

Delayed allergies in comprehensive care: enhancing clinical outcomes through functional lymphocyte response assays in primary management of chronic ill health. Original Internist, Dec. 2003

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Immune Defense and Repair Actions in Good and Ill Health

This article addresses our immune system's role in defense and repair. This fundamental approach to first line care is based on patient-specific, comprehensive, functional, ex vivo data. The role of immune system dysfunction in good health and chronic ill health are explored. Advanced assays that provide comprehensive determination of an individual's delayed allergy reactions are often able to get to the cause of "treatment resistant" issues.

Healthy resilience and disease resistance are reviewed. The causes of ill health, rather than their symptomatic consequences, are explored. Emphasis is on validated, successful approaches to sustainable remissions. Focus includes health maintenance, enhancement, or restoration based on clinically proven approaches. Clinically validated in randomized, controlled trials (RCT), this approach to repair immune responses and, thereby, restore health and achieve sustainable remissions in chronic illnesses are described herein. Let us start with the state of health.

When healthy, we are tolerant to the world around us. (1-4) This means we digest our food fully to molecular building blocks, enzyme-activating vitamins and minerals, as well as efficiently assimilated and utilized energy sources. (5,6) A healthy "transit time" from food consumption through digestion, assimilation, and waste elimination is an efficient 12-18 hour interval. (7) We can use transit time measurements as an overall assessment of digestive health. (7)

When healthy, any foreign immunoreactants (antigens) that gain entry are promptly identified, engulfed, and recycled by our ample supply of dendritic (phagocytic) surveillance cells. (4-7) A typical person has 5-50 billion dendritic cells at any moment. Each cell is capable, when functioning properly, of engulfing and recycling 50 infectious particles, pollen, or digestive remnants. This means 250 billion to 2.5 trillion immunoreactive items can be neutralized and recycled without infection or symptom provocation. This is a substantial reserve capacity. Further, our body processes all foreign

invaders in the same way. Our immune system makes no distinction between infectious agents, digestive remnants, and aeroallergens. This means that we are hospitable to infection and to irritative (histaminic) reactions from pollen (8) only when one or more of the following are present:

- 1) Essential nutrient deficits
- 2) Antioxidant depletion
- 3) Loss of buffering competence (cellular metabolic acidosis)
- 4) Toxin overload inhibiting ATP energy production
- 5) Immune overload from digestive immunoreactants

The types of foreign antigens that the immune system is responsible for neutralizing (when we are healthy) or defending against (when our immune defenses are burdened) include:

- 1) Infectious agents
- 2) Inhaled pollen or aeroallergens
- 3) Digestive remnants
- 4) Pathogenic dysbiotic organisms and parasite antigens

In contrast, when burdened by maldigested antigens or antigens from dysbiotic intestinal pathogens and parasites, our immune defenses are less able to neutralize infections or aeroallergens. (7-16) In this circumstance, our body defers needed repair, develops inflammation, and expresses the signs and symptoms of delayed allergic autoimmune and immune dysfunction pathologies. (1-7)

When healthy, we are:

- 1) Resistant to infection. Our dendritic system engulfs and degrades pathogens before they are able to proliferate within us.
- 2) Tolerant to allergens. Our dendritic and immune systems recycle foreign allergens before they are processed to induce acute or delayed allergic reactions.
- 3) Resilient if exposed to foreign antigens and haptens without adverse effects or symptoms of acute or delayed allergy. (Haptens are small molecules that bind to the body's own proteins, distort their structure, and render them immunoreactive. Examples of haptens include: xenobiotic chemicals, toxic minerals, and food colorings. (9))

When healthy, we have the following five lines of innate host defense:

- 1) Opsonins ("nature's antibiotics") and protective nutritives that inhibit pathogens produced by an abundance of healthy probiotic microflora. This includes flora on all body surfaces, from skin to mucosa. (10)

- 2) Adequate mucin production that traps and retains digestive remnants until they can be digested. (11)
- 3) Sufficient intestinal mucosal secretory IgA (sIgA) production to neutralize and inhibit pathogens and parasites. (12-14)
- 4) Mucosal macrophages and fibroblasts with the capacity to trap and recycle digestive remnants (and infectious agents) if they reach the intestinal or respiratory mucosa. (8)
- 5) Mucosally associated lymphocytic tissue (MALT; GALT; Peyer's patches) with lymphocytes present that process and neutralize reactive materials, either airborne, infectious, or digestive remnants. (15,16)

Only when these five primary defenses are disabled or persistently overloaded do we become susceptible to delayed allergic responses. (6-16) The most overworked (distressed) organ or system in the body is the most vulnerable to inflammation, i.e., swelling, discomfort, and mononuclear (lymphocytic) cell infiltrates. Symptoms are specific for the particular distressed organ(s) and system(s) in the body. (2-7,10-16)

When healthy, digestion processes foods completely, hydrolyzing them to:

- 1) Amino acids, di- and tripeptides,
- 2) Lipids and glycerides
- 3) Simple sugars
- 4) Nutrients, including antioxidants, minerals, and metabolic cofactors (5)

