while eroding the conditions for recovery is not promoting health. It is increasing allostatic load.

Salutogenesis therefore points beyond the clinic. Public health becomes the protection of generalized resistance resources. Clean air, safe water, nutritious food, adequate housing, education, social trust, ecological stability, meaningful work, equitable care, maternal-child protection, and climate resilience are not merely social goods. Social-determinants, environmental-health, air-quality, and climate-health frameworks all support this broader view: the conditions that protect health are distributed through institutions, environments, and public systems as much as through individual clinical care (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Marmot et al., 2008; World Health Organization, 2021). They are immune-coherence resources. They help populations complete adaptive cycles rather than accumulate unresolved biological stress.

At the civilizational level, this becomes decisive. A civilization that generates chronic perturbation while weakening resistance resources becomes anti-salutogenic. It produces bodies that must defend more, repair more, tolerate more, detoxify more, adapt more, and recover with fewer margins. It then interprets the resulting immune disease as isolated individual pathology. A life-coherent civilization would do the opposite: protect the conditions under which organisms

can maintain health cycles, complete healing cycles, and participate in life without chronic immune threat.

Salutogenesis thus prepares the ground for the health cycle and healing cycle. Before we can describe how the organism moves through biological phases of healing, we must understand that healing requires a field. The organism needs coherence, resources, time, rhythm, safety, nourishment, care, and meaning. Without these, even sophisticated immune mechanisms may remain trapped in unfinished work.

Health is not merely what remains when disease is absent. Health is generated. It is supported. It is resourced. It is lived.

And when those health-generating conditions are lost, the immune system may continue to defend long after life needs it to move again.

7. Naviaux's Health Cycle and Healing Cycle

Salutogenesis gives the coherence-and-resource field within which healing becomes possible. The next question is biological: how does the organism actually move through health, injury, healing, and return? For this, the distinction between the health cycle and the healing cycle is essential.

The organism is not normally in a state of continuous defence. Ordinary health is rhythmic. It involves wakeful activity, nourishment, digestion, movement, work, play, social connection, nature contact, learning, rest, detoxification, waste removal, sleep, repair, and renewed participation. These are not merely lifestyle variables around the edge of biology. They are the recurring conditions through which the organism maintains coherence.

The health cycle is the organism's ordinary rhythm of living.

This framing extends Naviaux's cell danger response biology by distinguishing ordinary health-cycle participation from the temporary protective reorganization that occurs during danger, injury, infection, or repair (Naviaux, 2014, 2020).

A healthy organism wakes, moves, eats, senses, relates, metabolizes, eliminates, repairs, sleeps, and begins again. It participates in the niche without losing itself. It encounters microbes, food antigens, pollutants, minor injuries, emotional demands, social signals, and environmental changes, yet it remains able to absorb, respond, and return. Immune activity is present throughout this cycle, but it does not dominate the organism's life. It remains integrated with metabolism, nervous system regulation, tissue maintenance, microbial ecology, endocrine rhythm, and behaviour.

In this sense, health is not immunological silence. It is immunological participation without pathological capture.

Modern immunology supports this view: immune activity is continuous in health through surveillance, tolerance, apoptotic-cell clearance, microbial negotiation, tissue repair, and readiness, rather than being present only during overt disease (Belkaid & Hand, 2014; Hooper et al., 2012; Medzhitov, 2008; Ravichandran & Lorenz, 2007).

The immune system is always active in health. It monitors barriers, clears apoptotic cells, maintains tolerance, samples microbial and dietary antigens, supports tissue repair, removes debris, surveils for malignant transformation, shapes microbiome relations, and maintains readiness. But this activity remains phase-appropriate. It does not seize the whole organism into prolonged defence. It supports ordinary living.

When perturbation exceeds the organism's routine adaptive capacity, the organism exits the health cycle and enters a healing cycle. This may occur after infection, injury, toxic exposure, surgery, trauma, overexertion, acute inflammation, allergen exposure, tissue damage, or major psychosocial stress. The organism shifts priorities. Ordinary activity is reduced. Energy is

reallocated. Inflammation, defence, containment, clearance, repair, and reorganization become dominant.

This exit from the health cycle is not disease by itself. It is often the beginning of healing.

The healing cycle is the organism's organized response to disruption. It begins when ordinary coherence has been disturbed and the organism must temporarily reorganize around protection and repair. Danger is sensed. Inflammatory pathways activate. Metabolism shifts. Mitochondria alter signalling and energy production. Barriers tighten or leak depending on context. Immune cells migrate. Coagulation and complement may participate. Pain and fatigue may reduce movement. Appetite may change. Sleep needs may increase. Behaviour may narrow. The organism becomes less available for ordinary participation because biological work must be completed.

The cell danger response provides a mechanistic basis for this temporary reorganization, linking mitochondrial signalling, metabolic shifts, inflammation, behaviour, and healing programs during threat or injury (Naviaux, 2014, 2020).

This temporary narrowing is adaptive when it serves completion. The problem begins when the healing cycle does not finish.

A coherent healing cycle moves through recognizable phases: perturbation, danger sensing, defence, containment, resolution, clearance, repair, remodelling, memory, adaptation, and reintegration. These phases are not always linear. They overlap, recur, and vary by tissue and disease. Yet the sequence captures an essential truth: healing is not complete when inflammation begins, nor when symptoms temporarily improve, nor when tissue is patched. Healing is complete only when the organism can re-enter ordinary health-cycle rhythms.

Healing is incomplete until the organism can return to living.

This interpretation also aligns with resolution biology: inflammation must actively terminate, debris must be cleared, and tissue must repair before functional restoration can occur (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

This is a central claim of life-coherent systems immunology. Disease emerges not only when healing fails to begin, but when healing cannot complete. The organism may become trapped in danger sensing, defence, containment, inflammation, proliferative repair, fibrotic remodelling, conservation, pain, fatigue, or memory. What should have been transitional becomes persistent. The healing cycle becomes a disease cycle.

This is why the health cycle and healing cycle must be considered together. If one sees only the healing cycle, inflammation may appear as the main problem. If one sees only the health cycle, rest, nourishment, sleep, movement, and social participation may appear as lifestyle advice. But when the two cycles are viewed together, a deeper clinical question appears: what prevents this organism from completing healing and re-entering health?

The answer may differ across patients. One patient cannot re-enter the health cycle because inflammation remains destructive. Another cannot re-enter because debris, immune complexes, damaged mitochondria, biofilms, toxins, or necrotic material remain uncleared. Another cannot re-enter because the tissue niche has entered fibrosis or remodelling. Another cannot re-enter because mitochondrial capacity remains constrained. Another cannot re-enter because autonomic regulation, pain, fatigue, or post-exertional symptom exacerbation prevents activity. Another cannot re-enter because the exposure continues. Another cannot re-enter because sleep, food, housing, care, or social safety remain insufficient.

The clinical task is to identify where the cycle is blocked.

The blockage may occur at different biological phases, including persistent danger signalling, unresolved inflammation, impaired clearance, mitochondrial constraint, fibrotic repair, neuroimmune sensitization, or failed functional re-entry (McEwen, 1998; Naviaux, 2014; Netea et al., 2016; Wynn & Ramalingam, 2012).

7.1 The Health Cycle

The health cycle is the recurrent rhythm through which the organism sustains ordinary coherence. It includes wakeful activity, nutrient intake, digestion, metabolism, waste and toxin removal, movement, tissue maintenance, social connection, nature contact, sensory engagement, learning, rest, and restorative sleep. These are not separate from immunity. They are the ordinary conditions of immune regulation.

Sleep, nutrition, movement, microbial ecology, clearance, and social conditions all influence immune regulation through metabolic, neuroendocrine, inflammatory, and behavioural pathways (Belkaid & Hand, 2014; Besedovsky et al., 2012; Hooper et al., 2012; McEwen, 1998).

Wakeful activity supports circulation, lymphatic movement, metabolic flexibility, muscular signalling, mitochondrial function, mood, and immune surveillance. Movement helps distribute fluids, mobilize lymph, maintain insulin sensitivity, support vascular function, prevent stiffness, and communicate mechanical information to tissues. Activity also allows the organism to participate in work, care, play, and meaning.

Nutrient intake supports immune cell production, barrier integrity, antioxidant systems, mitochondrial function, microbial ecology, and tissue repair. Food is not only fuel. It is information, substrate, microbial ecology, pleasure, culture, and relation. The immune system must learn food as tolerable and useful. When food systems become poor in nutrient density, high in ultra-processed exposure, contaminated, inflammatory, or socially insecure, the health cycle is strained.

Waste and toxin removal are equally central. The organism must remove metabolic byproducts, damaged proteins, apoptotic cells, immune complexes, excess inflammatory mediators, microbial products, bile waste, uremic toxins, damaged organelles, and environmental chemicals. Liver, kidney, gut, lymphatics, skin, lungs, autophagy, mitophagy, efferocytosis, mucociliary

clearance, and glymphatic flow all participate. A health cycle without clearance becomes congested.

Social connection is not an optional psychological add-on. Humans are relational organisms. Safety, belonging, touch, care, conversation, shared meaning, and trustworthy recognition affect autonomic tone, endocrine rhythms, inflammation, sleep, pain, behaviour, and treatment engagement. Social isolation and threat can become immune perturbations. Conversely, supportive relation can expand regulatory margins.

Nature connection also belongs in the health cycle. Light-dark rhythm, microbial exposure, movement outdoors, plant contact, clean air, temperature variation, visual complexity, and ecological belonging may all support organismic regulation. The organism evolved within ecological relations, not sealed indoor abstraction. Disconnection from nature is not merely aesthetic loss; it may alter immune, microbial, circadian, psychological, and behavioural regulation.

Restorative sleep is one of the most important immune-regulatory phases of the health cycle. Sleep supports immune memory, inflammatory regulation, glymphatic clearance, metabolic repair, hormonal rhythm, mitochondrial recovery, emotional processing, and tissue restoration. Sleep loss increases inflammatory tone, alters infection susceptibility, worsens pain, disrupts metabolism, and reduces resilience. A chronically sleep-deprived organism is less able to complete healing cycles.

Sleep is closely linked to immune memory, inflammatory regulation, metabolic repair, and glymphatic clearance, making sleep disruption a biologically meaningful constraint on recovery rather than merely a lifestyle issue (Besedovsky et al., 2012; Xie et al., 2013).

The health cycle can therefore be understood as a recurrent pattern of participation and restoration. The organism engages the world, takes in what it needs, removes what it must, relates, repairs, sleeps, and returns. Immune coherence depends on this rhythm.

When the health cycle is disrupted, immune disease becomes more likely to lock. A patient who cannot sleep, cannot rest, cannot move safely, cannot access nourishing food, cannot clear exposures, cannot breathe clean air, cannot feel socially safe, or cannot reduce allostatic load may remain biologically available for disease persistence. The immune system cannot complete healing in a life field that continually reopens danger.

This is where salutogenesis and allostasis converge: disrupted health-cycle conditions reduce resistance resources, increase allostatic cost, and narrow the organism's capacity to resolve, repair, and re-enter ordinary participation (Antonovsky, 1987; McEwen, 1998; Sterling & Eyer, 1988).

7.2 The Healing Cycle

The healing cycle begins when the organism's ordinary rhythm is interrupted by perturbation. This perturbation may be infectious, traumatic, toxic, metabolic, mechanical, psychosocial,

ecological, or iatrogenic. The organism exits ordinary health-cycle participation and enters a more focused biological state. The purpose is not long-term withdrawal, but temporary reorganization for protection and repair.

The first phase is perturbation and danger sensing. Cells detect microbial patterns, damage-associated signals, altered mechanics, redox changes, extracellular ATP, nucleic acids in abnormal compartments, crystals, toxins, hypoxia, or tissue disruption. Pattern-recognition receptors, inflammasomes, complement, sensory nerves, epithelial alarms, endothelial signals, macrophages, dendritic cells, mast cells, and mitochondria may participate. The organism recognizes that ordinary participation cannot simply continue unchanged.

Danger sensing is supported by pattern-recognition receptors, damage-associated signals, inflammasomes, complement, cytosolic nucleic-acid sensing, mitochondrial signals, and tissue alarms (Chen et al., 2016; Janeway, 1989; Matzinger, 2002; Ricklin et al., 2010; Schroder & Tschopp, 2010; West & Shadel, 2017).

The next phase is defence and containment. Inflammation mobilizes. Neutrophils, monocytes, macrophages, complement, antibodies, coagulation, antimicrobial peptides, fever, mucus, pain, and behavioural withdrawal may help contain spread and protect the organism. Metabolism shifts toward immune work. Energy is reallocated. The organism closes boundaries, reduces unnecessary activity, and focuses on survival.

Containment must then give way to resolution. Resolution is not passive fading of inflammation. It is an active biological process that limits further damage, changes lipid mediators, reprograms macrophages, restrains neutrophil recruitment, promotes efferocytosis, and prepares the tissue for repair. If resolution fails, inflammation persists even after the initial danger has changed.

Resolution is now understood as an active, regulated biological program involving lipid mediator class switching, macrophage reprogramming, neutrophil clearance, efferocytosis, and tissue repair signalling (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

Clearance follows and overlaps with resolution. The organism must remove dead cells, damaged mitochondria, immune complexes, fibrin, extracellular matrix fragments, toxins, microbes, biofilms, crystals, misfolded proteins, and inflammatory debris. Clearance is essential because unresolved debris becomes a continuing source of danger signals. Resolution without clearance is incomplete.

Clearance depends on efferocytosis, autophagy, mitophagy, lymphatic drainage, mucosal clearance, and organ-level waste handling; when these fail, debris can continue to signal danger (Ravichandran & Lorenz, 2007; Youle & Narendra, 2011).

Repair and remodelling then restore structure. Epithelial cells proliferate, fibroblasts deposit matrix, vessels remodel, nerves adapt, macrophages guide tissue reconstruction, and local stem or progenitor cells may participate. Repair must be sufficient to restore boundary integrity and function, but not so persistent that it becomes fibrosis. The organism must rebuild without overbuilding.

Repair requires coordination among macrophages, fibroblasts, epithelial cells, endothelial cells, extracellular matrix, and local tissue mechanics; when repair persists or overbuilds, fibrosis and functional restriction can result (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Memory and adaptation follow. The immune system updates readiness. Adaptive immune memory, trained innate states, tissue-resident memory cells, epigenetic marks, microbial changes, neural learning, behavioural caution, and metabolic adjustments may all persist after the acute event. Memory is essential for future protection, but it becomes pathological when it cannot update or relax.

Immune memory includes adaptive lymphocyte memory, trained innate immunity, tissue-resident memory, epigenetic priming, microbial shifts, and other durable changes that can protect future life or contribute to chronic readiness (Chuong et al., 2016; Netea et al., 2016; Virgin, 2014).

The final phase is reintegration. The organism returns to the health cycle. Sleep normalizes. Appetite returns. Movement expands. Pain decreases. Fatigue lifts. Tissue function improves. Social participation resumes. Immune activity remains present but no longer dominates the organism's life. The organism has not simply returned to the past; it has incorporated the event into its structure and continues living.

This is successful healing: not the erasure of perturbation, but reintegration after transformation.

7.3 Re-entry into the Health Cycle

Re-entry is the often-neglected endpoint of healing. Clinical care may focus on symptom reduction, laboratory normalization, imaging improvement, or acute stabilization. These are essential, but they are not the whole of recovery. A patient may have improved inflammatory markers and still be unable to walk, sleep, work, eat normally, think clearly, tolerate exertion, or participate in relationships. In such cases, the organism has not fully re-entered the health cycle.

Re-entry requires more than suppression. It requires restored rhythm.

Re-entry is therefore a salutogenic and biological endpoint: the organism must regain the resources, timing, tissue capacity, and regulatory confidence needed for ordinary participation (Antonovsky, 1987; Naviaux, 2014).

The organism must regain the capacity for wakeful activity without disproportionate crash. It must tolerate nourishment without excessive reactivity. It must clear waste without overload. It must sleep restoratively. It must move without threat. It must relate without overwhelming stress. It must inhabit environments that do not continually re-trigger defence. It must possess enough metabolic and mitochondrial reserve to support ordinary life. It must trust, biologically and experientially, that participation is safe enough.

This is why rehabilitation must be phase-sensitive. If re-entry is attempted too early or too forcefully, the organism may relapse. A patient with ongoing inflammation, post-exertional symptom exacerbation, active infection, unresolved anaemia, mitochondrial constraint,

autonomic instability, or severe allostatic load may not tolerate aggressive return to activity. Forced participation can become another perturbation. On the other hand, prolonged avoidance after the body is ready may sustain deconditioning, fear, stiffness, pain, social withdrawal, and loss of function.

The art is to find the threshold at which life can begin moving again without overwhelming the system.

Phase-sensitive rehabilitation is consistent with allostatic reasoning: an intervention that supports recovery in one phase may become an additional perturbation when reserve is low or when inflammatory, mitochondrial, autonomic, or tissue constraints remain active (McEwen, 1998; Naviaux, 2014; Picard et al., 2018).

Re-entry also requires trustworthy feedback. Patients need to understand which symptoms signal danger, which signal adaptive challenge, which signal deconditioning, which signal inflammation, and which require medical review. Without this orientation, they may oscillate between overexertion and fear. A coherent clinical explanation can help them participate in recovery with more discernment.

Re-entry is especially difficult in chronic immune disease because the organism may have lived for months or years in altered phase-states. The body may have adapted to restriction. Muscles decondition. Mitochondria shift. Sleep fragments. Pain pathways sensitize. Social roles shrink. Identity changes. Work capacity diminishes. Relationships reorganize around illness. The niche adjusts to disease. Recovery then requires not only biological change, but re-integration of life patterns.

Healing is incomplete until the organism can re-enter ordinary health-cycle rhythms.

This makes functional recovery — sleep, movement, appetite, cognition, social participation, exertional tolerance, and meaningful activity — a core marker of healing rather than a secondary outcome (Antonovsky, 1987; Naviaux, 2020).

7.4 Disease as Failure of Re-entry

Disease emerges not only when healing is incomplete, but when incomplete healing prevents re-entry into the health cycle. This statement reframes chronic illness. Disease is not always a continuous external attack or an ongoing primary defect. Sometimes it is the persistence of an unfinished healing phase that blocks return.

In chronic inflammatory disease, defence may not resolve. In post-infectious illness, the organism may remain in danger signalling, mitochondrial conservation, autonomic dysregulation, or immune memory after the pathogen is reduced or gone. In fibrosis, repair may fail to stop. In chronic pain, protection may persist after tissue danger has changed. In allergy, barrier alarm and type 2 immunity may remain ready to overrespond. In autoimmunity, recognition and clearance processes may remain misdirected. In chronic fatigue states, energy

conservation may become a long-term constraint. In recurrent infection, defence may not adequately initiate or sustain.

Each pattern represents a different failure of re-entry.

These failures can be linked to different mechanisms, including persistent inflammation, mitochondrial danger signalling, trained immunity, fibrotic repair, impaired clearance, type 2 barrier alarm, and neuroimmune conservation states (Naviaux, 2014; Netea et al., 2016; West & Shadel, 2017; Wynn & Ramalingam, 2012).

This explains why chronic immune disease often affects the whole life of the patient. The person is not merely carrying inflammation. They are living in a disrupted cycle. Sleep, appetite, movement, social participation, work, cognition, mood, sexuality, creativity, future planning, and identity may all be altered. The disease is not only in the tissue. It is in the interrupted rhythm of living.

A medicine focused only on disease suppression may miss this. Suppression can be necessary and lifesaving, but if it does not lead to resolution, clearance, repair, rehabilitation, and reintegration, the patient may remain biologically and existentially outside the health cycle. Conversely, lifestyle advice without control of active pathology may be inadequate or unsafe. The goal is not suppression versus support. The goal is sequenced phase restoration.

Sequenced phase restoration integrates suppression, resolution, clearance, repair, rehabilitation, and salutogenic support according to the organism's current state rather than treating these as competing therapeutic philosophies (Antonovsky, 1987; Fullerton & Gilroy, 2016; Naviaux, 2014; Serhan & Savill, 2005).

This brings us to the master distinction that will guide the rest of the paper: adaptive phase-shifting versus maladaptive phase-locking.

In health, the organism shifts phase according to need and then returns. In disease, a phase that should have been temporary becomes persistent, self-sustaining, or recurrent. The organism remains caught in unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration. The health cycle is not merely interrupted; it becomes difficult to re-enter.

The healing cycle becomes a holding pattern.

This is the biological and clinical heart of life-coherent systems immunology. The immune system's task is not to keep the organism permanently defended. It is to help the organism move through perturbation and back into life.

8. Allostasis, Allostatic Load, and Immune Resilience

If the health cycle describes ordinary organismic rhythm, and the healing cycle describes the organism's temporary reorganization after perturbation, then allostasis describes the adaptive process by which the organism changes state in order to remain viable. Health is not static homeostasis. It is not the maintenance of fixed internal values under all conditions. Health is the capacity to vary intelligently, to shift physiology according to need, and to return without accumulating unsustainable cost.

In a life-coherent systems immunology, health is best understood as affordable allostasis with preserved immune resilience and phase coherence.

This formulation draws directly on allostasis theory, which understands health as adaptive variation under demand rather than static equilibrium, and links it to immune resilience as the capacity to recover after perturbation (McEwen, 1998; Sterling & Eyer, 1988).

Homeostasis remains important. Blood pH, electrolyte balance, glucose range, oxygenation, temperature, blood pressure, and fluid balance must remain within viable limits. Yet the living organism does not maintain these values by staying the same. It maintains viability by changing. Heart rate rises with exertion. Cortisol rises with morning awakening and stress. Fever raises temperature during infection. Inflammation mobilizes after injury. Insulin shifts after eating. Sleep architecture changes after immune activation. Appetite falls during acute illness. Pain restricts movement after damage. Fatigue reduces energy expenditure when repair is needed.

The organism survives not by resisting change, but by changing in ways that preserve life.

Allostasis is therefore the physiology of adaptive variation. It is the organism's capacity to meet demands by altering endocrine, autonomic, immune, metabolic, mitochondrial, behavioural, and tissue states. It allows a person to wake, work, exercise, fight infection, digest food, respond to danger, repair wounds, grieve, learn, sleep, and recover. Allostasis is not pathology. It is the cost of living.

But all adaptation has cost. When demands are intense, repeated, prolonged, unpredictable, or insufficiently followed by recovery, allostatic cost accumulates. The organism must repeatedly mobilize defence, vigilance, inflammation, glucose, blood pressure, sympathetic tone, cortisol, mitochondrial reallocation, coagulation, and behavioural narrowing. If recovery is incomplete, these adaptive shifts become burdens. This accumulated cost is allostatic load.

Allostatic load is not simply stress. It is the embodied cost of repeated adaptation.

McEwen and Stellar introduced allostatic load to describe the cumulative physiological burden generated when adaptive systems are repeatedly activated or inadequately recovered (McEwen & Stellar, 1993; McEwen, 1998).

In immune terms, allostatic load may appear as elevated inflammatory tone, impaired resolution, reduced antiviral resilience, altered glucocorticoid sensitivity, disturbed sleep, metabolic

syndrome, hypertension, visceral adiposity, mitochondrial strain, barrier dysfunction, dysbiosis, pain sensitization, fatigue, impaired tissue repair, or increased flare susceptibility. It may also appear as vulnerability to both overreaction and underreaction: the organism becomes inflamed but less effective, vigilant but less resilient, reactive but less coherent.

This paradox is clinically familiar. Patients under chronic load may show both heightened inflammatory reactivity and poor recovery. They may flare easily but heal slowly. They may feel wired and exhausted. They may be hypersensitive to stimuli but vulnerable to infection. They may have pain amplification but reduced tissue capacity. They may respond strongly to minor perturbations yet fail to complete adaptive transitions. The organism is not simply too active or too weak. It is costly, strained, and poorly phase-coordinated.

Chronic load can alter inflammatory tone, glucocorticoid sensitivity, sleep, metabolism, mitochondrial function, vascular regulation, pain sensitivity, and behavioural capacity, thereby narrowing the organism's regulatory options (Barrett et al., 2016; Besedovsky et al., 2012; McEwen, 1998; Picard et al., 2018).

Allostatic load narrows immune possibility.

A low-load organism has margins. It can mount fever and recover. It can inflame and resolve. It can rest and repair. It can tolerate food, microbes, exertion, and ordinary social demand. It can adapt to environmental variation without losing rhythm. A high-load organism has fewer margins. The same perturbation becomes more expensive. A viral infection, allergen exposure, poor night of sleep, emotional shock, chemical exposure, overexertion, or dietary disruption may trigger disproportionate symptoms because the organism has little reserve.

This is why immune resilience depends on more than immune strength. Resilience is not the capacity to mount the largest response. It is the capacity to respond proportionately, resolve efficiently, clear effectively, repair adequately, remember appropriately, and re-enter the health cycle. A resilient immune system is not permanently activated. It is flexibly available.

Immune resilience therefore requires phase coherence. The organism must know when to surveil, when to inflame, when to contain, when to resolve, when to clear, when to repair, when to rest, when to remember, and when to re-enter. Disease appears when these phase transitions lose timing, sequence, proportionality, or reversibility.

Immune resilience is therefore not maximal immune strength, but coordinated timing among resistance, tolerance, resolution, clearance, repair, memory, and return to ordinary function (Medzhitov, 2008; Serhan & Savill, 2005).

8.1 Homeostasis and Allostasis

Homeostasis is the maintenance of key physiological variables within ranges compatible with life. It is essential, but it is not enough to describe living health. A homeostatic view can make the organism appear as if it is trying to remain unchanged. But organisms are not machines preserving fixed settings. They are living unities constantly adjusting to changing relations.

Allostasis expands the picture. It recognizes that the organism maintains viability through anticipatory and responsive change. Before waking, cortisol rises. Before exertion, heart rate and blood flow shift. During infection, temperature, metabolism, appetite, sleep, and immune activity change. During danger, sympathetic tone increases. During recovery, parasympathetic restoration, sleep, anabolic repair, and immune resolution become more important.

The organism changes state to preserve coherence.

Sterling and Eyer introduced allostasis as a way to understand adaptive regulation through change, later developed by McEwen into a framework for stress biology, physiological cost, and disease risk (McEwen, 1998; Sterling & Eyer, 1988).

This is central to immunology. An immune response is an allostatic event. It reorganizes the organism around defence, containment, clearance, and repair. It changes temperature, metabolism, sleep, appetite, vascular tone, pain, behaviour, endocrine regulation, and tissue function. The immune system is therefore not a local pathway responding in isolation. It participates in whole-organism allostasis.

Inflammation reorganizes metabolism, endocrine tone, sleep, appetite, vascular regulation, tissue function, and behaviour, making immune activation a whole-organism adaptive shift rather than a local pathway event alone (Medzhitov, 2008; Naviaux, 2014; O'Neill et al., 2016).

Inflammation is costly because it is allostatic. It reallocates energy. It alters insulin sensitivity. It changes mitochondrial function. It consumes amino acids, lipids, glucose, oxygen, and micronutrients. It produces oxidative and nitrosative stress. It changes mood, motivation, movement, and sleep. It increases vascular permeability. It recruits cells that may damage tissue while protecting the organism. It is necessary, but it must be time-limited and well resolved.

A life-coherent view does not ask whether inflammation is good or bad in general. It asks whether the inflammatory allostatic shift is appropriate to the perturbation, affordable for the organism, and able to transition toward resolution.

This phase-specific interpretation is supported by resolution biology, which emphasizes that inflammation's meaning depends on initiation, proportionality, termination, and transition to repair (Fullerton & Gilroy, 2016; Serhan, 2007).

8.2 Allostatic Load

Allostatic load accumulates when the organism must repeatedly adapt without adequate recovery. It may result from chronic infection, persistent inflammation, unresolved exposure, sleep disruption, psychosocial adversity, metabolic overload, environmental toxicity, pain, trauma, poverty, caregiving burden, climate stress, shift work, repeated flares, or the demands of chronic disease itself.

The immune system both contributes to and suffers from allostatic load.

Inflammation can increase load by altering metabolism, sleep, mood, vascular function, mitochondrial state, and tissue repair. At the same time, load can increase inflammation by disturbing neuroendocrine regulation, increasing oxidative stress, impairing barrier function, disrupting microbiota, sensitizing innate immune pathways, and reducing resolution capacity. The relation is circular. Load generates immune dysregulation; immune dysregulation generates more load.

This bidirectional loop is consistent with evidence linking chronic stress and allostatic load to inflammation, sleep disruption, metabolic strain, mitochondrial stress, pain, and altered immune regulation (Besedovsky et al., 2012; McEwen, 1998; Picard et al., 2018).

In chronic immune disease, this circularity may become self-sustaining. A flare disrupts sleep. Poor sleep increases inflammatory reactivity. Increased reactivity worsens pain and fatigue. Pain reduces movement. Reduced movement impairs lymphatic flow, insulin sensitivity, mitochondrial function, mood, and tissue resilience. Reduced function increases stress and social loss. Stress amplifies autonomic and inflammatory tone. The organism becomes locked in a costly adaptive pattern.

This is not merely "stress making disease worse." It is an organism-wide phase-lock in which repeated adaptation reduces the capacity for future adaptation.

This distinction helps avoid psychologizing stress while preserving its biological seriousness: allostatic load is embodied across immune, endocrine, metabolic, neural, vascular, and behavioural systems (Barrett et al., 2016; McEwen & Stellar, 1993; McEwen, 1998).

Allostatic load also helps explain why patients with chronic disease often have multi-system symptoms. Fatigue, brain fog, sleep disturbance, pain, dysautonomia, gastrointestinal sensitivity, mood changes, exercise intolerance, headaches, and heightened sensory reactivity may reflect distributed allostatic strain rather than unrelated complaints. This does not mean every symptom has the same cause. It means that systemic regulatory cost can express across many channels.

The clinician who recognizes allostatic load asks different questions. How long has the organism been adapting without recovery? What are the major load drivers? Which are biological, environmental, social, metabolic, infectious, inflammatory, psychological, or iatrogenic? Which can be reduced now? Which require longer-term change? What resources can be added? What phase transition is currently unaffordable?

This perspective also cautions against overly aggressive rehabilitation or treatment escalation without attention to reserve. An organism under high load may react poorly to interventions that would help a more resourced organism. Exercise, dietary change, medication shifts, detoxification attempts, exposure challenges, psychological work, or immune modulation may all become perturbations. The question is not whether they are good in general. The question is whether the organism can afford them now.

A phase-aware medicine begins where the organism is.

This principle follows from allostatic reasoning: interventions must be matched to current reserve, load, and transition capacity, because even beneficial interventions can become perturbations when the organism cannot yet afford them (McEwen, 1998; Sterling & Eyer, 1988).

8.3 Immune Resilience

Immune resilience is the capacity to meet perturbation without becoming trapped by it. It includes resistance, tolerance, resolution, clearance, repair, memory, and re-entry. It is not one function, but a coordinated pattern.

This coordinated pattern includes resistance to danger, tolerance of necessary relations, active resolution of inflammation, clearance of debris, repair of tissue, adaptive memory, and return to participation (Medzhitov, 2008; Serhan & Savill, 2005).

Resistance is the ability to limit pathogen burden, toxin impact, injury spread, or malignant transformation. Tolerance is the ability to limit damage while allowing necessary relations with food, microbes, pregnancy, tissue repair, and environmental exposure. Resolution is the ability to actively terminate inflammation. Clearance is the ability to remove debris, dead cells, immune complexes, damaged organelles, toxins, and microbial remnants. Repair is the ability to restore tissue integrity. Memory is the ability to learn without becoming fixed. Re-entry is the ability to return to ordinary health-cycle participation.

A resilient immune system must do all of these.

If resistance is strong but resolution fails, inflammation persists. If tolerance is strong but resistance fails, infection or malignancy may progress. If repair is strong but poorly regulated, fibrosis develops. If memory is strong but inflexible, allergy or autoimmunity may persist. If clearance fails, danger signals continue. If re-entry fails, the person remains ill even after the acute event has passed.

Immune resilience is therefore not reducible to immune activation. It is dynamic competence across the whole cycle.

This distinction is important because excessive activation can coexist with poor resolution, impaired clearance, inadequate repair, or failed re-entry; resilience requires coordination rather than amplification alone (McEwen, 1998; Serhan, 2007).

This also means that immune resilience can fail in different ways. One patient may have poor resistance and recurrent infection. Another may have poor tolerance and excessive inflammation. Another may have poor resolution and chronic inflammatory persistence. Another may have poor clearance and ongoing danger signalling. Another may have excessive repair and fibrosis. Another may have poor re-entry and prolonged post-infectious disability. These are different resilience failures requiring different interventions.

The language of resilience must therefore be used carefully. It should not become a demand placed on patients: “be more resilient.” It should become a diagnostic and therapeutic question: what would increase this organism’s capacity to adapt, recover, and re-enter life?

Sometimes the answer is medication. Sometimes it is rest. Sometimes it is nutrition. Sometimes it is sleep protection. Sometimes it is removal from exposure. Sometimes it is social support. Sometimes it is rehabilitation. Sometimes it is antimicrobial treatment, immunoglobulin replacement, biologic therapy, antifibrotic therapy, drainage, surgery, psychotherapy, pacing, or environmental reform. Often it is a sequence of supports that restores margins.

Resilience is not willpower. It is supported capacity.

This statement returns the concept of resilience to salutogenesis: resilient function depends on resources, relationships, environments, and institutions as well as biological mechanisms (Antonovsky, 1987; Commission on Social Determinants of Health, 2008).

8.4 Phase Coherence

Phase coherence is the temporal organization of immune life. It is the ability of the organism to move through biological phases in the right order, with the right intensity, for the right duration, and with the right exit signals.

Phase coherence integrates allostasis, resolution biology, and cell danger response biology by emphasizing timing, sequence, reversibility, and completion of adaptive responses (McEwen, 1998; Naviaux, 2014; Serhan, 2007).

The immune-metabolic phases of surveillance, danger detection, defence, containment, resolution, clearance, repair, memory, and re-entry must be coordinated. These phases overlap, but they cannot be randomly arranged without cost. Defence before detection is hypervigilance. Repair before clearance risks fibrosis or abscess. Memory without resolution risks chronic readiness. Resolution without adequate defence risks infection spread. Re-entry without repair risks relapse. Suppression without clearance risks persistence. Activation without rest risks collapse.

Phase coherence is therefore clinical timing embodied.

Many chronic immune diseases may be interpreted as phase incoherence. Asthma may involve repeated barrier alarm, type 2 inflammation, mucus, bronchial hyperresponsiveness, and airway remodelling. Rheumatoid arthritis may involve synovial immune activation, fibroblast transformation, autoantibody formation, complement, cytokines, pain, and tissue destruction in a recurrent inflammatory lock. Fibrosis may represent repair that does not exit. Long COVID may involve unresolved immune, vascular, mitochondrial, autonomic, viral, or inflammatory phase disturbances. Inflammatory bowel disease may involve barrier disruption, microbial dysregulation, immune activation, impaired tolerance, and failed mucosal healing. Chronic fatigue states may involve persistent conservation, post-exertional intolerance, autonomic dysregulation, and impaired re-entry.

The value of phase coherence is that it asks what transition has failed rather than only what marker is abnormal.

This protects biomarker interpretation from becoming static, because the same marker can indicate different biological meanings depending on phase, tissue, timing, and organismal context (Buck et al., 2017; Medzhitov, 2008; O'Neill et al., 2016).

An abnormal marker may mean different things depending on phase. Elevated inflammatory markers during acute infection may be appropriate. Persistent elevation during remission may suggest unresolved inflammation. Low inflammatory markers in a severely symptomatic patient may suggest that inflammation is not the only relevant phase, or that pathology lies in mitochondrial, autonomic, neuroimmune, fibrotic, clearance, or tissue-level processes. A positive autoantibody may indicate risk, disease, memory, or epiphenomenon depending on context. A cytokine may be driver, marker, compensatory signal, or failed resolution sign.

Phase coherence protects interpretation from becoming static.

8.5 Clinical Implications of Allostatic Reasoning

Allostatic reasoning asks clinicians to interpret disease not only by diagnosis, but by adaptive cost, reserve, and transition capacity.

This extends the clinical frame from disease activity alone to the organism's capacity to use treatment, recover from perturbation, and move toward the next coherent phase (Antonovsky, 1987; McEwen, 1998).

The central clinical questions become:

What demands are being placed on this organism?
What resources are available?
What adaptive responses are active?
What costs have accumulated?
What phase transition is needed?
What makes that transition unaffordable?
What can be reduced, restored, supported, or sequenced?

In practical terms, this means that chronic immune disease assessment should include not only disease activity, organ damage, and biomarkers, but also sleep, nutrition, movement capacity, pain, fatigue, infection history, exposure history, psychological threat load, social support, housing, work demands, medication burden, metabolic health, mitochondrial reserve, and recovery patterns. These are not distractions from immunology. They are part of the allostatic field in which immune regulation occurs.

Sleep, nutrition, movement, exposure, social support, housing, work demand, and metabolic health shape immune regulation through allostatic, inflammatory, neuroendocrine, and

behavioural pathways (Commission on Social Determinants of Health, 2008; McEwen, 1998; Rappaport & Smith, 2010; Wild, 2005).

Allostatic reasoning also supports treatment sequencing. A patient in destructive inflammation may need immediate suppression before lifestyle measures can matter. A patient under severe sleep disruption may not respond well until sleep is protected. A patient with ongoing exposure may not stabilize until the exposure is removed. A patient with post-exertional crashes may need pacing before conditioning. A patient with severe deconditioning may need rehabilitation once inflammation and energy constraints allow it. A patient with social insecurity may need practical support before self-management becomes feasible.

The question is not what is ideal in abstraction. The question is what the organism can use now.

This is the beginning of phase-state medicine. Allostasis shows that the organism changes to survive. Allostatic load shows that survival can become costly. Immune resilience shows that the organism must recover, not merely endure. Phase coherence shows that timing and sequence determine whether adaptation becomes healing or disease.

Phase-state medicine therefore applies allostatic and resolution reasoning to clinical sequencing: the same intervention may help or harm depending on whether the organism is in defence, containment, clearance, repair, conservation, or re-entry (McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005).

The next section therefore develops the master distinction directly: adaptive phase-shifting versus maladaptive phase-locking. This distinction gives the framework its central clinical grammar.

Health is resilient participation in coherent health cycles under changing conditions.
Healing is successful completion of salugenic phase transitions after perturbation.
Disease is maladaptive phase-locking that prevents re-entry into the health cycle.

This distinction synthesizes allostasis, salutogenesis, cell danger response biology, and resolution biology into a clinical grammar of adaptive state change versus failed transition (Antonovsky, 1987; McEwen, 1998; Naviaux, 2014; Serhan, 2007).

9. The Master Distinction: Adaptive Phase-Shifting versus Maladaptive Phase-Locking

The conceptual heart of life-coherent systems immunology is the distinction between adaptive phase-shifting and maladaptive phase-locking.

Health is resilient participation in coherent health cycles under changing conditions. Healing is successful completion of salugenic phase transitions after perturbation. Disease is maladaptive phase-locking that prevents re-entry into the health cycle.

This distinction gathers the previous sections into one clinical grammar. The organism normally moves through phases. It surveils, senses, defends, contains, resolves, clears, repairs, remembers, adapts, rests, and returns. These movements are not optional additions to immune life. They are immune life. The immune system exists not to keep the organism permanently defended, but to allow the organism to move through perturbation and return to participation.

Adaptive phase-shifting is the organism's capacity to change state when conditions require it and then change again when the conditions have changed. The organism does not remain in one mode. It becomes inflamed when inflammation is needed. It resolves when inflammatory work is complete. It repairs when structure has been damaged. It remembers when future readiness is useful. It relaxes vigilance when danger has passed. It returns to nourishment, movement, sleep, relation, learning, and ordinary life.

Adaptive phase-shifting is therefore not simply activation; it includes activation, proportionality, termination, recovery, and return to participation (McEwen, 1998; Serhan & Savill, 2005; Sterling & Eyer, 1988).

Maladaptive phase-locking occurs when this movement fails. A phase that should have been temporary becomes persistent, recurrent, self-sustaining, or excessive. The organism remains caught in unfinished defence, unfinished containment, unfinished clearance, unfinished repair, unfinished memory, or unfinished reintegration. It is not simply that a pathway is "on." It is that the organism cannot complete a transition.

Maladaptive persistence may involve inflammatory signalling, trained immunity, mitochondrial danger responses, fibrotic repair, impaired clearance, or neuroimmune conservation states that remain active beyond their adaptive window (Naviaux, 2014; Netea et al., 2016; West & Shadel, 2017; Wynn & Ramalingam, 2012).

This distinction is clinically powerful because it allows immune disease to be understood dynamically rather than only categorically. A disease label tells us what pattern medicine recognizes. A phase-lock asks what biological work remains unfinished.

The same disease category may contain different phase-locks. Asthma may involve barrier alarm, type 2 inflammation, mucus overproduction, airway hyperresponsiveness, remodelling, infection susceptibility, pollution sensitivity, or autonomic dysregulation in different proportions.

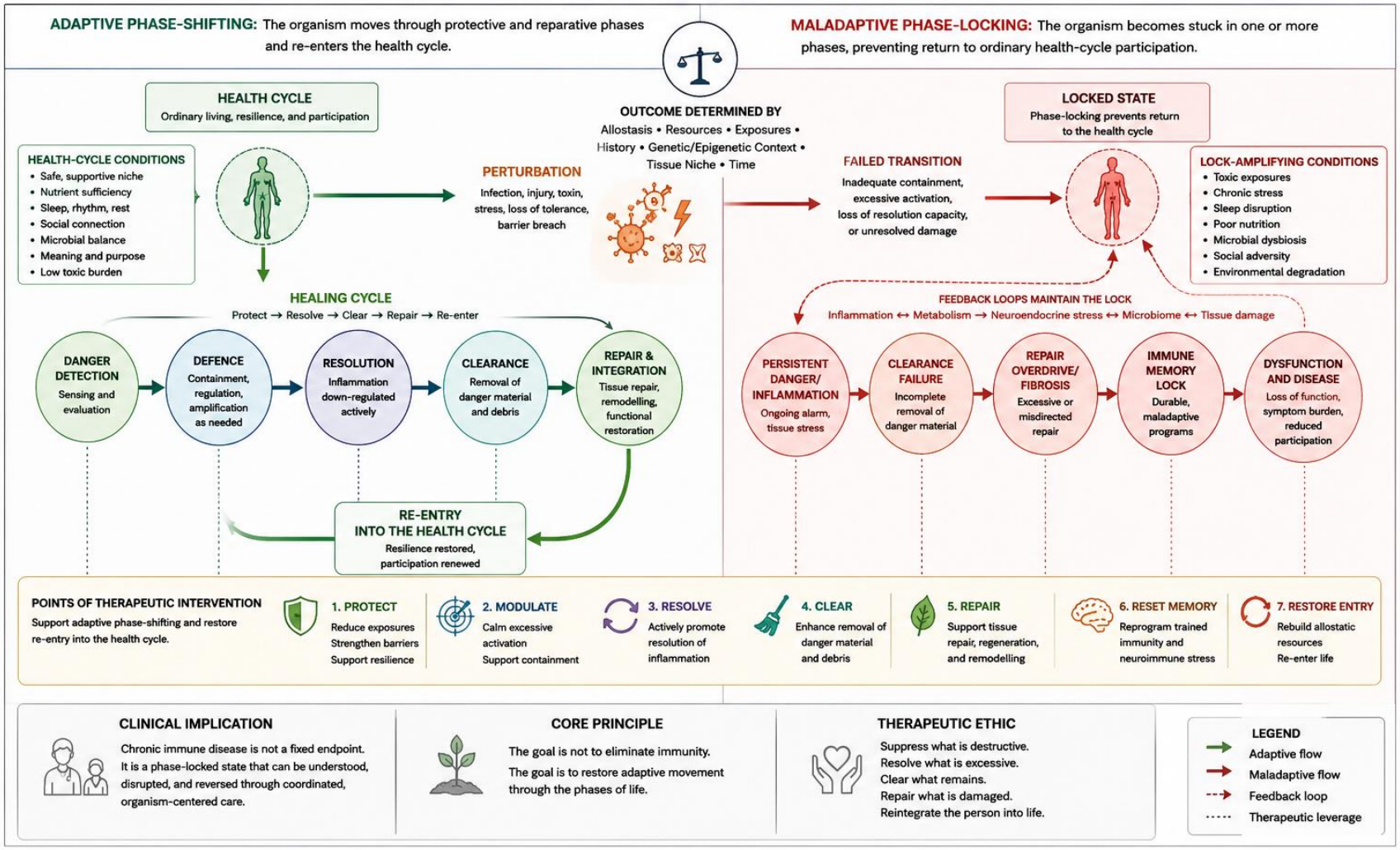
Rheumatoid arthritis may involve autoantibody formation, synovial macrophage activation, fibroblast transformation, complement, cytokine loops, pain sensitization, systemic inflammation, and impaired resolution. Inflammatory bowel disease may involve barrier disruption, microbial dysbiosis, impaired tolerance, excessive effector response, failure of mucosal healing, fibrosis, or altered gut-brain-immune signalling. Long COVID may involve viral persistence, immune memory, interferon dysregulation, mitochondrial constraint, endothelial dysfunction, dysautonomia, clotting abnormalities, mast-cell activation, microbiome change, or failed re-entry into activity.

The diagnosis matters. But the phase-state matters also.

The phase-lock concept therefore does not replace conventional diagnosis. It deepens clinical reasoning after diagnosis. It asks: What is the organism locked in? What transition is blocked? What mechanisms sustain the lock? What tissue niche gives it form? What exposures or histories keep it active? What would allow the next movement?

Figure 2. Adaptive Phase-Shifting Versus Maladaptive Phase-Locking

The Immune-Metabolic Phase Cycle, Healing Cycle, and Points of Therapeutic Intervention



Caption. Adaptive phase-shifting is the organism's capacity to move through protective and reparative phases after perturbation and then re-enter ordinary health-cycle participation. Maladaptive phase-locking occurs when one or more phases become persistent, recurrent, self-sustaining, or excessive, preventing completion of the healing cycle. The figure contrasts the adaptive sequence from health-cycle conditions through danger detection, defence, resolution, clearance, repair, and reintegration with locked states sustained by exposure, allostatic load, impaired clearance, repair-overbuild, immune memory, and feedback loops. Therapeutic intervention is therefore framed as phase restoration: protect, modulate, resolve, clear, repair, reset memory, and restore entry into life.

9.1 The Immune-Metabolic Phase Cycle

The immune-metabolic phase cycle can be described as a sequence of living transitions. These phases overlap and vary by tissue, disease, and context, but they provide a useful clinical map:

1. surveillance;
2. boundary sensing;
3. danger detection;
4. defence;
5. containment;
6. resolution;
7. clearance;
8. repair and remodelling;
9. memory and adaptation;
10. re-entry into the health cycle.

Surveillance is the background attentiveness of the organism. Immune cells, epithelial barriers, tissue macrophages, dendritic cells, complement, antibodies, sensory nerves, microbiota, stromal cells, and metabolic sensors continually sample the organism–niche field. Surveillance is not alarm. It is readiness.

Boundary sensing occurs at the interfaces where organism and niche meet: skin, gut, lung, genitourinary tract, vasculature, placenta, oral cavity, conjunctiva, lymphatics, and injured tissue. The organism senses what is entering, crossing, adhering, damaging, nourishing, or perturbing. Boundary sensing is where openness and protection first meet.

Danger detection begins when ordinary variation is evaluated as threat, injury, invasion, or dysregulation. Pattern-recognition receptors, inflammasomes, cGAS–STING, complement, epithelial alarmins, mitochondrial signals, extracellular ATP, HMGB1, uric acid crystals, mislocalized nucleic acids, oxidized lipids, microbial products, toxins, hypoxia, and mechanical injury may all participate. Danger detection shifts the organism from background surveillance toward active response.

Danger detection draws on pattern recognition, danger signalling, complement activation, inflammasome biology, cytosolic nucleic-acid sensing, mitochondrial signals, and tissue alarmins (Chen et al., 2016; Janeway, 1989; Matzinger, 2002; Ricklin et al., 2010; Schroder & Tschopp, 2010; West & Shadel, 2017).

Defence mobilizes protective force. Inflammation rises. Neutrophils, macrophages, mast cells, natural killer cells, complement, antibodies, T cells, cytokines, chemokines, coagulation, fever, mucus, antimicrobial peptides, and behavioural withdrawal may participate. Energy is redirected from ordinary activity toward protection. The organism closes, narrows, and concentrates.

Containment limits spread. Abscess formation, granulomas, fibrin deposition, mucus trapping, coagulation, tissue swelling, pain-limited movement, vascular changes, and cellular barriers may all help confine danger. Containment is adaptive when it prevents dissemination. It becomes pathological when it isolates unresolved material, sustains hypoxia, blocks drainage, or creates chronic inflammatory niches.

Resolution actively turns down inflammation. It is not passive disappearance. Specialized pro-resolving mediators, macrophage reprogramming, neutrophil apoptosis, efferocytosis, anti-inflammatory cytokines, regulatory T cells, lipid mediator class switching, and tissue-derived signals help terminate destructive immune activity. Resolution is the organism's transition from defence toward restoration.

Resolution is an active program involving specialized pro-resolving mediators, lipid mediator class switching, macrophage reprogramming, neutrophil apoptosis, efferocytosis, and tissue repair preparation (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

Clearance removes what would otherwise continue to signal danger. Apoptotic cells, necrotic debris, damaged mitochondria, immune complexes, crystals, biofilms, fibrin, extracellular matrix fragments, oxidized molecules, toxins, microbial remnants, and inflammatory mediators must be cleared. Without clearance, resolution cannot complete. The organism remains exposed to its own debris.

Efferocytosis, autophagy, mitophagy, lymphatic drainage, and organ-level waste handling are therefore not housekeeping alone; they are central to immune resolution and prevention of persistent danger signalling (Ravichandran & Lorenz, 2007; Youle & Narendra, 2011).

Repair and remodelling restore structure and function. Epithelial closure, angiogenesis, extracellular matrix deposition, fibroblast activation, macrophage guidance, stem or progenitor cell activity, nerve adaptation, and mechanical remodelling all participate. Repair is necessary, but it must end. When repair persists, fibrosis, stiffness, adhesions, strictures, vascular remodelling, airway remodelling, or organ dysfunction may result.

Repair is coordinated by macrophages, fibroblasts, epithelial and endothelial cells, extracellular matrix dynamics, and tissue mechanics; fibrosis can be understood as repair that fails to exit appropriately (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Memory and adaptation update future readiness. Adaptive immune memory, trained innate immunity, epigenetic changes, tissue-resident memory, fibroblast memory, microbial shifts, mitochondrial adaptation, neural learning, and behavioural caution all help the organism prepare for recurrence. Memory is protective when flexible. It is pathological when it becomes fixation.

Durable immune readiness may involve adaptive immune memory, trained innate immunity, tissue-resident states, epigenetic priming, viral or mobile-element history, and microbiome shifts (Chuong et al., 2016; Netea et al., 2016; Virgin, 2014).

Re-entry into the health cycle is the final test. Can the organism return to sleep, movement, appetite, digestion, social relation, work, play, creativity, learning, and ordinary rhythm? If not, healing remains incomplete.

This sequence is not a rigid ladder. It is a living cycle. Phases overlap, recur, branch, and sometimes operate differently in different tissues at the same time. But the sequence helps clinicians see that disease may arise not only from excessive activation, but from failed transition.

9.2 Adaptive Phase-Shifting

Adaptive phase-shifting is the successful movement through this cycle. The organism senses what is happening, shifts state, performs the necessary work, and then exits the phase when it is no longer needed.

A simple wound illustrates this. Tissue is injured. Danger signals are released. Inflammation begins. Bleeding stops. Neutrophils and macrophages clear microbes and debris. Pain protects the area. Resolution mediators rise. Macrophages shift toward repair. Fibroblasts deposit matrix. Epithelial cells close the surface. Collagen remodels. Sensitivity decreases. Movement returns. The organism remembers enough to protect the area but does not remain permanently inflamed. The health cycle resumes.

Acute infection follows a similar logic. The organism detects microbial invasion. Fever, fatigue, inflammation, and immune activation rise. The pathogen is contained and cleared. Inflammatory activity resolves. Damaged cells and debris are removed. Appetite, sleep, movement, and social participation normalize. Immune memory remains, but the person is not trapped in sickness behaviour.

Adaptive phase-shifting therefore requires both activation and exit. A system that cannot activate is vulnerable. A system that cannot exit is chronically ill.

This is the central contribution of resolution biology to phase-state reasoning: immune health requires not only capacity for activation, but also capacity for active termination, clearance, repair, and return (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

This point is essential. Many discussions of immune disease focus on overactivation, but underactivation and failed exit may coexist. A patient may have excessive inflammation but poor

pathogen clearance. Another may have chronic immune activation but impaired tissue repair. Another may have strong memory but weak resolution. Another may have suppression of one pathway while another phase-lock persists. Immune pathology cannot be reduced to “too much” or “too little.” It is often wrongly timed, wrongly placed, wrongly sustained, or wrongly sequenced.

Adaptive phase-shifting depends on biological margins. The organism must have sufficient energy, mitochondrial capacity, nutritional substrate, sleep, oxygenation, vascular flow, lymphatic drainage, microbial support, endocrine coordination, and social-environmental stability to move through the cycle. When margins are low, transitions become harder. The organism may begin a healing response but be unable to complete it.

Biological margins depend on allostatic reserve, mitochondrial capacity, sleep, nutrition, oxygenation, vascular and lymphatic function, microbial ecology, and supportive niche conditions (Besedovsky et al., 2012; McEwen, 1998; Picard et al., 2018).

This is why allostatic load predisposes to phase-locking. The overloaded organism can still respond, but response becomes costly. It may inflame but not resolve, defend but not clear, repair but overbuild, remember but not update, rest but not restore, or attempt activity but crash. The organism’s phase transitions become brittle.

Allostatic overload makes adaptive transitions more costly and less reversible, increasing the risk that defence, repair, memory, or conservation states persist beyond their useful period (McEwen, 1998; McEwen & Stellar, 1993; Sterling & Eyer, 1988).

9.3 Maladaptive Phase-Locking

Maladaptive phase-locking occurs when the organism remains trapped in one or more immune-metabolic phases. The lock may be molecular, cellular, tissue-based, neural, microbial, environmental, social, or allostatic. Most often, it is multi-level.

This multi-level reading is consistent with complex immune disease mechanisms in which molecular signalling, tissue niches, metabolism, microbiota, neural regulation, allostasis, and exposure history interact over time (Belkaid & Hand, 2014; McEwen, 1998; Naviaux, 2014; Netea et al., 2016).

A danger-detection lock occurs when the organism repeatedly evaluates signals as threat. This may involve epithelial alarmins, inflammasomes, DAMPs, PAMPs, cGAS–STING activation, mitochondrial stress, environmental exposures, or sensory-neural amplification. The organism remains primed for alarm.

Such locks may involve danger theory, inflammasome activation, cGAS–STING signalling, mitochondrial DAMPs, epithelial alarmins, and sensory-neural amplification (Chen et al., 2016; Matzinger, 2002; Schroder & Tschopp, 2010; West & Shadel, 2017).

A defence lock occurs when inflammatory pathways remain active beyond their useful window. Cytokines, immune cells, complement, antibodies, interferons, mast cells, neutrophils, macrophages, or T cells may continue to drive damage. The organism remains in battle mode even when battle has become self-injuring.

A containment lock occurs when the organism walls off danger but cannot clear or reintegrate. Granulomas, abscesses, biofilms, fibrinous deposits, immune complexes, chronic sinus disease, or poorly drained tissues may reflect containment that has become persistent. The organism has limited spread but not restored coherence.

A resolution lock occurs when inflammation cannot actively terminate. Specialized pro-resolving pathways may be insufficient, macrophage transitions may fail, neutrophil clearance may be impaired, or ongoing signals may prevent resolution. Inflammation remains because the exit program is blocked.

This is precisely the territory of resolution biology, where failure of pro-resolving mediators, efferocytosis, macrophage transition, and neutrophil clearance can sustain inflammatory persistence (Fullerton & Gilroy, 2016; Ravichandran & Lorenz, 2007; Serhan, 2007).

A clearance lock occurs when debris, damaged cells, immune complexes, crystals, toxins, biofilms, fibrin, senescent cells, damaged mitochondria, or misfolded proteins are not adequately removed. The organism continues to encounter uncleared material as danger. Resolution cannot complete because the field remains contaminated.

Clearance failure can sustain danger through uncleared apoptotic cells, damaged mitochondria, immune complexes, crystals, fibrin, biofilms, and other persistent material burdens (Ravichandran & Lorenz, 2007; West & Shadel, 2017; Youle & Narendra, 2011).

A repair lock occurs when repair persists beyond restoration. Fibrosis, airway remodelling, vascular thickening, adhesions, strictures, keloids, interstitial scarring, and chronic matrix stiffness may arise when the organism continues to build after building has become harmful. Repair becomes overprotection.

Fibrosis and pathological remodelling reflect persistent repair programs involving macrophage-fibroblast crosstalk, extracellular matrix deposition, TGF-β-related pathways, stiffness, and chronic tissue injury (Wynn et al., 2013; Wynn & Ramalingam, 2012).

A memory lock occurs when past danger remains biologically present as excessive readiness. Trained immunity, tissue-resident memory, autoantibodies, sensitized mast cells, fibroblast memory, epigenetic priming, pain memory, trauma physiology, or autonomic threat states may keep the organism responding to the present as if the past is still active.

A re-entry lock occurs when the organism cannot return to ordinary health-cycle participation.

