

Recent advances in integrative allergy care

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An integrative model of clinical allergy is proposed that incorporates clinical and experimental observations in the following three areas: (1) classical studies of IgE-mediated atopic response and, to a lesser degree, the other three types of Gell and Coombs' hypersensitivity responses; (2) an ecologic view of clinical allergy that includes sensitivity to environmental agents independent of the dose of the excitant; and (3) an expanded, integrative perspective of hypersensitivity responses that focuses on oxidative–dysoxygenative dysfunction (ODD) that profoundly influences sensitivity reactions included in the first two categories. The proposed integrative model has a strong explanatory power for many hitherto poorly understood aspects of clinical allergy. For instance, none of the Gell and Coombs' or other recognized types of hypersensitivity reactions explain why certain antigen exposures evoke strong responses under one set of conditions but not under another in the same atopic individuals. Beyond that, the proposed model provides a scientifically sound basis for adding to specific antigen immunotherapy nutritional, antioxidant, detoxification, and oxygenative therapies to enhance clinical benefits. *Curr Opin Otolaryngol Head Neck Surg* 2000, 8:260–266

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In 1983, I recognized spontaneity of oxidation in nature as the primary drive in all oxidative phenomena in nature and proposed it to be the primary mechanism for perpetuating oxidative molecular injury in biologic phenomena, including the human aging process [1]. In a series of publications that followed, I explored the issues of:

1. The fundamental oxygen order of human biology [2–5];
2. The impact of the molecular duality of oxygen on human health and disease [6];
3. Oxidative cell membrane injury [7];
4. Oxidative injury to intracellular matrix and mitochondria [8];
5. Oxidative phenomena in atopic disorders and multiple chemical sensitivity syndrome [7];
6. Stunted allergen-specific IgG response to immunotherapy in patients with chronic fatigue syndrome [9];
7. Morphologic changes of oxidative coagulopathy (observed in freshly prepared peripheral blood smears with high resolution [×15,000] phase contrast microscopy) in ischemic coronary artery disease [10];
8. The incidence and extent of oxidative coagulopathy in chronic fatigue syndrome, fibromyalgia and environmental illness [11,12];
9. Clinical evidence of oxidative injury to the hormone–receptor–response element–gene activation cascades [13];
10. Oxidative regression to primordial cellular ecology [14•]; and
11. Oxidative–dysoxygenative basis of fibromyalgia [15••].

In this article, the classical studies of atopy and the core clinical concepts of environmental medicine are briefly reviewed to provide a framework for presenting the integrative oxidative–dysoxygenative model of clinical allergy.

The classic atopic perspective

Modern concepts of allergy may be traced to Charles Robert Richet, who described anaphylactic reaction in 1902 [16]. Four years later, Von Pirquet introduced the term allergy (derived from the Greek words *allos* [other] and *ergia* [energy]) for an altered state of immune responsiveness or “changed reactivity” of an individual [17]. In 1911, Noon [18] introduced specific antigen immunotherapy. In 1923, Coca and Cooke [19] proposed the term atopy (derived from the Greek word

atopos, meaning strange or uncommon) for an abnormal state of hypersensitivity in an individual, rather than a hypersensitive response in a healthy individual, and believed that such sensitivity could not be transferred to animals or humans. Prausnitz and Kustner in 1921 laid the cornerstone for immunologic investigation of allergic phenomena by documenting the presence of a transferable skin-sensitizing factor in the serum of allergic individuals [20]. In 1964, Gell and Coombs [21] proposed their classification of four mechanisms of allergic reactions, Type-I reaction being the response mediated by the reaginic antibody. In the mid-1960s, Ishizaka *et al.* [22] established IgE as a new unique immunoglobulin on the basis of the following three principal criteria: its ability to bind the specific antigen, its unique antigenic determinants, and its correlation with biologic activity as demonstrated by the Prausnitz and Kustner (P-K) technique. In 1966, Wide *et al.* [23] described the radioallergosorbent (RAST) assay for semi-quantitative measurement of allergen-specific IgE antibodies and ushered in the era of *in vitro* diagnosis of allergy. In 1980, my colleagues and I demonstrated local IgE production in plasma cells in the nasal mucosa of atopic persons and in nasal polyps [24,25]. The same year, my colleague, Madhava Ramanarayanan, and I described micro-ELISA assays for allergen-specific IgE and IgG antibodies and, to achieve a higher level of assay sensitivity and specificity, developed a methodology for accounting for a range of variability in the nonspecific binding among individual antigens [26,27]. Using that assay, Hurst *et al.* [28] demonstrated the local production of allergen-specific IgE antibodies in the middle ear mucosa and firmly established such mucosa as the primary target of the atopic response.