Maldigestion, Dysbiosis, and Cumulative Intestinal Repair Deficits

All too often, digestion is impaired. This is independent of chronological age and dependent upon probiotic replenishment, distress hormones and neurochemicals, ingested toxins, and dietary fiber content. (17) In fact, maldigestion (incomplete breakdown of food ingested) and dysbiosis (unhealthy composition of microorganisms in the intestine) can generate appreciable quantities of immune-reactive and health-diminishing digestive remnants and pathogen products. (17)

These immune reactive digestive remnants can penetrate the intestinal mucosal barrier, particularly if it is more permeable due to cumulative repair deficits. (18,19) Immune-reactive digestive remnants exceed the mucosal lymphoid tissues ability to trap them. Digestive remnants, as foreign (immune-reactive) burdens, drain immune reserves, increase immune defense work, and delay or defer needed repair from routine "wear and tear" or injury. These immune reactive foreign "invaders" can enter systemic circulation where they provoke or make worse symptoms of ill health. (20-23)

Sources of Exposure to Immune Reactants

Although inhaled antigens are more commonly appreciated as sources of immune system challenge, the gut, by contrast, must process two to three orders of magnitude more foreign antigenic material than the respiratory tree over a typical human lifespan. A typical person processes 2-5 kg (5-11 lbs) of antigen via respiration pathways over a lifetime. While this is substantial, intestinal mucosa is presented with 100-500 times more. This means 500-2,500 kg (1,100-5,500 lbs = 0.55-2.75 tons) of foreign antigen need to be processed by the intestines over the same typical lifespan. (17-23)

This healthy resilience (homeostasis) is lost when maldigestion and dysbiosis persist. (10,24) This suggests the central importance of the role digestion plays in health and well-being. The consequences of these digestive disturbances are both subtle and profound and include the loss of the following five lines of innate host defense, particularly when essential nutrient deficits, toxin burden, and distress are also present.

This renders us:

- 1) Susceptible to delayed and acute allergic responses (1-6,25,26)
- 2) Hospitable to chronic infection (3-6,27)
- 3) Open to autoimmune or immune dysfunction conditions (28)
- 4) More at risk of inflammatory cardiovascular diseases linked to elevated C-reactive protein [CRP] (29,30) and increased homocysteine. (31,32) Similarly, other inflammatory markers, such as sedimentation rate (sed rate), microalbumin, ferritin and fibrinogen are elevated. This reflects the body's incomplete attempt to overcome repair deficits. (19-23,29,30)
- 5) More at risk of cancers related to loss of innate anti-cancer surveillance due to reduced NK and cytotoxic T-cell functions (33,34)

When these five lines of defense are overwhelmed, excess immune-reactive digestive debris or infectious agents may gain access to the lymphatic circulation. (35) Subsequently, as the lymph fluid is returned to the flowing blood through the thoracic duct, immunoreactive materials may gain access to the systemic circulation. (35,36) From there, a tissue or organ with increased permeability (repair deficit; inflammation) may become the focus for delayed immune reactions and lymphocytic infiltration. (21,23,37) Consequences of this include swelling, pain, and autoimmune syndromes. (28,38,39)

Clinical Importance of Immune Defense and Repair

Our immune defense and repair system is designed to defend us from foreign

invasion while retaining the reserves to repair us and carry immune system communication. This includes repair from daily wear and tear. (2-6,40) Although extensive, our immune system capacity is finite. (6,40) When we allow substantial and continuing amounts of digestive or inhaled immune reactors ("foreign invaders") to overload our immune defenses, our immune system becomes preoccupied with the primary work of defense. Repair is deferred until the "assault" is over. Too often, with each meal and due to contaminants in their air we breathe, preoccupation with defense becomes the routine. (25,26,37)

Repair, then, can become chronically deferred, particularly in distressed tissues or organs. This means that there is reduced synthesis of collagen, elastin, and basement membrane structural proteins. (40-43) When this occurs, our organs become more permeable. (26,37,38,44) This is clinically referred to as "leaky tissue" pathology. (45,46)

Since structural proteins are also important in cell communication and orientation, these important functions are impaired. (41-44) Figure 1 shows examples of clinical consequences of increased permeability (cumulative repair deficit) in specific sites of chronic distress

Consequences of Excess Burdens on Immune Defense and Repair Systems

Categories of items that can burden immune defenses when they are not properly handled by our digestive or respiratory processing systems include:

- 1) Foods, food preservatives, and colorants
- 2) Environmental chemicals (xenobiotics; xenoestrogens)
- 3) Molds and fungi
- 4) Medications
- 5) Pet danders
- 6) Toxic minerals

These burdens on our immune defense and repair systems are clinically actionable and can make an important difference in quality of life. (108-110) If we know which specific items are important for each individual to substitute or avoid, we can:

- 1) Take action to reduce the defense burden on each individual's immune system.
- 2) Systematically and comprehensively reduce the burden on our immune defense and repair system.
- 3) Facilitate rehabilitation and repair of immune system mechanisms. (108-111)
- 4) Show that the cumulative repair deficit in our body can be corrected. Tissues and systems become more structurally intact and permeability ("leaky tissue") is restored to a

healthy, low level where nutrients come in, wastes move out, and larger molecules and cells are excluded. (109-111)

A Functional, Comprehensive, Ex Vivo Clinically Validated Advance

The patient-specific lymphocyte response assay, LRA by ELISA / ACT, provides an advanced laboratory tool to address this clinical need. This is the first LRA that is ex vivo (using autologous plasma as the incubation medium and allowing lymphocyte reactions just as they occur inside the body) and uses an embedded enzyme in the lymphocyte surface to amplify the reaction allowing shorter incubation time, greatly enhanced detection signal, and enhanced reproducibility as described in detail below.