Memory locks may involve adaptive immune memory, trained innate immunity, tissue-resident cells, epigenetic priming, microbial shifts, pain memory, and autonomic threat learning (Chuong et al., 2016; Netea et al., 2016; Virgin, 2014).

The person remains limited by fatigue, post-exertional worsening, pain, sleep disruption, dysautonomia, fear of relapse, deconditioning, persistent symptoms, or environmental unsafety. The acute event may be over, but ordinary life remains biologically inaccessible.

These locks are not mutually exclusive. Chronic disease often involves several at once. Inflammatory bowel disease may involve barrier alarm, microbial dysbiosis, immune activation, impaired resolution, tissue repair, fibrosis, and altered gut-brain signalling. Chronic rhinosinusitis may involve barrier disruption, microbial communities, mucus, biofilms, type 2 inflammation, impaired drainage, and tissue remodelling. Rheumatoid arthritis may involve recognition lock, synovial inflammatory lock, fibroblast memory, pain lock, and systemic allostatic load. Long COVID may involve danger, viral, vascular, mitochondrial, autonomic, immune-memory, and re-entry locks in varying combinations.

The phase-lock concept therefore encourages pattern recognition without premature simplification.

This protects the framework from single-cause reductionism: chronic immune diseases often involve mixed mechanisms whose dominance may shift across time, tissue, exposure, and treatment phase (Belkaid & Hand, 2014; McEwen, 1998; Medzhitov, 2008; Netea et al., 2016).

9.4 Phase-Locking and the Organism–Niche Relation

A phase-lock is never purely internal. Even when molecular pathways are central, the organism remains embedded in a niche. Ongoing exposures, sleep disruption, food insecurity, damp housing, pollutants, infection recurrence, social threat, overwork, climate stress, medication effects, microbiome disruption, and lack of care can all maintain or deepen lock-in.

The organism may be trying to complete healing in a niche that continually re-injures it.

Phase-locking also links to exposome and social-determinants frameworks, where cumulative environmental, social, chemical, microbial, occupational, and climatic exposures shape disease risk and recovery capacity (Commission on Social Determinants of Health, 2008; Rappaport & Smith, 2010; Wild, 2005).

This matters because treatment directed only at internal pathways may fail if the external perturbation remains. A patient with asthma living in damp, moldy housing may receive inhaled corticosteroids and bronchodilators yet continue to flare. A patient with dermatitis exposed to occupational irritants may improve only temporarily. A patient with inflammatory disease under chronic sleep deprivation may remain unstable. A patient with recurrent infections in crowded or unsafe housing may not achieve durable resilience through medication alone. A patient with post-infectious illness forced into premature exertion may repeatedly crash.

This is not a rejection of pharmacology. It is a reminder that pharmacology enters an organism–niche system.

Pharmacologic treatment remains essential, but its effects are always mediated through the organism's phase-state, tissue context, allostatic load, exposure field, and recovery resources (McEwen, 1998; Medzhitov, 2008; Naviaux, 2014).

The same principle applies in reverse. Environmental or lifestyle interventions may fail if active pathology is not treated. Removing exposures will not be enough for aggressive vasculitis, severe lupus nephritis, uncontrolled inflammatory bowel disease, septic infection, advanced fibrosis, or destructive arthritis. A life-coherent approach refuses both narrow biomedical isolation and vague environmental reductionism.

The question is always phase-specific: What is locking the organism here, and at what level must intervention occur?

This phase-specific question preserves both biomedical precision and organism–niche reasoning: some locks require urgent suppression, others require clearance, exposure reduction, drainage, repair support, rehabilitation, sleep restoration, or social protection (Antonovsky, 1987; McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005).

9.5 Phase-State Clinical Reasoning

Phase-state clinical reasoning adds a second layer to diagnosis. The first layer asks: What disease or syndrome is present? The second asks: What phase-state is dominant, what transitions are blocked, and what conditions would allow movement?

This two-layer approach preserves conventional diagnosis while adding a process-oriented assessment of the organism's current regulatory state and transition capacity (McEwen, 1998; Naviaux, 2014; Serhan, 2007).

This reasoning might proceed through several questions.

Is the organism in active danger detection? Then the clinician looks for infection, injury, exposure, tissue damage, barrier disruption, mitochondrial stress, immune complexes, crystals, toxins, or inflammatory triggers.

Is the organism in destructive defence? Then suppression or targeted immune modulation may be necessary to prevent harm.

Is containment present without clearance? Then drainage, antimicrobial strategy, biofilm assessment, surgical evaluation, lymphatic support, or removal of persistent material may be relevant.

Is resolution impaired? Then the clinician asks why inflammation cannot terminate: ongoing trigger, metabolic constraint, insufficient pro-resolving pathways, macrophage dysfunction, persistent debris, sleep disruption, or tissue niche signalling.

Is clearance impaired? Then efferocytosis, autophagy, mitophagy, lymphatics, mucociliary clearance, glymphatic flow, renal and hepatic function, immune-complex handling, or environmental load may require attention.

Is repair excessive or disorganized? Then fibrosis, matrix remodelling, mechanical stress, TGF-β signalling, chronic injury, and rehabilitation become central.

Is memory fixed? Then trained immunity, autoantibodies, tissue-resident memory, mast-cell sensitization, pain memory, or autonomic threat learning may be involved.

Is re-entry blocked? Then pacing, rehabilitation, sleep, nutrition, social support, autonomic regulation, mitochondrial capacity, pain treatment, and gradual restoration of participation may become as important as suppressing inflammation.

This approach does not require every clinician to test every mechanism in every patient. It provides a grammar for asking better questions and organizing care.

The purpose is pragmatic clinical orientation, not exhaustive testing: phase-state reasoning should guide prioritization, sequencing, and interpretation without replacing evidence-based diagnosis or urgent treatment (Antonovsky, 1987; Medzhitov, 2008).

9.6 The Ethical Meaning of Phase-Locking

The language of phase-locking must be used carefully. It should never become another label imposed on the patient. A person is not “locked” in a moral or psychological sense. The organism is constrained by biological, historical, environmental, and relational conditions. Phase-locking is not a failure of will. It is a pattern of living regulation under constraint.

This ethical caution is consistent with salutogenic and allostatic reasoning: constrained regulation reflects the interaction between organismic capacity, stress burden, resources, history, and environment, not personal weakness (Antonovsky, 1987; McEwen, 1998).

This distinction protects patients from blame. A patient with chronic fatigue is not refusing activity; the organism may be unable to afford re-entry. A patient with allergy is not being irrational; the organism’s barrier and type 2 systems may be evaluating the environment as threat. A patient with autoimmunity is not attacking themselves in a psychological sense; immune recognition, clearance, tolerance, and tissue injury may be locked in destructive patterns. A patient with chronic pain is not imagining pain; neuroimmune protection may have become persistent. A patient with fibrosis is not “overhealing” by choice; repair biology has become self-sustaining.

The clinician’s task is not to judge the lock, but to understand and help loosen it.

This stance allows clinical rigor and compassion to coexist: the clinician takes suffering seriously, investigates mechanisms carefully, and supports the next adaptive transition without blaming the patient for being constrained (Antonovsky, 1987; Maturana & Varela, 1980).

This ethical stance is central to life-coherent medicine. It invites compassion without sentimentality and rigor without reductionism. It allows the clinician to take suffering seriously while still asking precise biological questions. It allows uncertainty without dismissal. It allows treatment without domination.

9.7 Transition to Mechanisms

The first three parts of this paper have developed the conceptual grammar: observer humility, organism-centered immune coherence, 5E immune cognition, preservation-development-coherence attractors, salutogenesis, health cycles, healing cycles, allostasis, immune resilience, and phase-locking.

The next task is to descend into mechanisms.

If immune disease is maladaptive phase-locking, then we must ask how phase-locks are installed, sustained, remembered, and expressed. How do molecular sensors participate in boundary evaluation? How do gene regulatory networks create immune-cell attractor states? How does viral and mobile genetic memory shape boundary-crossing information? How does metabolism write experience into chromatin? How do mitochondria set biological phase? How does the cell danger response become incomplete salugenesis? How do tissues give disease its form?

These questions take us from grammar into architecture.

The mechanisms that follow are not presented as disconnected pathways. They are the biological means by which the organism senses, evaluates, defends, resolves, clears, repairs, remembers, and sometimes becomes locked.

The move from conceptual grammar to biological architecture links organism-centered reasoning to molecular sensors, gene regulatory networks, immunometabolism, mitochondria, cell danger response biology, tissue niches, and immune memory (Buck et al., 2017; Naviaux, 2014; Netea et al., 2016; O'Neill et al., 2016).

The living cycle now descends into molecular life.

Part IV. Molecular, Cellular, and Evolutionary Foundations

10. Molecular Architecture: Sensors, Signals, and Regulons

If immune disease is maladaptive phase-locking, then the next question is mechanistic: how does the organism sense perturbation, evaluate boundary conditions, mobilize defence, regulate inflammation, repair tissue, remember danger, and sometimes become locked? The answer begins at the molecular level, but the molecular level must not be misunderstood as separate from the living organism. Molecules do not act in abstraction. They participate in the organism's embodied, embedded, enactive, extended, and evaluative boundary process.

Molecular sensors do not merely detect objects; they participate in the organism's evaluative boundary process.

This wider interpretation builds on pattern-recognition, danger, complement, inflammasome, and nucleic-acid sensing models, but situates them within an organism-centered account of boundary evaluation rather than isolated molecular detection alone (Chen et al., 2016; Janeway, 1989; Matzinger, 2002; Medzhitov & Janeway, 1997; Ricklin et al., 2010; Schroder & Tschopp, 2010).

This point is essential. Pattern-recognition receptors, cytokine receptors, antigen receptors, complement receptors, Fc receptors, mechanosensors, metabolic sensors, redox-sensitive transcription factors, inflammasomes, and nucleic-acid sensors are often described as if they simply recognize molecular targets. That is true, but incomplete. Their deeper biological role is to help the organism determine what kind of world it is presently inhabiting: safe enough, infected, injured, toxic, hypoxic, mechanically strained, metabolically overloaded, barrier-breached, virally invaded, or ready for repair.

The immune system's molecular architecture is therefore not a collection of isolated switches. It is a layered sensing-and-response network that helps the organism move between phases. These molecular systems help decide whether the organism remains in surveillance, shifts into danger detection, escalates to defence, contains spread, initiates resolution, clears debris, repairs tissue, updates memory, or returns to ordinary health-cycle participation.

When these molecular systems remain coordinated, they support adaptive phase-shifting. When they become excessive, insufficient, mislocalized, mis-timed, or unable to exit, they contribute to maladaptive phase-locking.

In this sense, molecular pathways can be understood as phase participants: they support adaptive transitions when coordinated, but contribute to chronic disease when activation, timing, localization, or termination fails (Medzhitov, 2008; Naviaux, 2014; Serhan, 2007).

10.1 Pattern-Recognition Receptors and Boundary Evaluation

Pattern-recognition receptors are among the core molecular systems through which the organism senses microbial presence, tissue damage, and altered internal conditions. Toll-like receptors, NOD-like receptors, RIG-I-like receptors, C-type lectin receptors, AIM2-like receptors, and other sensing systems detect molecular patterns associated with microbes, damaged cells, nucleic acids, crystals, toxins, or stress.

Pattern-recognition theory helped transform immunology by showing that innate immune systems detect conserved microbial and danger-associated molecular patterns rather than relying only on adaptive self/non-self discrimination (Janeway, 1989; Medzhitov & Janeway, 1997).

The older language of pathogen-associated molecular patterns and damage-associated molecular patterns remains useful. Microbial products may indicate invasion, colonization, dysbiosis, or misplaced organisms. Damage signals may indicate necrosis, stress, tissue rupture, mitochondrial injury, matrix damage, or failed clearance. But these signals do not carry fixed meaning in isolation. Their meaning depends on location, timing, dose, tissue, history, and the organism's present state.

A bacterial product in the gut lumen may be part of tolerated ecology. The same molecular pattern in the bloodstream may signal emergency. DNA inside the nucleus is ordinary. DNA in the cytosol may indicate viral infection, mitochondrial rupture, or cellular damage. Extracellular ATP may participate in normal signalling, but at high local concentrations after injury it may become an alarm. Uric acid may be a metabolic product, but crystals in tissue may activate inflammation. The issue is not simply the molecule. It is the molecule-in-context.

Pattern recognition is therefore boundary evaluation.

This boundary-evaluation framing preserves the insights of pathogen-associated and damage-associated sensing while emphasizing that immune meaning depends on compartment, tissue context, timing, dose, and organismal state (Matzinger, 2002; Medzhitov, 2008; Pradeu, 2012).

The organism is asking, in molecular form: Where is this signal? How much is present? What tissue is involved? Is there damage? Is the barrier intact? Has this been seen before? Are other alarms co-present? What metabolic state are we in? Is the organism safe enough to tolerate, or must it defend?

This is why the same receptor system can support health or disease. Pattern-recognition receptors are indispensable for host defence, microbial education, tissue repair, and immune readiness. But persistent or inappropriate activation can sustain chronic inflammation, autoinflammation, allergy amplification, autoimmune flares, fibrosis, metabolic inflammation, and post-infectious dysregulation. The molecular system that protects the organism can become part of the lock.

In phase-state terms, pattern-recognition receptors are especially important in surveillance, boundary sensing, and danger detection. They help determine whether the organism should remain open, become vigilant, or mobilize defence. When they are persistently stimulated by

ongoing exposure, uncleared debris, dysbiosis, damaged mitochondria, crystals, biofilms, or tissue injury, the organism may remain trapped in danger detection. It cannot return to ordinary health-cycle participation because the molecular field continues to say: danger is still present.

10.2 Antigenicity, Adjuvanticity, and Context

Antigenicity is the capacity of a molecule to be recognized by antigen receptors. But recognition alone does not determine immune meaning. The same antigen may be ignored, tolerated, responded to, remembered, or attacked depending on context. This is why adjuvanticity is so important. An antigen encountered with danger signals, tissue damage, infection, barrier disruption, or inflammatory co-stimulation may acquire a different meaning from the same antigen encountered in a tolerogenic context.

This helps explain why immune disease cannot be understood through antigen alone. Food proteins, pollen, commensal microbes, self-antigens, viral remnants, environmental particles, and tissue-derived molecules may become immunologically significant only when embedded in a broader alarm field. Barrier injury, epithelial cytokines, microbial products, toxins, pollutants, mitochondrial stress, inflammasome activation, or defective clearance may turn an otherwise tolerable signal into a trigger.

In organism-centered terms, the immune system is not simply asking, “What is this?” It is asking, “What does this mean here, now, under these conditions?”

This distinction matters for autoimmunity and allergy. Autoantigens are not necessarily sufficient to cause autoimmune disease. They may require inflammatory context, genetic susceptibility, defective clearance, molecular mimicry, tissue injury, epitope spreading, or loss of regulatory tolerance. Allergens are not merely foreign proteins. Many become allergenic in the context of epithelial barrier disruption, protease activity, pollutants, microbial changes, type 2 skewing, and developmental immune history.

The immune response is therefore not determined by the object alone. It emerges from antigen plus context plus history plus tissue state.

This context-dependent interpretation is central to danger and tissue-based accounts of immunity: antigen recognition becomes biologically consequential when coupled to co-stimulation, damage, inflammation, barrier disruption, or failed regulation (Matzinger, 2002; Medzhitov, 2008; Pradeu, 2012).

This is also why some immune responses become difficult to reverse. Once an antigen has been interpreted within a danger context, memory may preserve that interpretation. The organism may respond to later encounters as if the original danger remains present. This is protective when the remembered threat is real and recurrent. It is pathological when memory becomes inflexible, misplaced, or disproportionate.

Antigenicity gives the immune system specificity. Adjuvanticity gives that specificity biological urgency. Phase-locking occurs when urgency remains attached to signals that should have become tolerable, resolved, or forgotten.

This is especially relevant to allergic and autoimmune disease, where immune specificity becomes pathological only within a broader field of danger, tissue injury, memory, and regulatory failure (Matzinger, 2002; Medzhitov, 2008).

10.3 Inflammasomes and the Danger-Defence Transition

Inflammasomes are molecular platforms that translate danger detection into inflammatory defence. They respond to microbial products, crystals, ion fluxes, mitochondrial dysfunction, lysosomal damage, cytosolic perturbation, and other signs of cellular stress. Their activation can lead to interleukin-1β and interleukin-18 maturation, pyroptotic cell death, and amplification of local inflammation.

Inflammasomes provide a clear example of molecular phase transition: they convert sensed cellular stress or danger into inflammatory amplification through IL-1 family cytokines and pyroptotic pathways (Schroder & Tschopp, 2010).

In acute settings, inflammasomes are vital. They help mobilize defence against infection, respond to tissue injury, and alert the organism that cellular integrity has been breached. They are part of the transition from sensing to action.

But inflammasomes are also powerful generators of phase-locking. If inflammasome activation persists, the organism may remain trapped in danger and defence. Crystals, damaged mitochondria, metabolic stress, persistent infection, dysbiosis, pollutants, senescent cells, or impaired clearance can keep inflammasome pathways active. The result may be autoinflammatory disease, gout, metabolic inflammation, neuroinflammation, chronic tissue inflammation, or amplification of autoimmune pathology.

Inflammasome activation shows why clearance is inseparable from resolution. If the inflammasome is activated by material that remains uncleared, then anti-inflammatory treatment alone may quiet downstream signals temporarily but leave upstream danger intact. The organism continues to encounter the same molecular warning. The phase-lock persists.

Persistent inflammasome activation can therefore be understood as a danger-defence lock when crystals, damaged mitochondria, metabolic stress, infection, or uncleared debris continue to stimulate upstream sensing (Schroder & Tschopp, 2010; West & Shadel, 2017).

In clinical terms, inflammasomes help define a danger-defence lock. The organism is not merely inflamed. It is repeatedly receiving molecular evidence of cellular stress, damage, or mislocalized material. Treatment may require suppression, but also attention to the source of danger: crystals, metabolic overload, damaged mitochondria, infection, tissue injury, environmental exposures, or impaired clearance.

10.4 cGAS–STING and Nucleic-Acid Boundary Integrity

The cGAS–STING pathway is central to the organism's detection of cytosolic DNA. In one context, this is a powerful antiviral and antimicrobial defence system. DNA in the wrong cellular compartment may indicate viral infection, bacterial invasion, mitochondrial damage, nuclear rupture, micronuclei, senescence, or cellular stress. The pathway activates interferon and inflammatory programs that help defend the organism.

The cGAS–STING pathway is a major cytosolic DNA-sensing system linking misplaced DNA to interferon induction, innate immune activation, and inflammatory signalling (Chen et al., 2016).

But this same pathway can become pathological when nucleic-acid boundary integrity is chronically disturbed. Damaged mitochondria may release mitochondrial DNA. Genomic instability may generate micronuclei. Viral remnants, endogenous retroelements, impaired nucleic-acid clearance, cellular stress, and tissue injury may all contribute to persistent nucleic-acid sensing. The organism may behave as if viral invasion or internal rupture remains ongoing.

This creates a nucleic-acid/interferon lock.

Such locks may arise when cytosolic DNA, mitochondrial DNA, viral remnants, endogenous retroelements, senescence, or impaired clearance repeatedly activate antiviral-like programmes beyond their adaptive window (Chen et al., 2016; Chuong et al., 2016; West & Shadel, 2017).

Interferon responses are essential when viral defence is needed. They induce antiviral states, shape antigen presentation, activate immune cells, and restrict replication. Yet chronic interferon tone can impair tissue function, drive fatigue, alter haematopoiesis, amplify autoimmunity, and sustain systemic inflammatory symptoms. The problem is again not the existence of the pathway. The problem is failure of phase transition.

The organism must be able to enter antiviral defence and then exit. When nucleic-acid sensing persists, exit becomes difficult.

This has implications for autoimmune disease, post-viral syndromes, mitochondrial injury, senescence, and diseases involving endogenous mobile genetic elements. It also shows why mitochondria are immunologically central. Mitochondria are not merely powerhouses. Because of their bacterial ancestry and retained DNA, they can become sources of danger signals when damaged or misplaced. Mitochondrial injury can therefore blur the boundary between internal dysfunction and infection-like alarm.

The cGAS–STING system reminds us that immunity is deeply concerned with boundary location: not only what molecule is present, but where it is.

This reinforces the manuscript's central boundary-coherence claim: molecular identity is not sufficient; compartmental integrity and location are central to immune meaning (Chen et al., 2016; Pradeu, 2012; West & Shadel, 2017).

DNA in one compartment is self-maintenance. DNA in another compartment is alarm.

10.5 Fc Receptors, Complement, and Immune-Complex Meaning

Fc receptors and complement systems help translate antibodies and immune complexes into cellular action. They participate in pathogen clearance, opsonization, phagocytosis, immune-complex handling, inflammation, tissue injury, and communication between innate and adaptive immunity. They are essential for defence and clearance, yet they can become destructive when immune complexes persist, deposit, or activate complement in vulnerable tissues.

Complement and Fc-receptor pathways are key bridges between recognition, clearance, inflammation, and tissue injury, especially when immune complexes persist or deposit in vulnerable anatomical sites (Ricklin et al., 2010).

Antibodies are not simply markers of disease. They are molecular participants in boundary evaluation and memory. They can neutralize pathogens, tag targets for clearance, activate complement, guide phagocytosis, or, in pathological contexts, bind self-antigens and form immune complexes that drive inflammation.

Immune complexes illustrate the importance of clearance. If immune complexes are efficiently removed, they may be part of normal immune housekeeping. If they persist or deposit in vessels, kidneys, skin, joints, or other tissues, they become inflammatory signals. Complement activation then amplifies local injury. The organism becomes locked in a cycle of recognition, deposition, inflammation, and damage.

This is especially relevant to diseases such as systemic lupus erythematosus, vasculitis, immune-complex glomerulonephritis, serum sickness-like reactions, and some forms of chronic infection. The issue is not recognition alone. It is recognition plus persistence plus location plus inflammatory amplification plus insufficient clearance.

Fc-complement systems therefore participate in recognition/clearance locks. The organism has marked material for attention, but the resulting process cannot complete quietly. Instead, recognition becomes tissue injury.

This distinction helps explain why antibody presence alone is not equivalent to disease; pathology emerges when recognition becomes coupled to deposition, complement activation, inflammatory amplification, and insufficient clearance (Ricklin et al., 2010; Ravichandran & Lorenz, 2007).

Clinically, this supports the need to distinguish between autoantibody presence, immune-complex formation, complement consumption, tissue deposition, and active inflammatory damage. A positive antibody is not the same as disease. Disease emerges when molecular recognition becomes biologically consequential within tissue and phase-state context.

10.6 Mechanosensors and the Immunology of Force

Immune regulation is not only chemical. It is also mechanical.

Tissue mechanics, extracellular matrix properties, stromal activation, and fibroblast behaviour are increasingly recognized as active contributors to inflammation, repair, and fibrosis rather than passive background conditions (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Cells sense stiffness, stretch, pressure, shear, matrix composition, tissue architecture, and force. Mechanosensitive pathways involving integrins, cytoskeleton, ion channels, extracellular matrix, YAP/TAZ signalling, fibroblast activation, endothelial responses, and mechanically responsive immune cells help translate physical conditions into biological meaning.

This is crucial because tissues are not passive containers of immune activity. They are mechanically active niches. The synovium, enthesis, lung interstitium, skin, gut, blood vessels, fascia, and scar tissue all generate mechanical signals that shape immune behaviour.

Mechanical stress can be adaptive. Movement supports lymphatic flow, tissue remodelling, bone strength, vascular function, and metabolic health. But mechanical strain in a primed tissue can become inflammatory. Enthesis inflammation, synovial activation, airway remodelling, vascular stiffness, fibrosis, and chronic pain states may all involve immune-mechanical coupling.

Fibrosis is especially important here. As tissue stiffens, mechanical signals change. Stiffness can activate fibroblasts, alter macrophage behaviour, impair perfusion, affect epithelial cells, and maintain inflammatory repair loops. The tissue's physical state becomes part of the disease. Repair changes mechanics; altered mechanics sustain repair. This is enactive immunity at the tissue level.

Mechanosensors therefore help explain repair-overbuild locks. The organism attempts to stabilize damage by remodelling tissue, but the remodeled tissue generates signals that sustain further activation. The scar becomes a signal. The matrix becomes memory.

This is particularly important in fibrotic disease, where macrophage-fibroblast crosstalk, matrix stiffness, tissue remodelling, and persistent repair signalling can become self-reinforcing (Wynn et al., 2013; Wynn & Ramalingam, 2012).

This has clinical implications for rehabilitation, movement, physical therapy, antifibrotic strategies, occupational exposure, posture, breathing mechanics, and tissue loading. Movement may restore coherence when introduced at the right phase and dose. But excessive mechanical demand on an inflamed or energetically constrained tissue may worsen pathology. Again, timing matters.

10.7 Core Signalling Pathways as Phase Regulators

Several major signalling pathways help coordinate immune phase-states. NF-κB, interferon regulatory factors, JAK–STAT, mTOR, AMPK, HIF-1α, NRF2, TGF-β, YAP/TAZ, MAPK, and

related networks do not simply turn inflammation on or off. They help determine what biological phase a cell or tissue can enter, maintain, or exit.

NF-κB is central to inflammatory activation, survival signalling, cytokine expression, and stress response. It is essential for defence, but chronic NF-κB activation can sustain inflammatory lock-in.

Interferon regulatory factors coordinate antiviral and nucleic-acid responses. They support defence against viruses, but chronic activation can contribute to interferon-driven autoimmunity, fatigue, tissue dysfunction, and persistent immune activation.

JAK–STAT pathways translate cytokine signals into gene expression programs. They allow cells to respond to interferons, interleukins, colony-stimulating factors, and growth signals. Dysregulated JAK–STAT signalling can sustain inflammatory, allergic, autoimmune, or proliferative states.

mTOR senses nutrient, growth, energy, and immune signals. It supports anabolic growth, effector immune activity, and cellular activation. Excessive or mistimed mTOR activity may contribute to inflammatory activation, metabolic stress, and impaired autophagy.

AMPK responds to energy stress and helps promote catabolic balance, mitochondrial function, and metabolic adaptation. Its relation to mTOR helps cells decide whether conditions support growth, defence, conservation, or repair.

HIF-1α responds to hypoxia and metabolic shifts. It is important in inflamed tissues where oxygen demand, vascular changes, and cellular metabolism are altered. Hypoxia can sustain inflammatory and fibrotic states when unresolved.

NRF2 supports antioxidant defence, redox balance, detoxification, and cellular stress resilience. It helps determine whether oxidative stress remains adaptive or becomes damaging.

TGF-β participates in immune regulation, tolerance, tissue repair, fibrosis, and extracellular matrix remodelling. It is essential for healing, but persistent or excessive TGF-β signalling can drive fibrotic lock-in.

YAP/TAZ signalling links mechanical cues, tissue stiffness, cell growth, and repair responses. It helps explain how tissue architecture and mechanics shape immune and fibrotic states.

These pathways form part of the molecular grammar of phase regulation. Their meaning depends on timing and context. NF-κB activation during acute infection may be protective. Persistent NF-κB activation in tissue may be destructive. TGF-β may support resolution and repair after injury. Persistent TGF-β may drive fibrosis. mTOR may support effector function when energy is available. Chronic mTOR activation may impair autophagic clearance. NRF2 may protect against oxidative damage. Inadequate NRF2 response may allow stress to become inflammatory.

A pathway is not a disease. A pathway is a phase participant.

This framing prevents pathway reductionism: signalling systems such as NF-κB, interferon pathways, JAK–STAT, mTOR, AMPK, HIF-1α, NRF2, TGF-β, and related networks acquire meaning through timing, tissue context, metabolic state, and phase of response (Buck et al., 2017; Medzhitov, 2008; O'Neill et al., 2016).

10.8 Transcription-Factor Regulons and Immune-State Installation

Signals become durable when they alter gene expression programs. Transcription factors and regulons translate receptor activation, metabolic state, cytokine exposure, mechanical force, redox conditions, and tissue signals into cellular identity and function. They help install immune-cell states.

Durable immune-cell states arise through coordinated transcriptional, epigenetic, metabolic, and tissue-contextual regulation rather than through isolated receptor activation alone (Buck et al., 2017; Netea et al., 2016; O'Neill et al., 2016).

This is how temporary perturbation can become future readiness. A macrophage exposed to microbial products, interferons, hypoxia, lipids, crystals, apoptotic cells, or tissue signals may adopt distinct activation states. A T cell exposed to antigen, co-stimulation, cytokines, and metabolic cues may differentiate toward effector, regulatory, memory, exhausted, or tissue-resident programs. A fibroblast exposed to inflammatory and mechanical signals may become persistently activated. An epithelial cell exposed to allergens, pollutants, viruses, or injury may produce alarmins more readily. A mast cell may become sensitized. A microglial cell may become primed.

These state changes are not merely immediate reactions. They can persist through chromatin accessibility, enhancer priming, metabolic reconfiguration, and tissue memory. The organism becomes differently prepared for future encounters.

This altered readiness is central to trained immunity and tissue memory, where prior exposure changes chromatin accessibility, metabolic configuration, and future response thresholds (Netea et al., 2016).

In health, this is adaptive. Prior experience improves future response. In disease, it can install pathological attractors. The cell does not return fully to baseline. It remains primed, biased, sensitized, exhausted, fibrotic, inflammatory, or repair-oriented. Recurrent flares may then be understood not as entirely new events, but as reactivations of previously installed regulatory states.

This leads directly to the next section on gene regulatory networks and immune-cell state attractors. Molecular sensing begins the response, but gene regulation helps give it memory, stability, and recurrence.

10.9 Molecular Phase-Locking

The molecular architecture of immunity can become locked at multiple points.

Pattern-recognition receptors can remain stimulated by persistent microbes, dysbiosis, damaged tissue, environmental exposure, or uncleared debris.

Inflammasomes can remain active through crystals, mitochondrial dysfunction, lysosomal stress, metabolic overload, or chronic infection.

cGAS–STING and interferon pathways can remain active through persistent nucleic-acid signals, viral remnants, mitochondrial DNA, endogenous retroelements, or impaired clearance.

Complement and Fc receptor pathways can remain active through immune complexes, autoantibodies, chronic infection, or tissue deposition.

Mechanosensors can remain activated by stiffness, fibrosis, altered matrix, repetitive strain, or abnormal tissue architecture.

Transcription-factor regulons can stabilize inflammatory, fibrotic, antiviral, allergic, exhausted, or primed cell states.

Metabolic sensors can bias cells toward activation, conservation, growth, or shutdown.

Each of these molecular locks may correspond to a clinical phase-lock. Danger detection, defence, containment, resolution failure, clearance failure, repair-overbuild, memory fixation, and re-entry failure all have molecular correlates. The organism's inability to move is embodied in signalling networks.

Molecular phase-locking therefore provides the mechanistic underside of the clinical grammar: danger, defence, interferon activation, immune-complex injury, fibrosis, trained readiness, and failed clearance all have signalling correlates (Chen et al., 2016; Netea et al., 2016; Schroder & Tschopp, 2010; Wynn & Ramalingam, 2012).

Yet the molecular level is never the whole story. A molecular lock may be sustained by a tissue niche, exposure, infection, diet, sleep disruption, social stress, mechanical load, microbiome state, or treatment history. To treat the molecule without seeing the field may help, but may also leave the lock's conditions intact.

The goal is not to choose between molecular precision and organism-centered care. The goal is to integrate them.

10.10 Clinical Meaning

For clinical medicine, molecular architecture provides targets, but phase-state reasoning provides orientation.

This distinction supports targeted therapy without reducing treatment to pathway suppression alone; the clinical question remains which adaptive transition the intervention is meant to enable (Medzhitov, 2008; Naviaux, 2014; Serhan & Savill, 2005).

A JAK inhibitor, biologic therapy, corticosteroid, colchicine, antiviral, antimicrobial, antihistamine, mast-cell stabilizer, antifibrotic agent, antioxidant strategy, metabolic intervention, or complement inhibitor may all be appropriate in specific contexts. But the deeper question remains: what phase transition is this intervention intended to support?

Is the treatment suppressing destructive defence?
Is it reducing danger signalling?
Is it interrupting inflammatory amplification?
Is it allowing resolution?
Is it enabling clearance?
Is it preventing over-repair?
Is it reducing memory fixation?
Is it making re-entry possible?

When treatment is framed this way, pharmacology becomes part of phase restoration rather than merely pathway suppression.

This is also where humility remains necessary. Molecular biomarkers can guide care, but they do not speak for the whole organism. A cytokine level, antibody titre, gene signature, complement marker, mitochondrial signal, or inflammatory marker must be interpreted in context. A marker may indicate driver, consequence, compensation, risk, memory, or noise. The clinician must ask what it means in this tissue, in this patient, at this time, in this phase.

Molecular immunology is therefore indispensable, but it must remain answerable to the living cycle.

Biomarkers and molecular targets are most clinically meaningful when interpreted within tissue state, organismal history, allostatic load, recovery capacity, and health-cycle participation (McEwen, 1998; Medzhitov, 2008; Naviaux, 2014).

The organism senses through molecules, but it does not live as molecules alone. Its molecular architecture is the beginning of boundary evaluation, not the end of clinical understanding.

11. Gene Regulatory Networks and Immune-Cell State Attractors

If molecular sensors help the organism detect perturbation, gene regulatory networks help determine whether that perturbation becomes a passing response or a durable biological state. The immune system does not simply turn on and off like a switch. It changes cellular identity, readiness, memory, metabolism, and tissue behaviour through coordinated patterns of gene expression. These patterns can resolve after the threat has passed, or they can persist as altered immune-cell state attractors.

A flare is not always a new event; it may be the reactivation of a previously installed regulatory state.

This interpretation is consistent with trained immunity, tissue-resident memory, and epigenetic priming, where prior perturbations alter future response thresholds and make some inflammatory states easier to re-enter (Netea et al., 2016).

This is a crucial point for chronic immune disease. Patients often experience flares as if the body is "doing the same thing again." From a gene-regulatory perspective, this may be partly true. Prior perturbations can leave behind molecular readiness. Cells may not return fully to their previous baseline. Chromatin remains more open at certain inflammatory loci. Enhancers remain primed. Transcription factors become easier to recruit. Metabolic pathways remain biased. Tissue-resident cells remain sensitized. Fibroblasts remember position and injury. Macrophages, T cells, mast cells, epithelial cells, endothelial cells, and stromal cells may all carry traces of prior activation.

The organism's past becomes present as altered possibility.

Such altered possibility may be carried through chromatin accessibility, enhancer priming, immune-cell differentiation, tissue-resident cells, stromal memory, and metabolic reconfiguration (Buck et al., 2017; Netea et al., 2016; O'Neill et al., 2016).

Gene regulatory networks are the systems by which cells coordinate thousands of genes into meaningful biological programs. A macrophage does not activate one gene at a time in isolation. It enters a state. A T cell does not merely respond to antigen; it differentiates into a functional identity. A fibroblast does not simply deposit collagen; it can become part of a persistent repair program. An epithelial cell does not merely form a barrier; it can become an alarm-generating participant in chronic inflammation. These cell states are governed by networks of transcription factors, chromatin accessibility, cytokine exposure, metabolic substrates, mechanical cues, microbial signals, and tissue feedback.

In acute healing, this is adaptive. Cells must change state quickly. A macrophage must help detect danger, amplify defence, clear debris, resolve inflammation, and support repair. A T cell must expand, differentiate, perform effector functions, contract, and leave memory. A fibroblast must help close wounds and rebuild matrix. An epithelial cell must restore barrier integrity. Gene regulatory networks allow cells to move through these phases.

But in chronic immune disease, state transitions may fail. Cells may remain inflammatory, exhausted, fibrotic, hyperresponsive, antiviral, allergic, or repair-biased. Instead of flexible phase-shifting, the tissue becomes populated by cells that have settled into pathological attractors.

An attractor is a stable pattern toward which a system tends to return. In immune biology, this means that a cell or tissue may repeatedly return to the same inflammatory or repair state when perturbed. The state becomes easier to re-enter than to exit. This is one reason chronic disease can relapse after apparent improvement. The visible inflammation may settle, but the underlying regulatory landscape remains prepared for recurrence.

Remission, therefore, is not always reset.

Resolution biology supports this distinction: clinical quieting is not necessarily equivalent to active resolution, clearance, tissue reorganization, or restoration of a less relapse-prone regulatory landscape (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

This distinction is clinically important. Remission means that disease activity is currently reduced or absent by available clinical measures. Reset would mean that the regulatory architecture sustaining relapse has been substantially reorganized. A patient may be in remission but remain vulnerable because gene regulatory networks, tissue niches, immune memory, or environmental perturbations still favour reactivation. This helps explain why some patients flare after infection, stress, sleep disruption, toxin exposure, hormonal change, mechanical strain, or medication withdrawal. The trigger may be new, but the state it reactivates is old.

Chromatin accessibility is one mechanism by which such memory becomes possible. DNA is not equally available for transcription at all times. When chromatin opens around certain regulatory regions, genes become easier to activate. In immune cells, prior exposure to microbial products, cytokines, interferons, allergens, tissue damage, metabolic stress, or inflammatory mediators can make future responses faster or stronger. Enhancer priming allows cells to respond more readily to later signals. This is useful in host defence. It is dangerous when it sustains exaggerated or misplaced responses.

Trained immunity is a key example. Innate immune cells, once thought to lack memory, can develop long-lasting functional changes after exposure to certain stimuli. Monocytes, macrophages, natural killer cells, and progenitor cells may become more responsive after infection, vaccination, metabolic exposure, or inflammatory challenge. This can improve defence, but it can also amplify chronic inflammation. A trained innate system may respond to later perturbations with excessive force, even when the later trigger differs from the original one.

In this way, trained immunity is both adaptive memory and possible phase-lock.

Trained immunity demonstrates that innate immune cells and progenitors can acquire durable functional changes after prior exposure, improving defence in some contexts but amplifying chronic inflammation in others (Netea et al., 2016).

Tissue-resident memory adds another layer. Immune cells that remain in tissues after infection, inflammation, or injury can provide rapid local protection. In skin, gut, lung, synovium, brain, and other tissues, resident memory cells help the organism respond quickly to recurring threats. But they may also contribute to local disease recurrence. Psoriasis, inflammatory bowel disease, asthma, and other relapsing inflammatory disorders may involve tissue-resident cells that preserve local readiness long after the initial event has passed.

The tissue remembers through its cells.

Tissue-resident cells, stromal cells, fibroblasts, epithelial cells, macrophages, and local matrix conditions can preserve disease-specific readiness even after overt inflammation has quieted (Galli et al., 2011; Wynn et al., 2013; Wynn & Ramalingam, 2012).

Fibroblasts also remember. They are not merely structural support cells. They respond to cytokines, mechanical force, hypoxia, injury, growth factors, and matrix stiffness. In chronic inflammation, fibroblasts can adopt aggressive, inflammatory, invasive, or fibrotic phenotypes. They may maintain positional memory, meaning that their behaviour depends partly on the anatomical and developmental identity of the tissue they inhabit. Synovial fibroblasts, lung fibroblasts, gut stromal cells, skin fibroblasts, and vascular fibroblasts do not behave identically because they belong to different tissue worlds.

This helps explain why immune disease has form. The same systemic inflammatory signal does not produce the same disease everywhere. It is interpreted by tissue-specific regulatory landscapes. The synovium becomes rheumatoid synovitis. The skin becomes psoriatic plaque. The lung becomes interstitial fibrosis. The gut becomes mucosal ulceration or stricture. The vessel becomes vasculitis. Tissue-specific gene regulatory networks shape disease expression.

Chronic disease is therefore not only immune memory. It is tissue memory.

This distinction is particularly important for diseases in which local stromal, fibroblast, epithelial, endothelial, or matrix programmes shape recurrence and organ-specific disease expression (Wynn et al., 2013; Wynn & Ramalingam, 2012).

This perspective deepens the organism-centered view. The organism's history is not stored in a single place. It is distributed across immune cells, stromal cells, epithelial cells, endothelial cells, neurons, glia, mitochondria, microbiota, extracellular matrix, and tissue architecture. Each carries traces of prior coupling with the niche. Each can participate in future readiness or future lock-in.

Gene regulatory networks also connect immunity to metabolism. Cells require metabolic substrates to enter particular states. Effector immune activation often depends on glycolysis, anabolic metabolism, lipid synthesis, and mitochondrial signalling. Regulatory, memory, repair, or resolution states may depend on different metabolic patterns. Metabolites such as acetyl-CoA, NAD^+, α-ketoglutarate, succinate, fumarate, SAM, lactate, and reactive oxygen species can influence chromatin, transcription, and immune-cell function. Thus, metabolism does not merely fuel immune responses; it helps write them into gene regulation.

Immunometabolism shows that metabolic substrates and pathways influence chromatin, transcription, immune-cell differentiation, cytokine production, memory, and inflammatory readiness (Buck et al., 2017; O'Neill et al., 2016; Pearce & Pearce, 2013).

This means that chronic metabolic conditions can influence immune state attractors. Obesity, insulin resistance, nutrient deficiency, mitochondrial dysfunction, hypoxia, toxin exposure, and sleep disruption may alter the gene-regulatory conditions under which immune cells operate. The organism's metabolic field shapes what immune states are easy or difficult to enter.

This helps connect systemic metabolic conditions such as insulin resistance, hypoxia, nutrient deficiency, mitochondrial dysfunction, and chronic inflammation to immune-state attractors and relapse susceptibility (Buck et al., 2017; O'Neill et al., 2016; Picard et al., 2018).

Gene regulatory state attractors also help explain why treatment sometimes works incompletely. A targeted therapy may block a cytokine, receptor, or kinase and reduce active inflammation. But if the underlying cell-state landscape remains primed, disease may return when therapy is stopped. Conversely, early intervention may prevent pathological cell states from becoming entrenched. This supports the clinical intuition that timing matters: the same intervention may have different long-term effects depending on whether it is applied before or after tissue memory becomes stabilized.

This also reframes relapse. Relapse is not always simple recurrence of the original cause. It may be the reactivation of a stored regulatory possibility. The organism has learned a disease pattern. The pattern may be re-entered when conditions resemble, echo, or perturb the prior state.

A life-coherent clinical grammar therefore asks: Has this disease process installed a durable regulatory state? Is the current flare a new injury, an ongoing trigger, or reactivation of prior memory? Are tissue-resident cells sustaining local recurrence? Are fibroblasts maintaining repair-overbuild? Are innate cells trained toward excessive inflammation? Are epithelial barriers primed toward alarm? Are metabolic conditions maintaining the attractor? Is remission merely quieting, or is reset occurring?

The distinction between remission and reset becomes especially important.

Remission is the reduction or disappearance of active disease manifestations. It may be clinical, serological, imaging-based, histological, or symptomatic. Reset would mean a deeper reorganization of the regulatory architecture that made disease recurrence likely. Reset may require more than suppression. It may require resolution, clearance, tissue remodelling, metabolic restoration, microbial repair, exposure reduction, sleep normalization, rehabilitation, and time. In some diseases, full reset may not be achievable, and durable remission may be the realistic goal. But the distinction still clarifies clinical thinking.

The possibility of reset also must be treated carefully. It should not become an overpromise. Chronic immune diseases often involve genetic susceptibility, entrenched memory, tissue damage, environmental exposures, and ongoing risks. Some patients require long-term therapy. Some disease processes can be controlled but not fully reversed. A life-coherent framework

should not imply that all chronic immune disease can be reset if the correct holistic conditions are provided. That would be false and potentially harmful.

The more modest and useful claim is that chronic disease involves regulatory states, and treatment should ask whether it is merely suppressing expression or helping alter the state conditions that permit recurrence.

This distinction is clinically important because suppression may reduce current activity while leaving trained immunity, tissue memory, metabolic bias, or fibrotic niches capable of reactivation (Netea et al., 2016; Wynn & Ramalingam, 2012).

This has implications for biomarkers. A single inflammatory marker may not reveal whether the system remains primed.

Future regulatory-state profiles may therefore need to combine inflammatory markers with transcriptomic, metabolomic, mitochondrial, tissue, microbial, and functional indicators of phase-state and re-entry capacity (Buck et al., 2017; O'Neill et al., 2016; Picard et al., 2018).

Future medicine may need regulatory-state profiles: chromatin accessibility patterns, transcriptomic signatures, proteomic profiles, metabolomic states, mitochondrial markers, tissue imaging, microbiome ecology, and clinical measures of health-cycle re-entry. Such profiles could help distinguish active inflammation from primed remission, fibrotic repair from resolved healing, antiviral memory from chronic interferon lock, or tissue reset from temporary suppression.

But even advanced biomarkers must remain embedded in clinical context. A gene expression signature does not replace the patient. It becomes meaningful only when interpreted in relation to symptoms, tissue state, exposures, treatment, history, and function.

Gene regulatory networks also help make sense of why early-life conditions matter. Developmental exposures can shape immune architecture for decades. Microbial encounters, nutrition, stress, infections, pollutants, antibiotics, maternal health, birth mode, breastfeeding, housing, and social conditions may influence immune tolerance, barrier development, metabolic regulation, and inflammatory readiness. The organism's immune possibilities are built historically.

Developmental immune architecture is shaped by microbial exposure, nutrition, infection, stress, pollution, antibiotics, maternal-child conditions, housing, and wider social determinants of health (Belkaid & Hand, 2014; Commission on Social Determinants of Health, 2008; Hooper et al., 2012).

Adult immune disease may therefore reflect not only current triggers, but long developmental trajectories.

This does not mean destiny. Gene regulatory networks are dynamic. Cells can change. Tissues can remodel. Inflammation can resolve. Memory can update. Mitochondria can recover.

Microbiota can shift. Behaviour and environment can alter regulatory fields. Treatment can transform trajectories. But change is constrained by the depth and duration of prior state installation.

This is why chronic immune disease often requires patience and sequencing. A system that has been primed for years may not reset in weeks. A fibrotic tissue may not return to normal even when inflammation is controlled. A trained inflammatory state may require repeated absence of danger before it softens. A pain system may need gradual safe experience before it recalibrates. A microbiome may require time to reorganize. An immune system cannot simply be instructed to forget.

It must be given new conditions under which different gene regulatory patterns become possible.

This returns us to the organism–niche relation. Gene regulatory states are installed through coupling with the world. They are sustained through ongoing signals. They may be revised through altered coupling. Medication, food, sleep, movement, microbial exposure, toxin reduction, social safety, rehabilitation, infection control, and tissue repair all become inputs into the regulatory landscape. Clinical care itself participates in this re-patterning.

In summary, gene regulatory networks explain how immune experience becomes durable. They show how perturbation becomes readiness, how readiness becomes relapse, how remission may differ from reset, and how chronic disease can persist as a state attractor rather than a simple ongoing reaction. They allow us to understand flares not only as new events, but as reactivations of installed biological memory.

The next section extends this idea into evolutionary depth. If immunity is boundary-coherence, then viruses, endogenous viral elements, mobile genetic sequences, phages, exosomes, and horizontal gene transfer reveal that life has always been shaped by regulated boundary-crossing. The organism’s boundary is not a wall against information. It is a living membrane through which selected forms of information, danger, symbiosis, and memory pass.

12. Viral Memory, Virome, Mobile Genetic Elements, and Boundary-Crossing Information

If immunity is the organism's living boundary-coherence process, then viruses and mobile genetic elements reveal something fundamental: life has never been organized by sealed purity. Living systems have always been shaped by regulated boundary-crossing. Genetic material moves. Viruses enter cells. Phages shape microbial ecologies. Endogenous viral elements become part of genomes. Extracellular vesicles carry signals between cells. Mitochondria retain evolutionary traces of bacterial ancestry. Symbiosis, infection, integration, and defence are woven into the history of life.

Viruses and vesicles reveal that life is constituted by regulated boundary-crossing.

The virome, endogenous retroelements, viral integration, phage dynamics, and mitochondrial evolutionary ancestry all show that immune identity is historically layered rather than organized by sealed biological purity (Chuong et al., 2016; Lederberg, 2000; Virgin, 2014; West & Shadel, 2017).

This does not mean that all boundary-crossing is benign. Viral infection can injure, disable, transform, persist, reactivate, or kill. Mobile genetic elements can destabilize genomes. Viral remnants may trigger immune activation. Phages can reshape microbiome behaviour. Endogenous retroelements may participate in development, but they may also contribute to inflammation when dysregulated. Boundary-crossing is neither good nor bad in itself. Its meaning depends on regulation, context, timing, location, and consequence for organismic coherence.

The immune system therefore cannot be understood as a simple wall against outside information. It is a living system for discerning, regulating, incorporating, excluding, silencing, remembering, and sometimes being transformed by boundary-crossing information.

This deepens the critique of simple self/non-self immunology. The organism is not pure self defending against all non-self. It is a historically layered unity partly made from prior encounters with non-self. Microbial genes, viral sequences, symbiotic organisms, mitochondrial ancestry, maternal-fetal exchange, food-derived molecules, microbial metabolites, and environmental signals all participate in the organism's living structure. The immune system does not preserve identity by excluding everything foreign. It preserves identity by regulating participation.

In this sense, immunity is not anti-world. It is world-selective.

This argument extends post-self/non-self accounts of immunity by emphasizing regulated participation, contextual boundary management, and organismic integrity rather than simple exclusion of foreignness (Pradeu, 2012).

12.1 Viral Infection as Boundary Perturbation

A viral infection is one of the clearest examples of boundary disruption. A virus enters cells, uses host machinery, alters gene expression, activates innate sensing, provokes interferon pathways, reshapes metabolism, and may injure tissues directly or indirectly. The organism must respond quickly, because viral replication can turn cellular openness into vulnerability.

Acute antiviral immunity requires strong phase-shifting. Surveillance becomes danger detection. Nucleic-acid sensors activate. Interferons induce antiviral states. Natural killer cells, cytotoxic T cells, antibodies, complement, macrophages, dendritic cells, fever, fatigue, and behavioural withdrawal may participate. The organism narrows ordinary participation to defend cellular integrity.

Viral infection activates nucleic-acid sensing, interferon programmes, mitochondrial antiviral signalling, immune-cell recruitment, and metabolic reorganization, illustrating how boundary perturbation becomes whole-organism phase-shifting (Chen et al., 2016; Virgin, 2014; West & Shadel, 2017).

When this process works well, viral burden is reduced or cleared, inflammation resolves, damaged cells are removed, tissue repairs, memory is formed, and the organism re-enters the health cycle.

But viral infections can also install phase-locks.

Some viruses persist. Some remain latent and reactivate. Some leave behind antigenic remnants. Some alter tissue niches. Some trigger autoimmunity through molecular mimicry, bystander activation, epitope spreading, tissue injury, or defective clearance. Some induce chronic interferon tone. Some affect endothelial, neural, epithelial, mitochondrial, or immune-cell function. Some change the microbiome or reactivate other latent viruses. Some appear to initiate post-infectious syndromes in which the organism does not fully return to ordinary health-cycle participation.

From a phase-state perspective, the crucial question is not only whether a virus is present or absent. It is what viral encounter has done to the organism's boundary-coherence process.

Has viral sensing resolved? Has interferon tone normalized? Has mitochondrial function recovered? Has tissue damage been cleared? Has immune memory become protective or hypervigilant? Has the organism re-entered ordinary activity without post-exertional worsening? Has the niche changed in ways that continue to perturb the system?

This is especially important in post-viral conditions. The acute infection may be over, yet the organism may remain in altered immune, metabolic, vascular, autonomic, mitochondrial, or neuroinflammatory states. In such cases, the disease is not necessarily explained by ongoing viral replication alone. Nor can ongoing persistence always be excluded without evidence. The point is more nuanced: a viral perturbation can leave regulatory consequences that outlast the initial event.

The virus may be gone, reduced, latent, fragmented, or persistent. The organism's phase-state may remain changed.

This formulation allows post-viral disease to be considered without prematurely reducing it either to active viral replication or to non-biological symptoms; viral encounters may leave immune, mitochondrial, vascular, neuroimmune, or metabolic consequences that outlast the acute infection (Naviaux, 2020; Virgin, 2014; West & Shadel, 2017).

12.2 Endogenous Viral Elements and the Evolutionary Depth of Immunity

Endogenous viral elements show that viral encounters are not merely threats from outside. Over evolutionary time, viral sequences have entered germline DNA and become part of host genomes. Some remain silent. Some are regulatory. Some may be harmful if reactivated. Some have been domesticated for host functions.

One of the most striking examples is the role of syncytin genes, derived from retroviral envelope proteins, in placental development. Placenta formation depends on regulated boundary-crossing: maternal and fetal tissues must remain distinct yet intimately connected. Immune tolerance, invasion, exchange, vascular adaptation, and boundary regulation must be coordinated. A viral-derived function becomes part of mammalian reproduction.

Endogenous retroviral elements have been co-opted for host regulatory and developmental functions, demonstrating that viral ancestry can become constitutive of organismic life rather than remaining merely external threat (Chuong et al., 2016).

This is not an incidental curiosity. It reveals that living identity is historically composite. What was once foreign may become constitutive. What was once viral may become developmental. What was once boundary-crossing may become boundary-making.

The immune system therefore preserves an organism that is already a history of incorporations.

Endogenous retroelements and mobile genetic elements also require regulation. If normally silenced elements become transcriptionally active in inappropriate contexts, they may produce nucleic-acid signals that activate innate immune pathways. Cytosolic nucleic-acid sensing, interferon activation, inflammation, senescence, aging, cancer biology, and autoimmunity may all intersect with dysregulated mobile-element activity. The organism may interpret its own genomic echoes as viral-like danger.

Dysregulated endogenous retroelements can contribute to innate immune activation when normally silenced viral-like sequences become transcriptionally active or generate nucleic-acid signals (Chuong et al., 2016; Chen et al., 2016).

This creates a particularly subtle boundary problem. The signal is internal, but it resembles infection. It is self, yet it carries the form of ancestral non-self. The immune system responds not simply to identity, but to misplaced, unsilenced, or contextually abnormal information.

In phase-lock terms, endogenous retroelement activation may contribute to a viral/mobile-element boundary lock. The organism behaves as if viral boundary violation is ongoing, even when the source is internal genomic dysregulation, cellular stress, senescence, mitochondrial damage, or impaired epigenetic control.

This reinforces a central claim: immune disease often arises not because the organism fails to distinguish self from non-self in a simple way, but because boundary context becomes incoherent.

12.3 The Virome and Microbial Gene Flow

The organism does not live with bacteria alone. It lives with a virome: viruses that infect host cells, bacteria, fungi, and other members of the microbiome. Bacteriophages shape microbial populations, transfer genes, influence bacterial virulence, alter biofilm dynamics, and participate in gut and mucosal ecology. The virome is part of the extended immune niche.

The mammalian virome participates in physiology and disease by shaping microbial ecology, host immune tone, barrier function, and responses to perturbation (Virgin, 2014).

This matters because immune regulation depends on microbial ecology. The gut, airway, skin, and other surfaces are not merely colonized; they are ecologically organized. Bacterial, fungal, viral, and phage communities interact with epithelial barriers, mucus, metabolites, immune cells, diet, antibiotics, pollutants, and host genetics. Changes in one part of this ecology can alter immune tone.

Phages can reshape bacterial communities. Bacterial communities can alter metabolites. Metabolites can influence regulatory T cells, epithelial integrity, macrophage function, and inflammatory tone. Viral infections can disturb barriers. Antibiotics can alter bacterial ecology and indirectly affect phage dynamics. Diet can shift microbial substrate availability. Inflammation can change the ecological niche, favouring organisms adapted to inflammatory conditions. The immune system then responds to a niche partly shaped by its own prior response.

The virome therefore belongs to enactive and extended immunity. Immune action changes microbial ecology; microbial ecology changes immune action.

This reciprocal relation is consistent with microbiome-immunity research showing that microbial communities, metabolites, barrier function, and immune regulation are mutually shaping rather than linearly causal (Belkaid & Hand, 2014; Hooper et al., 2012; Virgin, 2014).

This helps explain why chronic inflammatory diseases may involve dysbiosis without dysbiosis being a simple root cause. Altered microbial communities may contribute to inflammation, result from inflammation, or both. The tissue and microbial ecology may become co-locked. Gut inflammation changes oxygenation, mucus, antimicrobial peptides, motility, and nutrient availability. These changes alter microbial communities. Altered communities then sustain barrier alarm and immune activation.

The organism is no longer responding to a fixed external microbiome. It is participating in an altered ecology that it helped bring forth.

12.4 Exosomes, Extracellular Vesicles, and Intercellular Boundary-Crossing

Boundary-crossing information is not limited to viruses. Cells communicate through extracellular vesicles, including exosomes and microvesicles, that carry proteins, lipids, nucleic acids, metabolites, and regulatory signals. These vesicles can transmit information between immune cells, epithelial cells, endothelial cells, neurons, stromal cells, tumour cells, microbes, and injured tissues.

Extracellular vesicles blur the boundary between cell autonomy and tissue communication. A cell's internal state can be packaged and sent outward. Other cells can receive that information and alter their behaviour. In inflammation, infection, cancer, tissue injury, pregnancy, metabolic disease, and repair, vesicles may amplify, regulate, or redirect biological processes.

From the organism-centered view, vesicles are part of distributed sense-making. They help tissues coordinate phase-state. A damaged cell can communicate distress. An immune cell can influence neighbouring cells. A tumour cell can shape its niche. A microbe or infected cell can alter host response. A resolving tissue may send signals that reduce inflammation or promote repair.

But vesicle signalling can also participate in lock-in. If vesicles carry inflammatory microRNAs, misfolded proteins, mitochondrial components, viral material, autoantigens, or pro-fibrotic signals, they may sustain pathology. They can extend local distress to distant sites. They can create systemic echoes of tissue injury.