The ecologic perspective

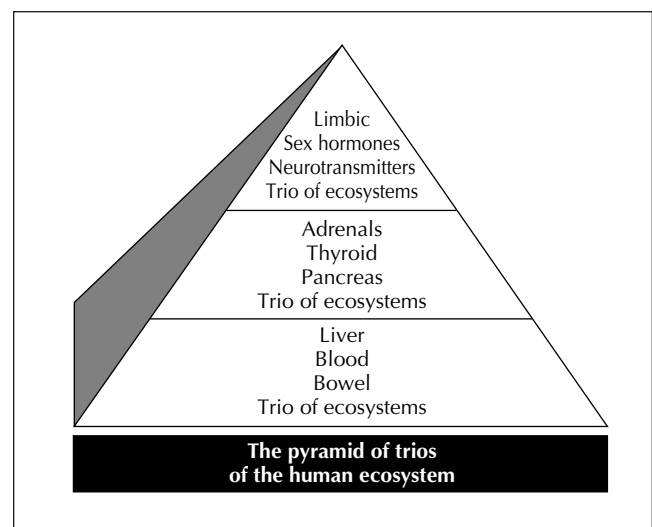
During the next two decades, a wide gulf developed between IgE researchers and clinical ecologists who focused on clinically verifiable patterns of hypersensitivity reactions that could not be explained on the basis of IgE-mediated or other immunologic sensitivity mechanisms. The discipline of clinical ecology was defined as the study of the effects of the environment on the individual by the pioneers of the field, including Randolph [29], Rea [30], and Waickman and Vojdani [31••]. Chemical sensitivity was defined as an adverse response of an individual to environmental chemicals at levels that are generally considered safe [32]. Thus, chemical sensitivity is independent of the dose of excitant. The core concept of chemical sensitivity holds that clinical expression of an adverse reaction is determined by the following: (1) the body tissue or organ involved; (2) the chemical nature of the excitant trigger; (3) the biochemical individuality of the person (the individual susceptibility of the person to a given excitant); (4) the length of

the exposure; and (5) the existence of concurrent but unrelated stressors as well as synergism among them (the concept of total load) [32]. Four general principles that govern the cause-and-effect relations in clinical ecology are (1) total load; (2) adaptation (first described by Selye [33] and including masking or acute toxicologic tolerance); (3) bipolarity consisting of an initial stimulatory phase followed by a depressive phase; and (4) biochemical individuality.

In my view, clinical ecology was an important advance beyond the classical atopy because it could explain a broad spectrum of clinical manifestations not accounted for by the latter. The IgE researchers continued to focus on issues of single-allergen sensitivity and consequences of specific immunotherapy in such disorders. The ecologists, although recognizing the theoretical merit of such work, found those findings to be of very limited clinical value because allergic persons invariably have multiple sensitivities. After decades of doubt and denial, the existence of multiple chemical sensitivity syndrome was finally acknowledged and its relevance to the management of the classical allergy understood [34–36].

During the early 1980s, many clinical observations led me to investigate the role of altered states of the bowel ecosystem on the clinical manifestations of hypersensitivity reactions [2,3]. For example, a marked improvement in symptoms of atopic dermatitis was observed in many patients with empiric therapies that putatively “restored the bowel health.” Relief of constipation was associated with relief of sinusitis headache in others.