When our immune defense and repair system is chronically overburdened, delayed allergic reactions occur. These are often technically referred to as delayed-type hypersensitivities [DTH]. Immune defense and repair is so important to survival, that our body has three distinct mechanisms of response. (112) Measuring the functional, clinically important immune-reactive triggers in all of these pathways gives us more precise and predictive information upon which to base our clinical management. These mechanisms include:

1) Humoral responses: Reactive or provocative antibodies. These may be mucosally associated IgA, recent IgM, or systemic memory IgG. It is important clinically to know if antibodies are protective and neutralizing (which are beneficial) or complement activating and symptom provoking (which are harmful). Knowing the presence of an antibody does not tell us its function. In the absence of functional information, people are often asked to substitute for many items to which they already have a protective, neutralizing, helpful IgG response. These Type II DTH (B-lymphocyte) responses can be specifically detected by functional autologous lymphocyte response assays (LRA) since only complement-activated, reactive antibodies "turn on" lymphocytes. (112) While short-term studies of ELISA IgG assays in clinical use have been published, some of which show short-term positive results, symptoms return after 3-6 months (based on reports from labs that perform ELISA IgG tests). No long-term successful outcome studies using ELISA IgG assays have been published.

Perhaps this is due to the fact that ELISA IgG assays are only a narrow component of the full delayed immune response spectrum. Other antibodies, immune complexes, and T-lymphocyte responses are not measured. In addition, ELISA IgG (EIA) assays do not differentiate functionally between the beneficial, neutralizing antibodies and the

symptom-provoking, reactive antibodies. This can lead to people substituting for items (foods or chemicals) for which they have a protective immune response and, thus, substitution is not needed. Further, this may be due to simple avoidance of nominally reactive items not addressing and resolving the underlying causes of the immune overload that lead to delayed immune responses. Thus new sensitivities may appear within a few months and, with them, the symptoms likely reappear. (113,114) Further, antibody tests do not tell us about the important other mechanisms of immune defense reaction noted below.

2) Immune Complex: IgM anti-IgG/antigen complexes--these are efforts by the body to mask and protect from reactive IgG antibodies. Only assays that detect immune complexes like functional lymphocyte response assays or Raji cell assays detect these Type III DTH responses. (112,115)

3) Cell-mediated responses: These are T-lymphocyte (CD4) responses. These are also known as Type IV DTH responses. (112,116,117)

Functional, Comprehensive, Autologous, Ex Vivo Immune System Measurements

Only a functional lymphocyte cell response assay (in contrast to a chemical detection of the presence or absence of an antibody without knowing its physiologic beneficial or harmful function) that is comprehensive (in measuring all delayed allergy mechanisms) can give us information on all these sources of immune reactions. This will be explored in more detail later in this article.

This is clinically important given the increasing:

- 1) Challenges to our digestion from poor dietary choices and restructured foods (118,119)
- 2) Chemical exposures in our environment (120,121)
- 3) Distress in our adaptation to the world as a biological tax from "high-tech living" (122-124)
- 4) Lack of restorative rest (125,126)
- 5) Deficit in satisfaction and joy of living (127,128)

It is not surprising that we have what has been described as an "epidemic of epidemics of autoimmune and immune dysfunction syndromes" that form the bulk of chronic ill health in our society. (129-131)

Chronic or excessive exposure to reactive substances can overwhelm our adaptive mechanisms for immune defense and repair. This results in further immune dysregulation

and dysfunction; (132,133) in already depleted protective reserves and resilience factors. (134,135) This can lead to:

- 1) Easy fatigability or chronic fatigue (136,137)
- 2) Hospitality to recurrent infections (colds, flu, ear infections, chronic viral syndromes, etc.) (27,138)
- 3) Chronic inflammatory (repair deficit) conditions and autoimmune syndromes (See Figure 1) (139,140)
- 4) Repair deficits that predispose to muscle (Fibromyalgia [FM]) (141) and visceral (Endometriosis; Endo) pain (142)

Thus, identification of the body's shift from healthy, non-reactive tolerance to delayed allergic (hypersensitivity, DTH) responses is essential to comprehensive, integrated health care. (109) First-line of care, actionable, clinical assessments for all people with chronic pain or autoimmune/immune dysfunction illnesses are now available. (108-110)

Why is this so fundamental to comprehensive or integrative care? Immune dysfunction is central to the basic mechanisms of inflammatory (really repair deficit) pain and chronic illness. Cumulative repair deficits lead to increased tissue permeability from decreased structural repair in that tissue. This is fundamental to the causes of over 1,000 autoimmune, immune dysfunction, and inflammatory cardiovascular diseases or syndromes. (143)