Extracellular-vesicle signalling therefore provides a mechanism by which local tissue states may become distributed across the organism, carrying proteins, lipids, nucleic acids, mitochondrial components, inflammatory signals, or pro-repair cues between cells and tissues (Amari & Germain, 2021; Robbins & Morelli, 2014; Yáñez-Mó et al., 2015).

This expands the concept of immune extension within the body itself. The organism's boundary-coherence process is not localized to one inflamed site. Signals travel. Tissue states communicate. A local disease can become systemic, and systemic states can reshape local disease.

12.5 Horizontal Transfer, Symbiosis, and the Porous History of Life

The deeper evolutionary lesson is that life develops through both boundary maintenance and boundary permeability. Cells, organisms, microbiomes, viruses, and ecosystems are not isolated substances. They are historically formed relations.

Mitochondria themselves are the result of ancient endosymbiosis. Their bacterial ancestry remains immunologically relevant because mitochondrial components can resemble microbial danger signals when misplaced. Mitochondrial DNA, cardiolipin, formyl peptides, reactive

oxygen species, and altered mitochondrial dynamics can all influence immune responses. The very organelles that support energy and phase-setting can become danger signals when damaged.

This is a profound example of evolutionary memory. What became internal remains capable of signalling as if foreign when boundary integrity fails.

Mitochondrial evolutionary ancestry helps explain why mitochondrial DNA, formyl peptides, cardiolipin, and other misplaced mitochondrial components can activate innate immune pathways and sterile inflammation (West & Shadel, 2017).

Horizontal gene transfer, viral integration, microbial symbiosis, and endosymbiosis all show that organisms are not sealed individuals in the simplistic sense. They are coherent unities composed through histories of regulated incorporation. The immune system must therefore manage a paradox: the organism is made of relations, yet must conserve itself as a distinct living unity.

Immune coherence is the regulation of this paradox.

It allows microbial partnership without infection, pregnancy without rejection, food tolerance without poisoning, tissue repair without fibrosis, memory without fixation, and openness without dissolution. Disease arises when this regulation fails: when boundary-crossing is excessive, misread, uncleared, unsilenced, unintegrated, or chronically defended against.

12.6 Viral and Mobile-Element Boundary Locks

A viral/mobile-element boundary lock occurs when the organism remains organized around viral-like danger, boundary invasion, nucleic-acid alarm, or unresolved informational crossing. This may occur through several mechanisms.

There may be persistent viral infection or latent viral reactivation. There may be residual viral antigen or RNA/DNA fragments that continue to stimulate immune sensing. There may be endogenous retroelement activation under stress, aging, epigenetic dysregulation, or impaired silencing. There may be mitochondrial DNA leakage after cellular injury. There may be extracellular vesicles carrying viral or danger-associated material. There may be microbiome phage shifts that alter bacterial behaviour and mucosal immunity. There may be impaired clearance of nucleic acids, apoptotic bodies, or immune complexes.

The common dynamic form is that the organism continues to receive signals of boundary-crossing information that has not been fully resolved.

Viral persistence, latent reactivation, endogenous retroelement activation, mitochondrial DNA leakage, and impaired nucleic-acid clearance can therefore all contribute to antiviral-like phase-locking in different contexts (Chen et al., 2016; Chuong et al., 2016; Virgin, 2014; West & Shadel, 2017).

Such locks may contribute to interferon-driven disease, post-viral syndromes, autoimmunity, chronic fatigue states, inflammatory flares, neuroimmune symptoms, vascular inflammation, or

tissue-specific pathology, depending on host context. The details must be investigated carefully in each condition. The framework should not overstate viral or mobile-element explanations. Rather, it identifies a plausible class of phase-locks in which nucleic-acid sensing, antiviral memory, mitochondrial damage, genomic instability, or viral ecology prevents return to health-cycle participation.

This is particularly important because viral explanations can become both underused and overused. Some patients with chronic illness may be dismissed when viral or post-viral mechanisms are not yet fully understood. Others may be given overly certain explanations without adequate evidence. A life-coherent approach requires disciplined openness: viral and mobile-element mechanisms are real and important, but their role must be demonstrated, contextualized, and distinguished from metaphor.

The organism-centered question remains: what boundary-crossing signal is active, where is it located, how is it being interpreted, and why has the organism not completed the transition?

This question keeps the analysis evidence-aware by distinguishing measurable viral, nucleic-acid, mitochondrial, or mobile-element mechanisms from metaphorical overextension (Pradeu, 2012; Virgin, 2014).

12.7 Clinical Implications

Clinically, this section supports a more nuanced approach to post-infectious and immune-mediated disease. The question is not simply whether an infection is active. It is whether the viral encounter has left the organism in an altered phase-state.

Assessment may need to consider acute infection history, latent viral reactivation, recurrent infections, immune deficiency, interferon signatures, autoantibodies, inflammatory markers, mitochondrial stress, tissue damage, endothelial involvement, microbiome disruption, sleep disruption, post-exertional symptom patterns, neurological symptoms, and environmental exposures. No single test will capture the whole field. The goal is to understand the dominant lock.

Treatment implications vary. Active viral replication may require antiviral or immune-based strategies. Latent reactivation may require different interpretation. Persistent inflammation may require immune modulation. Mitochondrial injury may require energy-conserving pacing and metabolic support. Impaired clearance may require attention to lymphatics, autophagy, efferocytosis, sleep, and organ function. Dysbiosis may require dietary, microbial, or antimicrobial care. Re-entry failure may require careful rehabilitation rather than forced exertion.

The point is not to treat every chronic immune disease as viral. The point is to recognize that viral and mobile genetic histories are part of immune boundary biology.

12.8 Transition to Immunometabolism

Viral memory, endogenous retroelements, mobile genetic elements, phages, exosomes, and mitochondria all show that the organism's boundary is informational as well as physical. The immune system regulates what enters, what is silenced, what is incorporated, what is remembered, and what is defended against.

But boundary regulation is not information alone. It is also energy. A cell cannot enter, maintain, or exit an immune phase without metabolic support. Defence, resolution, clearance, repair, memory, and re-entry all require distinct metabolic conditions. Experience is written not only into genes and immune memory, but into metabolic pathways and chromatin.

The next section therefore turns to immunometabolism and epigenetic memory: how metabolism writes experience into chromatin, and how chromatin makes experience re-activatable.

Immunometabolism and trained-immunity research show that metabolic state, substrate availability, chromatin accessibility, and epigenetic priming together shape immune-cell differentiation, inflammatory readiness, memory, and relapse potential (Buck et al., 2017; Netea et al., 2016; O'Neill et al., 2016; Pearce & Pearce, 2013).

13. Immunometabolism and Epigenetic Memory

If viral memory and mobile genetic elements show that immune life is shaped by boundary-crossing information, immunometabolism shows that immune life is also shaped by energy, substrate, redox state, and biochemical possibility. A cell cannot sense, defend, resolve, clear, repair, remember, or return without metabolic means. Every immune phase has a metabolic cost, and every metabolic state alters what immune phases are possible.

Metabolism writes experience into chromatin; chromatin makes experience re-activatable.

Metabolism links memory and chronic immune disease. Metabolism is not merely fuel supply. It is a regulatory language. Nutrients, oxygen, mitochondrial function, redox state, amino acids, lipids, glucose, lactate, acetyl-CoA, NAD^+, α-ketoglutarate, succinate, fumarate, SAM, ATP, and reactive oxygen species all help determine how immune cells behave. They influence transcription, chromatin accessibility, cytokine production, phagocytosis, antigen presentation, inflammasome activation, resolution, repair, and memory.

The immune system therefore does not simply “use” metabolism. It is metabolically enacted.

This is a central premise of immunometabolism: immune-cell activation, quiescence, differentiation, resolution, and memory are inseparable from metabolic programming (Buck et al., 2017; O’Neill et al., 2016; Pearce & Pearce, 2013).

A macrophage in an acutely inflamed tissue does not inhabit the same metabolic world as a macrophage clearing apoptotic cells during resolution. A proliferating T cell does not have the same metabolic demands as a resting memory T cell. A fibroblast laying down matrix in a hypoxic wound does not behave metabolically like a quiescent stromal cell. An epithelial cell under oxidative stress, a mast cell in an allergic tissue, a neutrophil in an abscess, or a microglial cell in a neuroinflammatory niche all interpret immune signals through metabolic conditions.

This is why immunometabolism belongs at the center of a phase-state framework. Immune phases are metabolic phases. Defence, resolution, clearance, repair, memory, and re-entry each require different energetic and biochemical conditions. When metabolism cannot support transition, the organism may become locked.

13.1 Metabolism as Phase Selection

Different immune states require different metabolic strategies. Rapid inflammatory activation often relies on glycolysis, even when oxygen is present, because glycolysis can support rapid ATP generation and provide intermediates for biosynthesis. Effector lymphocytes, activated macrophages, and inflamed tissues may shift toward metabolic programs that support proliferation, cytokine production, microbial killing, and inflammatory amplification.

By contrast, regulatory, resolving, memory, and repair-associated states may rely more heavily on mitochondrial oxidative metabolism, fatty acid oxidation, redox balance, autophagy, and

metabolic flexibility. These distinctions are not absolute. Immune cells are metabolically plastic, and the same pathway may have different meanings in different contexts. Yet the principle remains: the metabolic state of a cell helps determine what immune phase it can enter or exit.

A cell cannot resolve inflammation if it lacks the metabolic conditions for resolution. It cannot clear debris effectively if mitochondrial function, lysosomal function, autophagy, or phagocytic capacity are impaired. It cannot repair tissue without substrate, oxygen, vascular support, amino acids, and redox control. It cannot form healthy memory without appropriate energetic and transcriptional programming.

Metabolism therefore helps select immune possibility.

Different immune phases depend on different metabolic strategies, including glycolysis, oxidative phosphorylation, fatty-acid oxidation, autophagy, anabolic metabolism, and redox adaptation (Buck et al., 2017; O'Neill et al., 2016; Pearce & Pearce, 2013).

This becomes clinically important in chronic disease. A patient with insulin resistance, nutrient deficiencies, hypoxia, mitochondrial dysfunction, chronic sleep disruption, toxin exposure, chronic infection, or systemic inflammation may have immune cells biased toward certain states and away from others. The organism may be able to inflame, but not resolve; defend, but not repair; conserve energy, but not re-enter ordinary activity.

Metabolic constraint becomes phase constraint.

This provides a mechanistic bridge between metabolic syndrome, hypoxia, mitochondrial dysfunction, nutritional deficiency, sleep disruption, and the failure of immune cells or tissues to move from defence toward resolution, repair, or re-entry (McEwen, 1998; O'Neill et al., 2016; Picard et al., 2018).

13.2 Acetyl-CoA, Chromatin, and Inflammatory Readiness

Acetyl-CoA is a central metabolic intermediate linking nutrient state, mitochondrial function, lipid metabolism, and chromatin regulation. Histone acetylation generally makes chromatin more accessible, allowing genes to be more readily transcribed. In immune cells, changes in acetyl-CoA availability can influence whether inflammatory, reparative, regulatory, or memory-associated genes become accessible.

This means that nutrient flow and mitochondrial metabolism can alter immune readiness at the level of gene expression. A cell exposed to inflammatory stimuli in a particular metabolic context may open chromatin regions that later allow faster or stronger reactivation. Experience becomes written into the regulatory architecture of the cell.

In acute infection, this may be beneficial. The organism becomes more prepared for future threat. In chronic inflammatory disease, it can become pathological. Inflammatory loci remain primed. Cytokine production becomes easier to restart. Tissue cells remain alert. A minor perturbation can reactivate a large response because the chromatin landscape has been prepared.

This is one way metabolism participates in relapse.

Metabolic-epigenetic coupling helps explain why prior inflammatory experience can remain biologically reactivatable through chromatin accessibility and trained innate immune programmes (Netea et al., 2016; O'Neill et al., 2016).

13.3 NAD^+, Sirtuins, Repair, and Energetic Reserve

NAD^+ is central to redox reactions, mitochondrial metabolism, DNA repair, sirtuin activity, and cellular stress responses. It helps connect energy status to gene regulation and repair capacity. When NAD^+ availability is compromised, cells may have reduced capacity for mitochondrial function, stress resilience, genomic maintenance, and adaptive recovery.

In immune disease, this matters because chronic inflammation consumes energy and generates cellular stress. DNA damage, oxidative stress, mitochondrial dysfunction, infection, and repair demands can all increase metabolic burden. If the cell's redox and repair systems are strained, immune responses may become less coherent. Cells may remain inflammatory, senescent, exhausted, or unable to complete resolution.

NAD^+ biology therefore illustrates a wider principle: immune resilience requires energetic reserve.

Energetic reserve links mitochondrial function, stress adaptation, DNA repair, redox balance, and immune resilience, especially under chronic inflammatory or allostatic load (McEwen, 1998; Picard et al., 2018).

A system living at the edge of metabolic exhaustion cannot adapt flexibly. It may defend poorly, resolve slowly, repair incompletely, or become hypersensitive to minor perturbations.

This is especially relevant in fatigue states, chronic inflammatory disease, aging, metabolic syndrome, and post-infectious syndromes. The symptom of fatigue may reflect not simply subjective tiredness, but a whole-organism constraint in energy allocation and metabolic recovery. The organism may be protecting itself from expenditure it cannot presently afford.

13.4 α-Ketoglutarate, Succinate, Fumarate, and Immune-State Bias

Tricarboxylic acid cycle intermediates are not merely metabolic waystations. They can act as signalling molecules and epigenetic regulators. α-Ketoglutarate, succinate, and fumarate influence dioxygenases, histone and DNA demethylation, hypoxia signalling, inflammatory activation, and cellular differentiation.

Succinate can accumulate in activated inflammatory states and support inflammatory signalling, including stabilization of HIF-1α in certain contexts. Fumarate can influence redox and electrophilic stress pathways. α-Ketoglutarate can support demethylation and may favour different differentiation and regulatory programs depending on context.

The broader point is that metabolic intermediates help cells interpret their state. They indicate oxygen availability, mitochondrial function, substrate flow, stress, and biosynthetic demand. They influence whether chromatin remains open or closed, whether inflammatory genes remain accessible, and whether cells can transition toward repair or resolution.

In phase-state language, metabolic intermediates help determine whether the cell remains in defence, shifts toward resolution, or enters repair.

Metabolites such as succinate, fumarate, α-ketoglutarate, acetyl-CoA, SAM, and NAD^+ can therefore act as signals and cofactors linking metabolism to inflammatory gene expression and epigenetic regulation (Buck et al., 2017; O'Neill et al., 2016).

When these metabolic signals become chronically distorted, immune cells may become biased toward persistent inflammation, impaired tolerance, inadequate repair, or maladaptive memory. The inflammatory state is then not only signalled by cytokines. It is maintained by the metabolic architecture of the cell.

13.5 SAM, Methylation, and Durable Immune Memory

S-adenosylmethionine, or SAM, is a major methyl donor involved in DNA methylation, histone methylation, neurotransmitter metabolism, phospholipid synthesis, and many other biochemical processes. Through methylation, cells can alter gene expression patterns in durable ways.

In immune cells, methylation states can influence differentiation, tolerance, exhaustion, memory, inflammatory readiness, and regulatory function. These processes are shaped by nutrient status, one-carbon metabolism, folate, B vitamins, methionine availability, oxidative stress, inflammation, aging, and environmental exposures.

This does not mean that immune disease can be reduced to methylation imbalance in a simplistic way. Rather, methylation is one route by which metabolism and environment become durable biological structure. The organism's exposures, nutrition, inflammation, and developmental history can leave epigenetic marks that alter future immune possibility.

This is another way the niche enters the immune system.

Nutrient status, one-carbon metabolism, inflammation, oxidative stress, aging, and environmental exposures can all shape methylation and gene-regulatory patterns relevant to immune memory and differentiation (Netea et al., 2016; O'Neill et al., 2016).

13.6 Lactate, Hypoxia, and the Inflamed Tissue Niche

Lactate is often misunderstood as merely a waste product. In inflamed, hypoxic, or metabolically active tissues, lactate can become a signalling molecule. It may influence immune-cell behaviour, macrophage polarization, T-cell function, angiogenesis, tissue repair, and pain. High lactate environments may reflect intense glycolysis, reduced oxygen availability, vascular limitation, infection, tumour metabolism, or inflammatory burden.

Hypoxia is also common in inflamed tissues. Swelling, vascular disruption, high metabolic demand, microthrombi, fibrosis, and cellular infiltration can reduce oxygen availability. Hypoxia-inducible pathways then alter immune function, metabolism, angiogenesis, and tissue remodelling.

This matters because a tissue niche can metabolically trap immune cells. A hypoxic, acidic, lactate-rich, stiff, inflamed tissue may not permit easy resolution. Cells entering that niche are shaped by it. Macrophages, fibroblasts, epithelial cells, endothelial cells, and lymphocytes may adopt states suited to that local metabolic world. The niche becomes an attractor.

In clinical terms, this helps explain why local disease can persist even when systemic markers are modest. The tissue microenvironment may remain metabolically and mechanically organized around inflammation or repair.

Hypoxia, lactate, matrix stiffness, vascular disruption, and inflammatory metabolism can create local tissue niches that sustain immune and fibrotic states even when systemic markers are modest (O'Neill et al., 2016; Wynn & Ramalingam, 2012).

The organism's phase-lock is local, embodied in the niche.

13.7 ROS, Redox Signalling, and Damage

Reactive oxygen species are not simply damaging byproducts. At controlled levels, they participate in signalling, microbial killing, mitochondrial communication, transcriptional regulation, and adaptation. But when redox balance is lost, oxidative stress can damage proteins, lipids, DNA, mitochondria, membranes, and extracellular matrix. Damaged molecules can then become danger signals, sustaining inflammation.

Redox imbalance therefore links defence to damage. The organism produces oxidative signals to defend and communicate, but excessive or unresolved oxidative stress generates new material that must be cleared. If clearance and repair are insufficient, redox damage becomes part of the inflammatory loop.

This is a classic phase-lock pattern: defence creates debris; debris sustains danger; danger sustains defence.

Redox imbalance links mitochondrial stress, oxidative damage, danger signalling, inflammasome activation, and persistent inflammatory loops (Picard et al., 2018; West & Shadel, 2017).

NRF2 and related antioxidant-response systems help buffer this process. They support detoxification, glutathione metabolism, antioxidant defence, and cellular stress adaptation. When these systems are insufficient relative to load, the organism becomes more vulnerable to oxidative injury and inflammatory persistence.

Redox biology therefore connects toxins, pollutants, infection, mitochondrial dysfunction, inflammation, aging, and impaired repair. It also shows why "antioxidant" thinking must be

nuanced. ROS are not simply bad, and blanket suppression is not always appropriate. The goal is redox coherence: enough signalling and defence, not persistent oxidative injury.

13.8 Extracellular ATP and Danger-Energy Signalling

ATP is normally an intracellular energy currency, but when found extracellularly in high concentrations, it can function as a danger signal. It may indicate cell stress, injury, necrosis, mitochondrial damage, mechanical disruption, or inflammation. Purinergic signalling through ATP and its breakdown products helps regulate inflammasome activation, pain, vascular responses, immune-cell recruitment, clearance, and resolution.

This makes ATP a bridge between energy and danger. The molecule that powers life inside the cell becomes a warning signal outside the cell.

Extracellular ATP is a key feature of cell danger response biology, linking cellular stress, purinergic signalling, inflammation, pain, and impaired resolution in some contexts (Naviaux, 2014, 2020).

Extracellular ATP is therefore central to the cell danger response and to phase-locking. When cells are injured or stressed, ATP release may help alert the organism. But if extracellular ATP remains elevated, danger signalling may persist. Pain, inflammation, mast-cell activation, microglial activation, and impaired resolution may all be influenced by purinergic signalling in certain contexts.

A life-coherent view sees extracellular ATP not simply as a pathway target, but as a sign of boundary disturbance. Energy has appeared in the wrong place. The organism interprets this misplacement as danger.

13.9 Trained Immunity as Metabolic-Epigenetic Memory

Trained immunity links metabolism, epigenetics, and immune memory. Innate immune cells and their progenitors can undergo durable functional reprogramming after exposure to microbial products, vaccines, infections, metabolic stress, oxidized lipids, or inflammatory signals. These changes often involve both chromatin remodelling and metabolic rewiring.

This is adaptive when it improves future defence. It is maladaptive when it amplifies chronic inflammation or lowers the threshold for flares. A trained innate system may respond more strongly to later perturbations, even if those perturbations are not identical to the original stimulus.

Trained immunity is therefore a mechanism of phase memory.

Trained immunity links metabolic rewiring and epigenetic remodelling to durable innate immune readiness, providing a mechanism by which prior exposures alter future inflammatory thresholds (Netea et al., 2016).

It helps explain how the organism's prior encounters become future readiness. It also explains how chronic exposures, infections, metabolic overload, or inflammatory episodes may leave the immune system more reactive. The organism learns, but the learning may become too rigid.

This is especially relevant to atherosclerosis, metabolic inflammation, autoinflammatory disease, recurrent inflammatory flares, chronic infection, and possibly some post-infectious or environmentally triggered conditions. The precise role varies by disease, and overgeneralization should be avoided. But the principle is important: innate immune memory can be beneficial or pathogenic depending on context.

13.10 Immunometabolic Phase-Locking

Immunometabolic phase-locking occurs when the metabolic conditions required for phase transition are absent or distorted. The organism may be stuck not because it lacks immune signals, but because it lacks the metabolic possibility of moving.

A cell may remain inflammatory because glycolytic activation, succinate accumulation, NF-κB signalling, and chromatin accessibility sustain cytokine production. A macrophage may fail to clear debris because mitochondrial function, lysosomal function, or efferocytosis is impaired. A tissue may remain fibrotic because hypoxia, lactate, matrix stiffness, TGF-β, and altered mechanometabolism reinforce repair. A patient may remain fatigued because mitochondrial reserve, redox balance, sleep, and autonomic regulation do not support re-entry into activity.

The metabolic lock may be local, cellular, systemic, or organismal.

This multi-level metabolic lock can involve local tissue hypoxia, cellular mitochondrial constraint, systemic metabolic disease, allostatic load, sleep disruption, and neuroimmune energy conservation (McEwen, 1998; O'Neill et al., 2016; Picard et al., 2018).

This reframes many chronic symptoms. Fatigue, post-exertional worsening, brain fog, poor recovery, pain amplification, and inflammatory flares may reflect immune-metabolic constraints, not merely subjective experience. The organism may be unable to afford the next phase. It may defend because defence is metabolically installed; it may conserve because energy is constrained; it may fail to repair because substrate and signalling are insufficient; it may fail to re-enter activity because exertion exceeds mitochondrial and allostatic margins.

This does not imply one universal metabolic explanation for all chronic illness. It means immune phase-states are metabolically embodied.

13.11 Clinical Implications

Clinically, immunometabolism asks physicians to consider whether the patient's immune system has the energetic, nutritional, mitochondrial, redox, and metabolic conditions required for recovery. This includes attention to glucose regulation, insulin resistance, nutrient status, anaemia, oxygenation, sleep, mitochondrial stress, toxin burden, inflammation, infection, liver and kidney function, gut health, physical conditioning, and medication effects.

Treatment may include conventional disease control, metabolic risk reduction, sleep restoration, nutritional rehabilitation, graded or paced movement depending on phase-state, toxin reduction, mitochondrial support where evidence and safety permit, and careful avoidance of interventions that overtax a low-reserve organism.

The key clinical question is not “How do we boost metabolism?” or “How do we boost immunity?” Such language is too crude. The better question is: what metabolic conditions are needed for this organism to move from its current phase to the next coherent phase?

For one patient, reducing inflammation may restore metabolic flexibility. For another, improving sleep may lower inflammatory tone. For another, correcting iron deficiency, B12 deficiency, vitamin D deficiency, or protein malnutrition may be necessary for immune repair. For another, treating insulin resistance may reduce inflammatory load. For another, pacing may prevent repeated mitochondrial and allostatic crashes. For another, rehabilitation may restore metabolic reserve after inflammation has been controlled.

The intervention must match the phase.

Clinically, immunometabolic care should therefore avoid crude “boosting” language and instead identify the metabolic conditions needed for resolution, clearance, repair, or re-entry in the specific patient and phase-state (Buck et al., 2017; Naviaux, 2014; O’Neill et al., 2016).

13.12 Transition to Mitochondria

Immunometabolism leads naturally to mitochondria. Mitochondria sit at the intersection of energy, redox, apoptosis, innate immune signalling, antiviral defence, calcium regulation, metabolic phase selection, and cell danger responses. They do not merely power immune responses. They help determine what biological phase the cell can afford to enter, maintain, or exit.

The next section therefore turns to mitochondria as phase-setting organelles: not only engines of ATP, but central participants in immune coherence, danger signalling, conservation, repair, shutdown, and re-entry.

14. Mitochondria as Phase-Setting Organelles

Mitochondria are often introduced as the powerhouses of the cell. This is true, but insufficient. In immune biology, mitochondria are not merely generators of ATP. They are central participants in cellular phase selection, redox signalling, antiviral defence, inflammasome activation, apoptosis, mitophagy, metabolic adaptation, danger signalling, repair, conservation, and shutdown. They help determine whether a cell can afford to activate, defend, resolve, clear, repair, remember, or return.

Mitochondria do not merely power immune responses; they help determine which biological phase the cell can afford to enter, maintain, or exit.

Mitochondria link energy production, redox signalling, apoptosis, antiviral signalling, inflammasome activation, stress adaptation, and immune regulation, making them central to phase-state biology (Naviaux, 2014; Picard et al., 2018; West & Shadel, 2017).

This makes mitochondria essential to life-coherent systems immunology. If chronic immune disease is often a failure of phase transition, then mitochondrial function matters because phase transitions require energy, redox coordination, metabolic flexibility, and danger-signal regulation. A cell cannot move coherently from defence to resolution, from resolution to clearance, or from repair to reintegration if its mitochondrial state is constrained.

Mitochondria sit at the crossroads of energy and meaning. They sense nutrient availability, oxygen tension, calcium flux, infection, oxidative stress, cellular damage, inflammatory signals, and metabolic demand. They help decide whether the cell should produce energy efficiently, generate inflammatory signals, enter antiviral defence, conserve resources, initiate apoptosis, produce reactive oxygen species, support biosynthesis, or activate repair pathways. They are therefore not passive engines. They are phase-setting organelles.

This formulation is consistent with energetic and cell danger response models in which mitochondrial state helps determine whether cells defend, conserve, repair, or return to ordinary function (Naviaux, 2014, 2020; Picard et al., 2018).

14.1 Mitochondrial Allostasis

Mitochondria are dynamic. They divide, fuse, move, signal, change shape, alter membrane potential, adjust respiratory activity, produce reactive oxygen species, participate in calcium handling, and interact with the endoplasmic reticulum, nucleus, lysosomes, peroxisomes, and immune signalling complexes. Their function changes according to cellular demand.

This is mitochondrial allostasis: the adaptive adjustment of mitochondrial structure and function in response to changing conditions.

Mitochondrial allostasis extends allostatic reasoning to cellular energetics, emphasizing that mitochondrial structure and function change dynamically under stress, demand, inflammation, and repair (McEwen, 1998; Picard et al., 2018).

During acute immune activation, mitochondria may support inflammatory signalling, antimicrobial defence, reactive oxygen species production, and metabolic reprogramming. During resolution and repair, they may support oxidative metabolism, biosynthesis, redox balance, and restoration. During stress or danger, they may release signals that alert the immune system. During severe injury, they may participate in apoptosis or cellular shutdown.

Mitochondrial allostasis is healthy when these shifts are timely and reversible. A cell under threat changes mitochondrial behaviour, performs necessary work, and then returns toward a more sustainable metabolic state. Disease emerges when mitochondrial allostasis becomes overloaded, prolonged, fragmented, or unable to return.

A mitochondrion that remains in danger-signalling mode may sustain inflammation. A mitochondrion that cannot produce adequate energy may constrain repair and re-entry. A mitochondrion that generates excessive reactive oxygen species may damage cellular structures and create new danger signals. A mitochondrion that is not removed when damaged may become an ongoing source of immune activation. In each case, mitochondrial dysfunction becomes more than energy failure. It becomes phase distortion.

14.2 Mitochondria and Redox Coherence

Mitochondria are major sources and regulators of reactive oxygen species. These molecules are not simply harmful waste. At controlled levels, reactive oxygen species participate in signalling, antimicrobial defence, adaptation, and regulation of transcription. They help cells sense metabolic state, stress, infection, and damage.

But redox signalling requires coherence. Too little reactive signalling may impair defence and adaptation. Too much may damage proteins, lipids, DNA, membranes, mitochondria, and extracellular matrix. Damaged molecules can then become danger signals, activating pattern-recognition receptors, inflammasomes, and inflammatory pathways. Redox imbalance can therefore convert defence into damage.

This creates a common immune-metabolic loop: mitochondrial stress increases reactive oxygen species; reactive oxygen species damage cellular structures; damaged structures produce danger signals; danger signals sustain inflammation; inflammation further stresses mitochondria.

The organism becomes caught in a redox-inflammatory lock.

Redox-inflammatory loops connect mitochondrial stress, reactive oxygen species, tissue damage, danger signalling, and inflammatory amplification (Picard et al., 2018; West & Shadel, 2017).

Redox coherence is therefore not the elimination of oxidative activity. It is the regulated use of oxidative signalling without persistent self-damage. Mitochondria must generate enough redox signal to defend and adapt, but not so much that the cell becomes a source of continuing danger.

This has clinical relevance in chronic inflammation, metabolic disease, neuroimmune disorders, post-infectious illness, aging, environmental toxicity, and fibrotic disease. In all these contexts, mitochondrial redox state can influence whether the organism can move from defence toward resolution and repair.

14.3 Mitochondrial DNA as Internal Danger Signal

Mitochondria retain their own DNA, a trace of their bacterial ancestry. Under normal conditions, mitochondrial DNA is compartmentalized and does not provoke immune alarm. But when mitochondria are damaged, mitochondrial DNA may be released into the cytosol, extracellular space, or circulation. In the wrong location, it can be interpreted as a danger signal.

This is immunologically profound. What belongs inside the organism can become alarm when misplaced.

Mitochondrial DNA can activate innate immune pathways when released from its proper compartment, linking mitochondrial damage to cGAS–STING activation, inflammasome signalling, and sterile inflammation (Chen et al., 2016; West & Shadel, 2017).

Mitochondrial DNA can activate innate immune pathways, including cGAS–STING and other nucleic-acid sensing systems. It may also contribute to inflammasome activation and inflammatory amplification. The organism may read damaged mitochondrial material as evidence of infection-like danger because of its bacterial ancestry and nucleic-acid form.

This is not self/non-self recognition in a simple sense. Mitochondrial DNA is part of the organism, yet it can signal danger when released from its proper compartment. The immune issue is not identity alone, but boundary integrity and location.

This reinforces a central theme: immune coherence depends on regulated compartmentalization. DNA in the nucleus is ordinary. DNA in the cytosol may be alarming. Mitochondrial components inside healthy mitochondria support life. Mitochondrial components outside their proper location may signal damage. The immune system is sensitive not merely to what exists, but to where it appears.

Mitochondrial DNA release may therefore contribute to nucleic-acid/interferon locks, inflammasome locks, post-injury inflammation, autoimmunity, sepsis, trauma responses, and chronic inflammatory states. The organism remains inflamed because its own damaged energetic organelles are being interpreted as danger.

14.4 MAVS and Antiviral Signalling

Mitochondria also serve as platforms for antiviral signalling. The mitochondrial antiviral-signalling protein, MAVS, is located on the outer mitochondrial membrane and participates in responses to viral RNA sensed by RIG-I-like receptors. Through MAVS, mitochondria help organize interferon responses and antiviral defence.

This places mitochondria directly within the antiviral phase of immunity. They are not only supplying energy to immune cells. They are helping determine whether the cell enters an antiviral state.

This is adaptive when viral infection is present. The organism must respond quickly to viral replication, induce interferon-stimulated genes, restrict spread, activate immune cells, and coordinate cellular defence. But antiviral signalling must also exit. Persistent activation of antiviral pathways can contribute to chronic interferon tone, fatigue, tissue dysfunction, immune dysregulation, and post-infectious symptoms.

Mitochondrial stress may therefore blur antiviral defence and cellular danger. Damaged mitochondria can amplify innate immune signalling, while viral infection can damage mitochondria and alter cellular metabolism. The resulting loop may help sustain disease after the initial viral encounter.

In phase-state language, mitochondria participate in the entry into antiviral defence, but mitochondrial dysfunction may prevent clean exit from that phase.

Mitochondrial antiviral signalling illustrates how mitochondria function not only as energy organelles but as platforms for innate immune and interferon responses (Chen et al., 2016; West & Shadel, 2017).

14.5 Inflammasomes, Mitochondrial Stress, and Pyroinflammatory States

Mitochondria are also linked to inflammasome activation. Mitochondrial reactive oxygen species, mitochondrial DNA, altered membrane potential, cardiolipin exposure, ion fluxes, and mitochondrial damage can all contribute to inflammasome signalling in certain contexts. Inflammasomes then generate inflammatory cytokines and may induce pyroptotic cell death.

This is useful when cellular stress indicates infection or damage that requires defence. But when mitochondrial stress persists, inflammasome activation may become chronic. The organism remains in a danger-defence state because mitochondria continue to signal that cellular integrity is compromised.

This is especially relevant in metabolic inflammation, gout-like inflammatory states, autoinflammatory disease, tissue injury, neuroinflammation, environmental toxicity, and post-infectious conditions. It also links mitochondrial dysfunction to fatigue and pain, because inflammatory cytokines and danger signals can alter neural, metabolic, and behavioural regulation.

A mitochondrial-inflammasome lock is therefore a specific form of maladaptive phase-locking. The cell is not merely low in energy. It is signalling danger from its energy system.

This lock connects mitochondrial stress to inflammasome activation, pyroinflammatory signalling, metabolic inflammation, and sterile inflammatory persistence (Schroder & Tschopp, 2010; West & Shadel, 2017).

14.6 Mitophagy and Clearance of Damaged Mitochondria

If damaged mitochondria can become danger signals, then their clearance is essential. Mitophagy is the selective autophagic removal of damaged or dysfunctional mitochondria. It is one of the key processes by which the cell maintains mitochondrial quality and prevents mitochondrial debris from becoming inflammatory.

Mitophagy is therefore not only housekeeping. It is immune regulation.

Mitophagy is essential for mitochondrial quality control and for preventing damaged mitochondria from becoming persistent sources of reactive oxygen species, mitochondrial DNA, and inflammatory danger signals (West & Shadel, 2017; Youle & Narendra, 2011).

When mitophagy works well, damaged mitochondria are identified, sequestered, degraded, and recycled. This prevents excessive release of mitochondrial DNA, reactive oxygen species, and other mitochondrial danger-associated molecular patterns. It also allows the cell to renew its mitochondrial network and maintain metabolic flexibility.

When mitophagy is impaired, damaged mitochondria accumulate. They may produce excess reactive oxygen species, release danger signals, impair energy production, activate inflammasomes, stimulate nucleic-acid sensing, and contribute to cellular senescence or inflammatory persistence. The cell becomes unable to clear its own damaged energetic infrastructure.

This is a clearance lock at the organelle level.

This organelle-level clearance lock mirrors the larger healing-cycle principle that resolution cannot complete while danger material remains uncleared (Ravichandran & Lorenz, 2007; Youle & Narendra, 2011).

Mitophagy connects mitochondrial biology to the broader healing cycle. Resolution cannot complete without clearance. Clearance does not apply only to dead cells, immune complexes, toxins, or extracellular debris. It also applies inside cells, where damaged mitochondria must be removed before the cell can fully restore function.

Clinically, impaired mitophagy may be relevant to aging, neurodegeneration, metabolic disease, chronic inflammation, infection recovery, fatigue states, and inflammatory tissue damage. The precise therapeutic implications remain complex and condition-specific, but the principle is clear: a cell that cannot clear damaged mitochondria may remain immunologically alarmed.

14.7 Mitochondrial DAMPs and Sterile Inflammation

Mitochondrial danger-associated molecular patterns include mitochondrial DNA, cardiolipin, formyl peptides, ATP, reactive oxygen species, and other mitochondrial components that can signal injury when released or misplaced. Because mitochondria evolved from bacteria-like ancestors, some mitochondrial molecules resemble microbial signals to the immune system.

This helps explain sterile inflammation: inflammation that occurs without active infection. Trauma, ischemia-reperfusion injury, burns, surgery, strenuous tissue damage, toxins, crystals, hypoxia, and cellular necrosis can all release mitochondrial danger signals. The immune system responds as if a serious threat is present, even when no pathogen is driving the process.

Sterile inflammation is not mistaken inflammation in a simple sense. It is the organism responding to evidence of internal damage. But if mitochondrial DAMPs persist or clearance fails, sterile inflammation can become chronic.

This may be relevant in autoimmune flares, metabolic inflammation, vascular injury, chronic pain, tissue degeneration, and post-injury syndromes. The organism continues to respond because damaged internal material remains immunologically meaningful.

Mitochondrial DAMPs help explain sterile inflammation by converting internal damage, ischemia, trauma, toxins, or necrosis into immune alarm without requiring active infection (Naviaux, 2014; West & Shadel, 2017).

Again, the problem is not that the immune system is irrational. It is that the field continues to present danger signals, and the organism cannot complete the transition from danger detection to clearance and repair.

14.8 Mitochondrial Conservation and Shutdown

Not all mitochondrial phase-setting leads to inflammation. Sometimes mitochondria participate in conservation or shutdown. When the organism faces severe stress, infection, energy limitation, toxic exposure, or unresolved danger, cells may reduce energy expenditure, alter metabolism, lower activity, or enter protective states. At the organismal level, this may appear as fatigue, exercise intolerance, reduced motivation, sleepiness, cold intolerance, cognitive slowing, or post-exertional worsening.

These states can be adaptive in acute illness. The organism reduces non-essential expenditure so that defence, repair, and survival can continue. Fatigue during infection, for example, can protect the organism from wasting energy on ordinary activity when immune work is urgent.

But conservation becomes pathological when it cannot exit.

This links mitochondrial biology to cell danger response theory: acute energy conservation may be adaptive, but persistent conservation can prevent re-entry into ordinary activity and health-cycle participation (Naviaux, 2014, 2020; Picard et al., 2018).

In chronic post-infectious illness, chronic inflammatory disease, mitochondrial dysfunction, severe allostatic load, or unresolved exposure, the organism may remain in a low-energy protective state. The patient may experience profound fatigue, crashes after exertion, brain fog, autonomic instability, and inability to sustain ordinary activity. From a phase-state perspective, this may represent failed re-entry into the health cycle, with mitochondrial and allostatic systems continuing to evaluate activity as unaffordable.

This does not mean that all fatigue is mitochondrial, nor that all mitochondrial explanations are proven in every syndrome. It means that mitochondrial phase-setting provides a biologically plausible grammar for understanding why some organisms cannot simply be pushed back into activity.

Forced exertion in a conservation lock may worsen symptoms because the organism is being asked to spend energy it cannot yet afford. Conversely, indefinite inactivity can deepen deconditioning and reduce resilience once the organism is capable of rebuilding. The clinical challenge is timing: when to protect, when to pace, when to rehabilitate, and how to identify the threshold at which re-entry becomes possible.

14.9 Mitochondria, Repair, and Regeneration

Mitochondria also participate in repair and regeneration. Tissue repair requires energy, biosynthesis, redox control, calcium signalling, cell proliferation, matrix production, immune-cell transition, angiogenesis, and removal of damaged structures. Mitochondria support all of these processes.

Repair and regeneration require mitochondrial energy, redox coordination, biosynthesis, apoptosis control, and metabolic flexibility, making mitochondrial function central to tissue restoration (Naviaux, 2014; Picard et al., 2018).

Macrophage transitions during healing, fibroblast activity, epithelial regeneration, stem-cell function, endothelial repair, and muscle recovery all depend on mitochondrial state. If mitochondrial function is impaired, repair may be incomplete, delayed, excessive, or disorganized.

This connects mitochondrial dysfunction to fibrosis and poor healing. A tissue that cannot efficiently restore energy balance and redox coherence may remain inflamed or over-repair. Hypoxia, mitochondrial stress, TGF-β signalling, matrix stiffness, and inflammatory mediators may reinforce each other. Repair becomes prolonged because the energetic and signalling conditions for completion are absent.

Mitochondria therefore help determine whether repair restores coherence or becomes scar.

14.10 Mitochondrial Phase-Locks

Mitochondrial phase-locks can take several forms.

A danger-signalling lock occurs when damaged mitochondria continue releasing DAMPs, reactive oxygen species, or nucleic-acid signals.

An antiviral lock occurs when mitochondrial platforms such as MAVS remain tied to persistent interferon or viral-like signalling.

An inflammasome lock occurs when mitochondrial stress continues to activate inflammatory platforms.

A clearance lock occurs when mitophagy fails and damaged mitochondria accumulate.

A conservation lock occurs when the cell or organism remains in energy-protective shutdown.

A repair lock occurs when mitochondrial dysfunction prevents clean transition from tissue rebuilding to restored function.

A senescence-associated lock may occur when mitochondrial dysfunction contributes to cellular aging, inflammatory secretion, and tissue degeneration.

These locks can overlap. A patient may have mitochondrial stress that contributes to both inflammatory signalling and fatigue. A tissue may have mitochondrial dysfunction that drives both poor repair and fibrosis. A post-viral syndrome may involve antiviral memory, mitochondrial conservation, autonomic dysregulation, and impaired re-entry. A metabolic-inflammatory disease may involve mitochondrial overload, redox stress, inflammasome activation, and trained immunity.

The value of the mitochondrial lens is not that it explains everything. It is that it shows how energy, danger, and phase transition are inseparable.

14.11 Clinical Meaning

Clinically, mitochondria invite a careful question: does this organism have the energetic and signalling capacity to move to the next phase?

If the patient is in active infection or inflammation, mitochondrial changes may be part of necessary defence. If inflammation is chronic, mitochondrial damage may sustain danger. If fatigue dominates, mitochondrial conservation or impaired energy recovery may be part of the phase-state. If fibrosis progresses, mitochondrial dysfunction may contribute to repair failure. If post-exertional worsening occurs, energy allocation and recovery thresholds become central. If neuroimmune symptoms persist, mitochondrial signalling in immune cells, neurons, glia, endothelium, and muscle may be relevant.

This does not justify simplistic mitochondrial medicine. Many mitochondrial markers are difficult to interpret. Supplements are often overmarketed. Fatigue is multi-causal. Chronic illness should not be reduced to “mitochondrial dysfunction” without evidence. But neither should mitochondria be ignored. They are central to immune coherence.

A life-coherent approach treats mitochondrial support as part of phase restoration, not as a universal cure. This may include controlling inflammation, treating infection, protecting sleep, correcting nutrient deficiencies, reducing toxic exposures, managing metabolic disease, pacing exertion in low-reserve states, restoring movement gradually when appropriate, supporting oxygenation and vascular health, and avoiding interventions that impose excessive metabolic stress.

The goal is not to "boost" mitochondria indiscriminately. The goal is to restore mitochondrial coherence: the ability to generate energy, regulate redox, signal danger appropriately, clear damaged organelles, support repair, and permit re-entry into life.

14.12 Transition to the Cell Danger Response

Mitochondria lead directly to the cell danger response. When cells detect threat, injury, infection, toxin exposure, or metabolic disruption, they reorganize around defence and survival. Mitochondria participate in this reorganization through ATP release, redox signalling, metabolic shifts, membrane potential changes, innate immune activation, and energy allocation.

The cell danger response is therefore a phase transition.

This framing anticipates the cell danger response framework, where unresolved protective cellular states can sustain chronic illness when the organism cannot complete the transition from defence to repair and re-entry (Naviaux, 2014, 2020).

It is adaptive when temporary and completed. It becomes pathological when it persists, fragments, or blocks re-entry into the health cycle.

The next section examines the cell danger response, salugenesis, and incomplete healing: how disease may represent not only ongoing pathogenesis, but unfinished biological repair.

15. Cell Danger Response, Salugenesis, and Incomplete Healing

If mitochondria help set cellular phase, the cell danger response describes what happens when the cell enters a coordinated state of protection. A cell exposed to infection, injury, toxin, hypoxia, metabolic disruption, oxidative stress, mechanical strain, or severe perturbation does not merely continue ordinary function. It reorganizes. It changes metabolism, membrane signalling, redox state, mitochondrial behaviour, extracellular communication, inflammatory signalling, and resource allocation. It shifts from ordinary participation toward defence and survival.

The cell danger response is therefore not pathology in itself. It is a protective phase transition.

Naviaux's cell danger response framework describes coordinated metabolic, mitochondrial, redox, membrane, purinergic, and immune changes that help cells respond to threat, injury, infection, or stress (Naviaux, 2014, 2020).

Disease is not always ongoing pathogenesis; it may be incomplete salugenesis.

The distinction between pathogenesis and salugenesis reframes a large portion of chronic immune disease. Pathogenesis describes the processes by which disease is produced: infection, autoimmunity, inflammation, injury, toxicity, genetic defects, metabolic dysfunction, malignancy, or tissue damage. Salugenesis describes the biological processes by which healing is generated: containment, resolution, clearance, repair, remodelling, adaptation, and reintegration. Many chronic diseases may involve both. But some persistent illness may be driven less by ongoing attack alone than by incomplete healing. The organism has entered a protective response but cannot complete the transition back to ordinary health-cycle participation.

The cell danger response provides a molecular and cellular bridge between injury and healing. It begins as a survival program. The cell detects danger and changes state to protect itself and the organism. It may reduce ordinary functions, release alarm signals, alter ATP dynamics, change mitochondrial respiration, produce reactive oxygen species, activate innate immune pathways, shift metabolism, change membrane lipids, communicate with neighbouring cells, and participate in inflammation. These responses help contain damage and alert the wider tissue.

But what protects in the acute phase can become pathological when persistent. A cell that remains in danger mode cannot fully resume its ordinary role. An epithelial cell cannot simply maintain barrier and absorption if it remains in alarm. A muscle cell cannot support normal exertion if energy production remains constrained. A neuron cannot regulate normal signalling if threat physiology persists. A fibroblast cannot return to quiet matrix maintenance if repair signals remain active. A macrophage cannot complete clearance and resolution if danger signals continue to dominate.

The cell danger response is useful when it opens a healing cycle. It becomes harmful when it becomes the healing cycle's prison.

15.1 The Cell Danger Response as Protective Phase Shift

The first principle is that the cell danger response is adaptive. Cells must detect danger and protect themselves. When membranes are injured, pathogens invade, toxins accumulate, mitochondria fail, oxygen is limited, or DNA is damaged, ordinary function may become unsafe. The cell must shift into a protective state.

This shift can include reduced energy expenditure for non-essential functions, increased production of inflammatory mediators, release of extracellular ATP, activation of purinergic signalling, changes in mitochondrial dynamics, altered redox signalling, autophagy, mitophagy, unfolded protein responses, inflammasome activation, interferon signalling, and communication with immune and stromal cells. The cell becomes less focused on ordinary specialized function and more focused on survival, alarm, containment, and repair.

In acute injury or infection, this is coherent. The cell's distress participates in the organism's healing cycle. It alerts nearby cells, recruits immune support, limits spread, and helps coordinate tissue-level response. If the perturbation is resolved, the cell can then transition toward restoration or be removed if too damaged.

The danger response therefore belongs to salugenesis. It is part of how healing begins.

Cell danger response biology helps explain why danger signalling, inflammation, energy conservation, and altered cellular communication can be adaptive during acute healing but harmful when prolonged (Naviaux, 2014, 2020).

This is important because medicine often treats danger signals as though they are simply bad. But the organism does not generate danger responses without reason. Fever, inflammation, fatigue, pain, extracellular ATP release, cytokine production, and mitochondrial shifts may be costly, but they can also be protective. The clinical question is not whether danger responses should exist. The question is whether they are appropriate, proportionate, affordable, and able to exit.

15.2 Extracellular ATP and the Signal of Displaced Energy

Extracellular ATP is one of the most evocative signals in the cell danger response. Inside the cell, ATP is energy currency. Outside the cell, especially at high concentrations, ATP can signal injury, stress, membrane disruption, or danger. Energy in the wrong compartment becomes alarm.

This is a recurring theme in immunity: location matters. DNA in the nucleus is ordinary; DNA in the cytosol may be danger. Mitochondrial components inside mitochondria are functional; outside their proper location they may become inflammatory. ATP inside the cell powers life; outside the cell it can warn of damage.

Extracellular ATP participates in purinergic signalling, inflammasome activation, pain pathways, immune-cell recruitment, vascular responses, and tissue repair. It helps the organism know that

cells are stressed or injured. It is therefore an important bridge between cellular distress and tissue-level immune activation.

In acute healing, extracellular ATP can help mobilize response. But if ATP signalling persists, the tissue may remain in danger mode. Pain, inflammation, mast-cell activation, microglial reactivity, mitochondrial stress, and impaired resolution may all be sustained in some contexts. The cell's alarm becomes part of the lock.

This illustrates a general rule: danger signals are salugenic when they initiate completion, but pathogenic when they prevent completion.

15.3 From Inflammation to Proliferation to Differentiation

Healing is not a single event. It involves phases.

Resolution biology similarly emphasizes that inflammation must transition through active termination, efferocytosis, clearance, repair, and restoration rather than simply fading away (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

The cell danger response can be understood within a broader sequence that includes inflammation, proliferation, differentiation, repair, and reintegration.

Inflammation is the phase of alarm, defence, containment, and initial clearance. It mobilizes immune cells, vascular changes, cytokines, chemokines, complement, coagulation, and metabolic reallocation. It creates the conditions under which danger can be addressed.

Proliferation follows when cells expand, fibroblasts activate, epithelial cells migrate, endothelial cells form vessels, immune cells coordinate repair, and matrix is deposited. This phase rebuilds structure, but it remains immature and potentially unstable.

Differentiation and remodelling then restore specialized function. Cells return toward tissue-specific roles. Matrix is reorganized. Vessels mature. Nerves adapt. Barrier function improves. Mechanical properties normalize where possible. The tissue becomes less like a wound and more like a functioning organ.

Reintegration is the organismal endpoint. The tissue does not merely look repaired; it supports life again. Movement returns. Pain decreases. Energy improves. Sleep normalizes. Appetite, cognition, social participation, and ordinary rhythms recover. The organism re-enters the health cycle.

Disease can arise when any phase persists beyond its proper window. Persistent inflammation becomes chronic inflammatory disease. Persistent proliferation becomes hyperplasia, remodelling, or fibrotic expansion. Persistent repair becomes scarring. Persistent conservation becomes fatigue and shutdown. Persistent danger signalling becomes hypersensitivity. Persistent memory becomes hypervigilance or relapse.

The healing process becomes pathological when it cannot complete its own sequence.

15.4 Incomplete Salugenesis

Incomplete salugenesis occurs when the organism begins a healing response but cannot complete it.

This synthesis links salutogenic resources, cell danger response biology, resolution biology, and allostasis: healing can remain incomplete when triggers persist, clearance fails, energy is insufficient, repair overbuilds, or recovery conditions are absent (Antonovsky, 1987; McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005).

This may happen because the original perturbation remains, because damage is too extensive, because clearance fails, because energy is insufficient, because tissue mechanics become distorted, because exposures continue, because infection persists, because allostatic load is too high, or because the niche does not support recovery.

In incomplete salugenesis, the organism may still be trying to heal. But the attempt becomes chronic.

This reframes many disease patterns. Chronic inflammation may be incomplete transition from defence to resolution. Fibrosis may be incomplete transition from repair to functional remodelling. Persistent fatigue may be incomplete transition from conservation to re-entry. Chronic pain may be incomplete transition from protection to safe movement. Post-infectious illness may be incomplete transition from antiviral defence to health-cycle participation. Allergic disease may be incomplete transition from barrier alarm to tolerance. Autoimmunity may be incomplete transition from recognition and clearance to restored tolerance.

The disease is real. The damage is real. The suffering is real. But the process may still carry the form of unfinished healing.

This distinction is clinically important because it validates suffering while shifting treatment from symptom suppression alone toward identifying the unfinished biological transition (Naviaux, 2014; Serhan, 2007).

This is clinically useful because it changes the therapeutic question. Instead of asking only, “How do we suppress this abnormal process?” we ask, “What healing transition is incomplete, and what conditions would allow it to complete?”

Sometimes suppression is necessary to prevent damage. But suppression alone may not complete salugenesis. A patient with inflammatory bowel disease may need anti-inflammatory treatment, but also mucosal healing, microbial stabilization, nutritional repair, anaemia correction, sleep restoration, and reduction of triggers. A patient with fibrotic lung disease may need control of inflammation, avoidance of injury, antifibrotic strategy, oxygen support, pulmonary rehabilitation, and protection from further exposure. A patient with post-viral illness may need pacing, autonomic support, sleep protection, careful rehabilitation, and attention to immune,

vascular, mitochondrial, or infectious contributors. A patient with chronic sinus disease may need inflammation control, drainage, microbial assessment, barrier restoration, and environmental attention.

The point is that treatment must support completion, not only interruption.

15.5 Abnormal Persistence of Cell Danger Phases

The cell danger response can remain active in several ways.

First, danger may persist because the trigger remains. Ongoing infection, repeated allergen exposure, toxic exposure, damp housing, biofilms, crystals, immune complexes, metabolic overload, hypoxia, or mechanical injury may continue to stimulate alarm.

Second, danger may persist because debris is not cleared. Damaged mitochondria, apoptotic cells, necrotic material, fibrin, extracellular matrix fragments, immune complexes, oxidized lipids, misfolded proteins, and microbial remnants can all sustain inflammatory sensing if not removed.

Third, danger may persist because cellular memory has been installed. Gene regulatory networks, trained immunity, epigenetic marks, tissue-resident immune cells, sensitized mast cells, activated fibroblasts, or primed microglia may lower the threshold for reactivation.

Fourth, danger may persist because the organism lacks the energy or resources to exit. Mitochondrial dysfunction, nutrient deficiency, sleep disruption, anaemia, metabolic disease, severe allostatic load, or poor oxygenation may make resolution and repair unaffordable.

Fifth, danger may persist because the niche keeps re-entering the organism as perturbation. Polluted air, unsafe housing, chronic stress, social threat, food insecurity, climate heat, occupational exposure, or fragmented care may repeatedly reopen the healing cycle before it completes.

These are not mutually exclusive. Chronic illness often involves several at once. The cell danger response may be sustained by trigger, debris, memory, metabolic constraint, and niche incoherence simultaneously.

This complexity does not make the framework vague. It clarifies why single interventions may fail. If a patient's danger response is sustained by both active inflammation and ongoing exposure, treating only inflammation may produce partial benefit. If it is sustained by debris and impaired clearance, suppressing inflammation may reduce symptoms but leave danger material behind. If it is sustained by metabolic insufficiency, exertion-based rehabilitation may worsen the state. If it is sustained by memory, removal of the original trigger may not be enough.

The clinician must identify the lock's sustaining conditions.

Sustaining conditions may include persistent triggers, uncleared debris, trained memory, mitochondrial constraint, tissue damage, exposure, sleep disruption, allostatic load, or niche incoherence (McEwen, 1998; Naviaux, 2014; Netea et al., 2016; Picard et al., 2018).

15.6 Cell Danger Response and Chronic Fatigue States

The cell danger response is especially relevant to fatigue-dominant conditions. During acute illness, fatigue is often adaptive. It reduces activity, conserves energy, supports immune work, encourages rest, and limits exposure. But when the organism cannot exit conservation mode, fatigue becomes disabling.

From this perspective, fatigue is not merely lack of motivation. It may represent an organismal state in which energy allocation remains constrained by perceived or ongoing danger.

This interpretation is consistent with cell danger response biology, mitochondrial stress models, allostasis, sleep-immune regulation, and neuroimmune accounts of sickness behaviour and energy conservation (Besedovsky et al., 2012; McEwen, 1998; Naviaux, 2014; Picard et al., 2018).

Mitochondria, autonomic regulation, inflammatory signalling, sleep disruption, vascular function, neuroimmune pathways, and metabolic reserve may all participate.

Post-exertional symptom exacerbation is particularly important because it suggests that activity is not merely difficult; it may exceed the organism's current recovery capacity. The body responds to exertion as a perturbation that triggers worsening rather than adaptation. This indicates a re-entry lock. The organism cannot yet convert activity into conditioning because activity is still biologically interpreted as threat or excessive cost.

This does not mean that movement is unimportant. Movement is essential to health-cycle participation. But in a danger-response or conservation lock, movement must be reintroduced according to phase capacity. Premature forcing may deepen the lock. Indefinite avoidance may also become harmful if the organism is capable of gradual rebuilding. The clinical task is to determine timing, dose, threshold, and recovery pattern.

A life-coherent approach therefore distinguishes pacing from resignation. Pacing protects the organism while conditions for re-entry are restored. It is not the abandonment of recovery. It is the prevention of repeated injury during incomplete salugenesis.

Pacing is therefore framed not as avoidance, but as phase protection when the organism cannot yet convert exertion into adaptive conditioning without relapse or worsening (Naviaux, 2014; Picard et al., 2018).

15.7 Cell Danger Response and Fibrosis

Fibrosis can also be understood as incomplete salugenesis. In acute repair, fibroblast activation, extracellular matrix deposition, contraction, and tissue stabilization are necessary. The organism

must restore boundary integrity after injury. But when repair signals persist, fibrosis develops. The tissue becomes stiff, thickened, scarred, and functionally impaired.

Fibrosis is repair that cannot complete.

Fibrosis reflects persistent repair and remodelling programmes involving macrophage-fibroblast interactions, extracellular matrix deposition, mechanical stiffness, and failure to restore normal tissue function (Wynn et al., 2013; Wynn & Ramalingam, 2012).

