FOR IMMEDIATE RELEASE
Orthomolecular Medicine News Service, Feb 21, 2026

Systemic Leaky Barrier Syndrome (SLBS)

A Systems-Level Framework for Chronic Disease

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Over the past two decades, biomedical research has increasingly documented the loss of barrier integrity across multiple organ systems in chronic disease. Intestinal permeability ("leaky gut"), blood-brain barrier disruption, endothelial dysfunction, alveolar-capillary leakage, renal filtration injury, and skin barrier defects have typically been studied in isolation, within separate clinical and disciplinary silos.

In a recent preprint [1], *Systemic Leaky Barrier Syndrome (SLBS): A Systems-Level Framework for Chronic Disease* (Cheng, 2026), I proposed the term **Systemic Leaky Barrier Syndrome (SLBS)** as a unifying systems-level framework to integrate these observations across chronic disease.

SLBS describes a condition in which multiple biological barriers - intestinal, vascular, blood-brain, pulmonary, renal, hepatic, placental, and cutaneous - progressively lose structural and functional integrity due to shared upstream drivers. These include environmental toxins, chronic inflammation, oxidative and redox imbalance, micronutrient insufficiency, mitochondrial dysfunction, and impaired tissue repair capacity.

Across organ systems, barrier integrity depends on common structural and metabolic elements:

- Tight junction proteins
- Cytoskeletal support
- Extracellular matrix stability
- Endothelial and epithelial integrity
- Adequate cellular energy supply
- Redox-balanced repair systems

When these shared systems are stressed chronically, barrier resilience declines across multiple tissues simultaneously.

SLBS and Progressive Chronic Disease

This framework reframes chronic disease not as isolated organ failure, but as a systemic failure of barrier integrity and repair.

For example:

Chronic Kidney Disease

The kidney's filtration barrier depends on intact glomerular endothelium, basement membrane integrity, and podocyte structure. When redox imbalance, inflammation, and metabolic stress persist, filtration selectivity deteriorates. Albumin leakage and progressive nephron injury follow. What appears clinically as "renal failure" may reflect long-standing structural and oxidative compromise of the renal barrier system.

Hypertension

The vascular endothelium functions as a dynamic permeability and signaling barrier. Endothelial dysfunction - characterized by impaired nitric oxide signaling, increased permeability, oxidative stress, and inflammatory activation - precedes and drives sustained vascular stiffness and pressure dysregulation. High blood pressure, in this context, reflects loss of endothelial boundary regulation and structural vascular resilience.

Neuroinflammatory Disorders

Blood-brain barrier compromise permits peripheral inflammatory mediators and immune cells to enter neural tissue, amplifying oxidative stress and microglial activation.

Across these conditions, barrier breakdown functions both as an initiating factor and as a powerful amplifier of immune activation, inflammatory signaling, metabolic dysregulation, and iron-driven oxidative injury. Excess iron can cause ferroptosis and retinopathy leading to blindness [2]. A self-reinforcing cycle of tissue damage emerges.

The Cancer Connection

Genetic mutations and cellular transformation are real and important, but the tissue environment in which these mutations accumulate actively influences how cancer develops.

Healthy tissues maintain strict structural and functional boundaries:

- Epithelial layers maintain polarity and controlled proliferation

- Endothelial barriers regulate nutrient and oxygen delivery
- Extracellular matrix architecture constrains cell migration
- Immune surveillance operates within defined compartments

When these boundary systems are chronically disrupted - through inflammation, oxidative stress, micronutrient depletion, and impaired repair - the tissue microenvironment becomes destabilized.

Loss of boundary control contributes to:

- Persistent inflammatory signaling
- Increased oxidative DNA stress
- Impaired apoptosis and repair
- Degradation of extracellular matrix structure
- Increased vascular permeability
- Reduced immune containment

In this destabilized environment, genetically abnormal cells are more likely to survive, expand, invade, and eventually metastasize.

From a systems perspective, cancer progression can therefore be viewed as occurring in the context of advanced barrier and regulatory failure - not merely as an isolated genetic event. Barrier breakdown does not "cause" cancer in a simplistic sense. Rather, it creates conditions that lower structural and metabolic constraints on malignant progression.

This interpretation aligns cancer with other progressive chronic diseases within a shared upstream terrain of redox imbalance, structural degradation, and impaired repair capacity.

Clinical Implications

Importantly, SLBS does not replace disease-specific diagnosis or treatment. It complements conventional approaches by shifting attention upstream - toward:

- Barrier-centric biomarkers
- Structural resilience
- Redox balance
- Micronutrient sufficiency
- Mitochondrial energy support
- Inflammation control

Rather than waiting for organ-specific failure, earlier intervention aimed at preserving barrier integrity may help prevent multi-system progression.

A Systems-Level Construct

As with other systems-level constructs in medicine, SLBS is offered as a conceptual framework intended to stimulate research, refine clinical thinking, and encourage preventive intervention. Further work will be needed to:

- Delineate causal hierarchies
- Develop barrier-focused diagnostics
- Explore therapeutic strategies informed by this model

Orthomolecular medicine has long emphasized structural integrity, nutritional sufficiency, redox balance, and upstream causality. SLBS provides a modern systems framework that unifies these principles across biological barriers and chronic disease states.

References:

1. Cheng, R.Z. Systemic Leaky Barrier Syndrome (SLBS): A Systems-Level Framework for Chronic Disease. 2026. DOI: 10.20944/preprints202602.0069.v2; Available online: https://www.preprints.org/manuscript/202602.0069.

2. Li, L.; Dai, Y.; Ke, D.; et al. Ferroptosis: New Insight into the Mechanisms of Diabetic Nephropathy and Retinopathy. Front Endocrinol (Lausanne) 2023, 14, 1215292. DOI: 10.3389/fendo.2023.1215292.