If we can identify the items to which an individual reacts through all of the three delayed allergy (Types II, III, and IV DTH) pathways, we have the basis for more complete, accurate, predictive assessment and an individualized treatment plan. Of course, the person needs:

- 1) Adequate essential nutrients (143,144)
- 2) Competent detoxification mechanisms (145)
- 3) Distress adaptation (146,147) so that necessary repair is not blocked or inhibited when the defense burden is lifted (108-110)

Decrease in defense burden means identification and substitution for the ingested, inhaled, or absorbed sources of delayed allergic reactions. These sources include reactive antigens derived from what we eat, breathe, and contact, as well as from antigens shed by dysbiotic organisms. (108,109)

Antigen Cross Reactions and Antigen Mimics

Dysbiotic organisms, parasites, and fungi in the intestinal tract can shed antigens

that are identical to host proteins or food digestive remnants. Yersinia antigens cross reactivity with thyroid tissue antigens has been suggested as a potentiating variable in thyroiditis. (149) Sensitization to blood group B substance even in people who have had no prior transfusion is another example of antigenic cross reactivity. (150) A variety of phage infected bacteria (like hemolytic E. Coli) and anaerobic pathogens, as well as intestinal parasites have antigens that cross react with many antigens in foods. (151-154) Thus we can react to a substance we have never eaten due to cross-reactivity and antigen mimicry. By restoring healthy microflora and digestive competence, people lose their pathogen hospitality. (155) This improves clinical health and reduces the workload on the immune system. More attention can be given to repair and resilience than defense and delayed hypersensitivity-linked burdens that express as the symptoms of ill health. (156)

Substituting for the substances to which our immune system reacts is important for rebuilding reserves and reducing the load/distress on our immune system. This allows our physical economy to move from a state of "red alert" and hyperactivity to one of balance, regeneration, and repair. This shift is central to the restoration of health. (157) This shift is the basis for a sustainable remission in autoimmune and immune dysfunction conditions as the body seeks to restore immune tolerance, homeostasis and shift back to health from a fixed state of hypersensitivity/delayed allergic reactivity. (158)

Immune System Healthy Homeostasis

Are we able to restore tolerance, homeostasis, and sustainable good health? Based on clinical experience with symptom suppressive therapies, the maxim has become: Once reactive, always reactive. This is true as long as our therapy focuses on suppressing symptoms. (159) When we comprehensively identify and substitute for the reactive items, we allow immune defense and repair systems to repair and reset themselves to homeostatic tolerance. (108,109) Systematic success in community-based, randomized controlled trials [RCTs] in fibromyalgia with and without chronic fatigue [CFIDS], (95) as well as in type 1 and type 2 diabetes, supports the efficacy of this approach. (64) Clinical case successes in the full range of autoimmune and immune dysfunction problems are also consistent with this hypothesis. (108-110)

When we concurrently address the causes of these problems, our immune defense and repair system can reset itself to a tolerant, non-reactive state. A comprehensive approach that includes the following four elements is necessary to achieve healthy restoration of immune functions:

- 1) Comprehensive identification and substitution for specific delayed allergic sensitivities for the individual. These may be foods and food additives, environmental chemicals, medications, molds, toxic minerals, danders, or herbs.
- 2) Correct nutrient deficits
- 3) Restore detoxification systems
- 4) Reduce distress. It is our internal adaptation rather than the external events that determines if a stressor causes distress. Our internal responses may be learned or relearned in healthier, more resilient ways.

We can go by outcome results. Beyond statistics and predictive significance, clinical outcomes using the four integrated aspects above support the efficacy of this approach. The power of the approach in resolving the causes of autoimmune or immune dysfunction case by case (patient by patient) is becoming clearer as more clinical reports and successful randomized, controlled trials are reported. (3,108-110,160)

Meaning of Positive LRA by ELISA/ACT Results

- 1) Immune recognition: (161) Any of the delayed allergy pathways can be programmed into lymphocyte subsets for reaction.
- 2) Contaminant recognition: (162) We may think we react to an item when we react to a contaminant carried along in the production or processing of that food or chemical.
- 3) Cross reaction with identical reactive epitope from (163,164) nature is conservative. The same biological structure ("antigen") may exist in different systems and will cause a common reactivity. This is why, for example, people can have a transfusion reaction when they have never received blood before and why people can "react" to a food they have never ingested:
 - a) Gut pathogen
 - b) Related food family antigen (epitope)
 - c) Patient's tissue

A positive result on lymphocyte blastogenic or mitogenic response assays, for example, LRA by ELISA/ACT, can be due to one of three causes. These include immune recognition of a(n):

- 1) Antigen specific to the compound tested (161)
- 2) Identical antigen from another source, such as a pathogen, that sheds the same antigenic structure (164)
- 3) Non-specific reactivity due to generalized lymphocyte response, usually due to not

following the preparation instructions and being exposed to something that pre-activated the lymphocytes before they reach the lab (165)

Procedure, Method, and Clinical Results for LRA by ELISA / ACT Tests

The LRA by ELISA / ACT procedure is straightforward. It requires a 12-hour period of water only followed by a one-ounce blood draw. This is the amount of blood the bone marrow produces in about one hour.