At the cellular level, persistent TGF-β signalling, mechanical stiffness, hypoxia, mitochondrial stress, macrophage-fibroblast crosstalk, epithelial injury, endothelial dysfunction, and inflammatory mediators may keep repair programs active. The matrix itself becomes a signal. Stiff tissue activates mechanosensors, which sustain fibroblast activation, which increases stiffness. Repair becomes self-reinforcing.

This is a repair-overbuild lock.

Repair-overbuild links inflammation, tissue injury, TGF-β-related signalling, fibroblast activation, matrix stiffness, hypoxia, and altered mechanics into a self-reinforcing fibrotic phase-state (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Fibrosis shows why healing must include exit signals. Building is necessary, but overbuilding destroys function. The organism attempts to preserve structure, but preservation becomes constriction. The tissue survives at the cost of participation. A scar may protect against rupture, but too much scar prevents breathing, filtering, moving, absorbing, or contracting.

Clinically, this means that anti-inflammatory treatment may not be enough once fibrotic programs are installed. Antifibrotic strategies, mechanical considerations, rehabilitation, exposure removal, tissue protection, and early prevention of repeated injury may all be necessary. The best treatment for fibrosis is often preventing repair from becoming locked in the first place.

15.8 Cell Danger Response and Neuroimmune Sensitization

The cell danger response also intersects with neuroimmune sensitization. Pain, fatigue, sensory sensitivity, sleep disruption, brain fog, dysautonomia, and mood changes can all emerge when immune, neural, mitochondrial, and autonomic systems remain organized around threat.

Microglia, astrocytes, sensory neurons, autonomic circuits, mast cells, endothelial cells, cytokines, chemokines, mitochondrial signals, and extracellular ATP can participate in neuroimmune danger states. These systems are not separate from immunity. They help the organism regulate protection, movement, attention, arousal, and energy.

In acute injury or infection, neuroimmune sensitization is adaptive. Pain protects tissue. Fatigue reduces activity. Sensory changes may promote withdrawal. Autonomic shifts prioritize survival. But if these states persist, they narrow life. Ordinary stimuli become threatening. Movement

becomes costly. Sleep becomes fragmented. The organism remains prepared for danger even in relative safety.

This is not imaginary illness. It is embodied prediction and protection locked into neuroimmune regulation.

This interpretation connects neuroimmune symptoms with allostasis, interoception, sleep-immune regulation, mitochondrial stress, and threat physiology without reducing them to psychology alone (Barrett et al., 2016; Besedovsky et al., 2012; McEwen, 1998; Picard et al., 2018).

Treatment requires care. Dismissal worsens threat. Overmedicalization may also reinforce fixation. The organism needs trustworthy explanation, symptom control, pacing, inflammation treatment where needed, sleep restoration, autonomic support, gradual safe exposure, rehabilitation, relational safety, and careful attention to biological drivers. Neuroimmune re-entry must be earned by creating conditions in which the body can safely update its evaluation.

15.9 Salugenesis and Clinical Care

If incomplete salugenesis is central to chronic disease, clinical care must support the whole healing sequence. This does not mean abandoning disease-specific treatment. It means placing treatment within a larger question: what phase of healing is incomplete?

If danger is ongoing, the trigger must be addressed.
If defence is destructive, inflammation must be controlled.
If containment traps pathology, drainage or removal may be needed.
If resolution fails, inflammation must be guided toward termination.
If clearance fails, debris, damaged cells, toxins, or immune complexes must be removed or reduced.
If repair is incomplete, tissue restoration must be supported.
If repair is excessive, fibrosis must be restrained.
If memory is fixed, the organism must be helped to update.
If re-entry fails, rehabilitation must be carefully sequenced.

This is phase restoration in clinical form.

Phase restoration integrates suppression, resolution, clearance, repair, pacing, rehabilitation, and salutogenic support according to the patient's dominant phase-state rather than treating these as competing therapeutic logics (Antonovsky, 1987; Naviaux, 2014; Serhan & Savill, 2005).

Clinical care also becomes salugenic when it improves comprehensibility, manageability, and meaningfulness. A patient who understands their condition, has access to resources, and can see a path toward life is more likely to participate in healing. The physician's role is not only to prescribe but to help organize the field in which healing can complete.

This includes diagnosis, medication, monitoring, explanation, prioritization, coordination, reassurance, warning, referral, and partnership. It includes knowing when to act forcefully and when to avoid overwhelming the organism. It includes recognizing when the patient's life conditions make healing biologically unaffordable.

Clinical care is itself part of the organism–niche relation.

In salutogenic terms, care can support comprehensibility, manageability, and meaningfulness; in organism-centered terms, it becomes part of the patient's structural coupling with the healing environment (Antonovsky, 1987; Maturana & Varela, 1980).

15.10 Limits of the Cell Danger Response Frame

The cell danger response is a powerful concept, but it must be used carefully.

This caution is essential because the cell danger response is a useful phase-state concept, not a universal explanation for all chronic disease or a substitute for disease-specific diagnosis (Naviaux, 2020).

Not every chronic disease is best explained by persistent cell danger response. Not every symptom reflects incomplete healing. Some diseases are driven by genetic defects, malignancy, structural damage, active infection, severe autoimmunity, endocrine disorders, nutritional deficiency, toxic exposure, psychiatric illness, or other mechanisms requiring specific diagnosis and treatment.

The cell danger response should not become a universal explanation that erases disease specificity. It should not be used to dismiss active pathology or imply that patients can heal through mindset alone. It should not become a vague label attached to complex illness without evidence.

Its value is as a phase-state concept: a way of understanding how protective cellular programs can become persistent, how healing can remain unfinished, and why re-entry into health requires completion rather than suppression alone.

The framework remains strongest when it is tied to measurable mechanisms, clinical patterns, careful history, and therapeutic consequences.

15.11 Transition to Tissue Niches

The cell danger response occurs in cells, but disease is lived in tissues. Cells do not act in isolation. They belong to niches: synovium, enthesis, airway, gut, skin, vessel, kidney, lung interstitium, bone marrow, brain, and others. These tissues give immune disease its form. They provide mechanical, microbial, metabolic, vascular, neural, stromal, and developmental contexts that shape how immune phase-locks appear.

The next part therefore turns from molecular and cellular foundations to tissue niches, phase-locks, and disease expression.

The organism's immune story is not only written in molecules and cells. It is written in places.

The tissue-niche argument follows because immune mechanisms become clinically meaningful through the anatomical, mechanical, microbial, vascular, stromal, metabolic, and neural contexts in which they take form (Belkaid & Hand, 2014; Galli et al., 2011; Wynn et al., 2013).

Part V. Tissue Niches, Phase-Locks, and Disease Expression

16. Tissue Niches and Disease-Specific Regulatory Attractors

The molecular and cellular foundations of immune phase-locking are necessary, but they are not sufficient. Immune disease does not occur in pathways alone. It occurs in tissues. A cytokine becomes clinically meaningful in a place. An immune cell becomes pathogenic in a niche. A repair program becomes fibrosis in a specific organ architecture. A barrier alarm becomes asthma in the airway, eczema in the skin, colitis in the gut, or chronic rhinosinusitis in the sinus mucosa. The organism's immune story is therefore not only molecular or cellular. It is anatomical, mechanical, microbial, vascular, neural, developmental, and ecological.

Tissue-contextual immunology supports this shift: immune-cell function, inflammatory signalling, repair, microbial ecology, and tissue architecture acquire clinical meaning only within local anatomical and regulatory niches (Belkaid & Hand, 2014; Galli et al., 2011; Hooper et al., 2012; Wynn et al., 2013).

The tissue is not merely the target of immune disease; it is part of the regulatory circuit that gives disease its form.

This is especially evident where stromal cells, fibroblasts, macrophages, epithelial or endothelial barriers, extracellular matrix, and local repair programmes actively shape chronic inflammation and disease persistence (Galli et al., 2011; Wynn et al., 2013; Wynn & Ramalingam, 2012).

This is a decisive shift. In a simplified model, immune disease begins in the immune system and then attacks tissues. Sometimes this is partly true. Autoantibodies, autoreactive lymphocytes, immune complexes, complement, cytokines, and inflammatory cells may damage organs. But in many chronic immune-mediated diseases, the tissue is not passive. It shapes the disease process. It provides the signals, constraints, memory, mechanics, microbial relations, vascular conditions, stromal architecture, and repair programs through which immune activity becomes locally organized.

There is no generic inflammation. There is synovial inflammation, airway inflammation, mucosal inflammation, vascular inflammation, skin inflammation, renal inflammation, meningeal inflammation, interstitial inflammation, adipose inflammation, and fibrotic inflammation. Each has a different tissue grammar.

A life-coherent systems immunology must therefore ask not only which immune pathway is active, but where the pathway is active and what tissue world gives it meaning.

The same immune pathway may therefore have different consequences depending on timing, tissue, microbial context, mechanical load, vascular setting, and repair state (Belkaid & Hand, 2014; Medzhitov, 2008; Wynn et al., 2013).

16.1 The Tissue Niche as Regulatory Field

A tissue niche is more than an anatomical site. It is a regulatory field composed of resident immune cells, stromal cells, epithelial or endothelial barriers, extracellular matrix, nerves, vessels, lymphatics, microbiota where present, mechanical forces, oxygen gradients, metabolites, developmental patterning, local hormones, and prior injury history. Each tissue has its own way of sensing, defending, tolerating, repairing, and remembering.

This tissue-specific regulatory field helps explain why immune disease becomes organ-patterned rather than appearing as generic inflammation distributed evenly across the body (Belkaid & Hand, 2014; Galli et al., 2011; Wynn et al., 2013).

The gut must negotiate food, microbes, bile acids, peristalsis, mucus, epithelial turnover, immune tolerance, microbial metabolites, and barrier integrity. The airway must negotiate air flow, particles, viruses, allergens, pollutants, mucus, smooth muscle, epithelial alarms, and breathing mechanics. The skin must negotiate touch, microbes, temperature, chemicals, ultraviolet light, wounds, and social contact. The synovium must negotiate motion, load, vascularity, fibroblast activation, macrophage states, and joint mechanics. The enthesis must negotiate tensile force, bone interface, microdamage, IL-17 biology, and mechanical stress. The kidney must negotiate filtration, immune complexes, complement, vascular pressure, tubular injury, and metabolic waste. The lung interstitium must negotiate gas exchange, matrix architecture, immune surveillance, epithelial injury, and fibrotic repair. The brain must negotiate neural signalling, barriers, microglia, glymphatic clearance, vascular flow, and systemic inflammatory communication.

Because each tissue has different demands, the same immune signal does not have the same meaning everywhere.

Context-dependence is a core principle of immune regulation: cytokines, metabolic states, stromal responses, and repair programmes must be interpreted through tissue location, dose, timing, and organismal phase-state (Buck et al., 2017; Medzhitov, 2008; O'Neill et al., 2016).

A cytokine that supports defence in one tissue may promote destruction in another. A repair program that seals a skin wound may stiffen lung tissue disastrously. A neutrophilic response that helps clear bacteria in one compartment may damage the kidney or airway if persistent. A type 2 response that helps barrier repair and anti-parasitic defence may become allergy, asthma, polyposis, or eczema when locked. An interferon response that restricts viruses may become systemic fatigue, autoimmunity, or tissue dysfunction when persistent.

The tissue niche gives immune pathways their clinical face.

This is why tissue-niche reasoning is clinically necessary: molecular mechanisms become diseases only when they are installed in particular anatomical, stromal, microbial, vascular, neural, and mechanical worlds (Belkaid & Hand, 2014; Wynn et al., 2013).

16.2 Synovium: Inflammatory Memory in a Moving Joint

The synovium is a specialized tissue that lines joints and supports lubrication, movement, and exchange within the joint space. It is highly vascular, mechanically active, and populated by fibroblast-like synoviocytes, macrophages, endothelial cells, nerves, and immune cells. In health, it supports movement. In disease, it can become an inflammatory organ.

Rheumatoid arthritis illustrates how a tissue niche can become a disease-specific attractor. Autoantibodies, systemic inflammation, genetic susceptibility, mucosal immune events, smoking or other exposures, and immune dysregulation may all contribute. Yet the destructive disease takes form in the synovium. Synovial fibroblasts become activated. Macrophages produce inflammatory mediators. Blood vessels support cellular influx. The pannus invades cartilage and bone. Pain changes movement. Mechanical stress and inflammation reinforce one another. The joint becomes a self-sustaining inflammatory niche.

The synovium is therefore not merely attacked. It participates in the lock.

Synovial disease illustrates how resident stromal cells, macrophages, vascular remodeling, tissue-resident inflammatory states, and mechanical stress can sustain local inflammatory memory after systemic triggers fluctuate (Galli et al., 2011; Netea et al., 2016; Wynn et al., 2013).

Once synovial fibroblasts and macrophages enter persistent inflammatory states, the joint may remain primed even when systemic triggers fluctuate. Tissue-resident cells, matrix changes, vascular remodeling, and pain pathways preserve the disease pattern. A flare may then represent reactivation of a synovial attractor rather than a wholly new event.

Clinically, this supports early control of inflammation before destructive tissue memory becomes entrenched. It also supports rehabilitation once inflammation is controlled, because joint function is not restored by cytokine suppression alone. The tissue must return, as far as possible, to movement, strength, range, and participation.

16.3 Enthesis: Mechanical Stress and Immune Activation

The enthesis is the site where tendon, ligament, or capsule attaches to bone. It is a zone of mechanical transition. It absorbs force, transmits load, and experiences microdamage. Because of this, it is a natural site where mechanical stress, repair, and immune regulation meet.

In spondyloarthritis and related disorders, the enthesis may become a disease-defining niche. Mechanical stress, barrier immune events, microbial history, IL-17 and IL-23 pathways, stromal cells, bone remodeling, and local inflammation may converge. The result is not simply inflammation in a random tissue. It is inflammation at a mechanically specialized boundary.

The enthesis shows that immune disease can be mechano-immunological. Force matters.

Enthesitis is now understood as a key lesion in spondyloarthritis, where mechanical stress, stromal responses, bone remodelling, and IL-23/IL-17-associated immune pathways can converge at tendon, ligament, or capsular insertions into bone (Schett et al., 2017; Sherlock et al., 2012).

More generally, tissue mechanics, stromal activation, repair programmes, and extracellular matrix dynamics can shape inflammatory possibility and chronic tissue remodelling (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Force matters. Repetitive strain, microinjury, altered biomechanics, obesity, posture, gait, and tissue stiffness can all shape inflammatory possibility. Immune pathways respond not only to molecules, but to mechanical worlds.

In phase-lock terms, enthesitis may represent a mechano-inflammatory repair lock. The tissue repeatedly senses stress or microdamage, mobilizes repair and inflammation, but cannot fully reintegrate. Repair may lead to new bone formation, stiffness, pain, and altered mechanics, which then perpetuate the loop.

This helps explain why treatment may require both immune modulation and biomechanical attention. Suppressing inflammation without addressing mechanical context may be incomplete. Loading the tissue aggressively while inflammation is active may worsen the lock. Again, the question is timing and phase: what kind of movement helps this tissue re-enter function, and what kind of force reopens danger?

16.4 Airway and Sinus Mucosa: Barrier Alarm and Type 2 Locking

The airway and sinus mucosa are living interfaces with air, particles, microbes, allergens, pollutants, humidity, temperature, and viruses. Their immune function depends on epithelial integrity, mucus, cilia, antimicrobial peptides, resident immune cells, sensory nerves, smooth muscle, vascular tone, and microbial ecology.

Asthma, allergic rhinitis, chronic rhinosinusitis, and nasal polyposis illustrate how barrier tissues can become locked in type 2 immune patterns. Epithelial injury or stress may generate alarmins. Mast cells, eosinophils, type 2 innate lymphoid cells, Th2 cells, IgE, mucus production, smooth muscle reactivity, and tissue remodeling may follow. In acute contexts, type 2 immunity can support barrier defence and repair. In chronic contexts, it can narrow breathing, obstruct sinuses, produce mucus, amplify sensitivity, and remodel tissue.

The airway becomes a hyperresponsive boundary.

Barrier tissues such as the airway and sinus mucosa are immunologically active interfaces where epithelial injury, allergens, microbes, pollutants, mucus, sensory nerves, and type 2 immune programmes can become self-reinforcing (Belkaid & Hand, 2014; Galli et al., 2011; Hooper et al., 2012).

This is not merely “overreaction.” It is a tissue-niche state in which the organism evaluates ordinary air, particles, allergens, pollutants, or viral after-effects through alarm and repair pathways. The boundary becomes too ready to close. Bronchospasm, mucus, cough, sneezing, congestion, itch, and eosinophilic inflammation are embodied boundary responses. They protect by expelling, trapping, narrowing, or alerting, but when chronic they impair participation.

The extended niche is especially important here. Damp housing, mold, dust mites, combustion products, air pollution, occupational exposures, viral infections, climate change, pollen seasons, and indoor ventilation all shape airway immune states. Treating the airway without attending to air may be necessary but incomplete.

16.5 Skin: Visible Boundary, Microbial Ecology, and Social Surface

The skin is a barrier, sensory organ, microbial habitat, immune organ, thermal regulator, and social surface. It is where the organism meets touch, injury, temperature, sunlight, chemicals, microbes, allergens, and interpersonal visibility. Skin disease therefore carries biological and psychosocial weight.

Atopic dermatitis, psoriasis, urticaria, contact dermatitis, vitiligo, lupus rashes, vasculitic lesions, and scleroderma all illustrate different skin immune attractors. Barrier dysfunction, microbial shifts, type 2 inflammation, IL-17/IL-23 pathways, interferon signalling, mast-cell activation, immune complexes, vascular injury, fibroblast activation, and pigmentation-related autoimmunity may each give disease a different form.

The skin makes immune disease visible. This visibility can affect identity, shame, social participation, intimacy, and stress physiology. In an organism-centered framework, this matters. The skin is not only a biological boundary. It is also a relational boundary.

Skin disease illustrates how barrier immunity, microbial ecology, inflammation, itch, visible lesions, stress physiology, and social participation can interact within a single tissue-niche field (Belkaid & Hand, 2014; Hooper et al., 2012; McEwen, 1998).

Disease at the skin can alter how the organism-person inhabits the world.

Psoriasis illustrates tissue memory and inflammatory recurrence. Lesions often recur in previously affected areas. Skin-resident memory cells, keratinocyte activation, vascular changes, microbial factors, and mechanical injury can sustain local readiness. The tissue remembers the disease pattern.

Tissue-resident immune cells, epithelial activation, stromal changes, microbial shifts, local vascular patterns, and injury responses can preserve inflammatory readiness even after visible disease partially improves (Galli et al., 2011; Netea et al., 2016; Wynn et al., 2013).

Trauma to the skin can provoke lesions in susceptible individuals, showing how injury, repair, and immune memory interact.

Atopic dermatitis illustrates barrier-developmental vulnerability. Skin barrier disruption, itch-scratch cycles, microbial colonization, type 2 inflammation, allergens, irritants, and sleep disruption can form a self-sustaining loop. The organism scratches because it itches; scratching damages barrier; damaged barrier increases inflammation and microbial shifts; inflammation increases itch; sleep worsens; allostatic load rises. The disease is not only immune activation. It is a barrier-neural-microbial-behavioural lock.

16.6 Gut: Tolerance, Microbiome, Barrier, and Mucosal Healing

The gut is one of the most complex immune niches in the body. It must absorb nutrients while excluding pathogens, tolerate food while detecting toxins, cultivate microbes while preventing invasion, maintain mucus and epithelial turnover, regulate bile acids and metabolites, coordinate motility, and communicate with the nervous and endocrine systems.

Inflammatory bowel disease, celiac disease, food allergy, irritable bowel syndromes with immune features, post-infectious gut dysfunction, and gut-linked systemic inflammation all reveal the complexity of mucosal immune coherence.

In the gut, tolerance is not passive. It is active, ongoing, metabolically supported, microbial, epithelial, and immune-regulated. Regulatory T cells, IgA, mucus, epithelial junctions, antimicrobial peptides, dendritic cells, macrophages, microbial metabolites, short-chain fatty acids, bile acid signalling, enteric nerves, and motility all participate. When this system loses coherence, the gut may enter barrier alarm, microbial dysbiosis, chronic inflammation, ulceration, fibrosis, stricture, or hypersensitivity.

Gut immune tolerance is actively maintained through epithelial barriers, mucus, IgA, regulatory immune circuits, macrophages, dendritic cells, microbial metabolites, short-chain fatty acids, and continuous host–microbiota negotiation (Belkaid & Hand, 2014; Hooper et al., 2012).

Inflammatory bowel disease is not simply immune attack on the gut. It is a disorder of mucosal boundary-coherence involving genetics, immune pathways, microbiome, epithelium, diet, stress, infection history, and tissue repair. Clinical remission without mucosal healing may leave the tissue vulnerable. Mucosal healing is therefore a form of re-entry at the tissue level: the gut becomes able again to participate in nourishment without ongoing inflammatory capture.

The gut also demonstrates how local disease can become systemic. Microbial products, metabolites, inflammatory mediators, nutrient malabsorption, anaemia, immune activation, and gut-brain signalling can affect joints, skin, liver, mood, energy, and systemic inflammation. The gut niche is not confined to the gut.

Microbiome–immune interactions can influence mucosal inflammation, systemic immune tone, metabolism, barrier integrity, and distant tissue responses, making the gut a local and systemic immune niche (Belkaid & Hand, 2014; Hooper et al., 2012).

16.7 Vessel: Circulation, Immune Complexes, Endothelium, and Flow

Blood vessels are not passive pipes.

Endothelial regulation, complement activation, immune-complex handling, leukocyte trafficking, coagulation, shear stress, and vascular tone make the vessel wall an active immune-regulatory interface (Ricklin et al., 2010).

The endothelium senses shear stress, cytokines, immune complexes, complement, coagulation signals, hypoxia, metabolic stress, toxins, infection, and inflammatory mediators. It regulates permeability, leukocyte trafficking, clotting, vascular tone, tissue perfusion, and barrier function.

Vasculitis, atherosclerosis, thromboinflammation, antiphospholipid syndrome, immune-complex disease, endothelial dysfunction in infection, and microvascular complications all demonstrate the vessel as an immune niche. Vascular inflammation can damage organs not because every tissue is primarily diseased, but because perfusion, permeability, and clotting are altered.

The vessel is a boundary of flow.

Immune complexes may deposit in vessel walls. Complement may activate. Neutrophils may damage endothelium. Coagulation may amplify inflammation. Endothelial cells may become adhesive and pro-inflammatory. Tissue oxygenation may suffer. Microvascular dysfunction may contribute to fatigue, pain, cognitive symptoms, renal injury, skin lesions, lung disease, or post-infectious syndromes.

In phase-lock terms, vascular disease often involves recognition, complement, endothelial activation, coagulation, and clearance failure. The organism's attempt to handle immune material becomes damaging when that material lodges in flow structures. Circulation itself becomes a site of immune meaning.

16.8 Kidney: Filtration, Immune Deposition, and Silent Vulnerability

The kidney is a filtration, endocrine, metabolic, vascular, and immune-sensitive organ. It handles waste, fluid balance, electrolytes, blood pressure regulation, acid-base status, and hormonal signalling. Its glomeruli and tubules are exposed to circulating immune complexes, complement, toxins, metabolic stress, infections, and vascular injury.

Kidney immune disease can be clinically silent until significant damage has occurred.

Immune-complex deposition, complement activation, endothelial and glomerular injury, and impaired clearance can make filtration structures especially vulnerable to immune-mediated damage (Ricklin et al., 2010).

Lupus nephritis, immune-complex glomerulonephritis, vasculitis, IgA nephropathy, interstitial nephritis, complement-mediated disease, and infection-related kidney injury all show how immune processes become organized by filtration architecture.

The glomerulus is especially vulnerable to deposition and complement activation. Material circulating in blood can become trapped in filtration structures. What the organism fails to clear systemically may become kidney inflammation locally. This is a powerful example of how clearance failure becomes tissue disease.

The kidney also influences immune coherence systemically. Reduced kidney function impairs waste removal, alters metabolism, changes blood pressure, increases inflammatory burden, affects anaemia, and reduces physiological reserve. Kidney disease is therefore both a consequence and amplifier of allostatic load.

16.9 Lung Interstitium: Gas Exchange, Repair, and Fibrotic Constraint

The lung interstitium is a delicate tissue niche where gas exchange depends on thin barriers, elastic architecture, vascular flow, epithelial integrity, and precise matrix regulation.

Because gas exchange requires thin, compliant, highly organized tissue architecture, persistent epithelial injury, macrophage activation, fibroblast activity, matrix deposition, and failed repair can severely constrain lung function (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Inflammation and repair must be tightly controlled because excessive scarring impairs breathing.

Interstitial lung diseases demonstrate the danger of repair-overbuild. Repeated epithelial injury, immune activation, macrophage-fibroblast signalling, TGF-β pathways, environmental exposures, autoimmunity, viral injury, occupational particles, aging, and genetic susceptibility may converge. The tissue attempts to repair but becomes fibrotic. Stiffness increases. Gas exchange declines. Breath becomes effort.

The lung shows why repair is not automatically healing. Repair must restore function. If repair thickens the gas-exchange surface, it preserves tissue continuity at the cost of life participation. Fibrosis is therefore a tragic form of preservation: the organism closes and stabilizes, but breathing narrows.

Clinical care must therefore identify inflammatory, exposure, autoimmune, fibrotic, and mechanical components early. Once scarring is established, full reversal may be difficult. Prevention of repeated injury and interruption of fibrotic phase-locks become essential.

16.10 Bone Marrow: Haematopoietic Memory and Systemic Readiness

The bone marrow is not only a blood-cell factory.

Trained immunity research shows that prior inflammatory, infectious, or metabolic exposures can alter myeloid progenitors and haematopoietic programmes, shaping systemic inflammatory readiness over time (Netea et al., 2016).

It is an immune-memory and readiness organ. Haematopoietic stem and progenitor cells respond to infection, inflammation, stress, aging, metabolic signals, and trained immunity. Systemic perturbations can alter the production and bias of immune cells.

Chronic inflammation can shift haematopoiesis toward myeloid bias. Infection or inflammatory exposures can train progenitors. Aging can change marrow output. Metabolic disease can influence immune-cell production. Stress and neuroendocrine signals can affect mobilization. The organism's future immune responses are shaped before cells even enter tissues.

This means that phase-locking can occur upstream. A tissue flare may be supported by marrow-level readiness. An organism exposed to chronic inflammatory load may continuously produce cells predisposed to amplify inflammation. Systemic disease is therefore not only a sum of local tissue events. It includes altered production of immune possibility.

Bone marrow also matters in immunodeficiency, malignancy, anaemia of inflammation, mast-cell disorders, plasma-cell disease, and cytopenias. When the marrow is affected, the organism's capacity for defence, oxygen delivery, repair, and resilience is altered.

16.11 CNS and Neuroimmune Niches: Protection, Clearance, and Meaning

The central nervous system has a distinctive immune niche. It includes microglia, astrocytes, neurons, endothelial barriers, perivascular macrophages, meninges, cerebrospinal fluid, glymphatic clearance, autonomic regulation, and systemic immune communication. It is not immune-isolated, but immune-specialized.

Meningeal lymphatics, glymphatic clearance, microglial regulation, cerebrospinal-fluid dynamics, and sleep-associated metabolite clearance demonstrate that the CNS is immunologically specialized rather than simply immune-isolated (Aspelund et al., 2015; Louveau et al., 2015; Xie et al., 2013).

Neuroimmune disease, chronic pain, fatigue states, multiple sclerosis, autoimmune encephalitis, post-infectious syndromes, neuroinflammation, dysautonomia, and sickness behaviour all reveal how immune activity can alter cognition, mood, movement, sensation, sleep, and energy.

Microglia can become primed by infection, injury, aging, stress, or systemic inflammation. Sensory neurons communicate with immune cells. Mast cells can interact with nerves. Cytokines can alter brain function. Glymphatic clearance depends on sleep and vascular dynamics. Autonomic dysregulation can affect immune tone. The nervous system both shapes and is shaped by immune phase-states.

The CNS niche is especially important for re-entry. A patient may have resolved peripheral inflammation but remain limited by fatigue, brain fog, pain, dizziness, sleep disruption, or sensory sensitivity. These symptoms may reflect neuroimmune and autonomic locks that require their own phase-aware care.

The brain is also where biological meaning and lived meaning meet. Fear, uncertainty, dismissal, trauma, hope, trust, explanation, and relationship all affect neural regulation. This does not make immune disease psychological. It means that human immune coherence is inseparable from the organism-person's lived world.

16.12 Tissue Attractors and Disease Form

A disease-specific regulatory attractor emerges when a tissue niche repeatedly returns to a pathological pattern. The pattern may include immune cells, stromal cells, epithelial or endothelial states, matrix properties, nerves, vessels, microbes, metabolites, and mechanical forces.

Tissue attractors therefore link local architecture, resident cells, matrix, mechanics, metabolism, vascular flow, microbial relations, and immune memory into self-reinforcing disease patterns (Belkaid & Hand, 2014; Netea et al., 2016; Wynn et al., 2013).

Once established, the attractor becomes easier to re-enter.

This explains why diseases have recognizable forms. Rheumatoid arthritis tends to return to synovium. Psoriasis returns to skin. Asthma returns to airway. Inflammatory bowel disease returns to gut. Lupus may return to kidney, skin, joints, blood, or vessels. Spondyloarthritis returns to enthesis and axial structures. Fibrosis returns to injured interstitial architectures. Chronic sinusitis returns to mucosa and drainage spaces.

The disease is not merely in immune memory. It is in tissue memory.

Treatment must therefore address tissue attractors. Suppressing a cytokine may reduce inflammation, but the tissue may remain structurally, mechanically, or epigenetically prepared for relapse. Reversal may require mucosal healing, synovial quieting, barrier repair, fibrosis prevention, microbial stabilization, rehabilitation, clearance, and restoration of tissue function.

This is why functional recovery matters. A tissue is not healed simply because inflammation is lower. It is healed when it can participate in the organism's life again.

16.13 Transition to Phase-Lock Taxonomy

The tissue-niche view prepares the ground for a phase-lock taxonomy of immune-mediated disease. Such a taxonomy must be used humbly. These are observer distinctions, not boxes the organism inhabits. They are instruments for following the living process more faithfully.

The next section therefore identifies major phase-lock patterns: recognition and misrecognition locks, danger and inflammasome locks, nucleic-acid and interferon locks, viral and mobile-element boundary locks, barrier-type 2 locks, mechano-microbial enthesis/IL-17 locks, immune-complex vascular locks, trained-immunity locks, immunodeficiency-dysregulation locks, resolution and clearance-failure locks, repair-overbuild/fibrosis locks, and neuroimmune/allostatic pain-fatigue locks.

The goal is not to classify patients rigidly. The goal is to ask, with greater precision, what kind of unfinished immune work has taken form in this tissue, in this organism, in this niche.

17. Phase-Lock Taxonomy of Immune-Mediated Disease

The preceding sections have argued that immune-mediated disease cannot be understood only as pathway activation or diagnostic category. It must also be understood as a failure of biological transition: a phase of immune life that should have been temporary becomes persistent, recurrent, self-sustaining, or misdirected. The organism remains caught in unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration.

A phase-lock taxonomy can help clinicians and researchers follow these patterns more clearly. But it must be introduced with humility. These phase-locks are observer distinctions intended to help clinicians follow the living process more faithfully; they are not boxes the organism inhabits.

This preserves observer humility while allowing the taxonomy to function as a clinical instrument: useful for inquiry, sequencing, and pattern recognition, but never identical with the organism itself (Maturana, 1988; Maturana & Varela, 1980).

No patient is “a recognition lock,” “a type 2 lock,” “a fibrosis lock,” or “a neuroimmune lock.” These are not identities. They are clinical instruments. Their value lies in whether they help us ask better questions: What phase of immune life is dominant? What transition has failed? What tissue niche sustains the pattern? What exposures, memories, or constraints keep it active? What intervention might permit the next movement?

This taxonomy is therefore not meant to replace established diagnoses. Lupus, rheumatoid arthritis, asthma, psoriasis, inflammatory bowel disease, vasculitis, chronic rhinosinusitis, interstitial lung disease, immunodeficiency, long COVID, and other conditions remain clinically meaningful. The phase-lock taxonomy adds a second layer. It asks what regulatory lock is operating within or across these diagnoses.

The same patient may have more than one lock. A patient with lupus may have nucleic-acid/interferon activation, immune-complex vascular injury, impaired clearance, mitochondrial danger signalling, and fatigue-related neuroimmune load. A patient with asthma may have barrier-type 2 locking, viral-triggered interferon dysregulation, airway remodelling, and environmental exposure-locking. A patient with inflammatory bowel disease may have barrier disruption, microbial dysbiosis, trained immunity, impaired resolution, fibrosis, and allostatic burden. A patient with long COVID may have viral-memory signals, endothelial dysfunction, mitochondrial conservation, autonomic dysregulation, mast-cell activation, and re-entry failure.

The goal is not reduction to one lock. The goal is disciplined pattern recognition.

This protects phase-state reasoning from becoming another single-cause model; chronic immune disease often involves overlapping recognition, danger, clearance, repair, metabolic, tissue, exposure, and neuroimmune processes (Belkaid & Hand, 2014; McEwen, 1998; Medzhitov, 2008; Naviaux, 2014).

Figure 3. Phase-Lock Taxonomy: Dominant Locks, Drivers, Tissue Expressions, and Therapeutic Priorities

Maladaptive phase-locks arise when protective phases become excessive, incomplete, or unable to exit, preventing re-entry into the health cycle.

PHASE-LOCK (Locked Phase)	CORE DYNAMICS (Why It Locks)	TISSUE / CLINICAL EXAMPLES (Common Expressions)	KEY MECHANISMS & DRIVERS (Examples)	CLINICAL PATTERNS (Hallmarks)	THERAPEUTIC PRIORITY (Phase Restoration Focus)
1. Recognition Misrecognition (Identity Lock)	Persistent mis-evaluation of self, altered self, or harmless structures as threat.	Autoimmune diseases (e.g., SLE, RA, type 1 diabetes), graft rejection, vitiligo.	Breakdown of tolerance; altered antigen presentation; epitope spreading; molecular mimicry; aberrant B/T cell activation.	Autoreactivity, chronic flares, epitope spreading, relapsing inflammation.	Re-establish tolerance, reduce tissue damage, regulate recognition and co-stimulation.
2. Danger / Inflammasome (Pyroinflammatory Lock)	Persistent danger signalling and inflammasome activation without adequate resolution.	Gout, cryopyrin-associated periodic syndromes, CAPS, sterile inflammation states.	DAMP excess; ATP release; NLRP3 inflammasome activation; IL-1β/IL-18 amplification.	Recurrent flares, fever, pain, swelling, neutrophil recruitment, systemic features.	Reduce danger signalling, target inflammasome pathways, restore resolution.
3. Nucleic Acid / Interferon (Antiviral-Like Lock)	Persistent detection of nucleic acids or self-nucleic acid sensing with IFN dominance.	SLE, dermatomyositis, Aicardi-Goutières syndrome, some long viral states, chilblain lupus.	cGAS–STING activation; TLR3/7/9 signalling; endogenous retroelements; IFN-I signature.	IFN signature, fatigue, rashes, myalgias, cytopenias, photosensitivity, viral-like symptoms.	Reduce IFN drive, clear nucleic acid sources, restore immune quietude.
4. Barrier / Type 2 / Allergic (Barrier Alarm Lock)	Barriers remain activated; type 2 inflammation persists; repair and tolerance blocked.	Asthma, atopic dermatitis, chronic rhinosinusitis with polyps, eosinophilic esophagitis.	IL-4/IL-13 axis; epithelial alarmins (IL-33, TSLP); IgE; barrier microbiome dysbiosis.	Eosinophilia, mucus, itching, polyps, recurrent infections, food/environmental triggers.	Restore barrier ecology, reduce type 2 inflammation, promote tolerance.
5. Enthesis / IL-17 / Mechano-Inflammatory Lock	Mechanical stress–inflammation loop sustains IL-17/IL-23 axis and tissue activation.	Axial spondyloarthritis, psoriatic arthritis, reactive arthritis.	IL-23/IL-17 axis; entheseal stress; microdamage; barrier breach; innate lymphoid cell activation.	Enthesitis, axial pain, stiffness, psoriasis, dactylitis, uveitis.	Reduce mechano-inflammatory load, target IL-23/IL-17, restore barrier and tolerance.
6. Immune Complex / Vascular (Immune-Complex Lock)	Persistent immune-complex formation, deposition, and complement activation.	Lupus nephritis, vasculitides, cryoglobulinemia, serum sickness–like states.	Autoantibodies; complement activation; FC receptor signalling; impaired clearance.	Rashes, vasculitis, nephritis, low complement, circulating immune complexes.	Reduce immune complex formation, enhance clearance, control complement injury.
7. Trained Immunity / Epigenetic Reprogramming (Inflammatory Readiness Lock)	Innate cells remain epigenetically reprogrammed toward pro-inflammatory readiness.	Metabolic syndrome, atherosclerosis, NAFLD/NASH, chronic infections (e.g., TB), aging.	Metabolic reprogramming; H3K4me3/ H3K27ac; mTOR–HIF-1α–glycolysis; b-glucan, LPS exposures.	Low-grade inflammation, metabolic dysfunction, recurrent infections.	Reprogram metabolism, use epigenetic modulators, reduce persistent microbial stimuli.
8. Resolution / Clearance Failure (Debris-Persistence Lock)	Apoptotic and necrotic debris persist; resolution programs remain incomplete.	Long COVID, chronic rhinosinusitis, rheumatic disease, atherosclerosis.	Efferocytosis failure; Mertk/AXL defects; complement dysregulation; resolvins/ maresins deficiency.	Persistent inflammation, tissue swelling, fatigue, relapsing flares.	Enhance clearance, restore resolution mediators, complete the healing cycle.
9. Repair / Fibrosis / Matrix Overbuild (Repair-Overbuild Lock)	Repair programs become excessive; fibrosis replaces functional tissue.	Pulmonary fibrosis, liver fibrosis, systemic sclerosis, retroperitoneal fibrosis.	TGF-β/SMAD signalling; myofibroblast activation; ECM deposition; hypoxia.	Progressive stiffness, organ dysfunction, decreased reversibility.	Anti-fibrotic strategies, reduce TGF-β signalling, promote matrix remodelling.
10. Neuroimmune / Allostatic (Neuroimmune Lock)	Neuroimmune and allostatic systems remain in threat mode and cannot reset.	ME/CFS, fibromyalgia, POTS, long COVID, central sensitization syndromes.	Microglial priming; HPA axis dysregulation; vagal tone reduction; autonomic imbalance; cytokine–neurotransmitter interactions.	Fatigue, pain amplification, sleep disturbance, cognitive impairment, PEM.	Restore safety and rhythm, address autonomic tone, reduce neuroinflammation.

HOW PHASE-LOCKS ARISE

Perturbation → Adaptive Phase Shift → Failed Transition or Overactivation → Reinforcing Loops → Phase-Lock Established

UNIFYING PRINCIPLE

The goal is not simply to suppress symptoms. The goal is to restore the organism's capacity to complete the phases of protection, resolution, clearance, repair, and reintegration into life.

THERAPEUTIC ORIENTATION

Protect Health-Cycle Conditions · Shift / Modulate Excessive Activation · Resolve Inflammation · Clear Danger Material and Debris · Repair Function and Structure · Reset Memory and Stress Systems · Restore Re-entry Into Life

Caption. The phase-lock taxonomy is a clinical orientation map rather than a rigid disease classification. Each lock names a recurring pattern of unfinished immune work: recognition that remains damaging, danger sensing that cannot exit, antiviral-like alarm that persists, barrier repair that overreacts, mechanical and microbial cues that sustain IL-17–linked inflammation, immune-complex material that injures vascular or filtering structures, innate readiness that remains trained, clearance that fails, repair that overbuilds, or neuroimmune conservation that prevents re-entry. The taxonomy helps clinicians ask which regulatory process is dominant, which tissue niche gives it form, what mechanisms sustain it, and what therapeutic priority may help the organism move toward resolution, clearance, repair, and renewed participation.

17.1 Recognition and Misrecognition Lock

A recognition and misrecognition lock occurs when immune recognition becomes persistently directed toward targets that sustain tissue injury, inflammatory amplification, or loss of tolerance. In conventional language, this is the domain most closely associated with autoimmunity, but the phase-lock framing is slightly different. It does not simply ask whether the immune system has mistaken self for non-self. It asks why recognition has become biologically consequential, persistent, and damaging.

Autoantibodies, autoreactive T cells, epitope spreading, defective tolerance, impaired apoptotic-cell clearance, molecular mimicry, tissue injury, post-translational modification, and inflammatory co-stimulation may all contribute. But autoantibodies alone do not define the lock. Many people have detectable autoantibodies without active disease. Recognition becomes pathological when it enters a tissue, complement, Fc-receptor, inflammatory, or clearance context that sustains damage.

This reframes autoimmunity as more than mistaken self-recognition: pathology depends on tissue context, co-stimulation, complement activation, immune-complex handling, danger signalling, and clearance failure (Matzinger, 2002; Pradeu, 2012; Ricklin et al., 2010).

The organism is not simply “attacking itself” in a psychological or moral sense. That phrase can be misleading. More precisely, immune recognition has become attached to self-derived structures within a context of danger, failed clearance, tissue injury, or regulatory breakdown. What should have remained silent, tolerated, cleared quietly, or resolved becomes an ongoing focus of immune activity.

Systemic lupus erythematosus illustrates this pattern. Nuclear antigens, impaired clearance of apoptotic material, nucleic-acid sensing, autoantibodies, immune complexes, complement activation, interferon pathways, vascular injury, and tissue-specific susceptibility may interact. The disease is not reducible to one antibody or one pathway. It is a recognition-clearance-interferon-tissue lock.

Rheumatoid arthritis also involves recognition, but in a different tissue world. Autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies may precede clinical disease. Mucosal immune events, smoking, microbial factors, citrullination, genetic susceptibility, synovial inflammation, macrophage activation, fibroblast transformation, and cytokine loops may then converge. Recognition becomes clinically destructive when it participates in synovial phase-locking.

A recognition lock asks: What is being recognized? In what context did recognition become dangerous? Is there ongoing tissue injury generating antigen? Is clearance impaired? Are immune complexes forming? Has epitope spreading occurred? Is the tissue niche sustaining the response? Is the recognition marker pathogenic, predictive, incidental, or compensatory?

Treatment may require immune suppression, tolerance-oriented strategies, B-cell or plasma-cell targeting, complement modulation, cytokine inhibition, clearance support, tissue protection, and prevention of further injury. But the deeper goal is not merely to erase recognition. It is to prevent recognition from remaining coupled to destructive immune action.

17.2 Danger and Inflammasome Lock

A danger and inflammasome lock occurs when innate danger-sensing systems remain persistently activated. The organism continues to receive molecular evidence of cellular stress, crystals, microbial products, mitochondrial damage, lysosomal injury, ion flux, tissue disruption, or metabolic overload. Inflammasomes, especially when chronically engaged, can amplify IL-1β, IL-18, pyroptosis, neutrophil recruitment, and inflammatory cascades.

This lock is often associated with autoinflammatory conditions, gout, metabolic inflammation, recurrent fever syndromes, some sterile inflammatory disorders, and inflammatory amplification within broader autoimmune or degenerative disease. It is also relevant wherever damaged mitochondria, crystals, toxins, biofilms, senescent cells, or uncleared debris keep innate sensors activated.

The key feature is that the organism remains in danger detection and defence.

Inflammasome biology provides a molecular example of this lock, translating cellular stress, crystals, mitochondrial injury, lysosomal disruption, and microbial or sterile danger into IL-1-family inflammatory amplification (Schroder & Tschopp, 2010; West & Shadel, 2017).

Unlike recognition locks, which often involve antigen-specific memory and adaptive immune targeting, danger locks may be driven more by innate sensing and inflammatory thresholds. But the distinction is not absolute. Innate and adaptive immunity constantly interact. Autoimmune disease may contain inflammasome activation, and autoinflammatory disease may eventually shape adaptive responses.

A danger lock asks: What danger signal persists? Is there crystal deposition, mitochondrial injury, metabolic overload, chronic infection, dysbiosis, toxin exposure, tissue necrosis, lysosomal stress, or impaired debris clearance? Is the inflammasome protecting against a real

ongoing perturbation, or has it become self-sustaining? What would allow danger sensing to quiet?

Treatment may include targeted cytokine blockade, metabolic intervention, crystal reduction, infection control, exposure removal, mitochondrial protection, clearance support, and tissue repair. Suppression may be necessary, but the framework reminds us to look upstream. If the danger field remains active, inflammation may return when suppression is reduced.

17.3 Nucleic-Acid and Interferon Lock

A nucleic-acid and interferon lock occurs when the organism remains organized around antiviral-like alarm or misplaced nucleic-acid sensing. DNA or RNA in the wrong compartment, viral remnants, mitochondrial DNA, endogenous retroelement activation, defective nucleic-acid clearance, cellular stress, micronuclei, or immune complexes containing nucleic acids can activate pathways such as cGAS–STING, Toll-like receptors, RIG-I-like receptors, and interferon regulatory networks.

Interferon responses are essential for antiviral defence. They protect cells, activate immune responses, and restrict viral replication. But chronic interferon tone can become costly. It may contribute to fatigue, cytopenias, tissue dysfunction, autoimmunity, vascular inflammation, neuroimmune symptoms, and systemic inflammatory malaise.

In this lock, the organism behaves as if viral danger, genomic rupture, or nucleic-acid boundary violation remains present.

Cytosolic nucleic-acid sensing, cGAS–STING activation, mitochondrial DNA release, viral remnants, endogenous retroelements, and immune-complex delivery of nucleic acids can all contribute to persistent antiviral-like immune states (Chen et al., 2016; Chuong et al., 2016; West & Shadel, 2017).

Lupus is again a key example, but not the only one. Interferon signatures may appear in several autoimmune and inflammatory states. Post-viral syndromes may also involve persistent antiviral tone, though mechanisms vary and must be carefully demonstrated. Mitochondrial damage can contribute by releasing mitochondrial DNA. Senescent or stressed cells may activate nucleic-acid sensing. Endogenous retroelements may become insufficiently silenced.

The clinical question is not merely whether interferon is elevated. It is why the organism remains in an antiviral-like phase. Is there persistent infection? Viral reactivation? Mitochondrial injury? Defective apoptotic clearance? Endogenous retroelement activation? Immune-complex delivery of nucleic acids to immune cells? Tissue damage? Genetic predisposition? Drug effect?

Treatment may require disease-specific immune modulation, antiviral assessment where appropriate, control of upstream inflammation, clearance support, mitochondrial protection, or targeted pathway inhibition. But the phase-state aim is clear: help the organism exit persistent antiviral alarm when ongoing antiviral defence is no longer adaptive.

17.4 Viral and Mobile-Element Boundary Lock

A viral and mobile-element boundary lock overlaps with nucleic-acid/interferon locking but has a broader evolutionary and ecological meaning. It occurs when the organism remains perturbed by boundary-crossing information: persistent or latent viruses, viral remnants, endogenous retroelements, phage-mediated microbial shifts, extracellular vesicles carrying inflammatory material, mitochondrial DNA leakage, or impaired silencing of mobile genetic elements.

The immune system is not simply defending self against non-self. It is regulating information that crosses boundaries.

Virome biology, endogenous retroelements, phage-mediated microbial shifts, extracellular vesicles, and mitochondrial nucleic-acid signalling all illustrate that immune identity is historically porous and boundary-regulated rather than organized by sealed biological purity (Amari & Germain, 2021; Chuong et al., 2016; Virgin, 2014; Yáñez-Mó et al., 2015).

Viral and mobile-element locks occur when such information remains unsilenced, uncleared, mislocalized, reactivated, or repeatedly interpreted as danger.

This lock may be relevant in post-infectious illness, interferon-driven autoimmunity, chronic viral reactivation states, some neuroimmune syndromes, microbiome-related inflammation, and conditions involving persistent viral-like immune signatures. But the category must be used cautiously. Viral explanations can easily become speculative if not supported by evidence. The framework invites inquiry, not premature certainty.

A viral/mobile-element lock asks: Is there evidence of active infection, latent reactivation, residual antigen, viral RNA or DNA persistence, endogenous retroelement activation, phage-microbiome disturbance, or extracellular vesicle-mediated inflammatory signalling? Or is the viral language only metaphorical? What can be measured? What remains uncertain? What treatment consequences follow?

This lock is clinically useful when it prevents two errors: dismissing post-viral biology too quickly, and overclaiming viral persistence without evidence.

The category should therefore remain evidence-aware: viral or mobile-element language is useful only when it guides measurable inquiry and clinically responsible interpretation rather than speculative certainty (Pradeu, 2012; Virgin, 2014).

17.5 Barrier-Type 2 Lock

A barrier-type 2 lock occurs when epithelial surfaces and type 2 immune pathways remain organized around barrier alarm, expulsion, repair, and environmental sensitivity. The airway, skin, gut, and sinus mucosa are common sites. Epithelial alarmins, mast cells, eosinophils, basophils, IgE, type 2 innate lymphoid cells, Th2 cells, mucus production, itch, bronchial hyperresponsiveness, smooth-muscle reactivity, and tissue remodelling may participate.

Type 2 immunity is not inherently pathological. It supports defence against parasites, barrier repair, venom responses, mucus production, wound healing, and environmental boundary management. But when locked, it produces allergy, asthma, chronic rhinosinusitis, nasal polyposis, atopic dermatitis, food allergy, eosinophilic gastrointestinal disease, and related disorders.

The organism becomes too ready to close, expel, itch, swell, constrict, secrete, or remodel at the boundary.

Barrier-type 2 responses are shaped by epithelial surfaces, mast cells, eosinophils, IgE-related pathways, mucus, microbial ecology, allergens, pollutants, and tissue repair programmes (Belkaid & Hand, 2014; Galli et al., 2011; Hooper et al., 2012).

This lock is deeply extended into the niche. Air pollution, allergens, damp housing, mold, dust mites, occupational irritants, viral infections, climate change, food systems, skin products, antibiotics, microbial depletion, and epithelial injury can all shape type 2 readiness. Treating type 2 inflammation without addressing barrier conditions may produce incomplete control.

A barrier-type 2 lock asks: What boundary is alarmed? Is the epithelial barrier damaged? What exposures keep it activated? Are mucus, itch, bronchospasm, eosinophilia, IgE, mast cells, or alarmins dominant? Is there infection, dysbiosis, pollutant exposure, food trigger, or mechanical irritation? Has repair become remodelling?

Treatment may include allergen or exposure reduction, barrier repair, inhaled or topical anti-inflammatory therapy, antihistamines, leukotriene modulation, biologics targeting type 2 pathways, microbial and environmental care, and attention to sleep and stress where symptoms reinforce allostatic load. The aim is not simply to suppress allergy, but to restore a boundary that can remain open without alarm.

17.6 Mechano-Microbial Enthesis/IL-17 Lock

A mechano-microbial enthesis/IL-17 lock occurs when mechanical stress, barrier immune history, microbial signals, tissue repair, and IL-17-associated pathways converge in musculoskeletal boundary tissues such as entheses, joints, spine, skin, and gut-linked immune circuits.

This pattern is especially relevant to spondyloarthritis, psoriatic arthritis, enthesitis, axial inflammatory disease, and related conditions. The enthesis is a mechanical boundary. It is where force enters bone through tendon or ligament. Microdamage, repair, stromal activation, IL-17 biology, gut or skin immune signals, and genetic susceptibility may combine to produce chronic inflammation and new bone formation.

This lock shows that immune disease is not always driven by antigen recognition in the classic autoimmune sense.

Spondyloarthritis and enthesitis illustrate this principle: disease can arise from the convergence of mechanical load, entheseal stromal and immune cells, bone remodelling, microbial or barrier-linked immune history, and IL-23/IL-17-associated inflammatory pathways rather than from classic autoantibody-driven recognition alone (Schett et al., 2017; Sherlock et al., 2012).

It may arise from force, tissue stress, microbial ecology, and innate-like immune pathways interacting in a predisposed organism.

A mechano-microbial lock asks: What role do mechanical load, microdamage, gut or skin inflammation, microbial history, IL-17/IL-23 pathways, stromal cells, and repair programs play? Is the tissue being repeatedly asked to absorb force it cannot integrate? Is inflammation sustaining altered mechanics, and are altered mechanics sustaining inflammation?

Treatment may include immune modulation, physical therapy, load management, treatment of skin or gut disease, pain control, anti-inflammatory therapy, and rehabilitation sequenced to disease activity. Movement is necessary, but phase matters. Loading an actively inflamed enthesis may worsen injury; avoiding movement indefinitely may worsen stiffness and loss of function.

17.7 Immune-Complex Vascular Lock

An immune-complex vascular lock occurs when antigen-antibody complexes, complement activation, Fc-receptor engagement, endothelial activation, coagulation, and impaired clearance converge in vessels or filtration structures. The result may be vasculitis, glomerulonephritis, skin lesions, neuropathy, pulmonary haemorrhage, or systemic inflammatory injury.

This lock is about recognition material entering flow.

Complement activation, Fc-receptor engagement, immune-complex handling, endothelial activation, and tissue deposition make circulating recognition material clinically dangerous when clearance and vascular regulation fail (Ricklin et al., 2010).

The circulation distributes immune complexes. Vessels, glomeruli, skin, nerves, lungs, and other perfused tissues may become sites of deposition and inflammation. Complement activation may amplify injury. Neutrophils, macrophages, platelets, coagulation, and endothelial cells may participate. What began as immune recognition becomes vascular damage because clearance, deposition, and inflammatory amplification are misaligned.

A vascular immune-complex lock asks: What immune material is circulating? Is complement activated or consumed? Are vessels inflamed? Are kidneys filtering immune complexes? Is there infection, autoimmunity, cryoglobulin, drug reaction, malignancy, or persistent antigen source? Is clearance impaired?

Treatment may require urgent disease-specific intervention because vascular injury can threaten organs rapidly. Immunosuppression, complement modulation, antiviral or antimicrobial therapy, plasma exchange in select contexts, anticoagulation when appropriate, renal protection, and

removal of antigen source may be considered depending on disease. Here, phase-state reasoning must not delay decisive treatment.

17.8 Trained-Immunity Lock

A trained-immunity lock occurs when innate immune cells or progenitors become persistently primed toward exaggerated inflammatory responses. Prior infections, vaccines, microbial products, metabolic stress, oxidized lipids, chronic inflammation, environmental exposures, or tissue damage may alter chromatin accessibility, metabolism, and future responsiveness.

Trained immunity is adaptive when it improves host defence. It becomes pathological when it lowers the threshold for inflammation, amplifies responses to unrelated stimuli, or sustains chronic inflammatory readiness.

Trained immunity links prior exposure to durable innate immune readiness through epigenetic and metabolic reprogramming of innate immune cells and progenitors (Netea et al., 2016).

This lock may be relevant to atherosclerosis, metabolic inflammation, recurrent inflammatory flares, autoinflammatory conditions, chronic infection-associated inflammation, and possibly some post-infectious or environmentally triggered syndromes. It connects bone marrow, metabolism, innate immune memory, and systemic inflammatory tone.

A trained-immunity lock asks: Has the organism's innate immune system become too easily reactivated? Are monocytes, macrophages, natural killer cells, or progenitors primed? Are metabolic conditions such as insulin resistance, dyslipidaemia, obesity, or chronic infection sustaining the state? Are sleep disruption, stress, or pollutants reinforcing inflammatory readiness?

Treatment may require reducing inflammatory triggers, improving metabolic health, controlling infection, reducing exposure, addressing sleep and allostatic load, and using anti-inflammatory or pathway-specific therapy where indicated. The phase aim is to raise the threshold for inappropriate activation while preserving host defence.

17.9 Immunodeficiency-Dysregulation Lock

An immunodeficiency-dysregulation lock occurs when impaired defence and immune dysregulation coexist. This is an important category because immune deficiency is often imagined as simply "too little immunity." In reality, many immunodeficiency states involve recurrent infection, chronic inflammation, autoimmunity, lymphoproliferation, allergy, granulomas, malignancy risk, or tissue damage.

The immune system may be weak in one function and excessive in another.

This category protects against simplistic "too weak" versus "too strong" immune language by recognizing that impaired host defence, chronic infection, inflammation, autoimmunity, allergy, and tissue damage may coexist in dysregulated immune states (Medzhitov, 2008).

Failure to clear infection can sustain chronic immune activation. Recurrent infections can train or exhaust immune responses. Defective regulatory pathways can permit autoimmunity. Impaired antibody production can coexist with inflammatory complications. Barrier defects can produce both infection susceptibility and allergic inflammation. Genetic immune defects may produce paradoxical patterns of vulnerability and hyperactivation.

A dysregulation lock asks: Is the organism failing to defend, failing to regulate, or both? Are recurrent infections driving inflammation? Is immune deficiency masked by autoimmune or allergic features? Are immunosuppressive treatments worsening infection risk? Is replacement therapy, antimicrobial prophylaxis, vaccination strategy, or specialist immunology evaluation needed?

This category is clinically important because treating inflammation without recognizing immune deficiency can be dangerous. Conversely, treating infection repeatedly without recognizing underlying dysregulation may be incomplete. Phase-state reasoning must include both insufficiency and excess.

17.10 Resolution and Clearance-Failure Lock

A resolution and clearance-failure lock occurs when inflammation cannot actively terminate because the organism cannot clear what must be removed or cannot generate the signals required for resolution. Dead cells, damaged mitochondria, immune complexes, crystals, fibrin, biofilms, mucus, toxins, oxidized lipids, misfolded proteins, senescent cells, apoptotic bodies, and extracellular matrix fragments may remain in the tissue or circulation.