Figure 1. Schema of the Pyramid of Trios of Human Ecosystems



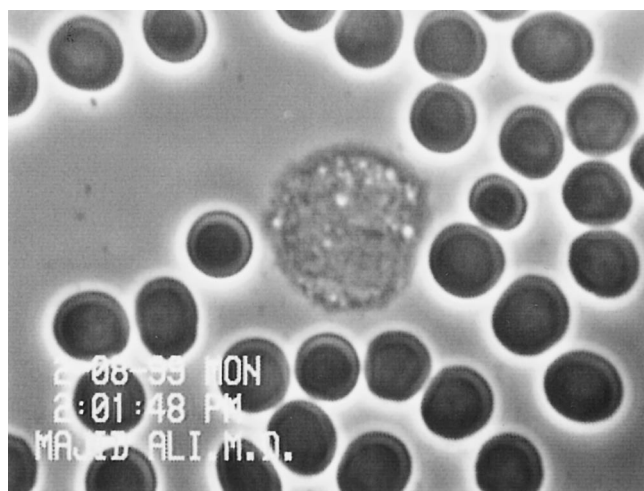
Shows the Schema of the Pyramid of Trios of Human Ecosystems that is used as a model for establishing clinical priorities for atopic patients with indolent chronic immune disorders such as chronic fatigue syndrome, fibromyalgia, and chemical sensitivity syndrome.

Symptoms of allergic rhinitis often subsided with antifungal therapies [11]. Such observations to the concept of altered states of bowel ecology as the basis for heightened hypersensitivity states.

The oxidative-dysoxygenative perspective

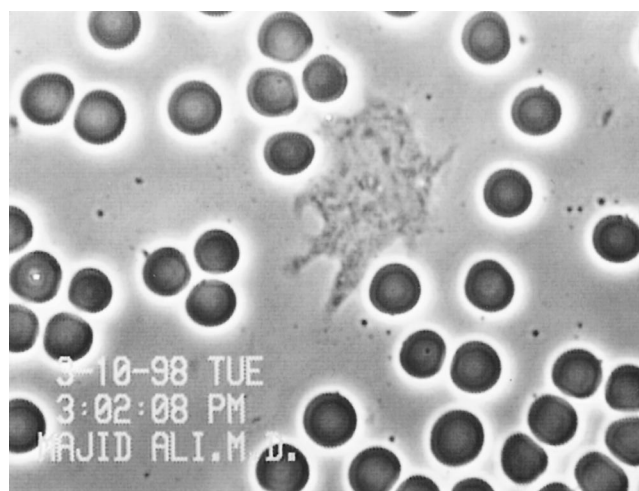
Notwithstanding the great advances in both classical allergy and clinical ecology, certain fundamental aspects of clinical hypersensitivity reactions remained unexplained. For instance, eczema lesions flare more in some weeks than in others in the same person. Lifestyle stressors exaggerate bronchospasm more on some days than on others in the same asthma patient. Symptoms of Crohn's colitis and ulcerative colitis remit and relapse for no apparent reason in most instances. Food sensitivity reactions vary over a broad range in the same individual. Allergic rhinitis becomes more intense on some days when pollen count is low and abates on days when pollen counts are high. The phenomenon of "spreading sensitivity reactions" (long vigorously denied by IgE researchers) is increasingly recognized in chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity syndrome. The molecular basis of the above cannot be understood on the basis of the known immunologic responses. Such considerations led me, in collaboration with my colleague, Omar Ali [37], and others [38], to look beyond those responses and focus on issues of redox homeostasis. Recently, I put forth an oxidative-dysoxygenative model as the molecular basis for fibromyalgia [15••]. Extended studies of freshly prepared peripheral blood smears with high resolution phase contrast microscopy led to the description and characterization of oxidative coagulopathy (Figs. 1–4) [4]. The oxidative nature of oxidative coagulopathy was

Figure 2. High resolution phase contrast photomicrograph



Shows a high resolution ($\times 15,000$) phase contrast photomicrograph of the freshly prepared peripheral blood smear of a healthy subject used as a control.

Figure 3. High resolution morphology of loose (soft) microclot

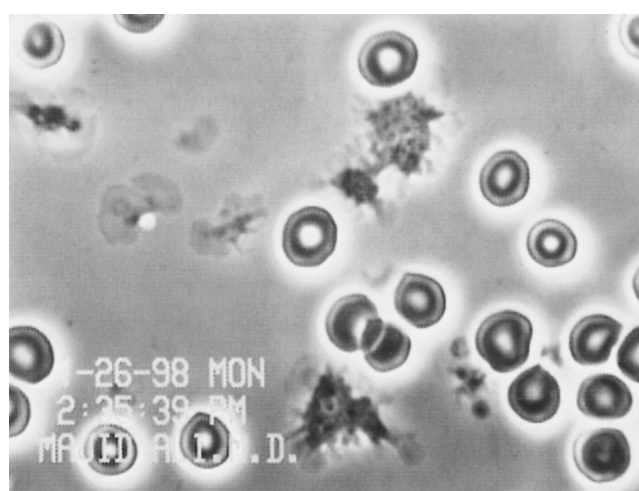


Shows high resolution morphology of loose (soft) microclot in the peripheral blood smears of a highly atopic 8-year-old girl with diffuse eczema.

established by its reversal by antioxidants in the early stages.