For accurate results certain substances need to be avoided for a few days. Steroid medications need to be avoided for four days. (166) A "steroid bridge" is available to help in this interim if needed. (165) Aspirin and antihistamines also stabilize lymphocyte membranes and reduce reactivity. (168,169) Aspirin and antihistamines need to be avoided for two days prior to drawing the blood sample.

The whole blood sample is sent to the lab via overnight courier. No processing of specimen is required. During transport the specimen is kept cool at 4-10[degrees] C so the cell metabolism is reduced. After receipt, the sample is centrifuged gently. The cell-rich plasma (CRP) is aspirated and aliquoted into microtiter plates precoated with the various substances (antigens/haptens) to be tested. (170)

An entire LRA assay can be performed on only 40[micro]l of CRP. The sample is incubated at 35[+ or -]2[degrees]C for three hours. This is long enough to measure the initial response when a lymphocyte recognizes a substance it has been pre-programmed to respond to as a delayed allergen. If the cell culture were continued for several days, DNA synthesis could be monitored by radioactive thymidine incorporation. If the cell culture were continued for several weeks, colonies of proliferated cells could be observed. After this brief incubation, the cells are examined to determine if enzyme activation has occurred. (171)

LRA by ELISA / ACT is unique. It is the first ELISA method to use the surface of a living cell (lymphocyte) as the source of the amplifying detection enzyme. (172) Each specimen has an internal positive and negative control performed as part of routine quality control. A >50% reactivity is considered a strong reaction, while a 5-50% reactivity is considered an intermediate reaction. Both of these reactions are equally burdensome to the immune system. Under optimal conditions, strong reactions take longer to reset. Typically, six months are needed to reset strong reactions while intermediate or moderate reactions can be reset in three months. A <5% cell reactivity is indistinguishable from background responses.

Validity, Reproducibility, Sensitivity, and Specificity

Validity or test accuracy can be defined as "the degree to which the results of a measurement correspond to the true state of the phenomenon being measured." (173) The classic way of determining the validity of a test is by comparing the observed measurement or results to some accepted, objective, physical "gold standard" method. (174,175) However, there is no such universally agreed upon standard for determining delayed hypersensitivity reactions. (176) Therefore, validity must be established by showing that the test results are predictive of, or are directly related to, clinically measurable or observable phenomena (signs and symptoms). In other words, does substitution for the reactive items detected by the tests bring clinical improvement for each individual. This is the clinical "gold standard." (177)

Regarding validity based on predictive value of clinical phenomena, the LRA by ELISA/ACT was performed on 81 consecutive cases of autoimmune or immune dysfunction syndromes. Entry criteria included persisting, treatment-resistant pathology for more than five years. Diagnoses of subjects included autoimmune conditions (rheumatoid diseases, multiple sclerosis [MS], asthma, ulcerative colitis [UC], eczema, psoriasis, lupus [SLE], thyroiditis, diabetes), and immune dysfunction conditions (fibromyalgia, and chronic fatigue [CFIDS]). (178)

Each person filled out two symptom questionnaires (the Cornell Medical Index Questionnaire and a Health Appraisal Questionnaire prepared by ELISA/ACT Biotechnologies) and rated the intensity of their primary symptoms on a scale of 1-100 prior to beginning the recommended ELISA/ACT program based on their individual LRA test results. To assess long-term outcomes, these same subjects again rated their primary symptom intensities at intervals over 6-30 months.

The results showed a primary symptom intensity of 77.4[+ or -]14.5 before and 26.4[+ or -]18.2 after 6-30 months of following this healing program ($p < .0001$). These results are based on real world "best efforts" to follow healing suggestions. This demonstrated clinical outcome successes, as well as statistically significant improvement, in this previously treatment-resistant group. (178) These results suggest a strong correlation between the reduction of symptom intensity and the substitution for reactive substances based on LRA by ELISA/ACT tests and compliance with the available treatment guide.

Test reliability or reproducibility is "the extent to which repeated measurements of a

relatively stable phenomenon fall closely to each other." (178) During the three year development phase of the LRA by ELISA / ACT tests, two procedures were utilized to establish reliability:

1) In over 100 separate instances, multiple samples were taken at the same time, from the same subject, and analyzed without the technician knowing their source. Results replicated with a variance of <3% with some occasional differences where a strong reaction was read as an intermediate or a marginal intermediate was read as not reactive. (179)

2) Blind split samples taken days to weeks apart in people following a stable diet and lifestyle also showed a <3% day-to-day variance in results in 100 samples thus obtained. (179)