Resolution is impossible without clearance.

Resolution biology emphasizes that inflammation must actively terminate through pro-resolving mediators, efferocytosis, macrophage transition, debris removal, and tissue repair preparation rather than simply fading away (Fullerton & Gilroy, 2016; Ravichandran & Lorenz, 2007; Serhan, 2007; Serhan & Savill, 2005).

This lock is central to the entire framework. The organism cannot simply decide to stop inflaming if the field remains full of danger material. Macrophages, efferocytosis, autophagy, mitophagy, lymphatics, mucociliary clearance, glymphatic flow, renal excretion, hepatic metabolism, bile flow, and tissue drainage all participate in clearance. If these processes fail, inflammatory signals persist.

A clearance-failure lock may be relevant to chronic sinusitis, non-resolving pneumonia, atherosclerotic plaques, gout, lupus, chronic wounds, neurodegenerative inflammation, post-infectious states, biofilm-associated illness, fibrosis, and chronic inflammatory tissues. It may also contribute to fatigue and malaise when systemic inflammatory debris remains active.

Treatment may require addressing the source of debris, supporting drainage, treating infection or biofilm where proven, controlling inflammation enough for clearance to proceed, improving

sleep, restoring lymphatic movement, correcting metabolic or organ dysfunction, and avoiding interventions that increase debris faster than the organism can clear it.

The key clinical question is: What has not been removed?

17.11 Repair-Overbuild and Fibrosis Lock

A repair-overbuild lock occurs when tissue repair persists beyond functional restoration. Fibroblasts, myofibroblasts, macrophages, epithelial injury signals, endothelial dysfunction, TGF-β, matrix stiffness, hypoxia, mechanical stress, and chronic inflammation may sustain extracellular matrix deposition and architectural distortion.

Fibrosis is not simply scarring. It is repair captured by preservation.

Fibrosis reflects persistent repair and remodelling programmes involving macrophage-fibroblast crosstalk, extracellular matrix deposition, matrix stiffness, hypoxia, epithelial or endothelial injury, and chronic inflammatory signalling (Wynn et al., 2013; Wynn & Ramalingam, 2012).

The organism attempts to stabilize injury, but the stabilizing response narrows function. Lungs become stiff. Liver becomes cirrhotic. Skin thickens. Airways remodel. Joints stiffen. Intestine strictures. Heart muscle scars. Kidney interstitium fibroses.

This lock shows that healing is not complete just because tissue has been filled in. Healing must restore participation. A fibrotic tissue may be structurally preserved but functionally constrained.

A fibrosis lock asks: What injury keeps repair active? Is inflammation ongoing? Is epithelial or endothelial injury persistent? Are exposures continuing? Is matrix stiffness sustaining fibroblast activation? Is hypoxia present? Is mechanical load appropriate or excessive? Can antifibrotic therapy, exposure removal, inflammation control, rehabilitation, or early intervention prevent progression?

Treatment must be realistic. Established fibrosis may not fully reverse. But progression may be slowed, function supported, injury reduced, and remaining tissue protected. The framework emphasizes early recognition of repair lock before irreversible architecture develops.

17.12 Neuroimmune and Allostatic Pain-Fatigue Lock

A neuroimmune and allostatic pain-fatigue lock occurs when immune, neural, autonomic, mitochondrial, endocrine, and behavioural systems remain organized around threat, conservation, or protection. The patient may experience pain, fatigue, post-exertional worsening, brain fog, dizziness, sensory sensitivity, sleep disturbance, temperature dysregulation, palpitations, gastrointestinal sensitivity, and reduced tolerance for ordinary activity.

This lock may appear in post-infectious syndromes, long COVID, chronic fatigue syndromes, fibromyalgia, dysautonomia, chronic pain states, migraine-associated immune sensitivity, inflammatory disease after apparent control, and trauma-linked physiological dysregulation. It

must be approached carefully because these patients are often dismissed, psychologized, or overmedicalized.

The lock is neither “all in the mind” nor reducible to one pathway.

Neuroimmune and allostatic symptoms can involve interoception, sleep disruption, mitochondrial energy constraint, inflammatory tone, autonomic regulation, pain sensitization, threat physiology, and cumulative adaptive burden (Barrett et al., 2016; Besedovsky et al., 2012; McEwen, 1998; Picard et al., 2018).

It may involve microglial priming, autonomic dysregulation, mitochondrial conservation, mast-cell activation, cytokine signalling, vascular dysfunction, sleep disruption, pain sensitization, interoceptive threat, endocrine changes, deconditioning, and allostatic load. The organism remains biologically organized around protection.

A pain-fatigue lock asks: Is the organism unable to afford activity? Is post-exertional worsening present? Is sleep restorative? Are inflammation, infection, anaemia, endocrine disease, mitochondrial constraint, autonomic dysfunction, medication effects, or environmental exposures contributing? What degree of movement is currently restorative rather than destabilizing? What would make re-entry safe?

Treatment requires sequencing. Active pathology must be investigated and treated. Sleep and autonomic regulation may need support. Pacing may be essential when exertion triggers relapse. Pain requires validation and management. Rehabilitation must be individualized and phase-aware. Explanation must reduce fear without implying symptoms are imaginary. The goal is gradual restoration of trustworthy participation.

17.13 Mixed Locks and Dominant Locks

Most chronic immune diseases involve mixed locks. The art of phase-state medicine is to identify the dominant lock at a given time.

A patient with asthma may be dominated by type 2 barrier lock during one season, viral-interferon lock after infection, repair-overbuild after years of remodelling, and allostatic lock during sleep disruption. A patient with lupus may be dominated by interferon lock during systemic flare, immune-complex vascular lock during nephritis, pain-fatigue lock during chronic symptom persistence, and clearance lock throughout. A patient with inflammatory bowel disease may shift from barrier-microbial lock to destructive defence to fibrosis lock over time.

The dominant lock changes the therapeutic priority.

This is why phase-state reasoning is sequential and pragmatic: the same diagnosis may require suppression, clearance, repair, exposure reduction, antimicrobial attention, metabolic support, pacing, or rehabilitation at different moments (Antonovsky, 1987; McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005).

If destructive inflammation dominates, suppressing it is urgent. If exposure dominates, removal matters. If clearance dominates, drainage and debris handling matter. If fibrosis dominates, anti-remodelling strategies matter. If re-entry failure dominates, rehabilitation and energy management matter. If immune deficiency dominates, antimicrobial and immune-support strategies matter.

This is why the same diagnosis can require different treatment logics at different times. Phase-state reasoning does not replace protocols, but it helps explain why protocol alone may not be enough.

17.14 Summary of the Phase-Lock Taxonomy

The phase-lock taxonomy can be summarized as follows:

Phase-lock pattern	Core unfinished process	Typical biological logic
Recognition/misrecognition lock	Tolerance, recognition, and clearance fail to resolve	Autoantibodies, autoreactive cells, immune recognition in danger context
Danger/inflammasome lock	Danger detection remains active	DAMPs, PAMPs, crystals, inflammasomes, IL-1 family activation
Nucleic-acid/interferon lock	Antiviral-like alarm cannot exit	Cytosolic nucleic acids, interferon tone, cGAS–STING, TLRs
Viral/mobile-element boundary lock	Boundary-crossing information remains unresolved	Viral persistence/reactivation, endogenous retroelements, vesicles, virome shifts
Barrier-type 2 lock	Barrier alarm and repair remain overactive	Epithelial alarmins, IgE, mast cells, eosinophils, mucus, type 2 inflammation
Mechano-microbial enthesis/IL-17 lock	Force, barrier history, and repair remain coupled to inflammation	Enthesis stress, IL-17 pathways, stromal activation, gut-skin-joint links
Immune-complex vascular lock	Recognition material damages flow structures	Immune complexes, complement, Fc receptors, endothelial injury
Trained-immunity lock	Innate readiness remains primed	Epigenetic and metabolic innate immune memory
Immunodeficiency-dysregulation lock	Defence and regulation fail together	Recurrent infection, autoimmunity, allergy, inflammation, immune defects
Resolution/clearance-failure lock	Inflammation cannot complete because debris remains	Efferocytosis, autophagy, mitophagy, lymphatics, drainage, waste removal

Phase-lock pattern	Core unfinished process	Typical biological logic
Repair-overbuild/fibrosis lock	Repair does not exit	TGF-β, fibroblasts, matrix stiffness, hypoxia, scarring
Neuroimmune/allostatic pain-fatigue lock	Protection and conservation prevent re-entry	Pain sensitization, fatigue, dysautonomia, mitochondrial conservation, allostatic load

This table should be treated as a map, not a cage.

As with all observer-made distinctions, the taxonomy is useful only if it improves clinical perception, supports evidence-aware care, and remains revisable in relation to the organism's actual course (Maturana, 1988; Maturana & Varela, 1980).

It helps orient clinical inquiry, but the organism remains more complex than any table can capture.

17.15 Transition to Clearance, Drainage, and Waste Removal

Among these locks, resolution and clearance failure deserve special attention because they cut across nearly every immune-mediated disease. Defence cannot end if danger material remains. Repair cannot complete if debris persists. Re-entry cannot occur if the organism is still burdened by inflammatory waste, damaged mitochondria, immune complexes, biofilms, toxins, crystals, mucus, fibrin, or uncleared matrix.

The next section therefore turns to clearance, drainage, and waste removal as central conditions of immune resolution.

In life-coherent systems immunology, healing is not only the control of inflammation. It is the completion of removal, repair, and return.

The transition follows directly from resolution biology and clearance biology: inflammation cannot complete its work until danger material, apoptotic cells, damaged organelles, immune complexes, and tissue debris are cleared or safely contained (Ravichandran & Lorenz, 2007; Serhan, 2007; Serhan & Savill, 2005; Youle & Narendra, 2011).

18. Clearance, Drainage, and Waste Removal

Resolution is impossible without clearance.

Resolution biology supports this principle: inflammation is actively terminated through coordinated mediator switching, efferocytosis, debris removal, macrophage reprogramming, and tissue restoration (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

Resolution biology emphasizes that inflammation must actively terminate through pro-resolving mediators, efferocytosis, macrophage transition, debris removal, and tissue repair preparation rather than simply fading away (Fullerton & Gilroy, 2016; Ravichandran & Lorenz, 2007; Serhan, 2007; Serhan & Savill, 2005).

This principle is simple, but it changes the entire grammar of immune disease. Inflammation cannot resolve merely because the organism wishes to stop inflaming. It can resolve only when the work that inflammation was mobilized to perform has been completed or sufficiently contained. Dead cells must be removed. Damaged mitochondria must be cleared. Immune complexes must be handled. Crystals, toxins, biofilms, fibrin, oxidized lipids, misfolded proteins, mucus, matrix fragments, microbial remnants, and necrotic debris must be processed, drained, metabolized, or sequestered safely. Without clearance, the tissue continues to present danger.

Clearance is therefore not a secondary housekeeping process. It is central to immune coherence.

Clearance links molecular, cellular, tissue, lymphatic, mucosal, renal, hepatic, and sleep-associated processes into a single requirement: the organism must remove or safely contain what would otherwise continue to signal danger (Ravichandran & Lorenz, 2007; Xie et al., 2013; Youle & Narendra, 2011).

Modern immunology often emphasizes activation: how the immune system detects danger, mobilizes inflammation, recruits cells, produces cytokines, generates antibodies, and attacks pathogens. These processes are essential. But equally important is the less dramatic work of removal. Healing requires not only the capacity to respond, but the capacity to finish. The organism must be able to remove what has become harmful, metabolize what can be metabolized, drain what must be drained, recycle what can be recycled, and restore a field in which ordinary life can resume.

If danger detection begins the healing cycle, clearance allows the healing cycle to complete.

18.1 Efferocytosis: Quiet Removal of the Dead

Efferocytosis is the process by which phagocytic cells, especially macrophages, engulf and clear apoptotic cells. It is one of the most important mechanisms of resolution. When cells die in an orderly way, they must be removed quietly. If apoptotic cells are not cleared efficiently, they can progress to secondary necrosis, release intracellular contents, expose nuclear material, activate innate immune sensors, and become sources of autoantigen and inflammation.

In health, efferocytosis is anti-inflammatory and pro-resolving. It removes cellular corpses while helping macrophages shift toward repair and resolution programs. It prevents the immune system from interpreting normal cell turnover as danger. It maintains tissue trust.

When efferocytosis fails, death becomes inflammatory.

Defective efferocytosis can allow apoptotic cells to progress toward secondary necrosis, expose intracellular antigens, activate innate sensors, and contribute to autoimmunity, chronic inflammation, and failed resolution (Ravichandran & Lorenz, 2007; Serhan & Savill, 2005).

This is especially relevant in diseases where apoptotic debris, nuclear antigens, autoantibodies, complement, and interferon pathways interact. If dying cells are not cleared quietly, their contents may become immunologically visible. Nuclear material may be bound by autoantibodies, form immune complexes, activate complement, stimulate Toll-like receptors, and amplify interferon responses. The organism then becomes inflamed not simply because cells die, but because death is not properly resolved.

Efferocytosis also matters in atherosclerosis, chronic wounds, lung inflammation, neuroinflammation, and tissue injury. In plaques, defective clearance of dead cells can contribute to necrotic core formation and persistent inflammation. In chronic wounds, failure to clear dead cells delays repair. In inflamed lungs, impaired clearance can sustain injury. In the nervous system, inadequate removal of cellular debris may prolong microglial activation.

The clinical principle is clear: inflammation cannot end if the dead remain immunologically active.

18.2 Autophagy and Mitophagy: Intracellular Clearance

Clearance is not only extracellular. Cells must also clear their own damaged components. Autophagy allows cells to degrade and recycle damaged proteins, organelles, pathogens, and cellular debris. Mitophagy, the selective removal of damaged mitochondria, is especially important in immune coherence because damaged mitochondria can release mitochondrial DNA, reactive oxygen species, cardiolipin, ATP, and other danger-associated molecular patterns.

If autophagy and mitophagy are impaired, the cell's interior becomes a source of ongoing alarm. Damaged mitochondria continue to signal danger. Misfolded proteins accumulate. Inflammasomes may be activated. Cytosolic nucleic-acid sensors may be stimulated. Cellular stress increases. The cell cannot fully return to ordinary function because its internal field remains contaminated by damaged material.

This is clearance failure at the subcellular level.

Autophagy and mitophagy maintain intracellular coherence by removing damaged proteins, organelles, pathogens, and mitochondria that might otherwise generate mitochondrial DNA, reactive oxygen species, inflammasome activation, or other danger signals (West & Shadel, 2017; Youle & Narendra, 2011).

Autophagy and mitophagy therefore connect metabolism, inflammation, aging, infection, neurodegeneration, autoimmunity, and fatigue. A cell that cannot clean itself cannot easily resolve. It may remain inflamed, senescent, energy-constrained, or prone to death. The organism then experiences this cellular failure as tissue dysfunction, inflammatory persistence, poor repair, or low resilience.

This is why clearance must be understood across scales: molecular, organellar, cellular, tissue, lymphatic, vascular, renal, hepatic, mucosal, and glymphatic.

18.3 Lymphatics: Drainage as Immune Infrastructure

The lymphatic system is essential for immune coherence. It drains interstitial fluid, transports immune cells, clears proteins and debris, returns fluid to circulation, supports antigen presentation, and maintains tissue homeostasis. Lymphatics are not merely passive drains. They are active immune-regulatory structures.

When lymphatic flow is impaired, tissues become congested. Fluid accumulates. Proteins, inflammatory mediators, immune cells, debris, and microbial products may persist locally. Swelling increases tissue pressure. Oxygen delivery may worsen. Cell migration changes. Inflammation can become harder to resolve.

Drainage is therefore part of resolution.

The lymphatic system is integral to immunity because it coordinates interstitial-fluid drainage, antigen transport, immune-cell trafficking, tissue-fluid homeostasis, and local immune regulation; impaired lymphatic function can therefore contribute to inflammatory persistence and failed clearance (Randolph et al., 2017).

This is visible in conditions such as chronic edema, lymphedema, chronic wounds, inflammatory arthritis, sinus disease, pulmonary inflammation, and post-surgical states. But lymphatic function is also relevant more broadly. Movement, breathing, skeletal muscle contraction, tissue mechanics, hydration, inflammation, fibrosis, and vascular function all influence lymphatic flow. An organism that cannot move, breathe well, or sleep may have impaired clearance capacity. A fibrotic tissue may obstruct drainage. A chronically inflamed tissue may overload lymphatic pathways.

In phase-state medicine, lymphatic impairment can become a clearance lock. The organism may have mobilized inflammatory work but cannot adequately remove the products of that work. The tissue remains swollen, painful, congested, or inflamed. The immune system continues to respond to material that should have been drained.

This helps explain why movement can support healing when appropriately timed. Gentle movement, breathing, and muscle activity can improve circulation and lymphatic flow. But in an actively inflamed or low-reserve organism, excessive movement may worsen symptoms. Again, the issue is phase: drainage support must match tissue capacity.

18.4 Mucociliary Clearance: The Airway's Removal System

The airway has its own clearance system: mucus production and ciliary movement. Mucus traps particles, microbes, allergens, pollutants, and debris. Cilia move mucus out of the airway. Cough helps expel what cannot be cleared quietly. This system is not incidental to immunity. It is one of the airway's primary immune functions.

When mucociliary clearance is impaired, the airway becomes a retention space. Mucus thickens or stagnates. Microbes persist. Biofilms may form. Inflammatory cells accumulate. Epithelial cells remain alarmed. Cough, congestion, wheeze, infection, and tissue remodelling may follow. The airway becomes locked in a cycle of mucus, inflammation, microbial persistence, and impaired drainage.

Chronic rhinosinusitis, bronchiectasis, asthma, chronic bronchitis, cystic fibrosis, post-viral airway disease, and recurrent respiratory infections all illustrate the importance of mucociliary clearance. In these conditions, inflammation is not only a matter of immune activation. It is often a matter of retained material.

The clinical question becomes: what cannot get out?

Mucociliary clearance is a primary innate defence mechanism of the airway, relying on coordinated mucus, airway-surface liquid, and ciliary movement to remove inhaled particles, pathogens, allergens, and pollutants; when this system fails, retained material can sustain infection, inflammation, obstruction, and airway remodelling (Bustamante-Marin & Ostrowski, 2017; Knowles & Boucher, 2002).

This shifts treatment logic. Anti-inflammatory therapy may be necessary, but so may hydration, airway clearance techniques, treatment of infection, reduction of irritant exposure, restoration of epithelial function, management of reflux where relevant, surgery for obstructed sinus drainage in selected cases, or biologic therapy when type 2 inflammation drives mucus and polyps. A blocked drainage pathway can keep inflammation alive.

18.5 Glymphatic Clearance: Sleep, Brain, and Waste Removal

The brain has specialized clearance systems, including glymphatic flow, perivascular drainage, cerebrospinal fluid dynamics, meningeal lymphatics, microglial clearance, and vascular exchange. These systems help remove metabolic waste, proteins, inflammatory mediators, and cellular debris. Sleep appears especially important for brain clearance and restoration.

This makes sleep an immune-clearance process, not merely rest.

Sleep-associated glymphatic clearance and meningeal lymphatic drainage support the idea that sleep participates in metabolite removal, neuroimmune regulation, and restoration of brain tissue environments (Aspelund et al., 2015; Louveau et al., 2015; Xie et al., 2013).

When sleep is disrupted, brain clearance may be impaired, inflammatory tone may rise, pain sensitivity may increase, cognition may worsen, mood may destabilize, and autonomic regulation may become strained. In chronic immune disease, post-infectious syndromes, chronic pain, neuroinflammatory states, and fatigue disorders, poor sleep can therefore become both consequence and cause of phase-locking.

A patient who cannot sleep cannot clear, repair, regulate, and re-enter normally.

This is not to imply that sleep alone cures immune disease. But it does mean that sleep protection is not optional "lifestyle advice." It is part of the biological infrastructure of resolution. Without restorative sleep, the organism's clearance and regulatory capacity are reduced.

18.6 Immune Complexes and Filtration Burden

Immune complexes are formed when antibodies bind antigens. In many contexts, they are cleared without harm. But when immune complexes persist, circulate, deposit, or activate complement, they can drive inflammation in vessels, kidneys, skin, joints, nerves, lungs, and other tissues.

This is a clearance problem as well as a recognition problem.

Immune complexes become pathogenic when recognition material persists, circulates, deposits, activates complement, engages Fc receptors, and overwhelms clearance or filtration systems (Ricklin et al., 2010).

The organism has identified material for immune handling, but that material is not being removed quietly. Instead, it deposits in vulnerable structures and becomes inflammatory. The kidney is especially vulnerable because filtration exposes glomeruli to circulating immune material. Vessels are vulnerable because immune complexes interact with flow, endothelium, complement, and leukocytes.

In systemic lupus erythematosus, cryoglobulinemia, immune-complex vasculitis, infection-related glomerulonephritis, serum sickness-like reactions, and some chronic infections, immune-complex handling becomes central. The inflammatory problem is not simply that antibodies exist. It is that antigen-antibody material becomes persistent, deposited, and damaging.

This reinforces the importance of asking: what is the organism failing to clear, and where is that failure becoming tissue injury?

18.7 Crystals, Particles, and Persistent Material

Some inflammatory triggers persist because they are physically difficult to remove. Uric acid crystals, calcium pyrophosphate crystals, cholesterol crystals, silica, asbestos, particulate pollution, microplastics, and other particles can activate innate immune pathways and remain in tissues. Their persistence can sustain inflammasome activation, macrophage frustration, fibrosis, or chronic inflammation.

Crystals and particles show that the immune system responds not only to biological signals, but to material burden.

Crystalline and particulate material can sustain innate immune activation, inflammasome signalling, macrophage frustration, and chronic tissue injury when it cannot be dissolved, cleared, or safely contained (Schroder & Tschopp, 2010; Wynn & Ramalingam, 2012).

Gout is a clear example. Uric acid crystals can activate intense innate inflammation. Acute flares may resolve, but if crystal burden remains, the organism remains vulnerable to recurrence. Anti-inflammatory treatment can control flares, but long-term reduction of urate burden addresses the material source. The phase-lock is not only inflammatory; it is crystalline.

Similar principles apply to occupational or environmental particles in lung disease. The organism may attempt to clear or contain particles, but if they persist, macrophages, fibroblasts, inflammasomes, and repair pathways may remain active. Containment can become fibrosis.

This matters because some immune locks cannot be resolved by signalling modulation alone. Persistent material may need to be reduced, dissolved, avoided, surgically removed, drained, metabolized, or isolated. The organism cannot resolve what remains physically present as danger.

18.8 Biofilms and Chronic Microbial Niches

Biofilms are structured microbial communities embedded in protective matrices. They can form on mucosal surfaces, wounds, sinuses, airways, teeth, implants, catheters, and other tissues or devices. Biofilms are difficult to eradicate because microbes within them may be metabolically altered, shielded from immune attack, resistant to antibiotics, and embedded in matrix.

Biofilms create a containment-clearance problem.

Biofilms are structured microbial communities embedded in self-produced matrices that can protect microbes from host defences and antimicrobial treatment, allowing persistent or recurrent infection and chronic inflammatory stimulation when clearance remains incomplete (Flemming & Wingender, 2010; Hall-Stoodley et al., 2004).

The organism may recognize microbial presence and mount inflammation, but clearance remains incomplete. The immune system continues to engage a microbial niche that it cannot fully remove. The result may be chronic low-grade inflammation, recurrent flares, tissue damage, mucus, drainage, pain, or fibrosis.

Chronic sinusitis, chronic wounds, bronchiectasis, dental disease, prosthetic infections, and some gastrointestinal or urogenital conditions may involve biofilm dynamics. The clinical challenge is that inflammation may persist because microbial communities remain protected within a local niche.

A biofilm lock asks: is there a persistent microbial structure that prevents clearance? Is drainage impaired? Is tissue architecture altered? Are antibiotics reaching the site? Is surgery, debridement, device removal, or local therapy required? Is inflammation helping containment but failing removal?

Again, the issue is not inflammation alone. It is incomplete clearance of a living niche.

18.9 Toxins, Biotoxins, and Exposure Burden

The organism must also handle chemical and biological toxins. These may include pollutants, heavy metals, pesticides, solvents, smoke, combustion products, endocrine disruptors, mycotoxins, algal toxins, bacterial toxins, and internally generated metabolic toxins. The evidence base varies greatly across exposures and conditions, so claims must be cautious and specific. But the general principle is sound: toxic burden can become an immune perturbation when exposure exceeds detoxification, repair, and clearance capacity.

Exposome and environmental-health frameworks support this cautious framing by treating disease risk as shaped by cumulative chemical, biological, physical, occupational, and social exposures across time (Rappaport & Smith, 2010; Wild, 2005; World Health Organization, 2021).

Toxins may damage barriers, alter mitochondria, induce oxidative stress, disrupt endocrine signalling, impair immune regulation, change microbiota, activate epithelial alarm, or injure tissues. If exposure continues, the organism may remain in danger detection or repair mode. If detoxification and excretion are impaired, internal burden may persist. If tissue damage occurs, secondary debris may sustain inflammation.

A life-coherent framework must avoid two opposite errors. The first is dismissing environmental exposure too quickly, as if modern immune disease occurs in a vacuum. The second is over-attributing complex illness to poorly verified toxin narratives. The appropriate stance is disciplined inquiry: what exposure is plausible, measurable, temporally related, biologically credible, and clinically actionable?

Exposure-linked clearance failure becomes clinically meaningful when reducing exposure or supporting standard detoxification pathways improves the organism’s ability to resolve and re-enter the health cycle.

18.10 Uncleared Matrix and Fibrotic Debris

Extracellular matrix is not inert scaffolding. It is biologically active. During injury and repair, matrix is deposited, degraded, crosslinked, stiffened, and remodelled. Matrix fragments can signal through immune receptors. Stiff matrix can activate mechanosensors. Excess matrix can obstruct diffusion, drainage, and movement. Damaged or uncleared matrix can sustain inflammation and fibrosis.

This means that repair itself generates material that must be reorganized.

If matrix remodelling is incomplete, the tissue may remain stiff, scarred, hypoxic, poorly perfused, and mechanically abnormal. Fibroblasts may continue to receive signals that repair is needed. Macrophages may remain activated. Lymphatic flow may be impaired. Nerves may become sensitized. The matrix becomes memory.

Extracellular matrix is biologically active: stiffness, fragments, crosslinking, hypoxia, fibroblast activation, and macrophage-fibroblast signalling can sustain inflammation, repair, and fibrosis (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Fibrosis is therefore both repair-overbuild and clearance failure. The organism has built tissue that it cannot adequately remodel back toward function.

This is important in lung fibrosis, liver cirrhosis, kidney fibrosis, systemic sclerosis, intestinal strictures, airway remodelling, cardiac scarring, adhesions, and chronic musculoskeletal injury. Treatment must address inflammation where present, but also matrix biology, mechanics, perfusion, oxygenation, and function.

18.11 Clearance and the Health Cycle

Clearance is not limited to disease states. It belongs to the health cycle. Daily life generates waste: metabolic byproducts, damaged proteins, used hormones, dead cells, microbial products, inhaled particles, food residues, oxidized molecules, and cellular debris. The organism must clear continuously through liver, kidney, gut, lungs, lymphatics, skin, autophagy, mitophagy, immune phagocytosis, mucociliary function, and sleep-associated brain clearance.

The health cycle therefore includes waste removal as a central phase.

Daily clearance depends on sleep, autophagy, mitophagy, immune phagocytosis, mucosal clearance, lymphatic flow, renal and hepatic function, gut motility, and ordinary movement, linking immune coherence to health-cycle rhythms (Besedovsky et al., 2012; Ravichandran & Lorenz, 2007; Xie et al., 2013; Youle & Narendra, 2011).

Wakeful activity generates metabolic demand. Food intake generates nutrients and byproducts. Movement mobilizes fluids. Sleep supports repair and clearance. Gut motility removes waste. Kidneys filter. Liver metabolizes. Lymph drains. Macrophages remove dead cells. Cells recycle their own damaged parts. This is ordinary immune coherence.

When the health cycle is disrupted, clearance suffers. Sleep loss impairs restoration. Sedentary immobility impairs lymphatic and metabolic flow. Dehydration, poor diet, constipation, kidney disease, liver disease, lung disease, chronic stress, and inflammation can all reduce clearance capacity. The organism then carries more unresolved material into the next day. Over time, this can reduce immune resilience.

This is why clearance connects clinical immunology with ordinary life conditions. Rest, sleep, movement, hydration, nutrition, organ function, breathing, and environmental quality are not decorative. They support the organism’s ability to finish biological work.

18.12 Clinical Translation: Asking What Has Not Been Removed

The clearance perspective gives clinicians a practical question: what has not been removed?

This question translates resolution biology into clinical reasoning: persistent inflammation may reflect not only ongoing activation, but also retained debris, infection, crystals, immune complexes, damaged mitochondria, mucus, toxins, matrix fragments, or biofilm-associated material (Ravichandran & Lorenz, 2007; Serhan, 2007; Youle & Narendra, 2011).

In a patient with persistent inflammation, what debris, trigger, infection, crystal, immune complex, damaged mitochondria, mucus, toxin, matrix, or biofilm remains? In a patient with recurrent sinus disease, is drainage impaired? In a patient with lupus nephritis, are immune complexes and complement driving filtration injury? In a patient with gout, does crystal burden persist? In a patient with chronic fatigue after infection, is there unresolved inflammatory, mitochondrial, autonomic, vascular, or sleep-related clearance impairment? In a patient with fibrosis, what repair material has become locked into tissue architecture?

This question does not replace diagnosis. It enriches it.

Clearance-oriented care may include disease-specific anti-inflammatory treatment, antimicrobial therapy when indicated, drainage, debridement, surgery, airway clearance, lymphatic support, sleep restoration, movement rehabilitation, hydration, renal and hepatic support, metabolic treatment, exposure reduction, antifibrotic therapy, and careful monitoring. The appropriate intervention depends entirely on the disease and phase-state.

The goal is not vague “detoxification.” It is specific removal of specific burdens through physiologically valid pathways.

18.13 Clearance Without Overload

A final caution is necessary. Supporting clearance does not mean pushing the organism aggressively. A low-reserve organism can be overwhelmed by excessive mobilization, exertion, dietary restriction, heat therapies, supplements, or detoxification protocols. If material is mobilized faster than it can be processed, symptoms may worsen. If inflammation is active, aggressive interventions can amplify injury. If the patient is fragile, even helpful changes may need slow sequencing.

Life-coherent clearance is non-forcing. It asks what the organism can safely process now.

This caution follows allostatic reasoning: interventions that mobilize burden faster than the organism can metabolize, drain, or repair may become additional perturbations in a low-reserve system (McEwen, 1998; Sterling & Eyer, 1988).

This is especially important in chronic illness communities where detoxification language is common but often imprecise. The framework should distinguish evidence-based clearance

mechanisms from speculative or unsafe protocols. The clinician's task is to protect the patient from both neglect and overintervention.

18.14 Transition to Exposure, Epidemiology, and Modern Niche Incoherence

Clearance brings the tissue-niche section to completion. The organism cannot resolve what remains present as danger, debris, burden, or blocked flow. But many modern exposures repeatedly introduce new burdens before prior healing has completed. Pollutants, damp buildings, toxins, sleep disruption, psychosocial adversity, climate stress, dysbiosis, ultra-processed food systems, infection pressure, and ecological instability can all become anti-salugenic when they prevent healing-cycle completion.

The exposome argument follows: recurrent environmental, microbial, social, chemical, nutritional, and climatic perturbations can prevent healing-cycle completion when they repeatedly introduce new burden before prior biological work has resolved (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Rappaport & Smith, 2010; Wild, 2005).

The next part therefore turns outward to exposure, epidemiology, and modern niche incoherence.

If Part V asked how immune disease takes form in tissues, Part VI asks why so many organisms may now be living in niches that repeatedly interrupt immune coherence.

Part VI. Exposure, Epidemiology, and Modern Niche Incoherence

19. Anti-Salugenic Exposure-Locks and the Exposome

The organism does not heal in abstraction. It heals in a niche. Every healing cycle unfolds within air, water, food, sleep, housing, work, microbial ecology, climate, social relation, medical care, chemical exposure, and meaning. These conditions may support the organism's return to the health cycle, or they may repeatedly interrupt it. When exposures recur faster than the organism can resolve, clear, repair, and reintegrate, the niche itself becomes anti-salugenic.

Anti-salugenic exposures are recurrent niche perturbations that prevent healing-cycle completion and block re-entry into the health cycle.

This framing extends exposome and environmental-health thinking by treating exposure not as a single external cause, but as the cumulative biological, chemical, physical, microbial, social, nutritional, occupational, climatic, and built-environment field through which organisms adapt, recover, or become locked (Rappaport & Smith, 2010; Wild, 2005).

This does not mean that every exposure causes disease, nor that chronic illness can be reduced to environmental triggers. The exposome is not a single-cause theory. It is the total field of biological, chemical, physical, microbial, social, nutritional, psychological, occupational, climatic, and built-environment conditions through which the organism is repeatedly perturbed. Some exposures are acute and overwhelming. Others are low-grade, cumulative, interacting, or meaningful only in vulnerable organisms. Some are measurable. Some are difficult to quantify. Some are well established. Others remain contested.

A life-coherent systems immunology treats exposure carefully: neither dismissed as irrelevant nor inflated into an all-purpose explanation.

The key question is not simply, "What exposure caused this disease?" The deeper question is: "What recurrent perturbations prevent this organism from completing healing and re-entering ordinary life?"

This shifts exposure assessment from linear causation toward organism–niche pattern recognition, where susceptibility, timing, dose, mixtures, tissue state, allostatic load, and recovery capacity all shape biological meaning (McEwen, 1998; Rappaport & Smith, 2010; Wild, 2005).

19.1 The Exposome as Organism–Niche History

The exposome is the lived history of the organism's encounters.

The exposome concept was introduced to complement the genome by emphasizing the totality of environmental exposures across the life course, including chemical, dietary, microbial, occupational, social, and other measurable or partially measurable conditions (Wild, 2005).

It includes pollutants, allergens, infections, diet, microbiome changes, medications, toxins, noise, heat, light, work rhythms, sleep disruption, psychosocial stress, trauma, housing quality, occupational exposures, climate instability, social adversity, and access to care. These exposures do not act on a blank organism. They are interpreted through genetics, development, immune history, tissue state, mitochondrial capacity, allostatic load, microbial ecology, and current phase-state.

The same exposure may therefore mean different things in different organisms.

Mold exposure in one person may cause no obvious illness; in another it may worsen asthma, sinusitis, allergy, migraine, fatigue, or inflammatory symptoms. Air pollution may trigger airway inflammation in one organism, vascular stress in another, and little apparent change in a third. A viral infection may resolve cleanly in one patient and precipitate prolonged dysregulation in another. Sleep disruption may be tolerated briefly by a high-reserve organism but destabilize one already under inflammatory load.

This variation should not be used to dismiss exposure. Nor should it be used to assume universal causality. It means that exposure must be understood relationally: exposure plus organism plus history plus tissue plus timing plus dose plus recovery capacity.

Exposure becomes anti-salugenic when it repeatedly reopens danger, adds burden, impairs clearance, disrupts repair, lowers resilience, or prevents re-entry into the health cycle.

This interpretation connects exposure science with allostasis and resolution biology: recurrent perturbation can become pathogenic when it exceeds regulatory margins, prevents recovery, or repeatedly interrupts the transition from defence to repair and re-entry (McEwen, 1998; Serhan & Savill, 2005; Sterling & Eyer, 1988).

19.2 Pollutants and Chemical Perturbation

Pollutants can perturb immune coherence through barrier injury, oxidative stress, mitochondrial dysfunction, endocrine disruption, epithelial alarm, altered microbiota, neuroinflammation, vascular dysfunction, and impaired repair.

Air-pollution and environmental-health frameworks support this multi-pathway view, showing that pollutants can act through airway injury, oxidative stress, vascular effects, inflammatory signalling, developmental vulnerability, and cumulative exposure burden (World Health Organization, 2021; Rappaport & Smith, 2010).

Air pollution, smoke, solvents, pesticides, heavy metals, combustion products, industrial chemicals, and indoor pollutants may all contribute depending on dose, duration, mixture, susceptibility, and context.

The immune system encounters pollutants first at boundaries: airway, skin, gut, vasculature, placenta. These boundaries must decide whether to tolerate, detoxify, expel, inflame, or repair. Recurrent pollutant exposure can keep epithelial cells in alarm, macrophages activated, mitochondria stressed, and tissues inflamed. In the airway, this may worsen asthma, rhinitis, chronic bronchitis, or post-viral reactivity. In vessels, it may contribute to endothelial dysfunction and inflammatory burden. In the developing organism, exposures may alter immune education and future regulatory margins.

The key phase-state question is whether pollutant exposure is acting as a repeated danger signal.

In phase-state terms, the relevant issue is not only the presence of a pollutant, but whether repeated exposure keeps boundary tissues, mitochondria, macrophages, epithelium, endothelium, or repair systems in a persistent defensive state (McEwen, 1998; Naviaux, 2014; West & Shadel, 2017).

If the organism is constantly asked to defend against inhaled, ingested, or absorbed chemical perturbations, the healing cycle may not complete. The body remains in low-grade repair and clearance work.

19.3 Dampness, Mold, and Contested Exposure Illness

Damp buildings and mold exposure require careful handling because they occupy a difficult clinical space.

Major reviews and public-health guidance recognize dampness and mould as important respiratory and allergic health concerns, while also distinguishing these established associations from broader systemic claims that remain more contested (Bush et al., 2006; Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

There is strong recognition that dampness and mold can worsen asthma, allergic rhinitis, respiratory symptoms, and some hypersensitivity conditions. Broader claims about systemic chronic inflammatory illness, neurocognitive symptoms, and multi-system disease are more contested and vary in evidentiary strength.

A life-coherent framework should therefore neither dismiss patient experience nor overstate certainty.

This evidence-strength posture allows clinically important damp-building illness to be investigated seriously while avoiding premature certainty about mechanisms, diagnostic labels, or treatment protocols where consensus remains incomplete (Bush et al., 2006; Institute of Medicine, 2004).

Dampness can alter indoor air quality, microbial fragments, volatile compounds, allergens, dust mites, and inflammatory exposures. For susceptible individuals, this may act as a recurrent boundary perturbation, especially in airway and sinus tissues. If the patient’s barrier systems,

immune history, mitochondrial reserve, sleep, or allostatic load are already strained, the same exposure may become more destabilizing.

The clinical question is not, “Does mold explain everything?” It is, “Is this environment repeatedly perturbing this organism, and is removal or remediation necessary for healing to complete?”

For some patients, environmental correction may be central. For others, it may be irrelevant. For many, it may be one contributor among infection, allergy, asthma, sinus disease, sleep disruption, psychosocial stress, and other exposures. Disciplined humility is essential.

The appropriate clinical stance is calibrated inquiry: assess exposure plausibility, respiratory and allergic disease, hypersensitivity conditions, differential diagnoses, remediation needs, and patient vulnerability without converting dampness or mould into a universal explanation (Bush et al., 2006; World Health Organization Regional Office for Europe, 2009).

19.4 Dysbiosis, Biofilms, and Microbial Niche Disruption

Microbial exposures are not only infections.

Microbiome research shows that microbial communities participate in immune education, barrier regulation, metabolic signalling, pathogen resistance, and inflammatory calibration rather than functioning only as sources of infection (Belkaid & Hand, 2014; Hooper et al., 2012).

The organism lives with microbial ecologies in the gut, airway, skin, oral cavity, genitourinary tract, and built environment. These ecologies educate immunity, support barrier function, produce metabolites, compete with pathogens, and shape inflammation. Antibiotics, diet, infection, stress, inflammation, pollutants, sanitation patterns, birth history, and environmental microbial diversity can all alter these ecologies.

Dysbiosis is not always a cause; it may be consequence, amplifier, or marker. But when microbial communities become unstable, inflammatory, invasive, or metabolically altered, they can sustain immune phase-locking. Barrier tissues may remain alarmed. Mucus may change. Biofilms may resist clearance. Microbial metabolites may shift immune tone. Inflammation may create a niche favouring microbes that further sustain inflammation.

The organism and microbiome can become co-locked.

This co-locking can occur when inflammation reshapes microbial ecology, altered microbial products sustain inflammation, biofilms resist clearance, and barrier tissues remain in alarm, creating reciprocal host–microbe reinforcement (Belkaid & Hand, 2014; Flemming & Wingender, 2010; Hall-Stoodley et al., 2004; Hooper et al., 2012).

This is especially relevant in inflammatory bowel disease, chronic rhinosinusitis, bronchiectasis, recurrent urinary symptoms, chronic wounds, atopic disease, and metabolic-inflammatory states. Treatment may require antimicrobial therapy in specific cases, but indiscriminate antimicrobial

use can worsen dysbiosis. Microbial care must therefore be precise, evidence-aware, and phase-sensitive.

The aim is not microbial purity. It is microbial coherence.

This distinction supports microbial stewardship: the goal is not indiscriminate antimicrobial suppression, but context-sensitive restoration of microbial relations that support barrier integrity, immune tolerance, and recovery (Belkaid & Hand, 2014; Hooper et al., 2012).

19.5 Sleep Disruption as Anti-Salugenic Exposure

Sleep disruption is one of the most common and underestimated anti-salugenic exposures.

Sleep is deeply linked to immune function, inflammatory regulation, metabolic repair, glymphatic clearance, and organismal recovery, making chronic sleep disruption a biological exposure rather than merely a behavioural habit (Besedovsky et al., 2012; Xie et al., 2013).

It impairs immune regulation, glymphatic clearance, metabolic flexibility, pain thresholds, mood regulation, endocrine rhythm, mitochondrial recovery, and inflammatory resolution. It also reduces the organism's ability to tolerate other exposures.

Sleep loss is not merely a lifestyle issue. It is a repeated interruption of the health cycle.

Recurrent sleep loss can increase allostatic load, alter neuroendocrine regulation, impair metabolic flexibility, increase pain sensitivity, and reduce the organism's capacity to complete inflammatory and repair cycles (Besedovsky et al., 2012; McEwen, 1998).

A patient who sleeps poorly cannot fully clear, repair, regulate, or re-enter. In chronic immune disease, sleep disruption may be caused by pain, itch, cough, dyspnoea, reflux, medications, anxiety, dysautonomia, night sweats, work schedules, caregiving responsibilities, noise, light, or unsafe housing. Whatever the cause, the result is reduced regulatory margin.

Sleep disruption can therefore turn manageable perturbations into destabilizing events. An allergen exposure after restorative sleep may be tolerated; the same exposure after repeated sleep loss may provoke flare. A viral illness may resolve in a rested organism but precipitate prolonged dysregulation in one already depleted. A rehabilitation effort may build capacity in one phase-state and trigger collapse in another.

Sleep protection is therefore not optional advice. It is immune infrastructure.

Treating sleep as immune infrastructure reframes rest as part of clearance, regulation, repair, and re-entry into the health cycle (Besedovsky et al., 2012; Xie et al., 2013).

19.6 Psychosocial Adversity and Threat Physiology

Psychosocial adversity becomes immunologically relevant when it is embodied as chronic threat, vigilance, helplessness, isolation, shame, uncertainty, or loss of control.

Allostatic and interoceptive models support this claim: chronic threat is biologically embodied through neuroendocrine, autonomic, inflammatory, behavioural, metabolic, and perceptual pathways (Barrett et al., 2016; McEwen, 1998; McEwen & Stellar, 1993).

This includes poverty, discrimination, violence, caregiving burden, unsafe relationships, work stress, social isolation, medical dismissal, trauma, and chronic uncertainty.

The point is not that immune disease is "psychological." The point is that human organisms regulate immunity through nervous, endocrine, metabolic, behavioural, and relational pathways. Chronic threat can alter sleep, cortisol rhythms, sympathetic tone, inflammatory signalling, pain sensitivity, eating patterns, microbiome, mitochondrial function, and treatment engagement. It can also reduce access to resources needed for healing.

Adversity becomes anti-salugenic when the organism cannot exit threat physiology.

When threat physiology persists, the organism may remain biased toward preservation, sympathetic readiness, inflammatory tone, poor sleep, pain amplification, and reduced capacity for repair or re-entry (Barrett et al., 2016; McEwen, 1998; Picard et al., 2018).

A patient who is unsafe, unbelieved, exhausted, impoverished, or socially isolated is being asked to heal while still defending. The immune system may remain biased toward preservation. The organism cannot afford openness, tolerance, repair, or re-entry because the niche continues to signal danger.

This insight must never be used to blame patients.

Social-determinants frameworks reinforce this ethical point: disease risk and recovery capacity are shaped by material conditions, structural inequities, care access, housing, work, safety, and dignity, not by individual willpower alone (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

It should direct attention to care, safety, dignity, social protection, and trustworthy clinical relationship as biological conditions of healing.

19.7 Climate Stress and Ecological Instability

Climate change and ecological instability are increasingly relevant to immune coherence.

Climate-health assessments identify heat, air pollution, wildfire smoke, vector shifts, flooding, food and water insecurity, displacement, and disaster-related stress as pathways through which climate change affects human health (Intergovernmental Panel on Climate Change, 2023).

Heat, storms, displacement, wildfire smoke, air pollution, changing pollen seasons, food insecurity, water contamination, vector-borne infections, flooding, damp housing, and psychosocial stress all alter organism–niche relations. These are not distant environmental issues. They enter bodies through breath, food, infection, temperature, sleep, stress, housing, and exposure.

Climate stress can worsen asthma, allergies, cardiovascular inflammation, kidney stress, heat illness, infectious risks, mental health, and chronic disease instability. It can also disrupt care systems and generalized resistance resources. A patient whose medication supply, housing, food, water, or clinic access is interrupted by climate events may experience biological consequences.

In life-coherent terms, climate instability reduces population-level salugenic capacity.

Climate instability increases perturbation load while weakening resistance resources such as housing, food security, water safety, healthcare access, sleep, and social stability (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023).

It increases perturbations while weakening recovery conditions.

This makes immune disease a civilizational signal. Bodies are registering ecological disorder.

This framing connects immune epidemiology to planetary health: bodies register ecological disruption through inflammatory, allergic, infectious, metabolic, respiratory, cardiovascular, and psychological pathways (Intergovernmental Panel on Climate Change, 2023; World Health Organization, 2021).

19.8 Food-System Disruption and Metabolic-Immune Load

Food is not only fuel. It is substrate, signal, culture, microbiome input, immune education, pleasure, and social relation.

Nutrition, microbiome ecology, metabolism, and immune regulation are closely coupled, with diet shaping microbial metabolites, barrier function, adipose inflammation, metabolic flexibility, and inflammatory tone (Belkaid & Hand, 2014; Buck et al., 2017; Hooper et al., 2012; O'Neill et al., 2016).

Food-system disruption can become anti-salugenic through ultra-processed diets, low fibre intake, micronutrient deficiency, food insecurity, pesticide exposure, additives, metabolic overload, obesity, insulin resistance, and loss of traditional food ecologies.

Metabolic-immune load arises when the organism is repeatedly exposed to nutrient patterns that impair metabolic flexibility, promote adipose inflammation, alter gut microbiota, increase oxidative stress, and reduce repair capacity. This does not mean that patients are to blame for diet-related disease. Food choices are shaped by affordability, availability, culture, marketing, work schedules, stress, policy, and food systems.

The immune system reads the food system through the gut, liver, adipose tissue, mitochondria, microbiome, and metabolism.

Food systems are linked to immunometabolism: nutrient quality, energy excess, fibre depletion, metabolic overload, microbiome disruption, and adipose inflammation can alter immune-state selection and recovery capacity (Buck et al., 2017; Hooper et al., 2012; O'Neill et al., 2016; Pearce & Pearce, 2013).

A life-coherent approach asks not simply what an individual should eat, but what food conditions allow organisms to maintain immune coherence. Nutrition advice matters, but food justice matters also.

Social-determinants research supports this wider frame by showing that food access, affordability, marketing, poverty, work schedules, and policy shape diet-related disease risk and recovery capacity (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

19.9 Exposure-Locks and Healing-Cycle Failure

Exposure-locks occur when recurrent perturbations repeatedly return the organism to earlier phases of the healing cycle.

This is the exposure-level expression of phase-locking: recurrent perturbations can repeatedly reactivate danger detection, defence, repair, conservation, or allostatic load before resolution and re-entry have completed (McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005).

A patient begins to resolve, but the exposure reactivates danger. A tissue begins to repair, but the environment re-injures it. The organism begins to re-enter activity, but sleep deprivation, pollution, infection, overwork, or stress pushes it back into conservation.

The result is a revolving door between partial healing and renewed defence.

Such cycling is consistent with an allostatic model in which repeated adaptation without sufficient recovery narrows regulatory margins and increases vulnerability to relapse (McEwen, 1998; McEwen & Stellar, 1993).

This is why chronic disease often feels cyclical. Patients may improve during rest, vacation, environmental change, medication, or reduced exposure, then relapse when returned to the same conditions. The relapse is not mysterious if the niche continues to recreate the perturbation field.

Exposure-locks may involve:

pollutants that sustain barrier alarm;
damp housing that worsens airway and sinus inflammation;
biofilms that prevent microbial clearance;
sleep disruption that blocks repair;
psychosocial threat that maintains allostatic load;

food insecurity or metabolic overload that reduces immune resilience;
climate stress that increases inflammatory burden;
occupational exposures that repeatedly injure tissues;
social conditions that make recovery unaffordable.

The clinical task is to identify which exposures are active, plausible, modifiable, and relevant to the patient's phase-state.

This keeps exposure assessment clinically disciplined: the relevant exposure is the one that is temporally plausible, biologically credible, modifiable, and connected to the patient's tissue niche, symptoms, and recovery trajectory (Rappaport & Smith, 2010; Wild, 2005).

19.10 Avoiding Exposure Reductionism

Exposure thinking must be disciplined because it can easily become reductionist.

Exposome thinking should widen inquiry without becoming a totalizing explanation; chronic immune disease still requires differential diagnosis, disease-specific mechanisms, and evidence-aware clinical judgment (Rappaport & Smith, 2010; Wild, 2005).

Not every chronic immune disease is exposure-driven. Genetics, developmental history, infections, autoimmunity, immune deficiency, malignancy, endocrine disease, structural damage, and stochastic events all matter. Some exposures are suspected but not proven. Some tests are unreliable. Some treatments marketed for exposure illness are unsafe or unsupported.

Life-coherent systems immunology must therefore avoid turning the exposome into a new dogma.

The correct use of exposure science is calibrated openness: exposure may matter, but claims must be proportionate to evidence, measurement quality, biological plausibility, safety, and treatment relevance (Bush et al., 2006; Institute of Medicine, 2004; Rappaport & Smith, 2010).

The correct stance is one of calibrated inquiry. Ask about exposures. Take the history seriously. Look for temporal patterns. Assess biological plausibility. Use validated tests where available. Distinguish established associations from hypotheses. Avoid blaming the patient. Avoid expensive speculative protocols. Intervene where the exposure is credible, harmful, and modifiable.

The goal is to remove anti-salugenic burden where doing so is likely to help the organism complete healing.

19.11 Clinical Translation

Clinically, exposure assessment belongs alongside diagnosis, biomarkers, tissue evaluation, and treatment planning.

This makes exposure assessment part of ordinary clinical reasoning rather than a replacement for it: environmental, occupational, microbial, dietary, sleep, stress, and social histories can help explain why healing does or does not complete (Commission on Social Determinants of Health, 2008; Rappaport & Smith, 2010; Wild, 2005).

The clinician may ask:

What environments worsen or relieve symptoms?
Are there airway, skin, gut, neurological, or systemic patterns linked to place, season, work, food, sleep, infection, or stress?
Does the patient live or work in damp, polluted, chemically intense, noisy, unsafe, or sleep-disrupting conditions?
Are there recurrent infections, biofilm-prone sites, or microbial exposures?
Are food access, nutrition, and metabolic health supporting or undermining recovery?
Is the patient repeatedly forced beyond energy capacity?
Are social or economic conditions making treatment unmanageable?

These questions do not replace laboratory testing or disease-specific care. They help identify why healing may not complete.

The aim is to identify modifiable anti-salugenic constraints while preserving diagnostic rigor, validated testing, and disease-specific treatment (Medzhitov, 2008; Rappaport & Smith, 2010).

Treatment may include exposure reduction, housing intervention, occupational protection, air filtration, smoking cessation, allergen control, mold remediation where indicated, sleep protection, antimicrobial or drainage strategies when appropriate, nutrition support, metabolic care, pacing, social support, and public health referral. Some of these interventions are clinical. Others require family, workplace, community, policy, or environmental action.

Exposure-locks are often not solvable by the patient alone.

Many exposure-locks require household, workplace, community, public-health, regulatory, or policy-level action because the relevant niche conditions exceed individual control (Commission on Social Determinants of Health, 2008; Marmot et al., 2008; World Health Organization, 2021).

19.12 Transition to CIRS as a Contested Case Study

The next section considers chronic inflammatory response syndrome, or CIRS, as a contested and clinically provocative case study of exposure-linked phase-locking.

The discussion should be anchored in evidence-strength framing: damp-building and mould-related respiratory disease are recognized concerns, while broader CIRS claims require more cautious interpretation (Bush et al., 2006; Institute of Medicine, 2004; Shoemaker & House, 2006; World Health Organization Regional Office for Europe, 2009).

It should not be treated as the foundation of this paper, nor as proof of a universal model. Rather, it can serve as an example of the difficulties that arise when patients report multi-system illness linked to environmental exposure, while the evidence base, diagnostic criteria, mechanisms, and clinical consensus remain debated.

CIRS is useful precisely because it forces humility.

Its usefulness here is methodological rather than foundational: it tests whether the framework can hold patient suffering, exposure plausibility, contested mechanisms, differential diagnosis, and caution about overclaiming at the same time (Bush et al., 2006; Shoemaker & House, 2006).

It asks medicine to hold several truths together: exposures can matter; patients can suffer profoundly; mechanisms may be incompletely understood; diagnostic frameworks may outrun consensus; dismissal can harm; overclaiming can also harm; and careful evidence-strength framing is essential.

The broader argument does not depend on CIRS. But CIRS can illuminate the challenge of thinking about anti-salugenic exposure-locks without either denial or dogmatism.

20. CIRS as a Contested Case Study of Exposure-Linked Phase-Locking

Chronic inflammatory response syndrome, or CIRS, occupies a contested position in contemporary medicine.

For that reason, CIRS should be discussed through a graded-evidence lens, distinguishing established damp-building respiratory risks from broader syndrome-level claims, proposed biomarkers, and treatment protocols that remain less settled (Bush et al., 2006; Institute of Medicine, 2004; Shoemaker & House, 2006; World Health Organization Regional Office for Europe, 2009).

It has been proposed as a multi-system illness arising in susceptible individuals after exposure to water-damaged buildings, mold, biotoxins, dinoflagellates, cyanobacteria, tick-borne infections, or other inflammatory environmental triggers. Its advocates describe a persistent innate immune and inflammatory state in which the organism cannot adequately clear or resolve the exposure-linked perturbation. Its critics question the strength of the evidence, the specificity of diagnostic criteria, the reliability of some proposed biomarkers, the breadth of causal claims, and the degree to which CIRS overlaps with better-established conditions such as asthma, allergic rhinitis, chronic sinusitis, hypersensitivity pneumonitis, mast-cell activation syndromes, post-infectious syndromes, chronic fatigue syndromes, depression, anxiety, dysautonomia, autoimmune disease, or medically unexplained symptoms.

For this paper, CIRS should not be used as the foundation of the argument. The broader framework of life-coherent systems immunology does not depend on accepting CIRS as a settled disease entity. Rather, CIRS is best used here as a contested and clinically provocative case study of anti-salugenic exposure-locking.

This placement protects the larger framework from depending on CIRS as a settled disease entity, while still allowing exposure-linked illness to be considered seriously and responsibly (Bush et al., 2006; Shoemaker & House, 2006).

Its value lies in the questions it forces medicine to ask. Can an environmental exposure repeatedly perturb susceptible organisms in ways that prevent healing-cycle completion? Can innate immune activation, impaired clearance, mitochondrial stress, neuroimmune symptoms, sleep disruption, autonomic changes, and tissue-specific vulnerability become linked in a persistent phase-state? Can patients suffer profoundly in ways that current diagnostic categories do not adequately capture? Can dismissal harm patients? Can overconfident explanatory systems also harm them? How should clinicians respond when patient experience, mechanistic plausibility, and formal consensus do not yet fully align?

These questions are not unique to CIRS. They arise throughout modern chronic illness medicine. CIRS is simply a concentrated example.

20.1 Why CIRS Is Clinically Provocative

CIRS is clinically provocative because it brings together several themes that are central to this paper: exposure, susceptibility, impaired clearance, inflammatory persistence, multi-system symptoms, contested evidence, and the difficulty of caring for patients whose suffering exceeds established categories.

These themes overlap with broader debates about damp-building illness, indoor air quality, respiratory disease, environmental exposure, chronic symptom syndromes, and evidence standards in complex illness (Bush et al., 2006; Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

Patients identified with CIRS commonly report combinations of fatigue, cognitive dysfunction, headaches, sinus symptoms, respiratory symptoms, muscle aches, joint pain, light sensitivity, sleep disturbance, mood changes, dysautonomia-like symptoms, gastrointestinal symptoms, temperature dysregulation, and heightened environmental sensitivity. These symptom patterns are not specific to CIRS. They overlap with many other conditions. That overlap is precisely why careful differential diagnosis is essential.