From our microscopic observations we inferred that oxidosis of blood (oxidative coagulopathy) is the primary mechanism that links redox disruptions of the bowel ecosystem with clinicopathologic consequences of oxidosis in all microecologic cellular and macroecologic tissue–organ ecosystems of the body [12,39]. Thus, changes of oxidative coagulopathy were deemed morphologic evidence of systemic dysregulation of the redox homeostasis. The role of such dysregulation in the pathogenesis and clinical symptomatology of allergic diathesis, to our knowledge, had not been explored. It

Figure 4. Zones of congealed plasma and microclots



Shows zones of congealed plasma (small arrows) and two microclots (larger arrows) in a 34-year-old atopic woman with fibromyalgia.

seemed self-evident to us that all mediator responses of hypersensitivity reactions would be greatly amplified by oxidative coagulopathy and its cellular consequences. The clinical manifestations of hypersensitivity states in such an oxidative–dysoxygenative context were seen as surface phenomena profoundly influenced by the foundational changes in redox homeostasis in the trio of the bowel, blood, and liver ecosystems.

Although the role of systemic oxidosis in clinical allergy, as reflected by microscopic changes in oxidative coagulopathy, had not been investigated, it is noteworthy that the role of local factors involved in redox homeostasis in nasal and bronchial allergy has drawn considerable attention. The nasal and bronchial mucosa excrete nitric oxide (NO), a ubiquitous and potent modulator of redox homeostasis [40–42]. Among its many biologic roles, NO also modulates ciliary motion [43]. Of direct relevance to the present discussion is the observed increased NO excretion in allergic rhinitis [44,45]. Topical use of an NO synthase inhibitor (N-nitro-L-arginine-methyl-ester [L-NAME]) in limited studies did not increase nasal cavity volume [46,47]. However, such findings do not in any way diminish the importance of the fundamental redox phenomena that underlie clinical symptomatology. Another line of evidence pointing to the importance of redox dysregulation in clinical allergy is increased immediate bronchial sensitivity to inhaled ozone [48]. In allergic asthma, the late phase responses to allergens also are enhanced by ozone exposure [49]. In normal subjects, ozone increases mast cell tryptase and the number of polymorphonuclear cells in the nasal lavage fluid. It seems safe to predict that future studies will uncover the oxidative–dysoxygenative underpinnings in all cellular and mediator allergic responses. Specifically, such responses include switch from proin-

flammatory and proallergic Th2 subtype T helper cells to allergy-inhibiting Th1 subtype and initiation of biochemical pathways mediated by cytokines (such as IL-4, IL-5, and GM-CSF) as well as monocyte chemotactic proteins (such as MCP-1, MCP-2, and MCP-3), which have been reviewed recently [50,51].

Integrative therapies for allergic disorders

My colleagues and I tested the theoretical validity of the proposed oxidative–dysoxygenative model of clinical allergy by conducting clinical outcome studies with integrative management plans that focused on all the relevant oxidative and dysoxygenative factors. Highly atopic patients with indolent disorders responded well only when broad-based redox-restorative therapies were vigorously administered. Specifically, such outcome studies included patients with chronic fatigue syndrome [11,37], fibromyalgia [52••], asthma [53], Crohn's disease [54], and young atopic women with oligomenorrhea and amenorrhea [13]. The clinical picture in patients in those studies was dominated by allergic symptoms and the presence of IgE antibodies with specificity for a host of mold and other inhalant allergy established with the previously described micro-ELISA assay [26]. Specifically, in the clinical outcome study of 44 consecutive patients with asthma that proved refractory to the standard bronchodilator therapies, regular use of drugs was discontinued in 77%, reduced by more than 50% in 9%, and by approximately 25% in the another 11% of subjects [53]. In the steroid-dependent subgroup of 11 patients, steroids were discontinued in 4 (35%) patients. In a study of 150 consecutive patients with fibromyalgia, the following data were reported: more than 90% relief of symptoms in 65.4% of patients, between 75% and 90% improvement in 19.3%, and less than 25% improvement in 10% [52••]. In the outcome