Confirmation of tests results in practice can best be achieved by demonstrating that clinical signs and symptoms remit when reactive substances are avoided. However, reactivity to a substance is not always synonymous with easily linked clinical signs and symptoms by the individual because of the delay between exposure and symptom provocation. This delay can be several hours to several weeks. (180,181) This is in contrast to Type 1 (IgE) hypersensitivity reactions (not tested for with LRA assays) or a psychologically programmed (distress) response. (182) In community-based randomized controlled studies of chronic, treatment-resistant fibromyalgia with or without chronic fatigue, the sustained improvements suggest predictive significance for LRA by ELISA / ACT tests. (64) Similar results in both type 1 and type 2 diabetics are also supportive of this comprehensive care technology breakthrough. (95) Clinical reports from a database of over 40,000 cases are further reinforcement of the value and validity of this comprehensive, functional, ex vivo approach. (108,109)

Clinical Application and Utility

Identification of LRA by ELISA / ACT reactions to over 420 substances makes this technique the most comprehensive available. Categories include foods and food additives, environmental chemicals, medications, molds, herbs, and danders. When these reactions are of a delayed nature, it is often clinically challenging, even with the most careful history, to make their determination. Use of this ex vivo technique allows the body to "speak for itself" under controlled laboratory conditions. (108,109)

LRA by ELISA / ACT tests are useful tools for identifying the reactive substances of delayed hypersensitivity by providing a comprehensive "immunologic finger-print" of our

delayed reactive substances. When these substances are identified, best efforts made to substitute for them, and a sensible repair program engaged, the reduced immunologic distress and repair deficit pathology can often be reversed, and sustainable remissions routinely occur.

Immunologic disrepair, despair, inflammation, and tissue destruction induced by delayed hypersensitivity reactions no longer mean chronic suffering and morbidity. A more scientific era of identifying the causes of ill health and comprehensively stimulating repair can open a bright chapter in comprehensive, integrated, evidence-based care and caring.

The LRA by ELISA / ACT optional lab director's interpretive treatment guide includes:

- 1) What to substitute based on the lymphocyte response assay results. In addition, clinical guidance is included on how to more easily substitute reactive substances and where hidden sources of exposure may reside.
- 2) Suggestions for an energizing, repair-promoting, "Alkaline Way" diet. This means a diet that has a net excess of buffering minerals that activate cell enzyme systems and alkaline amino acids compared to the metabolic acids produced.
- 3) Specific nutritional supplements based on the cell responses and a health appraisal questionnaire.
- 4) Health-supportive "healing actions" to engage the mind and body as the unit they are in the processes of health restoration.

Clinical Outcomes and Results

Ulcerative Colitis Case Success: (184) BG is a white, married man who presents with a 10-year history of severe pain with mucous/bloody stools (3-20/day). Prior therapy included:

- 1) Synthroid 0.125 mg/day for functional hypothyroidism
- 2) Dipentum 750mg BID
- 3) Cortisone/Butyrate enema 2-5 X/week +
- 4) Supplements taken include
 - a) High potency multi-vitamin
 - b) 2 gm/day buffered ascorbate
 - c) 120,000 IU 3X/week beta carotene
 - d) 800 IU E/day
 - e) 500 mg/day quercetin complex

f) Sialic acid 2 caps BID

5) A macrobiotic diet

Symptoms persisted on this regimen. His history includes psychotherapy, acupuncture, and homeopathy. Based on a clinical impression of candida overgrowth in the colon (candidiasis), a 6-month course of nystatin did not yield clinical improvement. Surgical removal of the bowel was recommended.

In October 1991, he obtained LRA by ELISA / ACT test results and started recommended plan. In January 1992, he was "85% better", off cortisone, and his Dipentum was reduced 50%. In June 1992, he was asymptomatic for three months, saying that the "last six months have been the best in last 10 years ... my ELISA / ACT plan made the difference." He has sustained improvement over the past decade.

Irritable Bowel Syndrome/Ulcerative Colitis Case Success: (185) AA presented as a 35-year-old, 67.5 kg white, married woman. Her blood pressure was 132/68, with a 10-year history of irritable bowel syndrome (IBS) and UC established by biopsy and barium enema in December 1983. Her IBS/UC remained clinically unresponsive to multiple therapies until 1990 that included:

- 1) Intensive management with azulfadene (0.5 gm QID)
- 2) Steroids with dosage based on symptoms
- 3) A variety of anti-inflammatory and cytokine blockers.

Annual sigmoidoscopies documented "cobblestone granuloma" from 8-25 cm in the colon. Patient reports excellent compliance with all therapeutic interventions. Lack of response to therapy was "frustrating and depressing."

In November 1990, she was clinically symptomatic with an ESR of 60. LRA by ELISA / ACT tests were performed. An unusually high number of reactive substances was noted (45 items). Substitution for reactions was associated with complete symptom remission after just one month. Follow up LRA by ELISA / ACT in November 1991, showed a 54% decrease in reactive items (20 items). Continuing in remission, she followed the updated plan. Further follow up LRA by ELISA / ACT in October 1992, showed a further reduction in reactions to 17 items. Subsequent tests revealed 3 reactive items out of 343 items tested. The patient remains asymptomatic at 10-year follow up.