But the symptom pattern also raises a legitimate organism-centered question: could some patients be trapped in a persistent danger-response state after recurrent environmental perturbation?

From a phase-lock perspective, the proposed CIRS pattern can be interpreted cautiously as an exposure-linked failure of re-entry. The organism encounters an environmental field that may include mold fragments, microbial volatile compounds, allergens, dampness-associated microbes, particulate matter, inflammatory debris, or other irritants. In susceptible individuals, the exposure may worsen barrier alarm, sinus and airway inflammation, mast-cell reactivity, sleep disruption, mitochondrial stress, neuroimmune activation, or allostatic load. If the exposure persists, the organism may repeatedly re-enter danger detection and defence before resolution and clearance can complete.

This does not prove CIRS as a specific syndrome. It shows why the question is biologically plausible enough to deserve careful, non-dismissive investigation.

This formulation preserves disciplined openness: biological plausibility and patient suffering warrant inquiry, but they do not by themselves establish diagnostic specificity or universal causality (Bush et al., 2006; Shoemaker & House, 2006).

20.2 Evidence-Strength Framing

The most important requirement in discussing CIRS is evidence-strength framing.

Evidence-strength framing is essential because claims about dampness, mould, indoor air, respiratory disease, systemic inflammation, biomarkers, and treatment protocols do not all have

the same evidentiary status (Bush et al., 2006; Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

Not all claims have the same evidentiary status.

Some claims are well established at a general level. Damp and mold-affected buildings can worsen asthma, allergic rhinitis, respiratory symptoms, hypersensitivity pneumonitis in susceptible individuals, and some other airway or allergic conditions. Poor indoor air quality can contribute to respiratory burden. Environmental exposures can matter clinically. Patients with chronic symptoms linked to buildings deserve serious assessment.

Dampness and mould are consistently associated with respiratory symptoms and asthma-related outcomes, while recognized hypersensitivity conditions require careful clinical evaluation and exposure assessment (Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

Other claims are plausible but less settled. Damp-building exposure may contribute to broader inflammatory, neuroimmune, or fatigue-dominant syndromes in some susceptible individuals, but mechanisms, diagnostic criteria, biomarkers, and treatment protocols remain debated. The relationship may differ across patients. Some may have allergic disease, asthma, chronic sinusitis, recurrent infection, migraine, sleep disruption, anxiety secondary to illness, occupational exposure, autoimmune disease, or other identifiable conditions. Others may have complex multi-system illness in which exposure is one contributor among several.

Still other claims require caution. Strong assertions that CIRS is a single unified cause of complex chronic illness, that specific commercial biomarker panels definitively diagnose it, that most multi-system symptoms in exposed patients are caused by biotoxin retention, or that standardized proprietary protocols are universally effective should not be accepted without careful evidence.

This caution is appropriate because broad causal claims, unvalidated biomarker panels, and standardized proprietary protocols may outrun current consensus and risk both medical and financial harm (Bush et al., 2006).

A life-coherent approach can therefore state the matter plainly: exposure-linked illness is real in some forms; damp-building and mold-related respiratory disease are clinically important; broader CIRS claims remain contested; patients should be evaluated seriously; and treatment should be grounded in evidence, safety, differential diagnosis, and careful follow-up.

20.3 CIRS as an Exposure-Lock Pattern

Used cautiously, CIRS can be interpreted as a possible exposure-lock pattern.

The word “possible” is important: this interpretation is a conceptual application of phase-lock reasoning, not proof that CIRS is a unified or settled disease entity (Bush et al., 2006; Shoemaker & House, 2006).

In such a pattern, the key clinical issue is not simply the presence of an exposure, but the organism's inability to complete the healing cycle while the exposure continues or while its effects remain biologically active.

The proposed lock may include several interacting elements:

First, there may be ongoing boundary perturbation. Damp indoor environments can affect airway and sinus mucosa, skin, eyes, and respiratory immune tone. Allergens, irritants, microbial fragments, and particulate matter can repeatedly stimulate barrier tissues.

Second, there may be inflammatory amplification. Epithelial alarm, innate immune activation, mast-cell reactivity, cytokine signalling, oxidative stress, or inflammasome-related pathways may contribute in susceptible patients.

Third, there may be impaired clearance. Sinus obstruction, mucus retention, biofilms, lymphatic congestion, poor sleep, reduced movement, or ongoing exposure may prevent removal of inflammatory material.

Fourth, there may be mitochondrial and metabolic strain. Chronic inflammation, poor sleep, toxin exposure, stress, and reduced activity can all reduce energy reserve and make re-entry into activity more difficult.

Fifth, there may be neuroimmune and autonomic involvement. Fatigue, brain fog, dizziness, sensory sensitivity, headaches, sleep disruption, and pain may reflect organism-wide threat physiology, but these symptoms remain non-specific and require careful evaluation.

Sixth, there may be allostatic load. The patient may live in uncertainty, experience repeated dismissal, lose work capacity, struggle financially, sleep poorly, and become socially isolated. These factors do not make the illness imaginary; they add physiological burden to an already strained organism.

Together, these elements form a plausible phase-lock pattern: recurrent exposure and organismal susceptibility combine with incomplete clearance, persistent danger signalling, and failed re-entry.

This synthesis should be read as a hypothesis-generating clinical pattern that requires differential diagnosis, exposure assessment, validated clinical evaluation, and careful treatment sequencing (Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

20.4 What CIRS Should Not Become

CIRS should not become a totalizing explanation.

The moment any contested syndrome becomes a totalizing explanation, it risks obscuring differential diagnosis, established disease entities, psychiatric and neurological comorbidities, environmental assessment, and patient-specific mechanisms (Bush et al., 2006).

The moment it is used to explain too much, it risks becoming another form of epistemic closure.

It should not replace differential diagnosis. Patients with fatigue, cognitive symptoms, respiratory symptoms, pain, and environmental sensitivity still need evaluation for anaemia, thyroid disease, sleep apnea, asthma, allergic rhinitis, chronic sinusitis, autoimmune disease, inflammatory disease, infection, medication effects, depression, anxiety disorders, dysautonomia, metabolic disease, renal or hepatic dysfunction, malignancy where appropriate, and other clinically relevant conditions.

This safeguard is clinically essential because fatigue, cognitive symptoms, respiratory complaints, pain, dysautonomia-like symptoms, and environmental sensitivity have broad differential diagnoses and cannot be safely assigned to one exposure label without evaluation.

It should not be used to dismiss conventional treatment. A patient with asthma needs asthma care. A patient with hypersensitivity pneumonitis needs appropriate pulmonary evaluation and exposure avoidance. A patient with autoimmune disease needs disease-specific management. A patient with chronic sinusitis may need ENT evaluation. A patient with sleep apnea needs sleep treatment. A patient with severe depression or anxiety needs compassionate mental health care. Exposure assessment does not cancel ordinary medicine.

It should not become patient blame. Patients should not be told they are sick because they failed to detoxify properly, failed to avoid every exposure, failed to follow a protocol perfectly, or failed to think correctly. Many environmental and housing conditions are outside individual control.

It should not become commercial exploitation. Patients with complex chronic illness are vulnerable to expensive tests, supplements, devices, and protocols that may not be validated. A life-coherent approach must protect patients from both dismissal and predation.

20.5 What CIRS Can Contribute

Despite these cautions, CIRS can contribute several important insights to a life-coherent systems immunology.

Its contribution is therefore not as a master diagnosis, but as a pressure test for whether medicine can integrate exposure, susceptibility, indoor air quality, respiratory disease, multi-system suffering, and uncertainty without either dismissal or overclaiming (Bush et al., 2006; Shoemaker & House, 2006).

First, it keeps exposure in view. Modern medicine often treats the body as if it were separable from housing, air, moisture, microbes, toxins, work, and environmental conditions. CIRS insists that the niche matters.

Second, it highlights susceptibility. Not everyone exposed to the same building becomes ill. This does not mean exposure is irrelevant. It means that exposure must be interpreted through

organism history, genetics, immune state, barrier integrity, allostatic load, and clearance capacity.

Third, it emphasizes persistence. Some patients do not recover simply by leaving an acute exposure or treating one symptom. Their organism may remain locked in inflammatory, neuroimmune, metabolic, or autonomic patterns that require sequenced care.

Fourth, it challenges dismissal. Patients with complex environmental illness are often told nothing is wrong because standard tests are normal. Yet normal standard tests do not prove that the organism is coherent. They may simply indicate that the measured variables did not capture the phase-state.

Fifth, it demands humility. CIRS reveals the difficulty of practicing medicine where mechanisms are plausible, patient suffering is real, but consensus remains incomplete.

These contributions can be retained without overclaiming.

This balance is the central reason to keep CIRS as a contested case study rather than as a foundation for the manuscript.

20.6 Clinical Approach to Suspected Exposure-Linked Phase-Locking

A life-coherent clinical approach to suspected exposure-linked phase-locking begins with careful listening.

Careful listening should be paired with exposure history, respiratory and allergic assessment, differential diagnosis, validated testing where appropriate, and practical environmental evaluation (Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

The clinician should ask about symptom timing, environmental patterns, building history, dampness, visible mold, occupational exposures, respiratory symptoms, sinus disease, asthma, allergies, infections, sleep, fatigue, cognitive symptoms, post-exertional worsening, medications, prior diagnoses, and relief away from the suspected environment.

The next step is differential diagnosis. Exposure may be relevant, but it should not stop the clinician from looking for other causes. Standard clinical evaluation should be guided by symptoms and risk. Respiratory symptoms may require pulmonary testing, allergy assessment, imaging, or ENT evaluation. Fatigue may require evaluation for anaemia, thyroid disease, sleep disorders, inflammatory disease, infection, renal or hepatic dysfunction, metabolic disease, medication effects, and mood disorders. Cognitive symptoms may require assessment of sleep, medications, migraine, mood, autonomic dysfunction, inflammatory disease, or neurological conditions.

Environmental action should be practical and proportionate.

For dampness and mould, proportionate action may include moisture control, remediation, ventilation improvement, exposure reduction, or relocation where clinically necessary, especially for asthma, allergy, hypersensitivity, and respiratory disease contexts (Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

If a patient has clear symptom worsening in a damp or mold-affected building, remediation, relocation, improved ventilation, moisture control, or avoidance may be appropriate, especially for asthma, allergy, sinus disease, or hypersensitivity conditions. The goal is not to create fear of all environments. It is to reduce credible anti-salugenic burden.

Treatment should then address the dominant phase-locks. If airway inflammation dominates, treat airway disease. If sinus obstruction and drainage failure dominate, address drainage and inflammation. If sleep disruption dominates, protect sleep. If post-exertional worsening dominates, use pacing and avoid forced rehabilitation until capacity improves. If autonomic symptoms dominate, evaluate and support autonomic regulation. If inflammatory disease is present, treat it. If anxiety or trauma has developed secondary to illness, provide care without implying that the illness is imaginary.

The clinical stance should be both validating and disciplined: “Your symptoms are real. Your environment may be contributing. We will evaluate carefully. We will address what is measurable and modifiable. We will not reduce everything to one cause. We will avoid unsafe or unsupported interventions. We will work toward conditions that allow your system to recover.”

This stance is the practical clinical expression of observer humility and evidence-strength framing.

20.7 CIRS and the Ethics of Uncertainty

CIRS forces medicine to confront the ethics of uncertainty.

The ethical problem is not uncertainty itself, but whether uncertainty is handled through dismissal, premature certainty, costly overtesting, unsupported protocols, or careful co-investigation.

There are two common failures.

The first is premature dismissal. Because CIRS is contested, some clinicians may dismiss all exposure-linked illness, assume symptoms are psychosomatic, or refuse to investigate environmental patterns. This can leave patients unsupported, exposed, and mistrustful.

The second is premature certainty. Because patients are suffering and conventional medicine may fail them, some practitioners may offer highly certain explanations, extensive unvalidated testing, costly protocols, or rigid causal narratives. This can also harm patients, financially, psychologically, and medically.

A life-coherent approach takes a different path. It allows uncertainty to remain open without becoming empty. It says: the evidence is incomplete; the patient's suffering is real; exposure may matter; other diagnoses must be considered; mechanisms should be investigated; interventions should be safe and proportionate; and the goal is recovery of life, not loyalty to a label.

This is observer humility applied clinically.

It requires clinicians to hold patient experience, differential diagnosis, evidence limits, exposure plausibility, safety, and proportionality together.

20.8 Why the Larger Framework Does Not Depend on CIRS

It is important to state clearly that life-coherent systems immunology does not stand or fall with CIRS. The framework is grounded in broader and better-established principles: immune regulation as organism–niche boundary-coherence, 5E organismic cognition, salutogenesis, allostasis, immune resilience, inflammation-resolution-clearance-repair cycles, tissue niches, mitochondrial signalling, immunometabolism, trained immunity, and phase-state reasoning.

CIRS is one possible example of exposure-linked phase-locking. It is not the master key.

The larger framework is anchored instead in broader and better-established literatures on autopoiesis, salutogenesis, allostasis, immunometabolism, mitochondrial signalling, resolution biology, tissue niches, trained immunity, exposure science, and public health (Antonovsky, 1987; McEwen, 1998; Naviaux, 2014; Netea et al., 2016; Serhan, 2007; Wild, 2005).

This distinction protects the paper. It allows CIRS to be discussed without making the whole argument vulnerable to the contested status of one syndrome. It also protects patients by preventing a single label from absorbing complex biological and clinical reality.

20.9 Transition to Immune Epidemiology

CIRS raises a larger question. What if exposure-linked phase-locking is not confined to a contested syndrome? What if rising burdens of asthma, allergy, autoimmune disease, inflammatory bowel disease, metabolic inflammation, post-infectious illness, chronic sinus disease, fibrosis, and chronic inflammatory disorders are, in part, epidemiological signals of changing organism–niche relations?

This does not imply one cause. It does not mean every immune disease is environmental. It does not deny genetics, infections, diagnostic improvements, or disease-specific mechanisms. It asks whether modern life is increasing perturbations while reducing the conditions required for immune coherence.

The next section therefore turns from the contested case of CIRS to immune epidemiology as organism–niche incoherence.

The central question becomes: are rising immune-mediated diseases telling us something about the world our bodies are being asked to live in?

The discussion now moves from contested exposure-linked illness to population-level organism–niche inquiry: immune epidemiology asks whether changing environments, food systems, microbial ecologies, social conditions, and climate stressors are altering immune coherence at scale (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Rappaport & Smith, 2010; Wild, 2005).

21. Immune Epidemiology as Organism–Niche Incoherence

The rising burden of immune-mediated disease cannot be understood through a single explanatory lens.

This caution is essential because apparent changes in disease burden may reflect improved diagnosis, changing classification, survival, reporting, access to care, true incidence changes, environmental shifts, and interactions among these factors.

Better diagnosis, changing classification, improved survival, increased clinical awareness, expanded testing, and altered reporting all contribute to apparent increases in many conditions. Genetics matters. Infections matter. Medications matter. Early-life development matters. Environment matters. Food systems matter. Social conditions matter. Climate matters. Microbial ecology matters. No single cause can explain the whole pattern.

Yet the pattern itself deserves attention.

Across many societies, clinicians and public health systems are seeing high burdens of allergic disease, asthma, eczema, inflammatory bowel disease, autoimmune disease, metabolic-inflammatory disease, chronic sinus disease, post-infectious syndromes, chronic pain-fatigue states, fibrotic disease, and other disorders involving immune dysregulation. These conditions differ mechanistically, but they share a larger question: are modern organism–niche relations increasingly disrupting the conditions required for immune coherence?

The rising burden of immune-mediated disease may be understood as an epidemiological signal of increasing organism–niche incoherence.

This interpretation should be read as a synthetic hypothesis, supported indirectly by literatures on the exposome, social determinants, microbiome disruption, metabolic inflammation, air quality, and climate-health risk rather than as a single-cause epidemiological claim (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Rappaport & Smith, 2010; Wild, 2005; World Health Organization, 2021).

This is not a single-cause theory. It is a multi-level pattern of increasing perturbation and reduced regulatory margins.

The framework therefore treats immune epidemiology as a pattern of interacting exposures, developmental histories, microbial ecologies, metabolic conditions, allostatic burden, climate stress, and health-cycle disruption (Belkaid & Hand, 2014; Hooper et al., 2012; McEwen, 1998; Wild, 2005).

21.1 Beyond Disease-by-Disease Fragmentation

Conventional epidemiology properly studies specific diseases: asthma, type 1 diabetes, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, lupus, psoriasis, atopic dermatitis,

allergic rhinitis, food allergy, long COVID, chronic obstructive pulmonary disease, metabolic syndrome, and many others. Each has its own diagnostic criteria, mechanisms, risk factors, and clinical course. Disease-specific study is indispensable.

The aim is not to replace disease-specific epidemiology, but to ask whether apparently distinct immune-mediated conditions may share upstream perturbation fields or reduced recovery conditions.

But disease-by-disease analysis can obscure shared background conditions.

If asthma rises, it may be attributed to allergens, pollution, viral infections, indoor air, epithelial vulnerability, or social conditions. If inflammatory bowel disease rises, attention may turn to diet, microbiome, antibiotics, urbanization, genetics, and immune regulation. If autoimmune disease rises, investigators may examine infections, hormones, pollutants, microbiome, vitamin D, smoking, obesity, and diagnostic change. If metabolic inflammation rises, food systems, inactivity, sleep disruption, stress, endocrine disruption, and adipose biology may be studied. If post-infectious syndromes rise, viral persistence, immune memory, vascular injury, mitochondrial dysfunction, autonomic regulation, and social recovery conditions may be examined.

These are all valid lines of inquiry. But when many immune-related conditions rise together or cluster across the life course, a wider pattern may be present.

The organism-centered question is: what kind of world is repeatedly shaping immune systems toward hyperreactivity, impaired tolerance, chronic inflammation, poor resolution, failed clearance, fibrotic repair, metabolic overload, or neuroimmune conservation?

This question integrates barrier biology, microbiome science, allostasis, immunometabolism, resolution biology, environmental exposure, and social determinants into a shared epidemiological frame (Belkaid & Hand, 2014; Hooper et al., 2012; McEwen, 1998; O'Neill et al., 2016; Serhan & Savill, 2005).

This question does not collapse diseases into one diagnosis. It asks whether multiple diagnoses may share upstream niche pressures.

21.2 Better Diagnosis and Real Increase

Any responsible account must begin by acknowledging that apparent increases in immune-mediated disease may partly reflect improved recognition.

This caution prevents the epidemiological argument from overstating trend data or mistaking improved ascertainment for true incidence increase.

Clinicians now diagnose conditions that were once missed. Laboratory testing is more available. Imaging is better. Classification criteria have changed. Patients are more aware. Electronic

records capture more diagnoses. Survival has improved in some diseases, increasing prevalence. Public health surveillance is stronger in some regions.

These factors matter.

But better diagnosis does not necessarily explain everything. In some conditions, there is evidence of genuine change in incidence or burden. Allergic disease, asthma, obesity-linked inflammation, inflammatory bowel disease in newly industrialized regions, and post-infectious chronic illness patterns all raise questions about changing organism–niche relations. Even where diagnostic change contributes, it does not negate the possibility that real exposures, developmental patterns, and regulatory conditions are shifting.

A life-coherent epidemiology therefore avoids both exaggeration and dismissal.

The appropriate position is to examine each disease and region carefully while also asking whether shared changes in exposure, development, microbial ecology, metabolism, and recovery conditions are contributing to broader immune burden (Belkaid & Hand, 2014; Hooper et al., 2012; Rappaport & Smith, 2010; Wild, 2005).

It asks, condition by condition, how much of the observed burden reflects detection, how much reflects true change, and how much reflects altered survival, classification, and access to care. But it also asks whether shared background pressures are increasing immune incoherence across multiple disease categories.

21.3 Barrier Disruption

Many modern immune diseases begin at barriers: gut, airway, skin, sinus mucosa, oral mucosa, genitourinary tract, placenta, endothelium, and blood-brain interfaces. These barriers are not walls. They are living interfaces where the organism negotiates exchange with the world.

Barrier disruption may therefore be one of the central epidemiological signals of organism–niche incoherence.

Barrier tissues are major immune-regulatory interfaces where pollutants, allergens, infections, diet, medications, microbes, stress, and environmental conditions can shape tolerance, inflammation, repair, and systemic immune tone (Belkaid & Hand, 2014; Hooper et al., 2012; Medzhitov, 2008).

Airway barriers are affected by air pollution, smoke, viral infections, indoor dampness, allergens, occupational exposures, climate-driven pollen changes, particulate matter, and poor ventilation. Skin barriers are affected by detergents, chemicals, climate, microbial change, scratching, dryness, occupational irritants, and altered early-life exposures. Gut barriers are affected by diet, antibiotics, infections, stress, alcohol, medications, microbiome changes, food additives, and metabolic inflammation. Endothelial barriers are affected by hypertension, diabetes, smoking, infection, pollution, inflammation, and vascular stress.

When barriers are repeatedly injured, the immune system is asked to evaluate the world through alarm. Food, microbes, pollen, particles, chemicals, and internal debris become more likely to be encountered in inflammatory contexts. Tolerance becomes harder. Type 2 inflammation, autoimmunity, dysbiosis, chronic sinusitis, asthma, eczema, food allergy, inflammatory bowel disease, and systemic inflammatory burden may all be shaped by barrier incoherence.

The barrier is where the world enters biology.

21.4 Microbiome and Virome Disruption

Immune systems develop and regulate in relation to microbial worlds.

Microbiota and virome research show that microbial communities and viral ecologies participate in immune education, barrier function, tolerance, pathogen resistance, metabolic signalling, and inflammatory calibration (Belkaid & Hand, 2014; Hooper et al., 2012; Virgin, 2014).

The microbiome and virome are not optional accessories. They participate in barrier education, metabolic signalling, immune tolerance, pathogen resistance, mucosal repair, and inflammatory calibration.

Modern life alters microbial relations through antibiotics, diet, sanitation, urbanization, C-section birth, formula feeding, reduced biodiversity exposure, indoor living, disinfectants, infection patterns, medications, food processing, environmental chemicals, and globalized lifestyles. Some of these changes are beneficial and lifesaving. Sanitation, antibiotics, and infection control have prevented immense suffering. But they also change microbial ecologies.

The challenge is not to romanticize premodern exposure or reject medical progress.

This caution preserves the benefits of sanitation, vaccination, antibiotics, and infection control while still allowing inquiry into microbial depletion, dysbiosis, ecological loss, and altered immune education.

The challenge is to understand how microbial depletion, dysbiosis, altered phage dynamics, and reduced ecological diversity may affect immune coherence.

A developing immune system needs microbial education without overwhelming infection. A mature immune system needs microbial partnership without dysbiosis or invasion. A damaged barrier needs microbial stability to repair. When microbial ecologies are repeatedly disrupted, the organism may lose some of the signals required for tolerance, resolution, and metabolic balance.

This may contribute to allergic disease, inflammatory bowel disease, metabolic inflammation, recurrent infections, and other immune disorders. The details vary, and causality is complex. But the broader principle is clear: immune epidemiology cannot be separated from microbial ecology.

This principle is supported by microbiome and virome research linking microbial ecologies to mucosal immunity, inflammation, metabolism, barrier integrity, and systemic immune tone (Belkaid & Hand, 2014; Hooper et al., 2012; Virgin, 2014).

21.5 Metabolic Overload

Metabolic overload is another major source of organism–niche incoherence.

Immunometabolism shows that metabolic state, nutrient availability, adipose inflammation, insulin resistance, mitochondrial stress, and gut microbial shifts can alter immune-cell function and inflammatory tone (Buck et al., 2017; O'Neill et al., 2016; Pearce & Pearce, 2013).

The immune system is metabolically sensitive. Adipose tissue, liver, muscle, gut, pancreas, vasculature, and immune cells are all involved in metabolic-immune regulation. When food systems produce chronic excess of energy-dense, nutrient-poor, ultra-processed, low-fibre, inflammatory, or metabolically disruptive diets, immune regulation changes.

Obesity, insulin resistance, fatty liver disease, dyslipidaemia, hyperglycaemia, and metabolic syndrome are not only metabolic disorders. They are inflammatory and immunological states.

Metabolic inflammation links adipose tissue, macrophage activation, cytokine signalling, endothelial dysfunction, mitochondrial stress, gut microbiota, and trained innate immune readiness (Buck et al., 2017; Netea et al., 2016; O'Neill et al., 2016; Picard et al., 2018).

Adipose tissue can become inflamed. Macrophages change. Cytokines rise. Endothelial function worsens. Mitochondrial stress increases. Gut microbiota shift. Trained immunity may be amplified. Infection outcomes may worsen. Autoimmune and inflammatory disease risks may be altered.

Metabolic overload narrows immune margins. The organism becomes less able to resolve inflammation, repair tissue, tolerate perturbation, and re-enter health-cycle rhythms. It may remain in low-grade defence and repair even without a classic infection or autoimmune trigger.

This is one reason immune epidemiology must include food systems, poverty, marketing, agriculture, work rhythms, stress, and urban design. Metabolic disease is not merely individual choice. It is organism–niche coupling through the political economy of food, time, work, and care.

This links immunometabolism to social determinants: metabolic risk is shaped by food systems, poverty, marketing, work schedules, stress, urban design, and access to health-generating resources (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

21.6 Allostatic Burden

Allostatic burden refers to the accumulated cost of repeated adaptation.

This follows allostatic-load theory, which describes the cumulative physiological cost of repeated or chronic adaptation across stress, immune, metabolic, cardiovascular, neuroendocrine, and behavioural systems (McEwen, 1998; McEwen & Stellar, 1993; Sterling & Eyer, 1988).

At population scale, allostatic burden increases when people live with chronic stress, insecurity, sleep disruption, overwork, violence, discrimination, poverty, caregiving strain, social isolation, trauma, climate anxiety, housing instability, and fragmented care.

The immune consequences are not metaphorical.

Chronic allostatic burden can alter inflammatory tone, glucocorticoid sensitivity, sleep, pain, appetite, metabolic health, autonomic regulation, and practical treatment capacity (Barrett et al., 2016; McEwen, 1998; Picard et al., 2018).

Chronic threat can alter inflammatory tone, antiviral responses, wound healing, pain sensitivity, cortisol rhythms, sympathetic activation, sleep quality, appetite, microbiome, and metabolic health. It can also reduce the practical capacity to follow treatment plans, rest during illness, access medication, attend appointments, or leave harmful environments.

At the population level, chronic allostatic burden can produce bodies that are simultaneously inflamed and depleted, vigilant and exhausted, reactive and poorly resilient.

This helps explain why immune disease is often socially patterned. Disease risk and outcomes are not distributed only by genes. They follow gradients of exposure, stress, housing, work, food, environment, access, and dignity. A life-coherent immune epidemiology must therefore attend to justice.

Health inequities are embodied through unequal distributions of exposure, stress, housing, food, work, care, dignity, and environmental protection (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

Immune coherence is easier to sustain when the niche protects life. It is harder when life is lived under chronic threat.

21.7 Exposure Accumulation

The modern organism is exposed to mixtures: air pollution, indoor pollutants, pesticides, plastics, solvents, heavy metals, endocrine disruptors, noise, artificial light at night, heat, occupational chemicals, food additives, medications, and microbial changes.

Exposome research emphasizes precisely this mixture problem: organisms experience cumulative, interacting exposures over time, even when research and regulation often assess exposures one at a time (Rappaport & Smith, 2010; Wild, 2005).

Each exposure may be studied separately, but the organism experiences them together.

Exposure accumulation matters because biological systems have thresholds, interactions, and limited clearance capacity. A low-level pollutant may be tolerated in a rested, nourished organism with low inflammatory burden. The same exposure may become destabilizing in a sleep-deprived, inflamed, metabolically strained organism living in a damp building after a viral infection. Cumulative exposures may reduce mitochondrial reserve, impair barrier function, increase oxidative stress, and lower the threshold for immune activation.

This is why the exposome must be interpreted relationally. It is not a list of toxins.

Exposure accumulation must be interpreted in relation to susceptibility, timing, mixtures, metabolism, clearance capacity, mitochondrial reserve, tissue vulnerability, and recovery resources (McEwen, 1998; Rappaport & Smith, 2010; Wild, 2005).

It is the cumulative perturbation field in which the organism tries to live, adapt, and heal.

21.8 Developmental Mismatch

Immune systems are shaped early.

Early-life immune development is shaped by microbial exposure, nutrition, infection history, antibiotics, stress physiology, pollutants, caregiving, and social conditions that influence barriers, tolerance, microbiome relations, and inflammatory thresholds (Belkaid & Hand, 2014; Commission on Social Determinants of Health, 2008; Hooper et al., 2012).

Pregnancy, birth, breastfeeding, microbial exposures, nutrition, infections, antibiotics, stress, pollutants, sleep, caregiving, and social safety all help configure immune regulation. Early-life development establishes barriers, tolerance, microbiome relations, metabolic pathways, neuroendocrine regulation, and inflammatory thresholds.

Developmental mismatch occurs when the conditions under which immune systems evolved or develop optimally diverge sharply from the conditions now encountered. This may include reduced microbial diversity, increased pollutants, altered diet, indoor living, disrupted sleep, high psychosocial stress, reduced outdoor exposure, excess hygiene in some contexts, high infection burden in others, and fragmented caregiving conditions.

The result may be immune systems less well calibrated for tolerance, defence, and repair.

This developmental framing supports prevention strategies that protect children from dangerous infections and toxins while supporting microbial education, nourishment, sleep, movement, attachment, nature contact, and social safety (Belkaid & Hand, 2014; Hooper et al., 2012; Marmot et al., 2008).

This does not mean returning to the past. The past included high infant mortality, infectious disease, malnutrition, and many forms of suffering. The goal is not nostalgia. The goal is life-coherent development: protecting children from dangerous infections and toxins while

supporting microbial education, nourishment, sleep, movement, play, attachment, nature contact, and social safety.

21.9 Climate and Ecological Instability

Climate and ecological instability intensify immune perturbations.

Climate change affects health through heat, air pollution, wildfire smoke, flooding, infectious disease shifts, food and water insecurity, displacement, mental health stress, and disruption of care systems (Intergovernmental Panel on Climate Change, 2023).

Heat stress, wildfire smoke, air pollution, changing pollen seasons, vector-borne infections, flooding, damp buildings, food insecurity, water contamination, displacement, and disaster-related trauma all alter immune conditions. Climate events also disrupt healthcare access, medication supply, housing, work, and sleep.

This means climate change is not only an environmental crisis. It is an immune-coherence crisis.

This framing is justified because climate stressors directly and indirectly affect respiratory, allergic, infectious, cardiovascular, renal, metabolic, psychological, and inflammatory disease burden (Intergovernmental Panel on Climate Change, 2023; World Health Organization, 2021).

Airway disease worsens with smoke and pollution. Allergic disease shifts with pollen and temperature. Infectious risks change with vector ranges and water conditions. Heat stresses cardiovascular, renal, and metabolic systems. Displacement increases allostatic load. Food and water insecurity impair resistance resources. Dampness after flooding increases respiratory burden. Ecological loss reduces biodiversity and microbial relations.

Bodies register ecological instability as inflammatory, allergic, infectious, metabolic, and psychological burden.

Ecological instability also threatens generalized resistance resources by disrupting housing, food, water, social stability, medication access, and healthcare continuity (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023).

A life-coherent immune epidemiology must therefore treat ecological protection as preventive medicine.

21.10 Reduced Health-Cycle Conditions

The health cycle requires sleep, movement, nourishment, waste removal, social connection, nature contact, restorative rhythm, and meaningful participation.

These health-cycle conditions overlap with salutogenic and allostatic resources: they help maintain coherence, reduce adaptive cost, support immune regulation, and enable recovery after perturbation (Antonovsky, 1987; McEwen, 1998; Sterling & Eyer, 1988).

Many modern environments undermine these conditions.

Sleep is disrupted by artificial light, shift work, stress, noise, screens, caregiving demands, economic pressure, pain, and illness. Movement is reduced by sedentary work, unsafe streets, car dependency, disability, pain, and time scarcity. Nourishment is undermined by food insecurity, ultra-processed diets, marketing, poverty, and loss of food culture. Waste removal is impaired by inactivity, dehydration, constipation, kidney disease, liver disease, poor sleep, pollution, and inflammation. Social connection is strained by isolation, digital substitution, migration, overwork, and fragmented communities. Nature contact is reduced by urbanization and ecological degradation. Meaningful participation is constrained by precarious work, illness, inequality, and social dislocation.

When health-cycle conditions are reduced, healing-cycle completion becomes harder.

Without sufficient sleep, movement, nourishment, clearance, safety, social support, and meaningful participation, the organism may enter defence repeatedly without completing resolution, repair, and re-entry (Antonovsky, 1987; McEwen, 1998; Serhan & Savill, 2005).

The organism may repeatedly enter defence but lack the ordinary rhythms required for resolution and re-entry.

This may be one of the most important epidemiological insights of the framework: chronic immune disease rises not only when exposures increase, but when health-generating cycles are weakened.

21.11 Immune Disease as Signal, Not Blame

To describe immune disease as organism–niche incoherence is not to blame patients for being ill.

This ethical clarification is necessary because social and ecological explanations can be misused unless they explicitly locate constraint in organism–niche conditions rather than in personal failure (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

It is the opposite. It recognizes that bodies are living in worlds that may not support coherence. A patient with asthma in polluted air, eczema in chemically harsh environments, inflammatory bowel disease in disrupted food systems, fatigue after infection without rest, or autoimmune disease under chronic stress is not personally failing. The organism is responding within constraints.

Nor does this framing blame society simplistically for every disease. Biology is complex. Randomness, genetics, infections, aging, and disease-specific mechanisms remain real. The point is that population patterns can reveal environmental, social, microbial, metabolic, and ecological conditions that repeatedly perturb organisms and reduce regulatory margins.

Immune epidemiology becomes a way of listening to bodies at scale.

Population immune patterns can therefore be read as early-warning signals of exposure burden, social inequity, ecological stress, metabolic disruption, microbial change, and weakened health-cycle conditions (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Wild, 2005).

If many bodies are inflamed, allergic, metabolically strained, fatigued, dysregulated, or unable to recover, the question is not only what drugs they need. It is what world they are being asked to inhabit.

21.12 Public Health Implications

A life-coherent immune epidemiology shifts public health priorities.

Public health must therefore protect not only against specific pathogens or individual risk factors, but also the ecological, social, microbial, nutritional, housing, occupational, and climatic conditions that shape immune coherence (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; World Health Organization, 2021).

Prevention cannot be limited to vaccination, screening, and individual risk counselling, although all are important. It must also protect the conditions under which immune coherence develops and recovers.

This includes clean air, safe housing, moisture control, healthy buildings, nutritious food systems, microbial stewardship, antibiotic stewardship, toxin regulation, climate adaptation, sleep-protective work policies, maternal-child support, outdoor play, nature access, social safety, equitable healthcare, occupational protection, and early treatment of inflammatory disease before tissue memory becomes entrenched.

Public health becomes phase prevention. It reduces perturbations, increases resistance resources, protects healing cycles, and supports re-entry into life after illness.

This connects public health directly to salutogenesis and allostasis: prevention includes protecting resources, reducing avoidable load, and supporting recovery before maladaptive phase-locks become entrenched (Antonovsky, 1987; McEwen, 1998).

This also means that healthcare systems must be designed to reduce fragmentation. Patients with complex immune disease often need coordinated care across primary care, immunology, rheumatology, pulmonology, gastroenterology, dermatology, neurology, rehabilitation, mental health, occupational medicine, environmental health, and social support. Fragmented systems increase allostatic burden and delay phase restoration.

A life-coherent public health system would ask: what conditions prevent immune disease from locking in the first place?

This question prepares the transition from immune epidemiology to clinical, public-health, and civilizational design.

21.13 Transition to Clinical, Public Health, and Civilizational Implications

The epidemiological argument completes the outward movement of the paper. We began with the organism, moved through immune cognition, health and healing cycles, molecular mechanisms, tissue niches, clearance, exposure, and contested environmental illness. We now see immune disease not only as a clinical event, but as a signal of organism–niche relations at multiple scales.

This multi-scale interpretation links clinical immunology to public health and civilizational design by treating disease patterns as embodied feedback from the conditions in which organisms must live, adapt, heal, and participate (Commission on Social Determinants of Health, 2008; Marmot et al., 2008; Wild, 2005).

The next part turns toward translation.

If chronic immune disease is maladaptive phase-locking, then diagnosis must become phase-state reasoning. Biomarkers must evolve toward regulatory-state profiles. Treatment must become phase restoration. Public health must protect health-cycle conditions. Civilization itself must be judged by whether its institutions support or undermine the conditions under which organisms can complete adaptive cycles.

This is the practical horizon of life-coherent systems immunology: to move from explanation to care, and from care to the conditions that make healing possible.

Part VII. Clinical, Public Health, and Civilizational Implications

22. Clinical Translation: Diagnosis as Phase-State Reasoning

If chronic immune disease is maladaptive phase-locking, then clinical diagnosis must do more than name the disease category. It must also identify the regulatory state in which the organism is caught. The conventional diagnosis remains essential. Lupus, rheumatoid arthritis, asthma, inflammatory bowel disease, psoriasis, chronic rhinosinusitis, vasculitis, immunodeficiency, interstitial lung disease, long COVID, and other conditions are not to be dissolved into vague systems language. They must be recognized, investigated, staged, monitored, and treated according to established clinical standards.

But a disease name alone may not tell us what transition has failed.

Name the disease, but also name the regulatory lock — while remembering that the lock is an observer tool, not the organism's identity.

This formulation preserves conventional diagnosis while adding a process-oriented layer of interpretation grounded in observer humility, allostasis, tissue-contextual immunology, resolution biology, and phase-state reasoning (Maturana, 1988; McEwen, 1998; Medzhitov, 2008; Serhan, 2007).

This is the clinical core of phase-state reasoning. The physician asks not only, "What diagnosis does this patient meet?" but also, "What is the organism doing now?" Is the organism in active danger detection, destructive defence, containment without clearance, failed resolution, impaired drainage, excessive repair, fixed memory, mitochondrial conservation, neuroimmune protection, or failed re-entry into the health cycle? What tissue niche gives the disease its form? What exposures or histories sustain it? What intervention would allow the next adaptive movement?

Diagnosis names the pattern. Phase-state reasoning follows the process.

The distinction is clinically important because disease categories organize care, while phase-state reasoning asks what transition has failed and what biological or niche conditions would allow movement toward recovery (Antonovsky, 1987; Naviaux, 2014; Serhan & Savill, 2005).

22.1 The Limits of Diagnosis Alone

A conventional diagnosis is powerful because it organizes knowledge. It links the patient's presentation to known mechanisms, prognosis, investigations, therapies, and risks. It allows clinical communication. It makes research possible. It protects against vagueness. Without diagnosis, care becomes impressionistic.

Yet diagnosis can also become too static. It may identify the disease but not the phase. A patient with rheumatoid arthritis may be in early inflammatory synovitis, erosive destructive disease, remission with residual pain, fibrotic stiffness, medication-related immunosuppression, or systemic allostatic exhaustion. These are not the same clinical situations. A patient with asthma may be in acute bronchospasm, chronic type 2 inflammation, fixed airway remodelling, viral-triggered flare, pollutant-induced barrier alarm, or anxiety-amplified dyspnoea. A patient with inflammatory bowel disease may be in active ulceration, post-inflammatory irritable bowel symptoms, fibrostenotic disease, dysbiosis, nutritional depletion, or systemic fatigue after inflammation has quieted.

The diagnosis remains the same, but the clinical task changes.

This is why static diagnostic labels should be complemented by assessment of disease activity, tissue state, repair status, allostatic burden, functional capacity, and re-entry into ordinary life (McEwen, 1998; Naviaux, 2014).

This is why phase-state reasoning matters. It prevents the diagnosis from becoming a flat label. It restores time, sequence, tissue, and transition to clinical judgment.

In this sense, phase-state reasoning extends diagnosis from classification toward clinical temporality: what is active, what is resolving, what remains uncleared, what has been damaged, and what sequence of care is needed next (Fullerton & Gilroy, 2016; Serhan, 2007; Wynn & Ramalingam, 2012).

22.2 Naming the Disease and the Lock

A phase-state diagnosis has two layers.

The first layer is conventional: What disease, syndrome, or clinical problem is present? This includes history, examination, laboratory testing, imaging, pathology, microbiology, physiology, and established diagnostic criteria. It asks: Is this asthma? Lupus? Vasculitis? Infection? Immunodeficiency? Inflammatory bowel disease? Fibrosis? Allergy? Malignancy? Endocrine disease? Medication toxicity? Psychiatric distress? Functional disorder? Something else?

The second layer is regulatory: What phase-lock is dominant? This asks: Is the main problem recognition/misrecognition, inflammasome danger, interferon tone, viral or mobile-element boundary activation, barrier-type 2 inflammation, mechano-inflammatory enthesitis, immune-complex vascular injury, trained innate readiness, immune deficiency with dysregulation, clearance failure, fibrosis, or neuroimmune pain-fatigue conservation?

These two layers must remain together. Naming the lock without naming the disease risks vagueness. Naming the disease without naming the lock risks static care.

This two-layer approach protects the framework from both reductionism and vagueness: mechanisms and diagnoses remain necessary, but they are interpreted within the organism's current regulatory state (Medzhitov, 2008; Maturana & Varela, 1980).

For example, a patient with lupus nephritis may require the conventional diagnosis of lupus nephritis because the condition can threaten kidney function and requires urgent evidence-based treatment. But phase-state reasoning adds that the patient may be in an immune-complex vascular-filtration lock, with nucleic-acid/interferon activation and impaired clearance. This helps explain why treatment may need to suppress immune injury, protect the kidney, monitor complement and urine sediment, reduce inflammatory load, support sleep and recovery, and prevent recurrent triggers.

A patient with long COVID may not fit one simple disease category. Phase-state reasoning may identify a dominant re-entry lock with mitochondrial conservation, dysautonomia, post-exertional worsening, neuroimmune sensitivity, sleep disruption, and possible viral or vascular contributors. This does not settle all mechanisms, but it guides care away from forced exertion and toward pacing, investigation of treatable contributors, sleep protection, autonomic support, symptom control, and careful rehabilitation when capacity allows.

This example should be framed cautiously as phase-state reasoning rather than as a settled mechanism: post-infectious illness may involve immune, mitochondrial, autonomic, vascular, sleep, and exertional-tolerance disturbances that require careful sequencing rather than forced reconditioning (McEwen, 1998; Naviaux, 2020; Picard et al., 2018).

A patient with chronic rhinosinusitis may have a barrier-type 2 lock, microbial biofilm or drainage lock, anatomical obstruction, allergic inflammation, or environmental exposure-lock. The phase-state distinction affects whether the priority is topical anti-inflammatory therapy, allergy management, antibiotics in selected cases, surgery for drainage, biologics, environmental remediation, or combined care.

22.3 Tissue Niche Assessment

Phase-state reasoning always asks where the lock has taken form. Tissue matters because the same immune process has different consequences in different places.

Tissue-niche reasoning is supported by evidence that stromal cells, epithelial and endothelial barriers, fibroblasts, macrophages, matrix, mechanics, microbiota, and resident immune states shape local disease expression (Belkaid & Hand, 2014; Galli et al., 2011; Wynn et al., 2013).

In the airway, inflammation can narrow breath, increase mucus, sensitize smooth muscle, and remodel tissue. In the gut, inflammation can ulcerate mucosa, impair absorption, alter microbiota, produce strictures, and affect systemic energy. In the kidney, immune deposition can silently damage filtration. In the vessel, complement and leukocytes can threaten perfusion. In the synovium, inflammation can erode cartilage and bone. In the lung interstitium, repair can become irreversible scarring. In the nervous system, immune activation can alter cognition, pain, sleep, autonomic function, and fatigue.

Therefore, diagnosis as phase-state reasoning asks: What is the tissue niche doing? Is it inflamed, damaged, obstructed, fibrotic, hypersensitive, infected, poorly drained, mechanically overloaded, metabolically strained, or failing to repair? Are local cells sustaining the lock? Are fibroblasts

activated? Is epithelial alarm present? Are resident immune cells primed? Are lymphatics impaired? Is the matrix stiff? Is microbial ecology altered?

This tissue-level inquiry prevents systems language from floating above clinical reality. The organism is always embodied in tissues.

This returns systems immunology to embodiment: immune processes are never abstract pathways alone, but are enacted through specific anatomical, microbial, vascular, mechanical, metabolic, and neural niches (Hooper et al., 2012; O'Neill et al., 2016; Wynn & Ramalingam, 2012).

22.4 Developmental and Historical Reasoning

The current phase-state is the result of history.

Immune history may be carried through adaptive immune memory, trained innate immunity, epigenetic priming, tissue-resident cells, microbial ecology, mitochondrial capacity, developmental exposures, and social or environmental conditions (Belkaid & Hand, 2014; Netea et al., 2016; Virgin, 2014).

Immune disease rarely begins at the moment of diagnosis. It may develop through genetic susceptibility, early-life exposures, infections, microbiome changes, trauma, pollutants, occupational exposure, sleep disruption, metabolic disease, pregnancy, hormonal transition, medications, injuries, surgeries, and previous inflammatory episodes.

A phase-state diagnosis therefore includes developmental history. When did symptoms begin? What preceded them? Was there infection, exposure, bereavement, injury, pregnancy, medication change, move to a new building, occupational shift, major stress, antibiotic use, travel, dietary change, vaccination, surgery, or environmental event? Did symptoms appear suddenly or gradually? Did they improve away from certain environments? Were there childhood allergies, recurrent infections, eczema, asthma, gut issues, autoimmunity, or family history? Has the disease relapsed in the same tissue? What does the organism seem to remember?

This is not an invitation to speculative causality. It is disciplined historical reasoning.

The aim is to identify biologically plausible temporal patterns without converting every prior exposure, infection, stressor, or life event into a presumed cause (Rappaport & Smith, 2010; Wild, 2005).

The goal is to understand how the present lock became biologically plausible. A post-infectious re-entry lock has a different history from a lifelong atopic barrier lock. A toxin-associated airway disease differs from genetic immunodeficiency. A menopausal autoimmune flare differs from childhood-onset autoinflammation. A recurrent joint flare after gut inflammation differs from purely mechanical injury. The past does not determine everything, but it helps identify the pathways through which the organism arrived here.

22.5 Exposure Ecology

Clinical translation also requires exposure ecology.

Exposure ecology extends the clinical history through exposome reasoning, asking how cumulative chemical, microbial, occupational, social, nutritional, built-environment, and climatic perturbations shape disease and recovery (Rappaport & Smith, 2010; Wild, 2005).

The physician asks what recurrent perturbations may be preventing healing-cycle completion. These may include allergens, pollutants, damp housing, occupational chemicals, infections, food triggers, medications, sleep disruption, overexertion, psychosocial threat, social isolation, climate heat, noise, light at night, microbial dysbiosis, or persistent antigen sources.

Exposure inquiry must be practical and evidence-aware. It should not become endless searching for hidden causes. The clinician should focus on exposures that are temporally related, biologically plausible, clinically actionable, and proportionate to the patient's symptoms and risks.

For example, in asthma and chronic rhinosinusitis, indoor air, dampness, allergens, smoke, occupational exposures, and viral triggers are clinically relevant. In inflammatory bowel disease, diet, antibiotics, infection, stress, and microbiome history may matter. In contact dermatitis, occupational and household exposures may be decisive. In hypersensitivity pneumonitis, exposure identification is central. In post-infectious syndromes, activity thresholds, sleep, and recurrent infection risk may matter. In recurrent infection, household crowding, immune deficiency, and exposure frequency may matter.

Exposure ecology asks: What keeps re-entering the organism as danger?

This question links exposure assessment to phase-locking: recurrent perturbations matter clinically when they repeatedly reactivate danger, impair clearance, disrupt repair, or prevent re-entry into the health cycle (McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005).

22.6 Allostatic Burden and Regulatory Margins

A phase-state diagnosis also assesses allostatic burden.

Allostatic burden captures the cumulative physiological cost of repeated adaptation and helps explain why the same disease may behave differently depending on sleep, stress, pain, metabolic load, social support, exposure, and recovery resources (McEwen, 1998; McEwen & Stellar, 1993; Sterling & Eyer, 1988).

The same disease behaves differently in an organism with ample margins compared with one under chronic load. Sleep disruption, pain, poverty, caregiving strain, trauma, overwork, metabolic syndrome, deconditioning, loneliness, medication side effects, repeated infections, or environmental exposure can reduce the capacity to heal.

The clinician should ask: How much adaptive cost is this organism carrying? Can the patient rest? Can they sleep? Can they eat nourishing food? Can they afford treatment? Can they attend appointments? Can they reduce exposure? Can they pace activity? Can they move safely? Can they trust care? Can they understand the plan? Can they recover after exertion?

These are not secondary concerns. They determine whether phase transition is affordable.

Phase transition is "affordable" only when biological reserve, social resources, metabolic capacity, sleep, safety, and care access are sufficient to support the next adaptive movement (Antonovsky, 1987; McEwen, 1998; Picard et al., 2018).

A treatment plan that ignores allostatic burden may fail because the organism cannot use it. A patient may be prescribed exercise when they need pacing, immunosuppression when infection is unrecognized, supplements when urgent inflammation requires treatment, or complex self-management when they lack sleep, money, transport, or support. Phase-state reasoning requires realistic care.

22.7 The Next Adaptive Transition

The most practical question in phase-state medicine is: What is the next adaptive transition?

This question translates the framework into clinical prioritization: suppress damage, clear burden, drain obstruction, restore sleep, support metabolism, slow fibrosis, pace exertion, rehabilitate capacity, or reduce exposure according to the dominant lock (Naviaux, 2014; Serhan, 2007; Wynn & Ramalingam, 2012).

Not the final cure. Not the whole life plan. The next transition.

For a patient in destructive inflammation, the next transition may be reduction of immune injury. For a patient with infection, it may be clearance of pathogen. For a patient with mucus retention, it may be drainage. For a patient with fibrosis, it may be slowing repair-overbuild and preserving function. For a patient with post-exertional worsening, it may be stabilization through pacing and sleep before reconditioning. For a patient with severe allostatic burden, it may be making the care plan manageable. For a patient with allergy, it may be reducing barrier alarm. For a patient with immune deficiency, it may be preventing recurrent infection. For a patient in remission with disability, it may be rehabilitation and re-entry.

This question protects care from becoming overwhelming. Complex chronic illness often has many problems. Phase-state reasoning prioritizes the transition that must occur before later transitions become possible.

The organism cannot always jump from disease to health. It may need to move from danger to containment, from containment to clearance, from clearance to repair, from repair to reconditioning, from reconditioning to participation. Good care respects sequence.

This sequencing is consistent with allostatic and resolution biology: an intervention that is helpful in one phase may be harmful if introduced before danger, inflammation, clearance, or repair constraints are addressed (McEwen, 1998; Serhan & Savill, 2005).

22.8 Clinical Care as Structural Coupling

Clinical care is itself structural coupling.

In autopoietic terms, clinical care becomes part of the organism's structural coupling with its niche; in salutogenic terms, it can strengthen or weaken comprehensibility, manageability, meaning, and trust (Antonovsky, 1987; Maturana & Varela, 1980).

The consultation is not outside the organism–niche relation. It enters the patient's world. A diagnosis can reduce chaos or increase fear. A medication can suppress damage or create new risks. A physician's explanation can restore coherence or deepen confusion. A care plan can become manageable or impossible. A follow-up appointment can generate trust or abandonment. The clinical relationship can become part of the patient's regulatory field.

This does not mean that kindness replaces science. It means that science is delivered through relationship.

For patients with chronic immune disease, especially those who have been dismissed, fragmented, or overtreated, the clinical encounter can either reduce or increase allostatic load. Being believed does not cure disease, but disbelief can worsen threat physiology and delay care. Clear explanation does not replace treatment, but confusion can increase fear and reduce adherence. Shared planning does not eliminate pathology, but it can make healing more manageable.

A life-coherent clinician therefore treats explanation, trust, pacing, and coordination as part of care, not decoration around care.

These relational dimensions are biologically relevant because confusion, fear, dismissal, fragmentation, and uncertainty can increase allostatic load, while coherent explanation and coordinated care can support recovery capacity (Antonovsky, 1987; McEwen, 1998).

22.9 Practical Template for Phase-State Diagnosis

A practical clinical template may include the following sequence:

First, establish the conventional diagnosis or differential diagnosis. Identify urgent conditions, organ threats, infection, malignancy, immune deficiency, inflammatory disease, endocrine disease, medication effects, and psychiatric or neurological contributors where relevant.

Second, identify the tissue niche. Determine where the disease is taking form: airway, gut, skin, synovium, enthesis, vessel, kidney, lung interstitium, marrow, nervous system, or multiple tissues.

Third, identify the dominant phase-lock. Ask whether the main pattern is recognition, danger, interferon, viral boundary, type 2 barrier alarm, mechano-inflammatory, immune-complex vascular, trained immunity, immune deficiency-dysregulation, clearance failure, fibrosis, or neuroimmune pain-fatigue.

Fourth, assess sustaining conditions. Look for persistent exposure, infection, debris, impaired drainage, sleep disruption, metabolic overload, mitochondrial constraint, allostatic burden, tissue memory, or treatment gaps.

Fifth, identify the next adaptive transition. Decide what must happen next for the organism to move: suppress, clear, drain, resolve, repair, protect, pace, rehabilitate, restore sleep, reduce exposure, support metabolism, or coordinate care.

Sixth, monitor for re-entry. Track not only biomarkers and organ measures, but also sleep, function, exertional tolerance, pain, fatigue, movement, appetite, social participation, and quality of life.

This template is not a substitute for clinical judgment. It is a scaffold for integrative reasoning.

Its value lies in guiding attention across conventional diagnosis, tissue niche, phase-lock, sustaining conditions, next transition, and functional re-entry without replacing disease-specific standards of care (Medzhitov, 2008; Naviaux, 2014).

22.10 Avoiding Misuse

Phase-state reasoning must not become a way to delay necessary treatment. A patient with rapidly progressive glomerulonephritis, severe asthma, sepsis, vasculitis, inflammatory bowel obstruction, severe lupus, anaphylaxis, or organ-threatening disease needs urgent evidence-based care. Systems language must not soften emergencies.

Phase-state reasoning must therefore remain subordinate to urgent clinical judgment whenever organ threat, sepsis, anaphylaxis, severe inflammation, malignancy, immunodeficiency, or rapidly progressive disease is possible.

It also must not become a way to psychologize unexplained symptoms. A neuroimmune or allostatic lock is not a euphemism for “not real.” It is a recognition that pain, fatigue, autonomic instability, and cognitive symptoms may arise from embodied regulation under constraint.

Nor should phase-state reasoning become an excuse for endless testing. The goal is better care, not diagnostic expansion without action. If a phase-lock distinction does not change understanding, prioritization, or treatment, it may not be useful.

The framework must remain pragmatic: does this distinction help the patient move?

This pragmatic test keeps the framework clinically accountable: distinctions are justified only when they improve understanding, prioritization, safety, sequencing, or care (Maturana, 1988; Maturana & Varela, 1980).

22.11 Transition to Biomarkers

Diagnosis as phase-state reasoning naturally leads to the question of measurement. If disease is not only a category but a regulatory state, then biomarkers must evolve beyond single molecules and static thresholds. Clinicians need ways to identify inflammatory phase, resolution capacity, clearance burden, mitochondrial stress, tissue remodelling, immune memory, microbial ecology, neuroimmune load, and health-cycle re-entry.

The future biomarker is not a single molecule; it is a regulatory-state profile.

A regulatory-state profile would integrate immune activity, metabolism, mitochondrial stress, clearance, repair, tissue state, microbial ecology, exposure context, allostatic burden, and function rather than isolating one marker from the organism's living process (Buck et al., 2017; O'Neill et al., 2016; Picard et al., 2018).

The next section therefore turns to biomarkers and phase-state medicine: how measurement might better reflect the living process clinicians are trying to guide.

23. Biomarkers and Phase-State Medicine

If chronic immune disease is not only a diagnostic category but a regulatory phase-state, then biomarkers must be reconsidered. A single laboratory value can be useful, sometimes decisive, but it rarely captures the living pattern of the organism. An elevated inflammatory marker may indicate infection, autoimmune activity, tissue injury, malignancy, metabolic inflammation, or recovery from damage. A positive antibody may indicate disease, risk, memory, or incidental recognition. A cytokine may be driver, consequence, compensatory signal, or epiphenomenon. A normal result may reassure, but it may also miss tissue-local, mitochondrial, neuroimmune, microbial, or functional phase-locks.

The future biomarker is not a single molecule; it is a regulatory-state profile.

This is a conceptual extension of systems immunology and immunometabolism: clinically meaningful measurement must capture patterns across immune signalling, metabolic state, tissue context, clearance capacity, and functional recovery (Buck et al., 2017; Medzhitov, 2008; O'Neill et al., 2016).

This does not mean that single biomarkers are obsolete. C-reactive protein, erythrocyte sedimentation rate, complement levels, autoantibodies, eosinophil counts, immunoglobulins, renal markers, liver enzymes, urinalysis, cytokines, ferritin, D-dimer, troponin, thyroid function, glucose, HbA1c, vitamin and mineral levels, and many other tests remain clinically important. In some cases, a single result can change management urgently. The point is not to abandon conventional biomarkers, but to situate them within a phase-state interpretation.

A biomarker becomes more useful when we ask: what phase of the organism's immune-metabolic cycle does this marker reflect? Does it indicate danger detection, defence, containment, resolution, clearance, repair, memory, exhaustion, fibrosis, immune deficiency, or failed re-entry? Is it systemic or tissue-local? Is it active or historical? Does it identify a treatable driver, a downstream consequence, or a compensatory response?