Table 1. General guidelines for nutrient and redox-restorative supplements for atopic patients with and without indolent immune disorders

	Atopic individuals without chronic indolent immune dysfunction	Atopic individuals with chronic indolent immune dysfunction
Vitamins	C, 1,000–2,000 mg E, 200–400 IU A, 5,000–7,500 IU D, 100–250 IU B-complex, 25–50 mg B12, 1,000 µg weekly for four weeks	C, 3,000–5,000 mg E, 400–800 IU A, 10,000–15,000 IU D, 100–250 IU B-complex, 30–50 mg B12, 1,000–5,000 µg weekly for four to six weeks
Minerals	Magnesium, 1,000–1,500 mg Calcium, 750–1,000 mg Potassium, 200–400 mg Chromium, 100–300 µg Selenium, 100–300 µg Molybdenum, 100–300 µg	Magnesium, 1,500–2,500 mg Calcium, 1,000–1,500 mg Potassium, 400–600 mg Chromium, 400–600 µg Selenium, 400–600 µg Molybdenum, 400–600 µg
Redox-restorative substances	Glutathione, 200–300 mg N-acetylcysteine, 200–300 mg Methylsulfonylmethane, 200–500 mg Lipoic acid, 100–200 mg Taurine, 500–1,000 mg Coenzyme Q10, 30–50 mg Pycnogenol, 50–100 mg	Glutathione, 600–800 mg N-acetylcysteine, 600–800 mg Methylsulfonylmethane, 1,000–1,500 mg Lipoic acid, 300–500 mg Taurine, 1,500–2,000 mg Coenzyme Q10, 100–150 mg Pycnogenol, 100–150 mg

Table 2. Composition of adjunctive nutrient and herbal protocols for the bowel**Bowel ecology protocol #1**

One billion spores of *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, and *Bifidobacterium* in a base of complex vegetable fiber, magnesium sulfate, vitamin B complex, L-histidine, L-arginine, pantethine, and aloe vera.

Bowel ecology protocol #2

Alfalfa, 500 mg; pau d'arco, 100 mg; allium, 100mg; licorice root extract, 200 mg.

Bowel ecology protocol #3

Calcium caprylate, 50 mg; magnesium caprylate, 50 mg; grapefruit seed extract, 25 mg; aloe vera, 1 mg; spirulina, 10 mg.

Bowel ecology protocol #4

Grapefruit seed extract, 50 mg; allium, 50 mg; pau d'arco, 500 mg.

Bowel ecology protocol #5

Par-quin, 150 mg; pau d'arco 150 mg; beet root fiber, 200 mg; guar gum, 100 mg.

Bowel ecology protocol #6

Echinacea, 200 mg; goldenseal root, 150 mg; astragalus root, 150 mg; burdock root, 150 mg.

study of menstrual dysfunction in 35 women with chronic fatigue syndrome, menstrual cycles were completely normalized in 12 of 14 women with amenorrhea of longer than 6 months duration and in 19 of 21 women with oligomenorrhea [13].

Data obtained with such trials provide significant support for the theoretical precepts for the proposed ODD hypothesis. Evidently, all such evidence must be considered indirect. It is noteworthy in this context, however, that the number of biologic variables in such syndromes is very large. It seems highly unlikely that studies can ever be designed in such a way that direct evidence for one-cause one-effect relations between intracellular oxidative–dysoxygenative phenomena and clinical symptomatology can be established.

Immunotherapy for IgE-mediated disorders

The precise diagnosis and the optimal management of IgE-mediated responses must be considered as the centerpiece of all integrative allergy management plans. The details of methodologies used at the Institute have been

Table 4. Composition of intramuscular protocol B

Nutrient	Concentration	Volume
Magnesium sulfate	500 mg/mL	3 mL
Calcium gly/lac	10 mg/mL	4 mL
Vitamin B ₁₂	10,000 µg/mL	0.5 mL

described previously [55,56]. The immunologic consequences of specific antigen immunotherapy were assessed by measuring allergen-specific IgG antibodies [27].