Colitis/Bronchitis/Glossitis/Fibromyalgia/CFIDS Case Success: (186) PR presented as a 60-year-old female with a 25-year history of chronic, treatment-resistant:

- 1) Ulcerative colitis established by biopsy and repeated barium enemas
- 2) Constipation with intermittent diarrhea
- 3) Post prandial "bloating"
- 4) Chronic fatigue immune dysfunction syndrome
- 5) Fibromyalgia
- 6) Insomnia
- 7) Bronchitis
- 8) Glossitis (recent onset)

Her treatment history included long term use of Prilosec (H2 blocker), Celexa (NSAID), and Allegra (H1 blocker).

In February 2002, she was evaluated using LRA by ELISA / ACT tests. Reactions were noted to 19 foods, food groups, and chemicals out of 377 items tested. Following her plan for one month she reported marked reduction in constipation, relief from postprandial bloating, and an energy level that was the "best it has been in years." An inadvertent exposure to dairy products in a cookie led to reappearance of symptoms. This verified to her the validity of the tests results and their link to her condition. After six months, she reported feeling "best I've felt in years." She was sleeping well (no insomnia), had regular bowel habits without bloating, constipation or diarrhea, muscle aches and pain were "minimal", and her concentration and memory were "much better." She continues to be asymptomatic at 15-month follow-up.

Fibromyalgia/CFIDS Case Success: (187) JA, a 44-year-old woman with treatment-resistant fibromyalgia and CFIDS for five years, reports:

- 1) "Unbearable upper back, thigh and calf muscle pain"
- 2) "Stiffness 'all over,' especially in the morning and after being at rest"
- 3) "Acquired depression"
- 4) Constipation (since childhood)
- 5) Pruritis (especially knees and elbows)
- 6) Memory and concentration problems
- 7) Sensitivity to chemicals, perfumes, odors
- 8) Menopause (premature, age 36)

JA went to rheumatologists, psychiatrists, and osteopaths without relief. She reported transient relief from chiropractic care.

Laboratory data was unremarkable except for first morning urine pH that was

consistently 5.5 suggesting cellular net acid excess (metabolic acidosis). JA was tested for delayed allergic responses (LRA by ELISA / ACT). She showed seven reactive substances out of 343 LRA cell cultures performed. Following the treatment guide, she did her best to eat 80% alkaline-forming foods (following the Alkaline Way Guide), took targeted supplements and followed healing actions. After six months, she reported "more than 75% reduction in back pain, stiffness is gone, and overall health is 90% better." Her constipation resolved; she felt optimistic and more emotionally stable. First morning urine pH was consistently in the 6.5-7.5 range suggesting correction of her cellular metabolic acidosis. Her summary: "The wind is at my back rather than in my face."

Separately, following her LRA by ELISA / ACT plan, Claire Musickant has reported her more than 10-year sustained remission from disabling fibromyalgia and CFIDS in her book *Fibromyalgia, My Journey to Wellness* (96) now in its second edition. We have published successful outcomes in a community-based, randomized controlled trial (RCT) based on 3- to 4-year outcome follow-ups. (97) Recent follow-up of those cases show continued improvement and sustained remissions now exceeding 10 years in over 85% of those cases.

Chronic Fatigue and Rhinitis Case Success: (188) SC presented as a 58-year-old woman who was "always sick and tired." She could not remember a time of feeling well. She reported:

- 1) "Perpetual colds and flu"
- 2) Recurrent headaches (? Sinusitis / Rhinitis)
- 3) CFIDS

Her treatment history included antihistamines (H1 blockers), antibiotics ("too numerous to count"), and decongestants.

She was evaluated using LRA by ELISA / ACT tests in June 2002. Reactions were observed to 10 of 377 items tested. After one month she reported that sleep gave rest and energy and that rhinitis / sinusitis symptoms were gone. After five months, she was asymptomatic and off all medications.

Asthma Case Success: (189) DK presents as a 25-year-old woman with a 22-year history of treatment-resistant asthma and chronic rhinitis. By high school, she regularly used three inhalers while receiving regular immunotherapy shots and taking H1 blockers (antihistamines).

LRA by ELISA / ACT tests were performed in August 2001. Reactions were noted to

12 out of 377 substances tested. After one month, rhinitis was gone and asthma was less symptomatic. Inhaler use with exercise remained. Follow-up at six months showed her symptom-free. Repeat tests found her reacting to only two of the initial items. As often happens when persisting maldigestion, dysbiosis, and intestinal wall repair deficits are present, new reactive items develop prior to full restoration of digestive and mucosal wall health. She continues to follow her plan of substitution for reactive items, an alkaline way diet, targeted supplements, and healing actions. She continues to be in remission.

Diabetes/Insulin Resistance Case Success: (190) BB presented as an 11-year-old boy with unremarkable development and insulin dependent type 1 diabetes. Typical blood sugars of 350 mg/dl and glycosylated protein (Hgb [A.sub.1]C) of 8 mg/dl. His uncle, a chiropractic physician, recommended niacinamide and acetylcholine. This provided transient benefit. Even on human insulin (Humulin) 10 U TID his blood sugars remained in the 300 mg/dl range.