Phase-state medicine therefore requires biomarkers that are dynamic, contextual, and multi-level.

Static values remain useful, but their meaning changes when interpreted through timing, tissue localization, disease phase, allostatic load, exposure, treatment, and re-entry capacity (McEwen, 1998; Naviaux, 2014).

23.1 From Static Markers to Regulatory Profiles

Many conventional biomarkers are static snapshots. They show what is measurable at one point in time. This is useful, but immune disease is temporal. A patient may flare and remit. A tissue may remain primed between flares. A marker may rise after damage has already occurred. Another may normalize while fatigue, pain, fibrosis, or post-exertional worsening persists. A single snapshot may miss the sequence.

A regulatory-state profile would aim to capture pattern rather than isolated value.

Such a profile would be longitudinal and integrative, tracking how immune activity, memory, metabolism, mitochondrial stress, tissue damage, repair, clearance, microbial ecology, neuroimmune regulation, and function change together over time (Netea et al., 2016; Picard et al., 2018; Serhan, 2007).

It would ask how inflammatory activity, immune memory, metabolic state, mitochondrial stress, tissue damage, repair, clearance, microbial ecology, neuroimmune regulation, and function relate to one another over time.

For example, in inflammatory bowel disease, the relevant profile may include symptoms, stool markers, endoscopic appearance, histology, anaemia, nutrition, microbiome context, inflammatory markers, imaging, fibrosis risk, and quality of life. In asthma, it may include symptoms, spirometry, eosinophils, IgE, FeNO where available, exacerbation history, allergen exposure, airway remodelling, sleep, and environmental triggers. In lupus, it may include autoantibodies, complement, urinalysis, renal function, interferon-related markers where available, symptoms, organ involvement, fatigue, infection risk, and treatment effects.

The point is that the biomarker profile should map the organism's phase-state, not merely confirm the label.

This protects measurement from becoming purely classificatory and reorients biomarkers toward the clinical question of what adaptive transition is needed next (Naviaux, 2014; Serhan & Savill, 2005).

23.2 Immune Signatures

Immune signatures may include cell counts, cell phenotypes, cytokines, chemokines, antibody patterns, complement activity, transcriptomic profiles, interferon signatures, T-cell states, B-cell states, innate immune activation, and markers of immune exhaustion or trained immunity.

These signatures are useful because immune-cell state, complement activity, cytokine patterning, interferon tone, and trained innate readiness can help identify dominant immune modes when interpreted in clinical context (Chen et al., 2016; Netea et al., 2016; Ricklin et al., 2010).

These signatures can help identify whether the organism is in antiviral alarm, type 2 inflammation, neutrophilic inflammation, immune-complex activation, autoinflammatory danger, immune deficiency, or regulatory failure.

But immune signatures require interpretation. A cytokine elevated in serum may not reflect what is happening in tissue. A transcriptomic signature may be influenced by infection, medication, circadian timing, stress, age, sex, and comorbidity. A high eosinophil count may reflect allergic disease, parasitic infection, drug reaction, eosinophilic disorder, or other causes. Low immunoglobulins may indicate primary immunodeficiency, medication effect, protein loss, malignancy, or other processes.

The value of immune signatures lies in pattern recognition tied to clinical context.

Their value depends on whether they help distinguish active danger, antiviral alarm, type 2 barrier activation, immune-complex injury, autoinflammation, deficiency, resolution failure, or treatment effect (Medzhitov, 2008; Schroder & Tschopp, 2010).

They should help answer: what immune mode is dominant, and what treatment logic follows?

23.3 Metabolic and Mitochondrial Markers

Because immune phase-states are metabolically embodied, metabolic and mitochondrial markers are central to future phase-state medicine.

Immunometabolism and mitochondrial stress biology show that immune-cell state, inflammatory readiness, repair, exhaustion, and re-entry capacity are shaped by metabolic programming and energetic reserve (Buck et al., 2017; O'Neill et al., 2016; Picard et al., 2018).

Conventional metabolic markers such as glucose, insulin resistance, lipids, liver enzymes, renal function, lactate in selected contexts, iron studies, B12, folate, vitamin D, thyroid function, and nutritional markers already provide important information about immune resilience and repair capacity.

More specialized mitochondrial markers remain more difficult to apply clinically. Mitochondrial function is tissue-specific, dynamic, and hard to infer from simple blood tests. Nevertheless, mitochondrial stress, redox imbalance, altered energy metabolism, post-exertional worsening, and impaired recovery are clinically important in many chronic conditions. Future medicine may develop better ways to assess mitochondrial phase-state, including cellular respiration assays, metabolomics, redox markers, mitochondrial DNA release, mitophagy markers, and integrated physiological testing.

The key is caution. Mitochondrial language should not outrun measurement.

This caution is important because mitochondrial dysfunction is tissue-specific and difficult to infer from simple blood tests; mitochondrial concepts should guide careful inquiry rather than become vague explanatory labels (Naviaux, 2020; Picard et al., 2018).

Fatigue does not automatically mean mitochondrial disease. Yet mitochondrial coherence should remain part of the interpretive field when patients show energy limitation, poor recovery, post-exertional worsening, inflammatory persistence, or repair failure.

23.4 Resolution and Clearance Markers

Current clinical medicine often measures inflammation better than resolution.

Resolution biology emphasizes that inflammation is actively terminated through pro-resolving mediators, neutrophil clearance, macrophage transition, efferocytosis, and tissue repair preparation (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

We can detect elevated CRP, ESR, cytokines, leukocytosis, ferritin, or tissue inflammation, but we less often measure whether inflammation is actively resolving, whether efferocytosis is adequate, whether debris is being cleared, whether lymphatic drainage is sufficient, or whether damaged mitochondria are being removed.

A life-coherent systems immunology needs better markers of resolution and clearance.

Future markers should help determine not only whether inflammation is present, but whether the organism is successfully clearing apoptotic cells, damaged mitochondria, immune complexes, mucus, debris, or fibrotic material (Ravichandran & Lorenz, 2007; Youle & Narendra, 2011).

Potential future markers may include specialized pro-resolving mediator profiles, macrophage state markers, efferocytosis capacity, autophagy and mitophagy indicators, circulating cell-free DNA or mitochondrial DNA, immune-complex burden, complement activation products, markers of neutrophil extracellular traps, lymphatic imaging, mucociliary function, glymphatic and sleep-related clearance indicators, and tissue-specific debris markers.

Clinically, some clearance problems are already assessed indirectly: urine sediment in nephritis, sputum production in airway disease, sinus imaging in drainage obstruction, kidney and liver function, ferritin and inflammatory patterns, imaging of abscess or effusion, and pathology showing necrosis or fibrosis. But the broader principle remains underdeveloped: resolution is not simply low inflammation. It is successful completion of inflammatory work.

23.5 Tissue Imaging and Structural Phase-State

Imaging is a biomarker of tissue phase-state.

Imaging and structural assessment are essential because blood markers may not capture local inflammation, fibrosis, obstruction, perfusion changes, remodelling, or tissue damage (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Ultrasound, MRI, CT, PET, endoscopy, histology, elastography, pulmonary function testing, echocardiography, vascular imaging, and other tools can show inflammation, obstruction, fibrosis, edema, perfusion, remodelling, erosion, thickening, and tissue damage.

Tissue imaging is especially important because blood markers may not reflect local disease. A patient may have active synovitis with modest systemic inflammation. A patient may have airway remodelling not captured by routine blood tests. A patient may have fibrotic progression despite limited inflammatory markers. A patient may have mucosal disease visible on endoscopy while symptoms fluctuate.

Phase-state medicine therefore asks imaging to answer temporal questions: Is the tissue actively inflamed? Is damage accumulating? Is repair becoming fibrosis? Is obstruction impairing clearance? Is perfusion altered? Is remodelling reversible or fixed? Is the tissue returning to function?

A tissue is not healed merely because a systemic marker improves. The tissue must regain participation in the organism's life.

This makes tissue function and structural recovery central endpoints of phase-state medicine rather than secondary consequences of systemic biomarker normalization.

23.6 Microbiome, Virome, and Exposure Markers

Microbiome and virome testing hold promise but must be used cautiously.

Microbiome and virome data are biologically relevant, but clinical interpretation remains context-dependent because microbial communities vary across time, tissue, diet, medication, infection history, and host state (Belkaid & Hand, 2014; Hooper et al., 2012; Virgin, 2014).

The microbiome is complex, variable, and context-dependent. Many commercial tests provide data that are difficult to translate into reliable clinical action. Yet microbial ecology is clearly relevant to immune regulation, especially in gut, skin, airway, sinus, oral, and genitourinary conditions.

Future biomarkers may better identify microbial configurations associated with inflammation, loss of diversity, pathogen overgrowth, biofilms, phage shifts, metabolite deficiency, barrier disruption, or treatment response. Metabolomic markers may be more clinically useful than taxonomy alone because microbial function often matters more than species lists.

Exposure markers are similarly complex. Some exposures can be measured directly, such as lead, certain occupational toxins, allergens, air pollution indices, or building assessments. Others are harder to quantify or interpret. The framework should encourage serious exposure assessment while avoiding speculative testing that lacks clinical validity.

The biomarker question should always be: does this measurement change care in a safe, evidence-aware way?

This question should govern microbiome, virome, exposure, mitochondrial, and commercial biomarker testing alike: measurement is justified when it improves safety, diagnosis, prioritization, or treatment decisions.

23.7 Health-Cycle Re-Entry Markers

Perhaps the most neglected biomarkers are markers of re-entry into the health cycle. Medicine often tracks disease activity but undermeasures recovery of life. A patient may have normalized

inflammatory markers yet remain unable to sleep, walk, work, think clearly, digest normally, tolerate exertion, maintain relationships, or participate meaningfully.

Health-cycle re-entry requires functional biomarkers.

Functional markers such as sleep, exertional tolerance, pain, fatigue, cognition, appetite, orthostatic tolerance, movement, social participation, and quality of life indicate whether biological improvement has translated into restored living (Antonovsky, 1987; Naviaux, 2020).

These may include sleep quality, activity tolerance, post-exertional symptom response, heart-rate variability where clinically useful, orthostatic tolerance, pain scores, fatigue measures, cognitive function, appetite, bowel regularity, respiratory capacity, exercise testing in appropriate contexts, rehabilitation milestones, work capacity, social participation, and patient-reported outcome measures.

These are not “soft” outcomes. They are indicators of whether the organism has re-entered ordinary living.

Treating function as central prevents medicine from mistaking biochemical improvement for completed healing when the person remains unable to participate in ordinary life.

A life-coherent medicine should treat them as central, while still grounding them in disease-specific safety.

23.8 Biomarkers as Instruments, Not Possessions

The observer-humility principle applies strongly to biomarkers.

Biomarkers are observer instruments: they reveal aspects of the organism, but they do not exhaust the living process and must be interpreted within history, tissue state, symptoms, exposure, treatment, and time (Maturana, 1988; Maturana & Varela, 1980).

A biomarker is an instrument, not the organism itself. It can reveal, guide, warn, or mislead. It may become overvalued because it is measurable. It may become undervalued because it is normal. It may be used to validate or invalidate patient experience too quickly.

A normal test does not prove that the organism is coherent. An abnormal test does not automatically prove causation. A marker must be interpreted within history, examination, tissue state, symptoms, function, exposure, treatment, and time.

The ethical risk is clear: patients with abnormal markers may be reduced to numbers, while patients with normal markers may be dismissed. Both errors violate life-coherent care.

The right question is: what does this marker help us see, and what remains unseen?

This question preserves both scientific rigor and humility by preventing normal markers from dismissing suffering and abnormal markers from becoming total explanations.

23.9 Toward Phase-State Dashboards

The long-term horizon is a phase-state dashboard for immune-mediated disease. Such a dashboard would not be a universal panel applied mechanically to every patient. It would be disease-specific and clinically tailored. Its purpose would be to integrate data across levels:

diagnostic category;
tissue niche;
current inflammatory activity;
immune signature;
metabolic reserve;
mitochondrial stress where measurable;
resolution and clearance indicators;
repair and fibrosis markers;
microbial or exposure context;
allostatic burden;
functional status;
health-cycle re-entry.

This dashboard would help clinicians ask: where is the organism in the immune-metabolic cycle, and what transition is needed next?

A phase-state dashboard should therefore remain clinically tailored and parsimonious, integrating only those measures that clarify current phase, risk, treatment sequence, or re-entry capacity (Naviaux, 2014; O'Neill et al., 2016; Serhan, 2007).

The danger, of course, is overcomplexity. A dashboard that overwhelms clinicians and patients would not be life-coherent. The goal should be elegant sufficiency: enough data to guide care, not maximal measurement for its own sake.

This principle protects patients from overtesting and protects clinicians from data overload while preserving the value of multi-level assessment.

23.10 Transition to Treatment

Biomarkers matter because treatment should be phase-directed. If the dominant state is destructive defence, suppression may be lifesaving. If the dominant state is impaired resolution, treatment must help inflammation complete. If the dominant state is uncleared debris, drainage or clearance is central. If the dominant state is fibrosis, anti-remodelling strategies matter. If the dominant state is mitochondrial conservation and failed re-entry, pacing and gradual restoration are necessary. If the dominant state is immune deficiency, strengthening defence and preventing infection may be priority.

The next section therefore turns to treatment as phase restoration.

The purpose of treatment is not merely to silence symptoms or normalize isolated markers. It is to help the organism move from its current locked state toward the next coherent phase of living.

The treatment discussion follows directly from phase-state medicine: biomarkers matter because they guide treatment toward suppression, resolution, clearance, repair, protection, pacing, rehabilitation, or re-entry according to the dominant lock (Naviaux, 2014; Serhan & Savill, 2005).

24. Treatment as Phase Restoration

If diagnosis becomes phase-state reasoning, then treatment becomes phase restoration. The purpose of care is not merely to suppress symptoms, normalize isolated biomarkers, or force the organism back to ordinary function. The deeper purpose is to help the organism move from a locked regulatory state toward the next coherent phase of living.

Suppression prevents damage; resolution completes inflammation; clearance removes danger material; repair restores structure; reintegration restores health-cycle participation.

This therapeutic grammar integrates conventional immune suppression with resolution biology, clearance, tissue repair, rehabilitation, salutogenesis, and health-cycle re-entry (Antonovsky, 1987; Fullerton & Gilroy, 2016; Naviaux, 2014; Serhan, 2007).

Together, these five phases provide the therapeutic grammar of life-coherent systems immunology. Each treatment should be understood in relation to the phase transition it is intended to support. In some patients, the immediate need is suppression of destructive immune activity. In others, the priority is removal of persistent exposure, treatment of infection, drainage of retained material, restoration of sleep, support for clearance, prevention of fibrosis, rehabilitation after deconditioning, or careful re-entry into movement and social life. The same disease may require different therapeutic logics at different times.

Treatment should therefore ask: what is the organism trying to complete, and what prevents completion?

This question helps align treatment with the organism's current phase-state rather than applying one therapeutic logic to every chronic immune condition (McEwen, 1998; Naviaux, 2014).

24.1 Suppression: Preventing Damage When Defence Becomes Destructive

Immune suppression has a central and legitimate place in phase restoration.

Suppression is life-serving when immune activity threatens organ function, tissue integrity, airway patency, vascular stability, or survival; in such cases, controlling destructive inflammation is a precondition for healing (Medzhitov, 2008).

In organ-threatening, tissue-destructive, or life-threatening immune disease, suppression may be urgent. Severe asthma, anaphylaxis, vasculitis, lupus nephritis, inflammatory bowel disease flare, autoimmune haemolysis, multiple sclerosis relapse, inflammatory arthritis with erosive risk, severe dermatitis, cytokine storm, or autoinflammatory crisis may require decisive intervention.

Suppression becomes life-coherent when immune defence has become destructive and must be restrained to preserve the organism.

This includes corticosteroids, conventional immunosuppressants, biologic therapies, small-molecule inhibitors, complement-targeted therapies, cytokine blockers, antihistamines, leukotriene modifiers, mast-cell stabilizers, and other disease-specific treatments. These therapies are not opposed to an organism-centered approach. They are often essential expressions of it. If the organism is damaging kidney, lung, vessel, gut, brain, skin, blood, or joint tissue through maladaptive immune activity, controlling that activity is a condition of healing.

The caution is that suppression is not the whole of restoration.

Suppression may reduce immediate injury without resolving tissue memory, debris, fibrosis, exposure, sleep disruption, metabolic constraint, or functional re-entry (Serhan & Savill, 2005; Wynn & Ramalingam, 2012).

Suppression can reduce damage, but it may not clear debris, resolve tissue memory, reverse fibrosis, restore mitochondrial reserve, repair barriers, normalize sleep, rebuild muscle, address exposure, or re-establish participation. Suppression may create the possibility of healing, but it does not always complete healing by itself.

The clinical question is therefore not whether suppression is good or bad. The question is whether suppression is necessary, sufficient, excessive, mistimed, or incomplete for the patient's current phase-state.

24.2 Resolution: Completing Inflammation

Inflammation does not end merely by being blocked.

Resolution is an active biological programme involving specialized pro-resolving mediators, macrophage transition, neutrophil apoptosis, efferocytosis, clearance, and tissue repair signalling (Fullerton & Gilroy, 2016; Serhan, 2007; Serhan & Savill, 2005).

In healthy healing, inflammation resolves through active biological processes. Resolution includes changes in lipid mediators, macrophage reprogramming, neutrophil apoptosis, efferocytosis, regulatory signalling, restoration of barrier integrity, and transition toward repair. If these processes fail, inflammation may persist even when the initial trigger has changed.

Resolution-oriented care asks how to help the organism complete inflammatory work.

In some cases, this requires removing the trigger. In others, it requires controlling excessive inflammatory amplification so that resolution can proceed. In others, it requires improving sleep, nutrition, metabolic health, tissue oxygenation, microbial balance, or drainage. Resolution is not a single treatment category. It is a phase transition that can be supported through several routes.

This perspective helps avoid a common therapeutic confusion. A patient may feel better when inflammation is suppressed, but relapse when treatment is reduced because the tissue never completed resolution. Another patient may have persistent symptoms despite low inflammatory markers because the problem is no longer active inflammation, but failed repair, fibrosis,

neuroimmune sensitization, or re-entry failure. Another may remain inflamed because an exposure, infection, crystal burden, or immune complex source continues to stimulate danger.

Resolution asks: has the inflammatory episode truly ended, or has it only been quieted?

This distinction matters clinically because symptom or marker suppression may mask unresolved triggers, uncleared debris, fibrotic repair, or incomplete re-entry.

24.3 Clearance: Removing Danger Material

Clearance is central to treatment because the organism cannot resolve what it continues to encounter as danger.

Clearance biology includes efferocytosis, autophagy, mitophagy, lymphatic drainage, mucociliary clearance, glymphatic clearance, filtration, microbial control, and removal or containment of persistent material burdens (Bustamante-Marin & Ostrowski, 2017; Randolph et al., 2017; Ravichandran & Lorenz, 2007; Xie et al., 2013; Youle & Narendra, 2011).

Dead cells, damaged mitochondria, mucus, immune complexes, crystals, fibrin, toxins, biofilms, necrotic tissue, misfolded proteins, matrix fragments, and microbial remnants can all sustain immune activation. Treatment must therefore ask what has not been removed.

Clearance-oriented care may include antimicrobial therapy where infection is present, surgical drainage when abscess or obstruction exists, airway clearance in bronchiectasis or mucus retention, sinus drainage where anatomy and inflammation block flow, urate-lowering therapy in gout, debridement of chronic wounds, removal of infected devices, support for renal or hepatic function, treatment of constipation or bile flow disorders where relevant, sleep restoration for glymphatic and systemic recovery, and rehabilitation that improves circulation and lymphatic movement.

The key is specificity. Clearance does not mean vague “detoxification.” It means identifying the burden and supporting physiologically valid pathways of removal.

This protects the framework from unsupported detoxification claims while preserving the legitimate importance of drainage, clearance, filtration, microbial control, and waste removal in immune recovery (Rappaport & Smith, 2010; Serhan & Savill, 2005).

This distinction protects patients. Many people with chronic illness are offered broad detoxification protocols that may be expensive, unsupported, or unsafe. A life-coherent approach does not dismiss toxic burden or clearance biology, but it insists on disciplined clinical reasoning. What burden is present? How do we know? Which pathway removes it? Is the intervention safe? Is the organism strong enough to tolerate it? Does it improve function?

Clearance must be non-forcing. A low-reserve organism can be worsened by aggressive mobilization, excessive exertion, extreme diets, heat exposure, supplement stacking, or rapid

medication changes. The goal is not to push material through the system at any cost. The goal is to restore the organism's capacity to process and remove what prevents resolution.

24.4 Repair: Restoring Structure Without Overbuilding

Repair is necessary because inflammation and clearance are not enough.

Repair requires coordinated activity among macrophages, fibroblasts, epithelial and endothelial cells, extracellular matrix, angiogenesis, metabolism, and mechanical signalling (Wynn et al., 2013; Wynn & Ramalingam, 2012).

Tissue must regain integrity. Barriers must close. Epithelium must regenerate. Vessels must stabilize. Matrix must remodel. Nerves must recalibrate. Muscles must rebuild. Mucosa must heal. Synovium must quiet. Skin must restore barrier function. Lung tissue must preserve gas exchange. Gut tissue must regain absorption and tolerance.

But repair must be guided. Repair that does not exit becomes fibrosis, stiffness, stricture, adhesion, airway remodelling, vascular thickening, scar, or chronic pain.

This is the therapeutic meaning of the repair-overbuild lock: repair must restore function without becoming a self-sustaining fibrotic or mechanical constraint (Wynn & Ramalingam, 2012).

Repair is healing only when it restores function and participation.

Treatment as repair may include nutritional restoration, correction of deficiencies, physical rehabilitation, wound care, pulmonary rehabilitation, mucosal healing strategies, barrier care, occupational therapy, graded strengthening when appropriate, antifibrotic therapy in selected diseases, control of repeated injury, and protection from ongoing exposure. It may also include psychological and relational repair when illness has disrupted trust, identity, and participation.

Repair requires timing. A tissue that is actively inflamed may not tolerate aggressive rehabilitation. A patient with post-exertional worsening may worsen if pushed too soon. A fibrotic tissue may need movement but within mechanical limits. A malnourished patient cannot repair well. A sleep-deprived patient cannot rebuild efficiently. A socially unsupported patient may not be able to carry out complex recovery plans.

The question is not simply, "How do we repair?" It is, "What repair is possible now, and what conditions must first be restored?"

24.5 Reintegration: Returning to the Health Cycle

The final therapeutic goal is reintegration.

Reintegration links treatment to salutogenesis: recovery is not complete until biological improvement supports sleep, movement, nourishment, relation, meaning, and participation (Antonovsky, 1987).

The patient is not healed simply because a marker improves, a flare quiets, or a tissue stabilizes. Healing is incomplete until the organism can re-enter health-cycle rhythms: sleep, movement, nourishment, digestion, waste removal, social relation, meaningful activity, nature contact, learning, creativity, care, and ordinary participation.

Reintegration is often the most neglected phase of treatment.

Many patients survive acute disease but remain outside life. They are less inflamed but still exhausted. Their joints are less swollen but still weak. Their lungs are stable but activity remains restricted. Their gut inflammation is quieter but food remains frightening. Their infection has cleared but exertion still causes relapse. Their skin is improved but social confidence is damaged. Their labs are normal but sleep, cognition, pain, and function remain poor.

Phase restoration asks medicine to care about this endpoint.

This endpoint-centered view prevents care from stopping at biomarker improvement when the organism-person remains unable to function or participate.

Reintegration may require pacing, rehabilitation, return-to-work planning, sleep treatment, pain management, autonomic support, social support, nutritional rebuilding, psychological care, environmental change, family education, and gradual restoration of confidence in the body. It also requires realistic expectations. Some patients may not return fully to prior function. Reintegration may mean a new life rhythm, adaptive supports, disability accommodation, or protection from relapse. The goal is not forced normality. The goal is the fullest coherent participation possible.

24.6 Exposure Removal and Niche Repair

Because immunity is extended through the niche, treatment may require changing the organism's conditions.

Exposure removal and niche repair are supported by environmental-health, exposome, indoor-air, and social-determinants frameworks that show recovery capacity is shaped by housing, air, food, work, safety, care access, and ecological conditions (Commission on Social Determinants of Health, 2008; Institute of Medicine, 2004; Rappaport & Smith, 2010; Wild, 2005).

A patient with asthma may need cleaner air. A patient with occupational dermatitis may need exposure protection. A patient with hypersensitivity pneumonitis may need removal from the antigen. A patient with damp-building-related respiratory disease may need remediation or relocation. A patient with sleep disruption may need changes in work rhythm, pain control, or household conditions. A patient with recurrent infection may need public health, housing, or immune evaluation. A patient with food insecurity may need social support before dietary advice can be meaningful.

Exposure removal is not alternative to medical treatment. It is often a precondition for medical treatment to work.

However, exposure thinking must remain proportionate. Not every symptom is exposure-driven. Not every exposure can be eliminated. Some avoidance strategies can shrink life, increase fear, or become socially and financially impossible. The therapeutic aim is not purity. It is reduction of credible anti-salugenic burden so the organism can complete healing.

Niche repair includes the social and environmental conditions that make recovery possible: safe housing, clean air, manageable work, social support, rest, food access, care coordination, and protection from repeated injury.

These conditions function as generalized resistance resources that make biological phase restoration more affordable (Antonovsky, 1987; Marmot et al., 2008).

These may not look like immunology, but they are part of the immune field.

24.7 Clinical Care as Structural Coupling

Clinical care is itself structural coupling.

The clinical encounter becomes part of the patient's organism–niche field, shaping threat, trust, meaning, comprehension, adherence, and recovery capacity (Antonovsky, 1987; Maturana & Varela, 1980).

The physician does not act from outside the organism–niche system. The clinician enters the patient's world as part of the niche. The diagnosis, explanation, treatment plan, relationship, follow-up, referral, medication, monitoring, and documentation all become perturbations that can either increase coherence or deepen distress.

A clear diagnosis may reduce chaos. A frightening label without explanation may increase threat. A medication may protect an organ. A poorly monitored medication may create fear or harm. A validating encounter may lower allostatic load. A dismissive encounter may increase it. A coherent care plan may make recovery manageable. A fragmented plan may overwhelm the patient.

This does not mean that kindness replaces treatment. It means that treatment is delivered through relationship, and relationship has biological consequences.

Relationship matters because clinical explanation, validation, coordination, and follow-up can alter allostatic burden and the patient's capacity to engage safely with care (McEwen, 1998).

For patients with chronic immune disease, the clinician's task includes orientation. The patient needs to know what is dangerous, what is uncertain, what is treatable, what must be monitored, what can be attempted safely, what should be avoided, and what the next step is. This restores comprehensibility and manageability. It can transform the patient's experience from helplessness to participation.

A life-coherent clinician therefore practices both precision and care. The goal is not to dominate the organism into compliance, but to participate skillfully in conditions that allow the organism to move.

24.8 Minimum Sufficient Force

A phase-restoration approach favors minimum sufficient force.

Minimum sufficient force means matching the strength and timing of intervention to the organism's phase-state, reserve, risk, and capacity for transition (McEwen, 1998; Naviaux, 2014).

This does not mean weak treatment. It means the right amount of force for the phase-state. Severe vasculitis may require strong immunosuppression. Anaphylaxis requires immediate intervention. Sepsis requires urgent treatment. Severe asthma requires decisive airway management. Minimum sufficient force in these contexts may be high.

But in low-reserve, post-infectious, neuroimmune, or allostatic states, excessive force can worsen lock-in. Overexertion, rapid medication changes, extreme diets, aggressive detoxification, overstimulation, or premature rehabilitation may exceed the organism's capacity. Minimum sufficient force may mean pacing, stabilization, sleep restoration, small changes, and careful monitoring.

The principle is not "less is always better." The principle is fit.

In high-risk destructive phases, fit may require aggressive treatment; in low-reserve re-entry states, fit may require stabilization, pacing, and gradual restoration.

The intervention should be strong enough to change the phase-state, but not so forceful that it creates new injury or overwhelms regulatory margins. This is a clinical expression of non-forcing action: not passivity, but timing-sensitive intervention.

24.9 Sequencing Care

Treatment as phase restoration is fundamentally sequential.

Sequencing reflects the biological fact that danger detection, defence, containment, resolution, clearance, repair, memory, and re-entry require different conditions and interventions (Naviaux, 2014; Serhan, 2007).

Different phases require different interventions.

In active destructive disease, first prevent irreversible damage.
In persistent danger, identify and reduce the trigger.
In containment failure, prevent spread.
In containment lock, support drainage or removal.

In unresolved inflammation, promote resolution.
In clearance failure, remove debris or burden.
In repair failure, support tissue restoration.
In repair-overbuild, restrain fibrosis and protect function.
In memory lock, reduce reactivation and help the organism update.
In re-entry failure, restore capacity gradually.

This sequence may loop. A patient may improve, flare, return to suppression, then resume repair. Another may need exposure reduction before medication works. Another may need inflammation control before rehabilitation. Another may need sleep restored before immune regulation improves. Another may need urgent organ protection before broader life conditions can be addressed.

The clinician must therefore revisit the phase-state repeatedly. Treatment is not a one-time plan. It is an adaptive process.

This makes treatment an iterative process of reassessment, response, monitoring, and adjustment as the organism's dominant lock changes over time.

24.10 Integrating Conventional and Life-Coherent Treatment

Life-coherent systems immunology is not a rejection of conventional medicine.

It depends on the diagnostic, pharmacological, surgical, rehabilitative, preventive, and emergency capacities of conventional medicine, while asking how each intervention supports phase transition.

It depends on conventional medicine's diagnostic and therapeutic power. Antibiotics, antivirals, vaccines, immunosuppressants, biologics, surgery, inhalers, antihistamines, antifibrotics, anticoagulants, immunoglobulin replacement, renal protection, pulmonary care, dermatological care, gastroenterological care, rheumatological care, neurology, rehabilitation, and emergency medicine remain indispensable.

The contribution of the life-coherent frame is integration. It asks how these tools support phase transition. It also asks what conventional care may miss if it focuses only on suppression or disease labels.

A biologic may reduce inflammation, but the patient may still need rehabilitation. Surgery may improve drainage, but the patient may still need barrier care and exposure reduction. Antimicrobials may treat infection, but the patient may need microbiome recovery. Steroids may quiet inflammation, but the patient may need bone protection, metabolic monitoring, and sleep support. Antifibrotic therapy may slow scarring, but the patient may need pulmonary rehabilitation and avoidance of further injury.

Good medicine is not either mechanistic or holistic. It is phase-appropriate, evidence-aware, organism-centered, and life-serving.

24.11 Avoiding Therapeutic Errors

The phase-restoration framework helps identify common therapeutic errors.

These errors arise when treatment targets one phase while ignoring the organism's actual sequence, reserve, tissue state, clearance burden, or re-entry capacity (McEwen, 1998; Naviaux, 2014).

One error is suppressing without asking what remains uncleared. This may quiet inflammation but leave debris, exposure, infection, crystal burden, biofilm, or tissue damage active.

Another error is supporting lifestyle without controlling destructive pathology. This may delay necessary treatment and permit irreversible damage.

A third error is rehabilitating before the organism can tolerate re-entry. This may worsen post-exertional states or active inflammatory injury.

A fourth error is avoiding all activity after the organism is ready. This may deepen deconditioning and fear.

A fifth error is treating biomarkers rather than patients. This may normalize numbers while function remains poor.

A sixth error is treating symptoms as purely subjective when they may reflect phase-state physiology.

A seventh error is treating every symptom as evidence of ongoing danger, thereby reinforcing fear and medical overreach.

Phase restoration asks medicine to avoid both neglect and excess. The guiding question remains: what helps this organism move coherently now?

This keeps treatment accountable to timing, proportionality, safety, and the next adaptive transition.

24.12 The Ethical Aim of Treatment

The ethical aim of treatment is not only survival, although survival is fundamental. It is restored participation in life.

Clinical ethics therefore links to salutogenesis: treatment should remain answerable to the patient's capacity to live, relate, act, recover, and participate meaningfully (Antonovsky, 1987).

The patient wants to breathe, sleep, move, eat, think, work, love, create, care, belong, and hope. Immunology must remain answerable to these ends.

A therapy that improves a marker but leaves the person unable to live requires further thought. A therapy that reduces symptoms but increases long-term harm requires caution. A care plan that is scientifically elegant but impossible for the patient to enact is not coherent. A diagnosis that organizes treatment but becomes the patient's identity must be held lightly.

Treatment should help life move again.

This does not mean cure is always possible. Some diseases are chronic, progressive, relapsing, disabling, or only partially reversible. Life-coherent care does not promise what medicine cannot deliver. It seeks the best possible movement under real constraints: less damage, more function, fewer flares, better sleep, safer activity, restored dignity, clearer understanding, and greater participation.

24.13 Transition to Public Health

Treatment as phase restoration applies at the individual level, but many phase-locks are sustained by conditions beyond the clinic.

The transition to public health is supported by social-determinants, exposome, environmental-health, and climate-health frameworks showing that recovery depends on conditions distributed beyond clinical care (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Marmot et al., 2008; Wild, 2005).

Clean air, safe housing, healthy food, sleep-protective work rhythms, microbial stewardship, toxin regulation, climate adaptation, social support, and equitable care all shape whether organisms can complete healing cycles.

This leads directly to public health.

If clinical treatment helps one organism move from lock to coherence, public health protects the conditions under which whole populations can maintain health cycles and complete healing cycles. The next section therefore reframes public health as protection of health-cycle conditions at population scale.

25. Public Health as Protection of Health-Cycle Conditions

If clinical care helps individual organisms move from phase-locking toward coherence, public health protects the conditions under which whole populations can maintain health cycles, complete healing cycles, and avoid preventable immune dysregulation. Public health is therefore not external to immunology. It is immunology at the scale of air, water, housing, food, work, microbial ecology, climate, social protection, and care systems.

Public health is the protection of health-cycle conditions at population scale.

This reframes public health as the protection of generalized resistance resources: clean air, water, housing, food, sleep, microbial stewardship, climate stability, social protection, and accessible care (Antonovsky, 1987; Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

This reframing matters because immune-mediated disease is often treated as an individual clinical problem after it has already become biologically established. A patient develops asthma, eczema, inflammatory bowel disease, autoimmune disease, chronic sinusitis, post-infectious illness, metabolic inflammation, or fibrotic disease, and the health system responds with diagnosis, medication, specialist referral, monitoring, and rehabilitation. These are necessary. But by the time clinical disease appears, organism–niche incoherence may already have been accumulating for years.

Public health asks what could have protected the organism before lock-in occurred.

This question shifts prevention upstream, toward the conditions that reduce perturbation, preserve regulatory margins, and support healing-cycle completion before chronic disease becomes entrenched (McEwen, 1998; World Health Organization, 2021).

It asks whether children are growing in conditions that support immune tolerance, microbial education, sleep, nourishment, movement, safety, and barrier health. It asks whether adults live in environments that allow recovery after infection, injury, stress, pregnancy, surgery, or inflammatory flare. It asks whether buildings, workplaces, food systems, climate policies, and healthcare systems reduce or increase immune perturbation. It asks whether societies generate chronic danger and then medicalize the resulting biological consequences.

A life-coherent public health system would not wait for bodies to become inflamed, allergic, exhausted, fibrotic, or dysregulated before acting. It would protect the cycles that allow immune coherence to develop and recover.

25.1 Clean Air as Immune Protection

Clean air is one of the most fundamental public health conditions for immune coherence.

This follows directly from the airway's role as a living immune boundary exposed continuously to particles, allergens, microbes, smoke, combustion products, and pollutants.

The airway is a living boundary. It encounters particles, allergens, viruses, pollutants, temperature shifts, humidity, smoke, mold fragments, combustion products, and occupational exposures with every breath. When air is chronically polluted, the organism is repeatedly perturbed at one of its most exposed interfaces.

Air pollution can injure epithelium, increase oxidative stress, worsen asthma, amplify allergic inflammation, alter immune responses to infection, contribute to cardiovascular and vascular inflammation, and increase allostatic burden. Indoor air matters as much as outdoor air. Dampness, poor ventilation, smoke, cooking fumes, cleaning chemicals, dust, occupational particles, and mold-related exposures can all influence respiratory and immune health.

Clean air policy is therefore not merely environmental regulation. It is boundary medicine.

At the population level, clean air reduces recurrent danger detection. It lowers the burden on epithelial surfaces, macrophages, mucociliary clearance, antioxidant systems, and inflammatory pathways. It allows the airway to remain open to the world without being chronically forced into defence.

25.2 Safe and Healthy Housing

Housing is an immune niche.

Housing affects respiratory health, indoor air, dampness, mould, allergens, crowding, sleep, stress, thermal safety, social stability, and exposure burden (Institute of Medicine, 2004; World Health Organization Regional Office for Europe, 2009).

It shapes air quality, sleep, microbial exposure, temperature, humidity, stress, crowding, safety, social stability, and exposure to pests, allergens, chemicals, and dampness. Unsafe housing can become anti-salugenic because it repeatedly interrupts health-cycle conditions.

Damp buildings may worsen respiratory and allergic disease in susceptible people. Crowding can increase infectious exposure. Poor ventilation can concentrate pollutants. Heat and cold stress can burden cardiovascular, respiratory, and metabolic systems. Noise and insecurity disrupt sleep. Housing instability increases chronic threat and allostatic load. Chemical exposures from building materials, cleaning products, pesticides, and indoor combustion may add further burden.

Healthy housing is therefore not a social luxury. It is immune infrastructure.

Public-health evidence supports the claim that safe, stable, dry, ventilated, and non-toxic housing protects respiratory, allergic, infectious, sleep, and stress-related health.

A life-coherent public health approach would treat moisture control, ventilation, safe materials, clean indoor air, pest control, thermal comfort, noise reduction, and housing security as part of

immune disease prevention. The clinic can prescribe inhalers, biologics, antihistamines, antibiotics, and steroids, but if the patient returns each night to a niche that reopens danger, healing remains incomplete.

25.3 Food Systems and Metabolic-Immune Coherence

Food systems shape immune coherence through nutrition, metabolism, microbiome, inflammation, endocrine function, mitochondrial capacity, and social life.

Immunometabolism and microbiome research support this connection: diet and food systems shape metabolic inflammation, microbial metabolites, barrier function, adipose biology, and immune-cell state (Belkaid & Hand, 2014; Buck et al., 2017; Hooper et al., 2012; O'Neill et al., 2016).

Public health cannot treat diet only as individual choice. What people eat depends on affordability, availability, culture, marketing, agriculture, work schedules, stress, cooking facilities, education, and policy.

A life-coherent food system would support nutrient density, microbial diversity, metabolic stability, food security, cultural appropriateness, and reduced exposure to harmful contaminants. It would protect children's development, reduce ultra-processed dietary dominance, improve access to fibre-rich and minimally processed foods, and support communities in maintaining food practices that nourish rather than destabilize immune regulation.

Metabolic disease is not separate from immune disease. Insulin resistance, obesity, fatty liver disease, nutrient deficiencies, and food insecurity all affect immune resilience. They alter inflammation, repair, infection risk, mitochondrial function, and recovery capacity. A population living in a food system that promotes metabolic overload while undermining nourishment will carry higher immune-regulatory burden.

Nutrition policy is therefore immunology at scale.

25.4 Microbiome-Protective Policy

The microbiome and virome are part of immune development and regulation.

Microbiota and virome research show that microbial and viral ecologies shape immune education, mucosal tolerance, pathogen resistance, metabolism, inflammatory tone, and barrier function (Belkaid & Hand, 2014; Hooper et al., 2012; Virgin, 2014).

Public health must therefore protect microbial relations without romanticizing infection or rejecting hygiene. The aim is not exposure to dangerous pathogens. It is healthy microbial education, ecological diversity, and prudent stewardship.

Antibiotic stewardship is central. Antibiotics save lives, but unnecessary or poorly targeted use can disrupt microbial ecosystems and contribute to resistance. Microbiome-protective policy

includes appropriate prescribing, infection prevention, vaccination, food-system reform, reduced environmental antimicrobial contamination, support for breastfeeding where possible, careful neonatal care, and protection of microbial diversity through outdoor play, healthy food, and reduced environmental degradation.

Sanitation remains essential. Clean water, sewage control, hand hygiene, and infection prevention are among the great achievements of public health. But microbial protection in the modern age requires balance: prevent dangerous infection while preserving the ecological conditions that help immune systems learn tolerance and resilience.

A life-coherent approach does not ask society to choose between sterility and infection. It asks for microbial wisdom.

25.5 Sleep-Protective Rhythms

Sleep is a public health condition, not merely a private habit.

Sleep is linked to immune function, inflammatory regulation, metabolic repair, memory, glymphatic clearance, pain sensitivity, and recovery capacity (Besedovsky et al., 2012; Xie et al., 2013).

Work schedules, artificial light, noise, stress, housing insecurity, caregiving burdens, digital design, school start times, shift work, economic precarity, and pain all shape sleep. When societies normalize chronic sleep disruption, they weaken immune resilience.

Sleep supports inflammatory regulation, infection defence, glymphatic clearance, metabolic repair, emotional regulation, mitochondrial recovery, tissue healing, and memory. Populations deprived of restorative sleep are more vulnerable to immune dysregulation, metabolic disease, pain amplification, mental distress, poor recovery, and reduced resilience after infection.

Public health must therefore protect sleep through labor policy, housing standards, noise regulation, school and work scheduling, education, clinical screening for sleep disorders, and cultural recognition that rest is biological infrastructure.

A society that treats sleep as expendable should expect immune consequences.

This follows from the biological role of sleep in immune regulation, allostatic recovery, and clearance.

25.6 Toxin Reduction and Chemical Safety

Modern organisms encounter many chemical exposures across air, water, food, consumer products, workplaces, and waste streams.

Exposome research emphasizes that disease risk is shaped by cumulative chemical, biological, physical, occupational, and social exposures across the life course (Rappaport & Smith, 2010; Wild, 2005).

Not all exposures are equally harmful, and risk depends on dose, timing, mixture, susceptibility, and route. But public health has a responsibility to reduce preventable toxic burden, especially where exposures affect children, pregnant people, workers, marginalized communities, and those with chronic disease.

Chemical safety is immune protection because toxins can injure barriers, alter endocrine function, stress mitochondria, change microbial ecology, increase oxidative burden, disrupt development, and impair repair. Occupational health is especially important because workers may face repeated exposures that become anti-salugenic over time.

A life-coherent approach favors precaution where evidence of harm is credible, surveillance where uncertainty remains, and protection of those least able to avoid exposure.

This balances public-health precaution with evidence-strength discipline, especially for children, workers, pregnant people, marginalized communities, and people with chronic disease.

It rejects both chemical denial and indiscriminate fear. The public health task is disciplined reduction of avoidable burden.

25.7 Climate Adaptation as Immune Prevention

Climate adaptation is now part of immune disease prevention.

Climate-health assessments identify heat, wildfire smoke, flooding, vector-borne infection, food and water insecurity, displacement, and care disruption as major pathways through which climate instability affects health (Intergovernmental Panel on Climate Change, 2023).

Heat waves, wildfire smoke, floods, damp buildings, vector-borne infections, food insecurity, water contamination, displacement, pollen shifts, and disaster-related stress all alter immune risk. Climate instability increases perturbations while reducing recovery conditions.

A life-coherent public health system would prepare for these immune consequences. It would protect vulnerable populations during heat events, improve air filtration during smoke episodes, prevent mold and dampness after floods, strengthen infectious disease surveillance, secure food and water systems, support displaced communities, and maintain continuity of care during disasters.

Climate policy is therefore not only ecological or economic. It is preventive medicine.

Climate adaptation protects immune coherence by reducing perturbation load and preserving housing, food, water, sleep, care access, and recovery conditions (Intergovernmental Panel on Climate Change, 2023).

Bodies breathe, drink, eat, sleep, work, and heal inside climate conditions. When climate becomes unstable, immune coherence becomes harder to sustain.

25.8 Early-Life Protection

Early life is a sensitive window for immune development.

Early-life immune development is shaped by microbial exposure, nutrition, infection, antibiotics, stress, pollutants, caregiving, sleep, housing, and social conditions (Belkaid & Hand, 2014; Commission on Social Determinants of Health, 2008; Hooper et al., 2012).

Pregnancy, birth, infancy, childhood nutrition, microbial exposure, sleep, attachment, infection, antibiotics, pollution, stress, housing, and play shape immune tolerance and resilience. Public health should therefore prioritize early-life conditions as immune-coherence foundations.

This includes maternal health, prenatal care, reduced toxic exposures, safe birth, breastfeeding support where possible, appropriate vaccination, infection prevention, nutrition, outdoor play, reduced air pollution, stable housing, caregiver support, sleep protection, and early treatment of allergic, respiratory, developmental, and inflammatory conditions.

The goal is not to eliminate all perturbation from childhood. Immune systems need learning, play, microbial encounter, movement, and adaptation. The goal is to prevent overwhelming, toxic, or chronically unsafe perturbation while supporting developmental richness.

Children need protected openness: enough world to learn, enough safety to develop.

25.9 Equitable Access to Care

Immune coherence depends on timely, trustworthy, affordable care.

Health equity frameworks show that access to care, medication, diagnostics, rehabilitation, environmental assessment, and social support shapes disease burden, complications, and recovery opportunity (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

Delayed diagnosis allows disease to become entrenched. Fragmented care increases allostatic burden. Inaccessible medication allows flares, damage, and disability. Dismissive care worsens mistrust and delays treatment. Overly complex systems make healing unmanageable.

Equity is therefore not only a moral principle. It is biological.

Inequity becomes embodied through delayed diagnosis, higher exposure, chronic stress, fragmented care, food insecurity, housing instability, and reduced recovery resources.

Populations with less access to care often carry higher inflammatory burden, more advanced disease, more complications, and fewer opportunities for early phase restoration.

A life-coherent health system would reduce barriers to primary care, specialist care, diagnostics, medications, rehabilitation, mental health support, environmental health assessment, and social services. It would coordinate care for complex chronic illness rather than forcing patients to navigate fragmented systems alone.

Care access protects phase transitions. When care is delayed, disease locks deepen.

25.10 Public Health as Anti-Phase-Locking

Public health can be understood as anti-phase-locking at population scale.

It reduces the probability that organisms will enter persistent defence, unresolved inflammation, impaired clearance, repair-overbuild, or failed re-entry by protecting upstream conditions of resilience and recovery (Antonovsky, 1987; McEwen, 1998).

It reduces the probability that organisms will become trapped in persistent danger, defence, repair, or re-entry failure.

Vaccination prevents dangerous infections and reduces immune burden. Clean water prevents pathogen exposure. Sanitation reduces infectious load. Air quality regulation reduces barrier injury. Housing policy reduces recurrent respiratory and allostatic perturbation. Food policy supports metabolic and microbial coherence. Antibiotic stewardship protects microbial ecology. Occupational safety reduces repeated injury. Climate adaptation reduces ecological shocks. Social protection reduces chronic threat. Early-life support improves developmental immune calibration. Accessible care prevents acute disease from becoming chronic lock-in.

This is the public health meaning of life-coherent systems immunology: reduce unnecessary perturbation, increase regulatory margins, support healing-cycle completion, and protect health-cycle participation.

25.11 Avoiding Individualization of Public Health Failure

One of the most important ethical implications is that medicine must not individualize public health failure.

Social-determinants research supports this ethical stance: risk and recovery are distributed through housing, air, work, food systems, income, education, safety, discrimination, and care access (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

If a patient's asthma is worsened by polluted air, the answer cannot be only better inhaler technique. If a child's eczema is worsened by housing conditions, the answer cannot be only topical therapy. If metabolic inflammation is driven by food deserts and ultra-processed food systems, the answer cannot be only willpower. If sleep is destroyed by shift work and economic precarity, the answer cannot be only sleep hygiene. If post-infectious recovery is undermined by lack of sick leave, the answer cannot be only self-management.

Clinical care remains necessary, but public health must address the conditions that keep bodies locked.

This is not to deny personal agency. Individuals can often make meaningful changes. But individual agency is always exercised within conditions. Public health expands the field of possible agency by making healthy choices realistic, affordable, safe, and socially supported.

This keeps personal agency within its proper context: individuals act, but they act inside enabling or disabling conditions.

25.12 Public Health Dashboards for Immune Coherence

A life-coherent public health system would need dashboards that track more than disease prevalence.

Such dashboards would function as early-warning systems for the conditions that produce immune burden: exposure, housing, food, sleep, occupational risk, climate vulnerability, care access, and social isolation (Wild, 2005; World Health Organization, 2021).

It would monitor health-cycle conditions and anti-salugenic exposures.

Such dashboards might include air quality, indoor dampness, housing security, food access, sleep disruption, occupational exposures, antibiotic use, green space, climate vulnerability, childhood asthma rates, allergic disease, autoimmune incidence, inflammatory bowel disease, metabolic health, post-infectious disability, healthcare access, social isolation, and environmental toxin burden.

The purpose would not be surveillance for its own sake. It would be early warning. Rising asthma in a district may signal air or housing problems. Rising inflammatory bowel disease may invite investigation of food systems, antibiotics, urbanization, and microbial ecology. Rising post-infectious disability may signal inadequate recovery protections. Rising heat-related illness may signal climate adaptation failure.

Population immune patterns can reveal where the niche is failing life.

25.13 From Public Health to Civilizational Design

Public health sits between clinical medicine and civilization.

It translates biological needs into institutional responsibilities, making visible how air, water, food, housing, work, climate, care, and social protection become embodied (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

It translates biological needs into institutional responsibilities. It recognizes that bodies require conditions: air, water, food, housing, sleep, care, safety, microbial relations, ecological stability, and meaningful participation.

But many determinants of immune coherence lie beyond the health sector. They are shaped by economic systems, urban planning, agricultural policy, labor law, education, housing markets, energy systems, chemical regulation, climate policy, media environments, and political priorities. Public health can identify these conditions, but civilization decides whether to protect them.

This leads to the final outward movement of the paper.

If chronic immune disease reflects, in part, organism–niche incoherence, then a life-coherent civilization would be one whose institutions protect the conditions under which organisms can complete adaptive cycles.

This prepares the civilizational argument by extending public-health reasoning to the larger systems that organize exposure, recovery, and participation.

A pathogenic civilization would be one that normalizes chronic perturbation and then treats the resulting phase-locks as isolated individual disorders.

The next section therefore turns to civilizational implications: toward life-coherent systems.

26. Civilizational Implications: Toward Life-Coherent Systems

A life-coherent systems immunology begins in the clinic but cannot remain there. If immune disease is partly a disorder of organism–niche coherence, then the conditions that shape immunity extend beyond cells, tissues, patients, and even health systems. They include the organization of housing, food, work, air, water, climate, technology, economics, education, law, public knowledge, and care. The immune system is embodied in the organism, but the organism lives inside civilization.

A civilization is life-coherent when its institutions protect the conditions under which organisms can complete adaptive cycles; it becomes pathogenic when it normalizes chronic perturbation and then medicalizes the resulting phase-locks.

The civilizational frame extends social-determinants, exposome, climate-health, and salutogenic reasoning to institutional design: institutions shape whether organisms can maintain health cycles, complete healing cycles, and participate in life (Antonovsky, 1987; Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Wild, 2005).

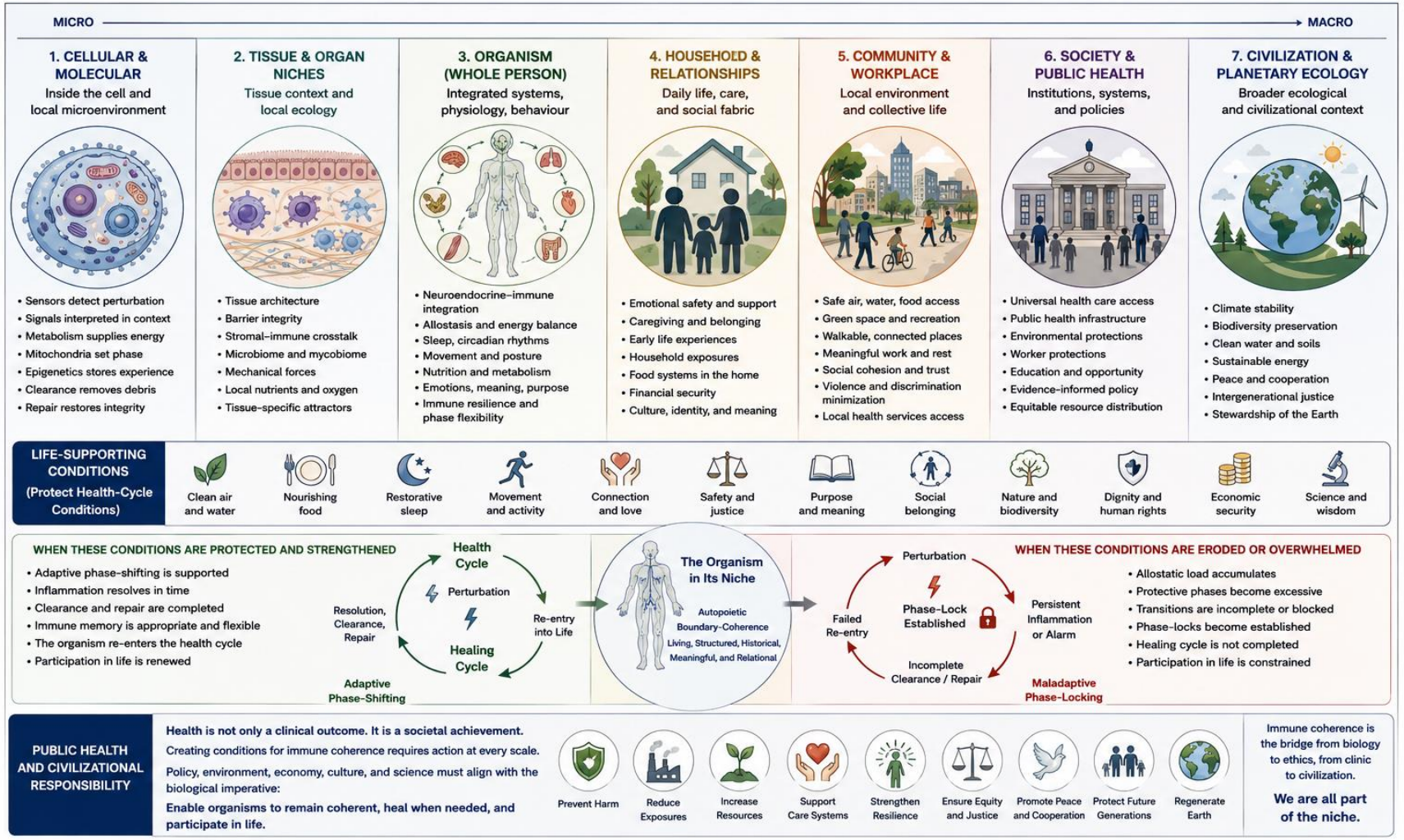
This is not a metaphor. Civilizational arrangements enter bodies through exposure, stress, sleep, diet, microbial ecology, pollution, infection, work rhythms, housing, social safety, medical access, ecological stability, and meaning. These conditions shape immune development, allostatic load, mitochondrial reserve, barrier function, inflammation, tolerance, repair, and recovery. A society does not stand outside biology. It becomes biology.

This is the civilizational expression of embodiment: social, ecological, economic, and institutional arrangements enter physiology through exposure, stress, development, sleep, food, care, microbial ecology, and allostatic load (McEwen, 1998; Marmot et al., 2008).

The question is therefore not only how medicine treats immune disease, but what kind of world repeatedly produces immune incoherence.

Figure 4. From Clinic to Civilization: The Extended Immune Niche and Conditions for Immune Coherence

Immune coherence is built across nested scales of life and sustained by life-supporting conditions that enable adaptive phase-shifting and healing.



The extended immune niche is the totality of conditions that shape immune activity across scales of life. Protecting and strengthening these conditions is the foundation of life-coherent medicine and a healthy civilization.

Caption. Immune coherence is shaped across nested scales, from cellular and molecular regulation to tissue niches, whole-organism physiology, household relations, community conditions, public health systems, and planetary ecology. The figure shows that immune activity is not confined to the body but is extended through the conditions that make adaptive phase-shifting, healing-cycle completion, and health-cycle participation possible. When life-supporting conditions such as clean air and water, nourishing food, restorative sleep, movement, care, social belonging, safety, justice, biodiversity, economic security, and public health infrastructure are protected, organisms are more able to resolve, clear, repair, and re-enter life. When these conditions are eroded or overwhelmed, allostatic load accumulates, phase-locks become more likely, and chronic immune disease appears as a signal of organism–niche incoherence.

26.1 Civilization as Extended Immune Niche

Modern civilization functions as an extended immune niche.

The "extended niche" includes material and institutional conditions that shape immune development and recovery, including air, food, housing, work, microbes, toxins, climate, care, and social safety (Commission on Social Determinants of Health, 2008; Rappaport & Smith, 2010; Wild, 2005).

It determines what people breathe, eat, drink, touch, fear, tolerate, metabolize, work through, sleep within, and recover from. It determines whether children develop in conditions of microbial richness or microbial depletion, nourishment or ultra-processing, outdoor play or indoor confinement, safety or chronic threat. It determines whether adults can rest when ill, access care, avoid toxic exposures, live in healthy buildings, recover after infection, and participate meaningfully in community.

The immune system reads these conditions continuously.

Air pollution is read through airway epithelium, macrophages, oxidative stress, vascular inflammation, and asthma exacerbation. Food systems are read through gut microbiota, insulin signalling, adipose inflammation, mitochondrial function, and metabolic load. Housing is read through sleep, dampness, allergens, crowding, temperature, safety, and indoor air. Work systems are read through circadian rhythm, stress physiology, injury, chemical exposure, and recovery time. Climate instability is read through heat stress, smoke, infectious risk, displacement, food insecurity, and ecological anxiety. Social inequality is read through allostatic load, access to care, inflammation, trauma, and reduced resistance resources.