Adjunctive nutrient, herbal, and oxygenative therapies

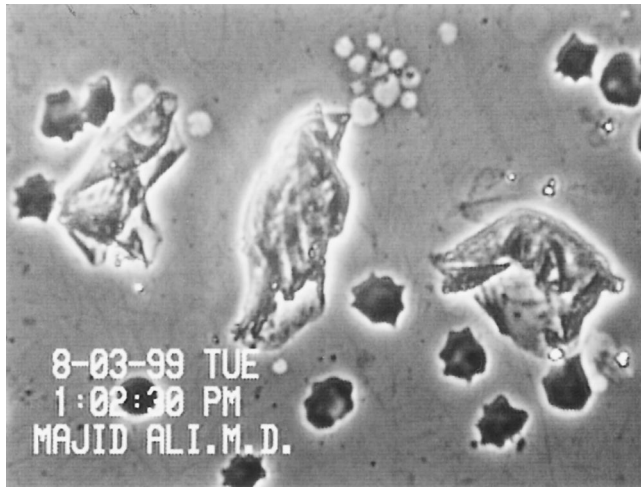
The clinical outcome in allergy treatment is markedly enhanced if issues of lifestyle, stress, and the ecologic integrity of the bowel, blood, and liver ecosystems are addressed. This becomes a critical issue when allergy symptomatology is a major part of diverse chronic immune disorders such as fibromyalgia, Crohn's colitis, multiple sclerosis, and multiple chemical sensitivity syndrome. The details of integrative management protocols in use at the Institute and clinical outcome data obtained with those plans have been previously described [9–14•]. Figure 5 shows the schema of an ecologic model in use at the Institute to assist clinicians in establishing therapeutic priorities as well as for patient education. Extensive clinical experience has led me to the conclusion that the bowel, blood, and liver ecosystems form the foundation of human redox, enzymatic, and detoxification defenses. My colleagues and I prescribe nutrient, herbal, and oxygenative protocols for restoring the various ecosystems of the body for individual patients in light of the total clinical context, rather than blinded and controlled trials of individual therapeutic agents. The latter approach, we have pointed out earlier, negates the very essence of the integrative approach to clinical problems. In this section, some salient aspects of antioxidant, herbal, and oxygenative protocols are included for the general interest of the reader (Tables 1–4). Table 1 shows our recommendations for atopic but generally healthy persons as well as those with chronic immunologic disorders, such as chronic fatigue syndrome, fibromyalgia, and chemical sensitivity syndrome. In selected cases, individualized parenteral nutrient support is very beneficial. Intramuscular protocols A and B may be given on alternate weeks for 4–6 weeks in selected cases (Tables 3 and 4).

Summary

The proposed integrative model of clinical allergy evolved in three phases of the author's experimental and clinical work. In the first phase, the focus was on classical immunology in general and on *in vitro* methodologies for the diagnosis of IgE-mediated disorders in particular. In the second phase, the focus shifted to ecologic issues concerning the allergic individual. In the third phase, emphasis was on issues of oxidosis and dysoxygenosis that greatly amplify IgE-

Table 3. Composition of intramuscular protocol A

Nutrient	Concentration	Volume
Magnesium sulfate	500 mg/mL	1.5 mL
Calcium glycerate/lactate	10 mg/mL	1.5 mL
Vitamin B ₁₂	10,000 µg/mL	0.5 mL
Vitamin B complex	*	1 mL
Pantothenic acid	250 mg/mL	0.5 mL
Pyridoxine	100 mg/mL	0.5 mL
Zinc	5 mg/mL	0/6 mL
Molybdenum	25 µg/mL	0.5 mL
Selenium	40 µg/mL	0.4 mL
Multivitamin	*	0.5 ML

Figure 5. Morphologic features of three microplaques

Illustrates the morphologic features of three microplaques formed when micro-clots in the circulating blood are compacted into microplaques with layered appearance.

mediated responses. Further, allergic symptomatology was seen within the broader context of oxidative–dysoxygenative injury to the bowel, blood, and liver ecosystems. A case is made for adding adjunctive nutrient, herbal, and redox-restorative therapies to the specific antigen immunotherapy for improving clinical outcome. Such adjunctive therapies were found to be especially beneficial in cases in which allergic symptomatology is associated with microscopic evidence of oxidative coagulopathy and clinical features of persistent fatigue, myalgia, abdominal symptoms, and cognitive dysfunctions.

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