Civilization becomes immune environment.

This means that immune disease cannot be fully understood if civilization is treated as background. The patient's biology is not confined to the patient's skin. It includes the structures that shape perturbation and recovery. When those structures repeatedly injure, overload, deprive,

or destabilize organisms, the clinic receives the downstream effects as asthma, allergy, autoimmune disease, metabolic inflammation, chronic fatigue, depression, pain, infection vulnerability, fibrosis, or multimorbidity.

Medicine then treats the phase-locks that civilization helped make likely.

26.2 The Medicalization of Chronic Perturbation

One of the central failures of modern systems is the medicalization of chronic perturbation.

Social-determinants and exposome frameworks support this critique by showing that downstream clinical disease often reflects upstream exposure, deprivation, stress, environmental degradation, and lack of protective resources (Commission on Social Determinants of Health, 2008; Marmot et al., 2008; Wild, 2005).

Societies expose organisms to disrupted sleep, polluted air, processed food, social insecurity, climate stress, toxic chemicals, noise, indoor isolation, sedentary work, microbial disruption, overwork, and fragmented care. Then, when bodies become inflamed, dysregulated, exhausted, allergic, or metabolically strained, the problem is often assigned to the individual patient.

The patient becomes the site of treatment, while the niche remains largely unchanged.

This is the civilizational analogue of treating inflammation without asking what keeps reactivating danger.

This does not mean that medication is unnecessary. On the contrary, medication may be lifesaving. The problem is not that medicine treats disease. The problem is that civilization continues to generate disease-producing conditions while asking clinical medicine to manage the consequences downstream.

A life-coherent civilization would not abandon medical treatment. It would reduce the need for preventable treatment by protecting health-generating conditions upstream.

It would ask why so many children require inhalers, why allergic disease is so common, why autoimmune diseases cluster, why metabolic inflammation is widespread, why post-infectious recovery is difficult, why fatigue and pain syndromes proliferate, why sleep is broken, why food systems produce illness, why housing makes people sick, and why ecological instability increasingly enters clinical practice.

The aim is not to blame civilization in a vague way. It is to identify specific institutional patterns that generate anti-salugenic exposure and reduce regulatory margins.

26.3 Economy as Immune Determinant

The economy is one of the most powerful immune determinants because it organizes access to food, housing, work, rest, healthcare, time, safety, and environmental protection.

Economic arrangements become embodied through food access, housing security, work conditions, exposure distribution, healthcare affordability, stress burden, and recovery time (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

When economic systems prioritize throughput, extraction, productivity, consumption, and profit without sufficient regard for biological limits, bodies absorb the cost.

Precarious work disrupts sleep and recovery. Low wages constrain food and housing choices. Unsafe workplaces expose bodies to chemicals, dust, stress, injury, and heat. Lack of sick leave forces infected or inflamed bodies to continue working before healing is complete. Food markets promote ultra-processed products that undermine metabolic and microbial coherence. Housing markets leave people in damp, crowded, polluted, or insecure homes. Healthcare markets can make diagnosis and treatment unaffordable.

The immune system experiences these economic arrangements as allostatic burden.

Allostatic load provides the biological bridge between economic insecurity and immune vulnerability by linking chronic demand to inflammatory, metabolic, neuroendocrine, sleep, and behavioural pathways (McEwen, 1998; McEwen & Stellar, 1993).

A life-coherent economy would be judged by whether it supports the biological preconditions of health: adequate rest, nourishing food, clean environments, safe work, social security, healthcare access, childhood development, ecological stability, and time for care. Economic productivity that depends on chronic depletion is not truly productive. It converts life capacity into short-term output while externalizing the costs into clinics, families, ecosystems, and future generations.

26.4 Law, Policy, and the Protection of Biological Margins

Law and policy define what forms of exposure, burden, and deprivation are permitted. They regulate air quality, water safety, chemicals, workplace conditions, housing standards, food systems, pharmaceuticals, healthcare access, environmental protection, labor rights, disability accommodations, and climate response. They determine whether immune coherence is protected as a public good or left to individual struggle.

Biological margins are not only personal. They are politically organized.

Law and policy influence biological margins through air-quality standards, housing codes, labor protections, chemical regulation, food policy, disability rights, healthcare access, and climate adaptation (Commission on Social Determinants of Health, 2008; World Health Organization, 2021).

A patient with chronic immune disease needs margins: time to rest, access to medication, clean air, safe housing, nourishing food, reduced exposure, reliable care, and social support. If law and policy do not protect these margins, the patient is asked to heal under impossible conditions. The organism remains in defence because the niche continues to demand defence.

A life-coherent legal order would treat preventable exposure and deprivation as health harms.

This follows from the public-health principle that preventable environmental and social conditions can become embodied as disease risk and recovery constraint.

It would strengthen housing codes, air-quality regulation, occupational protection, food policy, climate adaptation, disability rights, and access to care. It would recognize that immune disease prevention is not only a matter of clinical guidelines, but of institutional design.

26.5 Technology and the Immune Field

Technology also shapes immune coherence.

Technologies alter the immune field when they change sleep, movement, exposure, food systems, attention, social connection, pollution, diagnostics, care access, and public-health surveillance.

Some technologies protect life: vaccines, antibiotics, biologics, imaging, clean water systems, air filtration, assistive devices, telemedicine, diagnostics, and public health surveillance. Others can increase burden: sedentary design, artificial light at night, addictive digital platforms, pollution-intensive production, chemical proliferation, ultra-processed food technologies, and infrastructures that disconnect people from sleep, movement, nature, and social presence.

The question is not whether technology is good or bad. The question is whether technology serves life-cycle coherence.

A life-coherent technological system would ask whether its tools support sleep, movement, clean environments, microbial wisdom, care access, reduced exposure, ecological repair, and meaningful participation. It would design for biological rhythm rather than continuous extraction of attention and labor. It would use data to identify population-level perturbation and support early intervention, while protecting privacy, dignity, and equity.

Technology should extend the organism’s capacity for health, not deepen its phase-locks.

26.6 Education and Immune Literacy

Civilization also shapes immunity through knowledge.

Immune literacy connects biological knowledge to lived conditions, helping people understand how sleep, food, infection, air, stress, housing, microbes, climate, and care affect healing capacity.

People need immune literacy: not technical expertise alone, but practical understanding of how sleep, food, infection, air, stress, movement, housing, microbes, climate, medication, and care affect the body’s capacity to heal.

Current education often separates biology from lived conditions. Students may learn organs and systems without learning how social, ecological, and economic arrangements become embodied. Patients may learn disease labels without understanding phase transitions, recovery rhythms, or the difference between suppression, resolution, clearance, repair, and reintegration. Clinicians may be trained deeply in pathways but less consistently in organism–niche reasoning.

A life-coherent education would teach that health is generated through conditions. It would teach children, patients, clinicians, policymakers, and communities how living systems maintain coherence, how chronic perturbation becomes disease, and why care must operate across scales.

Immune literacy can reduce fear. It can also increase responsibility.

Education becomes life-coherent when it increases comprehensibility, manageability, and meaningful participation rather than simply transmitting technical information (Antonovsky, 1987).

A population that understands the immune consequences of polluted air, sleep disruption, food degradation, unsafe housing, and climate instability is better equipped to demand life-protecting institutions.

26.7 The Civil Commons as Immune Infrastructure

The civil commons includes the shared institutions and resources that protect life: public health, clean water, sanitation, education, healthcare, housing standards, environmental protection, food safety, labor protections, social security, public knowledge, ecological stewardship, and systems of care.

These shared protections function as population-level resistance resources, reducing exposure, increasing resilience, and making health-cycle participation more widely possible (Antonovsky, 1987; Commission on Social Determinants of Health, 2008).

These are not merely social supports. They are immune infrastructure.

They reduce unnecessary danger. They increase resistance resources. They support healing-cycle completion. They protect vulnerable bodies. They prevent private suffering from becoming the only site where public failures appear.

When the civil commons is strong, organisms have better chances of maintaining immune coherence. When it is weakened, privatized, underfunded, captured, or ignored, bodies bear the burden individually. The wealthy may purchase cleaner air, safer food, better housing, and specialized care. The poor are left with higher exposure and fewer margins. Immune incoherence then follows social gradients.

A life-coherent civilization must therefore strengthen the civil commons as a biological necessity.

This links public institutions directly to organismic health: when common protections weaken, biological risk is individualized and unequally distributed.

26.8 Civilization as Salugenic or Anti-Salugenic

Civilizations can be evaluated by whether they are salugenic or anti-salugenic.

A salugenic civilization protects the conditions required for healing-cycle completion; an anti-salugenic civilization increases perturbation while weakening recovery resources (Antonovsky, 1987; Naviaux, 2014).

A salugenic civilization protects the conditions that allow organisms to heal. It reduces preventable exposure, supports sleep, nourishes bodies, protects microbial ecology, ensures care, stabilizes climate, safeguards childhood, provides meaningful work, protects time for recovery, and reduces chronic threat. It helps healing cycles complete.

An anti-salugenic civilization does the opposite. It increases perturbation while reducing recovery. It normalizes exhaustion, pollution, ultra-processed food, insecurity, isolation, ecological instability, chemical burden, and fragmented care. It then treats the resulting biological distress as individual pathology.

The distinction is not utopian. It is diagnostic.

It asks whether institutions expand or consume the biological margins required for organisms to defend, resolve, clear, repair, and re-enter life.

Every policy can be asked a life-coherent question: does this help organisms complete adaptive cycles, or does it increase chronic perturbation? Does it protect health-cycle rhythms, or does it disrupt them? Does it expand regulatory margins, or does it consume them? Does it support recovery after illness, or does it force premature re-entry into demand? Does it reduce exposure, or does it distribute exposure onto the least powerful?

These questions bring immunology into ethical and political focus.

26.9 Chronic Immune Disease as Civilizational Feedback

The rising burden of immune-mediated disease may be read as civilizational feedback.

This should be interpreted as a synthetic hypothesis rather than a single-cause claim: disease patterns may reflect interacting changes in exposure, microbiome, food systems, allostatic burden, climate stress, care access, and health-cycle conditions (Belkaid & Hand, 2014; Intergovernmental Panel on Climate Change, 2023; McEwen, 1998; Wild, 2005).

Bodies are not merely failing individually. They may be reporting that the organism–niche relation has become incoherent at scale.

Asthma reports air and barrier stress. Allergy reports altered immune education and boundary alarm. Metabolic inflammation reports food-system and activity incoherence. Autoimmune disease may report complex interactions among genetics, infection, microbiome, toxins, stress, and immune regulation. Post-infectious illness reports inadequate recovery conditions and unresolved immune-metabolic transitions. Fibrosis reports repeated injury and failed repair. Chronic pain-fatigue states report allostatic and neuroimmune overload. Multimorbidity reports cumulative loss of margins.

This does not mean each disease has a simple social cause. It means disease patterns are signals.

This caution prevents civilizational analysis from becoming reductionist while preserving its value as population-level pattern recognition.

A wise civilization listens to bodily signals before collapse deepens. It asks what must be changed in the conditions of living, not only what must be prescribed after disease appears.

26.10 Medicine's Civilizational Role

Medicine has a civilizational role, but it must be carefully understood.

Medicine's role is not to solve all social and ecological problems, but to bear witness to how they enter bodies and to advocate for conditions that make healing possible (Commission on Social Determinants of Health, 2008; Marmot et al., 2008).

Physicians and health systems cannot solve all social, ecological, and economic problems. They should not be expected to repair civilization alone. But medicine can bear witness to embodiment. It can show how policies enter bodies. It can document exposure, inequality, delayed care, climate harms, food-system disease, occupational injury, and housing-related illness. It can advocate for conditions that make healing possible.

Medicine can also refuse to individualize preventable suffering. It can say: this child's asthma is not only a pulmonary problem; it is also an air and housing problem. This patient's metabolic inflammation is not only a lifestyle problem; it is also a food-system problem. This worker's chronic airway disease is not only a personal vulnerability; it is an occupational exposure problem. This post-infectious patient's relapse is not only poor coping; it is also a recovery-time problem. This community's immune burden is not only medical; it is ecological and social.

This is not politicization of medicine in a partisan sense. It is fidelity to biological reality.

The claim is grounded in embodiment: policies, exposures, institutions, and inequities are biologically consequential.

26.11 Life-Coherent Systems

A life-coherent system is one that remains answerable to the conditions of life.

In this manuscript, those conditions are biological, ecological, social, and institutional: clean air and water, food, housing, sleep, movement, care, microbial ecology, climate stability, dignity, and meaningful participation (Antonovsky, 1987; Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023).

It does not measure success only by output, growth, profit, speed, control, or technological expansion. It asks whether living beings can breathe, eat, sleep, move, relate, learn, repair, participate, and flourish without chronic overload. It asks whether ecosystems can regenerate. It asks whether institutions protect future generations. It asks whether economic activity serves life or consumes it.

Applied to immunology, life-coherent systems would protect:

clean air and water;
healthy food and microbial ecologies;
safe housing and buildings;
sleep and circadian rhythms;
movement and nature contact;
social belonging and dignity;
exposure reduction and chemical safety;
climate stability and adaptation;
timely healthcare and rehabilitation;
childhood development and maternal health;
work rhythms compatible with recovery;
public knowledge and trust.

These are not sentimental ideals. They are biological requirements.

If organisms require these conditions to complete adaptive cycles, then institutions that undermine them become pathogenic. Institutions that protect them become salugenic.

26.12 Avoiding Overreach

The civilizational argument must be made carefully.

This caution is necessary because modern medicine, sanitation, vaccination, antibiotics, surgery, maternal care, diagnostics, and public health have reduced suffering dramatically, even as some modern systems generate new burdens.

It should not imply that all immune disease is caused by civilization, that premodern life was healthier, or that modern medicine is merely compensating for modern harms. Such claims would be false. Many modern advances have reduced suffering dramatically: vaccination, antibiotics, sanitation, surgery, intensive care, biologics, maternal care, public health, diagnostics, nutrition, and clean water systems have saved countless lives.

The question is not modernity versus nature. The question is life coherence.

Some modern systems are profoundly salugenic. Others are anti-salugenic. The task is not rejection of modern civilization, but reorientation of its systems toward the conditions that living beings require.

This framework also should not imply that civilizational change replaces clinical care. A patient with severe lupus, asthma, vasculitis, infection, or inflammatory bowel disease needs treatment now. Civilizational reform may prevent future burden, but it does not substitute for immediate care. Life-coherent medicine must work at both levels: treat the patient and transform the conditions that make such illness more likely.

26.13 The Horizon of Immune Coherence

The horizon of life-coherent systems immunology is therefore wider than immunology, but not less precise. It begins with the immune system as the organism's living boundary-coherence process. It follows that process through molecular sensors, gene regulatory networks, metabolism, mitochondria, cell danger responses, tissue niches, clearance systems, exposure ecology, and public health. It then recognizes that the ultimate niche is civilization itself.

The immune system asks, at every scale: under these conditions, can life remain coherent?

The scale-bridging question gathers the manuscript's central concepts: autopoiesis, boundary-coherence, allostasis, salugenesis, phase restoration, public health, and civilizational design (Antonovsky, 1987; Maturana & Varela, 1980; McEwen, 1998; Naviaux, 2014).

If the answer is yes, the organism can protect, tolerate, repair, remember, and participate. If the answer is no, the organism enters defence, closure, inflammation, conservation, fibrosis, or collapse. Disease is often the body's way of showing that the conditions for coherent life have failed.

A life-coherent civilization would take that signal seriously.

26.14 Transition to Limits, Humility, and Conclusion

The civilizational implications bring the argument to its widest scale. But the wider the framework becomes, the more humility it requires. A unifying grammar can illuminate, but it can also overreach. It can integrate mechanisms, but it can also blur distinctions. It can inspire clinical and public health action, but it can also become another totalizing story if not carefully bounded.

The final part therefore returns to limits, evidence strength, and observer humility.

The mechanisms described in this paper are sufficient to define a unifying grammar, but not sufficient to close inquiry.

This methodological limit follows from observer humility: explanatory frameworks are useful only insofar as they clarify phenomena, guide responsible action, remain open to correction, and

avoid becoming totalizing descriptions of the organism itself (Maturana, 1988; Maturana & Varela, 1980).

The task now is to state clearly what the framework can and cannot claim, where evidence is strong, where it is emerging, where it is contested, and how life-coherent systems immunology can remain open, rigorous, and clinically responsible.

Part VIII. Limits, Humility, and Conclusion

27. Evidence Strength, Limits, and Required Humility

A framework that moves across autopoiesis, immunology, metabolism, mitochondria, tissue niches, exposure ecology, public health, and civilization must be held with unusual care. Its strength is integration. Its danger is overreach. The more levels a framework connects, the more easily it can begin to sound more certain than the evidence permits. A life-coherent systems immunology must therefore return explicitly to observer humility.

The mechanisms are sufficient to define a unifying grammar, but not sufficient to close inquiry.

This is the proper status of the framework. It is a grammar for seeing immune-mediated disease as an organism–niche process of boundary coherence, adaptive phase-shifting, and maladaptive phase-locking. It does not claim to be a final theory of immunity. It does not replace disease-specific mechanisms. It does not erase conventional diagnosis. It does not reduce immune disease to stress, exposure, mitochondria, microbiome, trauma, or civilization. It offers a way to organize many valid mechanisms into a clinically meaningful pattern: living systems become ill when adaptive processes cannot complete their transitions.

That claim is useful, but it must remain open.

The framework should therefore be treated as a synthesis and hypothesis-generating clinical grammar, not as a closed theory or replacement for disease-specific evidence.

27.1 The Framework Is Not Final Truth

Life-coherent systems immunology is a conceptual and clinical framework.

Its conceptual foundations draw on autopoiesis, enactive cognition, salutogenesis, allostasis, cell danger response biology, resolution biology, immunometabolism, trained immunity, tissue-niche science, exposure science, and social determinants of health (Antonovsky, 1987; Maturana & Varela, 1980; McEwen, 1998; Naviaux, 2014; Netea et al., 2016; Serhan, 2007; Wild, 2005).

It proposes a way of seeing. It gathers multiple bodies of knowledge into a coherent grammar: autopoiesis, structural coupling, 5E cognition, salutogenesis, allostasis, immune resilience, immunometabolism, mitochondrial signalling, trained immunity, resolution biology, tissue niches, clearance, exposure ecology, and public health.

But coherence is not proof.

Conceptual coherence can organize inquiry, but empirical validity requires testable claims, careful measurement, clinical outcome assessment, and revision in light of evidence.

A framework can be elegant and still require testing. It can be clinically useful and still incomplete. It can reveal patterns and still miss important exceptions. It can help generate hypotheses without settling them.

The language of boundary-coherence, phase-locking, salugenesis, and health-cycle re-entry should therefore be used as an interpretive tool, not as a doctrine.

These terms are strongest when they remain connected to measurable biology: barrier function, immune tolerance, inflammation, resolution, clearance, repair, allostatic load, mitochondrial state, tissue remodelling, and functional recovery (McEwen, 1998; Naviaux, 2014; Serhan & Savill, 2005; Wynn & Ramalingam, 2012).

Its value must be judged by whether it improves clinical reasoning, generates testable hypotheses, prevents harm, supports patient care, and helps medicine see what narrower categories may miss.

27.2 Categories Are Observer-Made

The paper began with observer humility, and it must end with the same discipline.

In Maturana's terms, scientific explanations arise within domains of distinctions made by observers, and those distinctions must be judged by the coherence of the operations they make possible rather than by possession of an observer-free view of reality (Maturana, 1988).

Autoimmunity, autoinflammation, allergy, fibrosis, resolution, clearance, salugenesis, phase-locking, and even "immune system" are distinctions made by observers. They are useful only insofar as they help us coordinate more accurate, compassionate, and life-serving action.

The organism does not inhabit our categories. It lives.

This applies equally to the phase-lock taxonomy proposed in this paper. Recognition locks, inflammasome locks, interferon locks, type 2 barrier locks, fibrosis locks, and neuroimmune pain-fatigue locks are not natural boxes into which patients can be placed. They are clinical instruments for following process.

Vaz's Maturanian observer-dependent immunology reinforces this final caution: immunological explanations remain observer-made distinctions that must remain answerable to the organism's actual living process (Vaz, 2022).

This makes the phase-lock taxonomy an instrument of clinical orientation, not a natural kind taxonomy or an identity imposed on the patient (Maturana & Varela, 1980; Pradeu, 2012).

They must not become identities imposed on patients or substitutes for diagnosis.

A patient is not “a phase-lock.” A patient is a living organism-person whose immune, metabolic, neural, microbial, tissue, social, and ecological relations have become constrained in particular ways.

27.3 The Framework Does Not Replace Diagnosis

No life-coherent grammar should delay or dilute diagnosis. Patients still require careful evaluation for infection, malignancy, autoimmune disease, autoinflammatory disease, immunodeficiency, allergy, asthma, inflammatory bowel disease, vasculitis, endocrine disease, renal disease, liver disease, neurological disease, psychiatric illness, medication effects, toxic exposure, genetic disorders, and other clinically significant conditions.

Phase-state reasoning is a second layer, not a replacement.

It should deepen ordinary diagnosis by adding temporal, tissue, exposure, allostatic, clearance, repair, and functional-recovery questions after urgent pathology and disease-specific categories have been appropriately considered (McEwen, 1998; Medzhitov, 2008; Serhan, 2007).

It helps ask what transition has failed after the disease is named or while the differential diagnosis is being developed. It does not justify vague diagnosis, excessive testing, or bypassing established standards of care. In urgent disease, phase-state language must not slow decisive treatment. Severe asthma, sepsis, anaphylaxis, rapidly progressive glomerulonephritis, vasculitis, severe inflammatory bowel disease, organ-threatening lupus, meningitis, malignancy, or serious immunodeficiency must be treated with appropriate urgency.

The framework deepens clinical reasoning only when it remains disciplined by ordinary medicine.

Its clinical legitimacy therefore depends on preserving differential diagnosis, guideline-informed care, specialist referral when needed, validated testing, and urgent treatment for organ-threatening disease.

27.4 Not All Chronic Disease Is Immune Disease

The framework focuses on immune-mediated and immune-involved illness, but not all chronic disease is primarily immune disease. Some conditions are mainly structural, genetic, degenerative, endocrine, malignant, neurological, psychiatric, vascular, toxic, nutritional, or iatrogenic. Many involve immune processes secondarily, but that does not mean immunity is the primary driver.

A life-coherent approach must resist immunological imperialism.

Immune mechanisms may participate in many chronic conditions, but participation is not the same as primary causation; clinical reasoning must distinguish primary drivers, secondary immune involvement, comorbidity, and downstream inflammatory consequences (Medzhitov, 2008).

To say that the immune system participates in organismic coherence does not mean that every symptom is immune dysregulation. Fatigue may arise from anaemia, hypothyroidism, sleep apnea, depression, medication effects, malignancy, renal disease, liver disease, heart failure, infection, inflammatory disease, or many other causes. Pain may arise from structural injury, neuropathy, inflammation, central sensitization, vascular disease, malignancy, or psychosocial trauma. Brain fog may arise from sleep disruption, medications, mood disorders, neuroinflammation, metabolic disease, infection, endocrine disease, or vascular causes.

The framework should widen inquiry, not prematurely narrow it around immunity.

This safeguard protects the framework from becoming another reductionism, replacing molecular reductionism with immunological or systems reductionism.

27.5 Avoiding Overstatement of CIRS and Exposure Claims

CIRS and broader exposure-linked illness require particular caution.

Dampness, mould, and poor indoor air are recognized public-health and respiratory concerns, but broader syndrome-level claims, biomarker panels, and treatment protocols require careful evidence-strength framing (Bush et al., 2006; Institute of Medicine, 2004; Shoemaker & House, 2006; World Health Organization Regional Office for Europe, 2009).

Environmental exposures can matter greatly. Damp buildings, mold, air pollution, occupational chemicals, allergens, toxins, infectious agents, and poor indoor air can contribute to real disease. Patients with exposure-linked symptoms deserve careful, respectful evaluation.

But not every multi-system illness is caused by mold, biotoxins, pollutants, or hidden exposure. Some proposed tests lack validation. Some treatment protocols are expensive, burdensome, or unsupported. Some claims exceed available evidence. Clinicians must distinguish established environmental disease from plausible but uncertain mechanisms and from speculative narratives.

The correct stance is disciplined openness.

Disciplined openness means taking exposure-linked suffering seriously while distinguishing established environmental disease from plausible hypotheses and speculative narratives (Bush et al., 2006; Rappaport & Smith, 2010; Wild, 2005).

Do not dismiss exposure. Do not absolutize it. Ask what is known, what is measurable, what is plausible, what is modifiable, what else must be ruled out, and what intervention is safe.

CIRS can serve as a case study in exposure-linked phase-locking, but it should not become the foundation of the whole framework.

The framework is better grounded in broader literatures on exposure science, allostasis, immunometabolism, mitochondrial danger signalling, resolution biology, tissue niches, and public health (McEwen, 1998; Naviaux, 2014; O'Neill et al., 2016; Serhan, 2007; Wild, 2005).

27.6 Avoiding Overstatement of Virome and Mobile-Element Claims

Viruses, endogenous retroelements, phages, extracellular vesicles, and mitochondrial nucleic acids are biologically important.

These domains are supported by virome biology, endogenous retroelement research, extracellular-vesicle biology, and mitochondrial innate immune signalling, but their clinical significance varies by disease, tissue, timing, and measurable mechanism (Amari & Germain, 2021; Chuong et al., 2016; Virgin, 2014; West & Shadel, 2017; Yáñez-Mó et al., 2015).

They illuminate the deep history of boundary-crossing information. They may contribute to autoimmunity, interferon activation, post-infectious syndromes, microbial ecology, and inflammatory disease.

But their clinical significance must be demonstrated carefully in each condition. It is easy to move too quickly from plausible mechanism to broad explanation. Viral persistence, retroelement activation, phage dysbiosis, extracellular vesicle signalling, and mitochondrial DNA release are not universal explanations for chronic illness.

The framework should use these mechanisms as part of an open research grammar, not as proof that every chronic immune disease is driven by hidden viral memory or mobile genetic activity.

This caution preserves the value of boundary-crossing information while preventing virome, retroelement, vesicle, or mitochondrial-DNA language from becoming a universal explanation.

27.7 Distinguishing Metaphor from Measurable Biology

The language of coherence, boundary, phase, lock, memory, and re-entry is partly conceptual.

Conceptual language is useful when it organizes measurable biology, but it must be translated back into mechanisms, markers, tissue states, clinical patterns, and outcomes.

It helps organize biological processes. But it must remain connected to measurable phenomena wherever possible.

“Boundary-coherence” may refer to barrier integrity, immune tolerance, compartmentalization, epithelial function, endothelial regulation, microbial ecology, and tissue repair.

These biological referents connect the boundary concept to barrier immunology, microbial ecology, complement, tissue repair, and immune identity rather than leaving it as metaphor alone (Belkaid & Hand, 2014; Hooper et al., 2012; Medzhitov, 2008; Pradeu, 2012; Ricklin et al., 2010).

“Phase-locking” may refer to persistent inflammation, impaired resolution, fibrotic remodelling, trained immune states, mitochondrial conservation, neuroimmune sensitization, or failed functional recovery.

These referents link phase-locking to allostatic load, trained immunity, resolution failure, mitochondrial danger response, fibrosis, and neuroimmune conservation rather than to a vague systems metaphor (McEwen, 1998; Naviaux, 2014; Netea et al., 2016; Serhan, 2007; Wynn & Ramalingam, 2012).

“Memory” may refer to adaptive immune memory, epigenetic priming, tissue-resident cells, fibroblast memory, pain memory, or organismal history.

These terms are useful when they clarify biology. They become dangerous when they float free as poetic substitutes for evidence.

A life-coherent systems immunology should therefore translate its metaphors back into mechanisms, observations, biomarkers, clinical patterns, and testable claims.

This translation discipline is essential for acceptance by clinicians, immunologists, and policymakers because it keeps the framework accountable to evidence, measurement, safety, and practical action.

27.8 Avoiding Patient Blame

One of the most important ethical limits is the avoidance of patient blame.

Social-determinants and allostatic-load frameworks help protect against blame by showing that disease risk and recovery capacity are shaped by material, relational, environmental, economic, and physiological constraints beyond individual willpower (Commission on Social Determinants of Health, 2008; Marmot et al., 2008; McEwen, 1998).

If immune disease is described as organism–niche incoherence, patients must not be made responsible for having failed to achieve coherence. The organism is shaped by genetics, development, infection, exposure, housing, food systems, stress, work, trauma, climate, inequality, and access to care. Much of this lies outside individual control.

Similarly, if disease is described as unfinished healing, patients must not be told that they are failing to heal because they lack meaning, positivity, discipline, or correct behaviour. Salutogenesis is not positive thinking. Salugenesis is not willpower.

Salutogenesis concerns coherence, meaning, manageability, and resistance resources; it should not be reduced to optimism or moral strength (Antonovsky, 1987).

Phase restoration is not moral achievement.

The patient is not at fault for being locked. The task of care is to understand the constraints and help create conditions for movement.

This also means that lifestyle recommendations must be offered with humility. Sleep, food, movement, pacing, stress regulation, and exposure reduction matter, but they are not equally

accessible to all. Advice that ignores poverty, caregiving, unsafe housing, disability, work demands, trauma, or social isolation can become another burden.

Lifestyle recommendations must therefore be matched to real constraints, available resources, social support, and the patient's current phase-state (Antonovsky, 1987; Commission on Social Determinants of Health, 2008; McEwen, 1998).

27.9 Avoiding Anti-Biomedical Misuse

The framework must also avoid being used against biomedicine.

Life-coherent systems immunology depends on the achievements of biomedical science; its purpose is integration, not rejection.

It should not encourage patients to reject immunosuppressants, biologics, antibiotics, vaccines, surgery, inhalers, antivirals, antifibrotics, immunoglobulin replacement, or other evidence-based treatments when these are indicated.

Life-coherent medicine is not anti-pharmacological.

Pharmacological, surgical, rehabilitative, antimicrobial, immunological, and preventive interventions can all be life-coherent when they are evidence-based, phase-appropriate, and directed toward preventing damage or enabling recovery (Medzhitov, 2008; Serhan & Savill, 2005).

It asks what role a treatment plays in phase restoration. Sometimes suppression is precisely what life requires. Sometimes antimicrobial therapy is essential. Sometimes surgery is the necessary path to drainage or repair. Sometimes vaccination prevents dangerous immune burden. Sometimes biologic therapy prevents irreversible organ damage.

The problem is not conventional medicine. The problem is conventional medicine when it becomes too narrow to see the organism–niche process. The solution is not rejection, but integration.

Integration means preserving biomedical precision while widening attention to tissue context, allostatic load, exposure ecology, functional recovery, and the conditions required for healing-cycle completion.

27.10 Avoiding Holistic Overreach

The opposite error is holistic overreach.

Holistic overreach occurs when relational or systems language becomes so expansive that it obscures pathology, delays necessary treatment, or implies that all disease can be resolved by balance, meaning, or lifestyle change.

A framework that speaks of organism, meaning, niche, and civilization can be misused to imply that all disease is relational, all treatment should be gentle, or all pathology can be resolved by restoring balance. This is false.

Some disease requires aggressive treatment. Some tissue damage is irreversible. Some genetic defects cannot be overcome by changing the niche. Some infections kill without antimicrobials. Some autoimmune diseases destroy organs without immunosuppression. Some cancers require surgery, chemotherapy, radiation, immunotherapy, or targeted treatment. Some psychiatric conditions require medication and specialist care. Some patients do not recover despite excellent care.

Life-coherent medicine must remain truthful about limits.

Truthfulness about limits is part of clinical care: some conditions require urgent suppression, antimicrobial therapy, surgery, organ support, specialist treatment, or long-term disease-specific management.

It should support hope without promising cure.

27.11 Evidence Strength Across the Framework

Different parts of the framework rest on different levels of evidence.

Evidence-strength framing should therefore distinguish established mechanisms, plausible integrations, emerging science, contested syndromes, speculative extensions, and original synthesis.

The existence of immune pathways, tissue niches, cytokines, complement, pattern-recognition receptors, mitochondria, inflammasomes, resolution processes, fibrosis pathways, metabolic inflammation, and public health determinants is well established.

These domains are supported by mature literatures in innate immunity, complement biology, immunometabolism, mitochondrial immune signalling, resolution biology, fibrosis, microbiome science, and social determinants of health (Belkaid & Hand, 2014; Buck et al., 2017; Janeway, 1989; Medzhitov, 2008; O'Neill et al., 2016; Ricklin et al., 2010; Serhan, 2007; West & Shadel, 2017; Wynn & Ramalingam, 2012).

The integration of these mechanisms into a phase-locking grammar is conceptual and synthetic.

It should therefore be presented as an organizing framework that requires further empirical testing, clinical refinement, and disease-specific validation.

It is plausible and clinically useful, but it requires further development and testing.

Some domains, such as trained immunity, immunometabolism, mitochondrial immune signalling, resolution biology, microbiome science, and post-infectious syndromes, are rapidly

evolving. They are strong enough to inform the framework, but not always mature enough for definitive clinical translation in every condition.

Other domains, such as CIRS, broad biotoxin illness, commercial microbiome interpretation, detoxification protocols, and some virome or retroelement claims, require greater caution.

These areas should be discussed through explicit evidence-strength language so that clinical openness does not become premature certainty.

A responsible paper should make these differences visible. It should not present all mechanisms with equal certainty.

27.12 Research Implications

The framework suggests several research directions.

First, phase-state biomarkers are needed.

Such biomarkers should distinguish active inflammation, impaired resolution, clearance failure, mitochondrial conservation, trained immune readiness, fibrosis, neuroimmune sensitization, and health-cycle re-entry (Buck et al., 2017; Naviaux, 2014; Netea et al., 2016; O'Neill et al., 2016; Serhan, 2007).

Second, longitudinal studies are needed.

Longitudinal designs are essential because immune disease is temporal: flare, remission, repair, relapse, exposure, treatment response, and functional recovery cannot be understood from isolated time points alone.

Chronic immune disease is temporal. Single time-point measurements miss phase transitions. Studies should track patients through flare, treatment, remission, repair, relapse, and functional recovery.

Third, tissue-niche studies are needed.

Tissue-niche studies should examine resident immune cells, stromal and fibroblast programmes, epithelial and endothelial states, microbial ecology, matrix, mechanics, vascular flow, and local metabolism (Belkaid & Hand, 2014; Galli et al., 2011; Wynn et al., 2013).

Blood biomarkers alone may not capture local disease. Synovium, gut mucosa, airway epithelium, skin, lung interstitium, kidney, vessel, and nervous system each require tissue-specific analysis.

Fourth, exposure and recovery studies are needed.

Such studies should integrate exposome science with recovery conditions, including sleep, housing, pollutants, food systems, allostatic load, climate stress, microbial ecology, and access to care (Commission on Social Determinants of Health, 2008; Rappaport & Smith, 2010; Wild, 2005).

Research should investigate not only what triggers disease, but what prevents healing-cycle completion: sleep disruption, housing, pollutants, food systems, allostatic load, climate stress, and access to care.

Fifth, treatment trials should measure re-entry.

Re-entry outcomes should include function, exertional tolerance, sleep, pain, fatigue, cognition, social participation, and quality of life alongside biomarkers and organ measures (Antonovsky, 1987; Naviaux, 2020).

Sixth, public health research should examine immune disease as a signal of niche incoherence, integrating environmental, social, microbial, metabolic, and clinical data.

This research direction links immune epidemiology to social determinants, climate-health, environmental exposure, food systems, microbial ecology, and health-system design (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Marmot et al., 2008; Wild, 2005).

27.13 Clinical Cautions

For clinicians, the framework should be used as a guide to inquiry, not as a rigid protocol.

Its clinical value lies in improving differential reasoning, sequencing, and care coordination without replacing established diagnostic pathways, disease-specific guidelines, or urgent medical evaluation.

It can help organize complex cases, especially when patients have overlapping inflammation, fatigue, pain, exposure sensitivity, tissue damage, and functional loss. But it should not replace differential diagnosis, guidelines, specialist referral, or evidence-based treatment.

Clinicians should ask phase-state questions while remaining alert to red flags. Weight loss, fever, night sweats, organ dysfunction, neurological deficits, severe pain, bleeding, immunosuppression, recurrent infections, abnormal imaging, renal abnormalities, severe inflammatory markers, hypoxia, chest pain, or rapidly progressive symptoms require standard medical evaluation.

Systems thinking must not become a reason to miss dangerous disease.

27.14 Patient Communication

The framework also requires careful patient communication.

Communication should increase comprehensibility, manageability, and meaningful participation without implying that illness is self-created or that recovery depends on willpower (Antonovsky, 1987).

Terms such as “phase-locking” and “unfinished healing” can be helpful if they reduce fear and increase understanding. They can also be misunderstood. Patients should not hear that their illness is imaginary, self-created, or a failure to move on. They should hear that the body may be stuck in protective processes that once had a purpose but now need help to complete or update.

A useful clinical explanation might be:

“Your body appears to be caught in a protective state. The goal is not to force it, and not to ignore it, but to understand what is keeping it there and help it move safely to the next phase.”

This kind of explanation validates suffering while preserving hope and agency.

This communication style is clinically important because validation, explanation, and shared orientation can reduce threat, support trust, and make care more manageable.

27.15 Required Humility

The required humility is therefore fourfold.

This humility follows from the same observer discipline introduced at the beginning of the manuscript: the organism exceeds the framework, evidence exceeds plausibility, patients exceed categories, and complexity exceeds any single level of explanation (Maturana, 1988; Maturana & Varela, 1980).

First, humility before the organism: the living body exceeds every framework.

Second, humility before evidence: plausible mechanisms must not be overstated.

Third, humility before patients: suffering must be believed even when mechanisms are incomplete.

Fourth, humility before complexity: no single level of explanation is sufficient.

Life-coherent systems immunology is strongest when it remains open, revisable, evidence-aware, clinically grounded, and ethically careful.

This is the methodological posture that allows the framework to integrate without closing inquiry.

28. Conclusion: Toward Organism-Centered Life-Coherent Systems Immunology

Immunity is not merely defence.
It is not merely self/non-self recognition.
It is not merely inflammation.
It is not merely molecular signalling.
It is the organism's living boundary-coherence process.

This formulation integrates autopoiesis, enactive cognition, immune identity, pattern-recognition theory, danger theory, tissue-contextual immunology, and resolution biology into an organism-centered clinical grammar (Janeway, 1989; Maturana & Varela, 1980; Matzinger, 2002; Medzhitov, 2008; Pradeu, 2012; Serhan, 2007; Varela et al., 1991).

This paper has proposed a re-seeing of immune-mediated disease from the side of the living organism. Conventional immunology remains indispensable. Its categories, mechanisms, diagnostics, and treatments are among the great achievements of modern medicine. Autoimmunity, autoinflammation, allergy, infection, immunodeficiency, fibrosis, chronic inflammation, and post-infectious illness are clinically necessary distinctions. Yet they do not fully describe what the organism is doing. They name where the patient has arrived more clearly than how the living process became locked there.

Life-coherent systems immunology begins from a different question: how does an organism conserve coherence while remaining open to the world?

This question is rooted in autopoietic and enactive biology, where living systems conserve identity through ongoing structural coupling with their worlds rather than by remaining closed or passively instructed (Di Paolo et al., 2018; Maturana & Varela, 1980, 1987; Varela et al., 1991).

The organism must defend without becoming permanently defended. It must tolerate without becoming vulnerable. It must repair without overbuilding. It must remember without fixation. It must respond to danger without losing the capacity to re-enter ordinary life. Immune health is therefore not immune silence, nor maximal immune strength, nor permanent tolerance. It is coherent movement between protection and participation.

This view connects immune health to allostasis, tolerance, resolution, repair, and re-entry rather than to one fixed immune state (McEwen, 1998; Serhan & Savill, 2005; Sterling & Eyer, 1988).

From this perspective, chronic immune disease can be understood as maladaptive organism–niche phase-locking.

This synthesis draws together allostatic load, cell danger response biology, trained immunity, mitochondrial danger signalling, resolution failure, tissue remodelling, and failed re-entry into a dynamic clinical grammar (McEwen, 1998; Naviaux, 2014; Netea et al., 2016; Serhan, 2007; West & Shadel, 2017; Wynn & Ramalingam, 2012).

The organism enters a protective, inflammatory, reparative, metabolic, or neuroimmune phase that may have been adaptive at first, but that can no longer complete its transition. Defence does not resolve. Clearance does not complete. Repair does not reintegrate. Memory does not update. Conservation does not release. The healing cycle becomes a holding pattern.

This is the central phase-locking claim: an adaptive response becomes disease when it persists beyond its proper window, cannot complete its transition, or prevents return to ordinary participation.

This reframing does not replace disease-specific medicine.

It should be read as an additional layer of clinical reasoning that preserves conventional diagnosis while asking what regulatory process is locked and what transition is needed next.

A patient with lupus still needs lupus care. A patient with asthma still needs asthma care. A patient with inflammatory bowel disease, vasculitis, chronic sinusitis, interstitial lung disease, immunodeficiency, long COVID, psoriasis, rheumatoid arthritis, or allergic disease still needs careful diagnosis, monitoring, and treatment. But phase-state reasoning adds a second layer. It asks what regulatory process is locked, what tissue niche sustains it, what history installed it, what exposures maintain it, what resources are missing, and what next transition would allow life to move again.

The framework also invites a deeper clinical humility.

This humility follows from the observer-made nature of diagnostic categories and from the ethical need to keep the patient larger than the label, biomarker, pathway, or phase-lock (Maturana, 1988; Maturana & Varela, 1980).

The organism does not live inside our categories. It does not call itself autoimmune, allergic, fibrotic, inflamed, salugenic, or phase-locked. These are observer distinctions. They are useful only if they help us see more faithfully, act more wisely, reduce suffering, and support life. The patient is never the diagnosis, never the biomarker, never the pathway, and never the lock. The patient is a living organism-person whose biology, history, tissue worlds, relationships, exposures, and possibilities exceed every map we draw.

The practical implication is that treatment should become phase restoration.

Phase restoration integrates suppression, resolution, clearance, repair, pacing, rehabilitation, exposure reduction, niche repair, and reintegration according to the organism's current state (Antonovsky, 1987; Naviaux, 2014; Serhan & Savill, 2005).

Suppression is necessary when immune activity is destructive. Resolution is needed when inflammation cannot complete. Clearance is required when debris, damaged mitochondria, immune complexes, toxins, mucus, crystals, biofilms, or matrix fragments remain. Repair is needed when tissue integrity is lost. Reintegration is needed when the organism cannot return to sleep, movement, nourishment, relation, work, creativity, and ordinary participation.

The goal is not to force the organism into health, but to create the conditions under which the next coherent movement becomes possible.

At the public health level, the same logic expands.

Public health becomes the protection of the conditions that allow populations to maintain health cycles and complete healing cycles: clean air, safe housing, nutritious food, microbial stewardship, sleep, toxin reduction, climate adaptation, early-life protection, and equitable care (Commission on Social Determinants of Health, 2008; Intergovernmental Panel on Climate Change, 2023; Marmot et al., 2008; World Health Organization, 2021).

Bodies do not heal in abstraction. They heal in air, housing, food systems, microbial ecologies, work rhythms, social relations, climate conditions, and care systems. Clean air, safe housing, nourishing food, sleep, microbial stewardship, toxin reduction, climate adaptation, early-life protection, and equitable care are not peripheral to immunology. They are the population-level conditions under which immune coherence develops, recovers, and remains possible.

At the civilizational level, chronic immune disease becomes a signal.

This signal should be interpreted cautiously, not as a single-cause claim, but as a population-level invitation to examine exposure burden, allostatic load, food systems, microbial ecology, climate stress, public health infrastructure, and weakened recovery conditions (McEwen, 1998; Rappaport & Smith, 2010; Wild, 2005).

When many organisms are inflamed, allergic, exhausted, metabolically strained, fibrotic, dysregulated, or unable to recover, the question is not only what medications they require. It is also what world they are being asked to inhabit. A civilization becomes life-coherent when its institutions protect the conditions under which organisms can complete adaptive cycles. It becomes pathogenic when it normalizes chronic perturbation and then medicalizes the resulting phase-locks.

The framework must remain modest.

Its value lies in integration without closure: it helps organize established, emerging, and contested mechanisms while preserving diagnosis, evidence strength, clinical safety, and humility.

It is not a final theory. It does not explain all chronic disease. It does not make CIRS, virome mechanisms, mitochondrial dysfunction, exposure, stress, microbiome disturbance, or civilization into a single master cause. It does not replace established diagnosis or evidence-based treatment. Its value lies in its capacity to integrate without closing inquiry: to help clinicians, researchers, patients, and public health systems see immune disease as a living process rather than a static label.

Life-coherent systems immunology therefore offers a grammar of unfinished living.

That grammar is grounded in the claim that chronic immune disease often reflects unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration rather than a single isolated immune error.

Chronic immune disease is not merely inflammation to suppress, nor merely error to correct, nor merely a pathway to block. It is often an organism–niche coherence process caught in unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration.

The task of medicine is to understand the lock without making it the patient's identity.

This ethical task preserves observer humility while keeping care oriented toward the person's next possible movement.

The task of treatment is to support the next adaptive transition.
The task of public health is to protect the conditions that make such transitions possible.
The task of civilization is to stop producing preventable chronic perturbation faster than bodies can heal.

Life-coherent systems immunology reframes chronic immune disease as unfinished living: not merely inflammation to suppress, but an organism–niche coherence process that has become locked in unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration — and now requires conditions, signals, relationships, and care that allow life to move again.

Back Matter

Appendix A. Phase-State Clinical Reasoning Template

This appendix provides a practical template for translating life-coherent systems immunology into clinical reasoning. It is not a diagnostic substitute, treatment protocol, or replacement for established guidelines. It is an orienting instrument for asking what phase of immune life may be dominant, what transition has failed, and what conditions may be needed for the organism to move again.

The central clinical question is:

What is this organism trying to complete, and what is preventing completion?

A.1 Conventional Diagnosis or Differential Diagnosis

The first task is always ordinary clinical medicine. The clinician must identify the disease, syndrome, or differential diagnosis using history, examination, appropriate laboratory testing, imaging, pathology, microbiology, physiology, and specialist assessment where needed.

Possible diagnostic domains include infection, autoimmune disease, autoinflammatory disease, allergy, asthma, inflammatory bowel disease, vasculitis, immunodeficiency, fibrosis, malignancy, endocrine disease, renal or hepatic disease, neurological disease, medication effect, toxic exposure, psychiatric illness, structural injury, or other relevant conditions.

Phase-state reasoning begins after, or alongside, this diagnostic work. It must never be used to bypass urgent evaluation.

A.2 Tissue Niche

The next question is where the immune process has taken form.

Relevant tissue niches may include airway, sinus mucosa, gut, skin, synovium, enthesis, vessel, kidney, lung interstitium, bone marrow, central nervous system, peripheral nerves, lymphatics, adipose tissue, or multiple interacting tissues.

The clinician asks:

What tissue is inflamed, damaged, obstructed, sensitized, fibrotic, infected, poorly drained, or unable to repair?
What local niche features sustain the process?
Are epithelial, endothelial, stromal, neural, microbial, vascular, lymphatic, or mechanical factors involved?

A.3 Dominant Phase-Lock

The clinician then identifies the dominant regulatory lock. This does not replace the diagnosis. It names the living process that appears to be stuck.

Possible locks include:

recognition/misrecognition lock;
danger/inflammasome lock;
nucleic-acid/interferon lock;
viral/mobile-element boundary lock;
barrier-type 2 lock;
mechano-microbial enthesis/IL-17 lock;
immune-complex vascular lock;
trained-immunity lock;
immunodeficiency-dysregulation lock;
resolution/clearance-failure lock;
repair-overbuild/fibrosis lock;
neuroimmune/allostatic pain-fatigue lock.

These are observer distinctions, not identities. Their purpose is to help follow the organism's process more faithfully.

A.4 Sustaining Conditions

The clinician then asks what keeps the lock active.

Possible sustaining conditions include ongoing infection, persistent exposure, barrier injury, dysbiosis, uncleared debris, damaged mitochondria, immune complexes, biofilms, crystals, mucus retention, impaired drainage, fibrotic matrix, sleep disruption, metabolic overload, mitochondrial constraint, allostatic burden, social threat, occupational exposure, medication effects, or fragmented care.

The key question is:

What keeps re-entering the organism as danger, burden, or constraint?

A.5 Next Adaptive Transition

The most important therapeutic question is the next adaptive transition.

Does the organism need suppression, defence, containment, drainage, resolution, clearance, repair, remodelling, rest, pacing, rehabilitation, exposure reduction, metabolic support, sleep restoration, social support, or re-entry into ordinary participation?

The goal is not to force complete recovery in one step. The goal is to identify the next coherent movement.

A.6 Monitoring Re-Entry

Monitoring should include both disease-specific markers and life-cycle markers.

Disease-specific markers may include inflammatory markers, autoantibodies, complement, imaging, organ function, tissue healing, microbial assessment, pulmonary function, renal indices, endoscopy, or other appropriate measures.

Life-cycle markers include sleep, fatigue, pain, movement tolerance, post-exertional response, appetite, digestion, cognition, mood, social participation, work capacity, relational life, and quality of life.

Healing is incomplete until the organism can re-enter health-cycle participation.

Appendix B. Phase-Lock Taxonomy Summary

The following table summarizes the major phase-locks proposed in the paper. It is intended as a clinical and research orientation device, not as a rigid classification system.

Phase-lock pattern	Core unfinished process	Typical biological logic	Clinical question
Recognition/misrecognition lock	Tolerance, recognition, and clearance fail to resolve	Autoantibodies, autoreactive cells, immune recognition in danger context	What is being recognized, and why has recognition become damaging?
Danger/inflammasome lock	Danger detection remains active	DAMPs, PAMPs, crystals, inflammasomes, IL-1 family activation	What danger signal persists?
Nucleic-acid/interferon lock	Antiviral-like alarm cannot exit	Cytosolic nucleic acids, interferon tone, cGAS–STING, TLRs	Why does the organism remain in antiviral alarm?
Viral/mobile-element boundary lock	Boundary-crossing information remains unresolved	Viral persistence/reactivation, endogenous retroelements, vesicles, virome shifts	What boundary-crossing signal remains active or uncleared?
Barrier-type 2 lock	Barrier alarm and repair remain overactive	Epithelial alarmins, IgE, mast cells, eosinophils, mucus, type 2 inflammation	What boundary has become too reactive?
Mechano-microbial enthesis/IL-17 lock	Force, barrier history, and repair remain coupled to inflammation	Enthesis stress, IL-17 pathways, stromal activation, gut-skin-joint links	What role do mechanical load and barrier immune history play?
Immune-complex vascular lock	Recognition material damages flow structures	Immune complexes, complement, Fc receptors, endothelial injury	What immune material is circulating, depositing, or activating complement?
Trained-immunity lock	Innate readiness remains primed	Epigenetic and metabolic innate immune memory	Has innate immunity become too easily reactivated?
Immunodeficiency-dysregulation lock	Defence and regulation fail together	Recurrent infection, autoimmunity, allergy, inflammation, immune defects	Is the organism both vulnerable and inflamed?
Resolution/clearance-failure lock	Inflammation cannot complete because debris remains	Efferocytosis, autophagy, mitophagy, lymphatics, drainage, waste removal	What has not been removed?
Repair-overbuild/fibrosis lock	Repair does not exit	TGF-β, fibroblasts, matrix stiffness, hypoxia, scarring	Has repair become structural constraint?
Neuroimmune/allostatic pain-fatigue lock	Protection and conservation prevent re-entry	Pain sensitization, fatigue, dysautonomia, mitochondrial conservation, allostatic load	Is the organism unable to afford ordinary participation?

Appendix C. Health Cycle, Healing Cycle, and Phase Restoration

The framework distinguishes three related processes: the health cycle, the healing cycle, and phase restoration.

C.1 The Health Cycle

The health cycle is the organism's ordinary rhythm of living. It includes wakeful activity, nourishment, digestion, movement, waste removal, social connection, nature contact, rest, sleep, tissue maintenance, and meaningful participation.

Immune activity is present throughout the health cycle, but it does not dominate the organism's life. It supports surveillance, tolerance, clearance, repair, and readiness while allowing ordinary participation to continue.

C.2 The Healing Cycle

The healing cycle begins when perturbation exceeds ordinary adaptive capacity. The organism temporarily exits ordinary participation and reorganizes around protection and repair.

The healing cycle includes:

surveillance;
boundary sensing;
danger detection;
defence;
containment;
resolution;
clearance;
repair and remodelling;
memory and adaptation;
re-entry into the health cycle.

Disease emerges when this cycle cannot complete.

C.3 Phase Restoration

Treatment as phase restoration asks what transition is needed now.

Suppression prevents damage.
Resolution completes inflammation.
Clearance removes danger material.
Repair restores structure.
Reintegration restores health-cycle participation.

The clinical art lies in sequencing. Some patients need urgent suppression. Others need drainage, clearance, sleep protection, exposure reduction, pacing, rehabilitation, antifibrotic care, antimicrobial therapy, metabolic support, or social protection. Most need a coordinated sequence.

Appendix D. Glossary of Core Terms

Allostasis
The organism's adaptive variation in response to changing demands. Health is not static homeostasis, but the capacity to change state while preserving viability.

Allostatic load
The accumulated cost of repeated or prolonged adaptation without adequate recovery.

Autopoiesis
The self-producing organization of living systems. An autopoietic organism continuously conserves the organization that makes it a living unity.

Boundary-coherence
The organism's dynamic capacity to remain itself while remaining open to exchange with the world.

Cell danger response
A protective cellular phase-shift in which cells reorganize metabolism, signalling, mitochondrial function, and communication in response to threat, injury, infection, or stress.

Clearance
The removal, processing, drainage, recycling, or safe containment of material that would otherwise sustain danger signalling.

Coherence
Adaptive coordination across biological, tissue, organismal, relational, and ecological levels. Coherence does not mean stillness; it means flexible, life-serving movement.

Efferocytosis
The quiet phagocytic clearance of apoptotic cells, especially by macrophages, supporting resolution and preventing inflammatory debris accumulation.

Exposome
The cumulative field of environmental, microbial, chemical, social, nutritional, occupational, climatic, and built-environment exposures encountered by an organism.

Health cycle
The ordinary rhythm of living through activity, nourishment, waste removal, relation, rest, sleep, repair, and participation.

Healing cycle
The organism's temporary reorganization after perturbation through danger sensing, defence, containment, resolution, clearance, repair, memory, and re-entry.

Immune coherence
The immune system's capacity to defend, tolerate, resolve, clear, repair, remember, and re-enter ordinary life in a timely and proportionate way.

Maladaptive phase-locking
A persistent or recurrent regulatory state in which an adaptive immune phase becomes stuck and prevents re-entry into the health cycle.

Organism–niche unity
The inseparable relation between a living organism and the niche in which it develops, adapts, heals, and participates.

Phase restoration
Treatment aimed at helping the organism move from a locked state toward the next coherent biological phase.

Phase-state medicine
Clinical reasoning that asks not only what disease is present, but what regulatory phase the organism is currently locked in.

Resolution
The active biological termination of inflammation and transition toward clearance, repair, and restoration.

Salugenesis
The biological generation of healing through resolution, clearance, repair, remodelling, adaptation, and reintegration.

Salutogenesis
The generation and maintenance of health through coherence, resources, meaning, manageability, and life-supporting conditions.

Tissue niche
The local regulatory field in which immune disease takes form, including resident cells, matrix, vessels, nerves, barriers, microbes, mechanics, metabolism, and history.

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Dr. Bichara Sahely is a physician, systems thinker, and independent scholar whose work integrates internal medicine, public health, ecology, social theory, and life-value philosophy. He trained in biology at Dalhousie University and in medicine and internal medicine at the University of the West Indies, with additional clinical electives at the University of Toronto. His professional work has spanned clinical medicine, environmental health, public policy, water quality, and regional capacity development in the Caribbean.

Dr. Sahely's current writing explores life-coherent medicine, civilizational health, autopoiesis, social and ecological determinants of health, and the conditions under which living systems can conserve coherence, repair injury, and flourish. His work seeks to bridge clinical practice, systems biology, public health, and life-serving institutional design.

Back Cover Synopsis

Modern immunology has transformed medicine, yet many chronic immune-mediated diseases remain difficult to understand through diagnostic categories alone. Autoimmunity, allergy, autoinflammation, fibrosis, chronic inflammation, and post-infectious illness describe important clinical patterns, but they do not always explain how the living organism became stuck there.

Life-Coherent Systems Immunology offers a new organism-centered grammar. It reframes immunity not primarily as war against non-self, but as the organism's living boundary-coherence process: the way a living being conserves identity while remaining open to a changing world.

The central claim is that many chronic immune diseases can be understood as maladaptive organism–niche phase-locks. The organism enters a protective state — defence, inflammation, containment, repair, memory, or conservation — but cannot complete the transition back into ordinary living. Disease becomes unfinished healing: unfinished defence, unfinished clearance, unfinished repair, or unfinished reintegration.

Moving across autopoiesis, 5E cognition, salutogenesis, allostasis, immunometabolism, mitochondria, tissue niches, exposure ecology, public health, and civilization, this paper proposes a clinically useful framework for phase-state reasoning and phase restoration.

The result is a medicine of deeper seeing: name the disease, but also understand the living process that has become locked — and the conditions required for life to move again.