In January 2003 he was evaluated using LRA by ELISA/ACT tests. Reactions were noted to 13 of 377 items tested. Following his plan for five months, he was reported to have fasting blood sugar (FBS) in the 80-125 mg/dl range on only 6 U Humulin TID; two-hour post prandial blood sugar (2[degrees] PP BS) in the 120-150 mg/dl range; and glycosylated protein (Hgb [A.sub.1]C) reduced to 5.1 mg/dl.

In a community-based, randomized, controlled trial (RCT), we noted systematic improvements in these same markers in both type 1 and type 2 diabetics. (191)

Thyroiditis Case Success: (192) EO presented as a 35-year-old mother of three with an unremarkable presentation except for 18 kg (40 lb) excess over her lean target weight. She reports that she always has "to push ... to get through the day." Observations include:

- 1) First morning basal temperatures that fluctuate between 96.7-97.3 over a one-month observation period.
- 2) Thin, slow-growing, coarse hair and nails
- 3) Easy fatigue (? CFIDS)
- 4) High personal standards "rarely met"
- 5) Loss of lateral margins of eyebrows
- 6) Marital distress

While previous thyroid tests had been "OK," measurement of free hormone and concurrent TSH had not previously been reported. Data include:

- 1) Free T3 of 120 pg/dl

- 2) Free T4 of 0.5 ng/dl
- 3) TSH of 12
- 4) TRF with a peak TSH of 92 [micro]IU at 30 minutes
- 5) Microsomal antibodies >2048:1
- 6) Anti-thyroid antibodies >4096:1
- 7) Cholesterol of 325 mg/dl
- 8) Triglycerides of 280 mg/dl
- 9) Two-hour post prandial blood sugar (2[degrees] PP BS) 186 mg/dl
- 10) Two-hour post prandial insulin (2[degrees] PP Insulin) 80 IU

She was evaluated using LRA by ELISA / ACT tests and she was found to react to four items and one food group out of 343 items tested. She was started on a comprehensive program of substitution for reactive items, Alkaline Way diet, targeted supplementation, and healing actions. In addition, two grains of desiccated thyroid daily were initiated. Follow up at six months found her "more energetic and pleased with ... nails and hair." She had lost 10 kg (22 lbs) "without dieting." Data included:

- 1) Free T3 of 430 pg/dl
- 2) Free T4 of 0.9 ng/dl
- 3) TSH of 5.2
- 4) Microsomal antibodies 8:1
- 5) Anti-thyroid antibodies 8:1
- 6) Cholesterol of 220 mg/dl
- 7) Triglycerides of 150 mg/dl
- 8) Two-hour post prandial blood sugar (2[degrees] PP BS) 108 mg/dl
- 9) Two-hour post prandial insulin (2[degrees] PP Insulin) 16 IU

Further follow up at one year included repeat of LRA by ELISA / ACT tests. She was found reactive to only two of 343 items tested. She had now lost 18 kg (40 lbs) and was at her lean body weight. Basal morning temperatures were within the healthy range. Data included:

- 1) Free T3 of 380 pg/dl
- 2) Free T4 of 1.1 ng/dl
- 3) TSH of 4.4
- 4) Microsomal antibodies were not detected
- 5) Anti-thyroid antibodies were not detected
- 6) Cholesterol of 190 mg/dl

- 7) Triglycerides of 145 mg/dl
- 8) Two hour post prandial blood sugar (2[degrees] PP BS) 94 mg/dl
- 9) Two hour post prandial insulin (2[degrees] PP Insulin) 150 IU

Conclusions

These cases illustrate the broad applicability of this fundamental approach to the first line management of autoimmune, immune dysfunction, and chronic inflammatory syndromes. The benefits of functional, comprehensive ex vivo LRA by ELISA / ACT tests and clinical outcome results are the following:

1) It is time to consider these and related functional, patient-specific, clinically actionable tests and treatment guides first line therapy for comprehensive care of chronic autoimmune, immune dysfunction, and inflammatory conditions.

2) Comprehensive, functional, ex vivo tests for all delayed immune pathways give clinically predictive and useful information to guide therapy. Up to 420 LRA assays can be performed on just one ounce of whole blood. This is more comprehensive and less time consuming than provocative testing. This is more specific and functional than serum ELISA IgG tests in that it measures reactive antibodies of all types (IgA, IgM, and IgG).

3) LRA assays detect only reactive, symptom-provoking antibodies in contrast to serum ELISA IgG tests that are fundamentally different. ELISA IgG tests are not functional. As a serum test, ELISA IgG measures presence or absence of antibody regardless of function. Both neutralizing, protective, and beneficial, as well as reactive, symptom-provoking, and harmful, antibodies are measured. The assay procedure cannot distinguish between them. This means unnecessarily avoiding items with a protective antibody response. ELISA IgG tests measure only immunoglobulin G class antibodies. Other reactive antibody classes (IgA and IgM), immune complex reactions (IgM anti-IgG antigen), and T-lymphocyte (helper cell) responses are not detected due to intrinsic limitations of the ELISA IgG procedure.

4) People respond to a group of items that are specific to them rather than to their condition or disease state.

5) Substituting for common items rather than the individual's full range of responses gives short term, transient improvements (at best). This is because the full burden on the immune defense and repair system is not sufficiently lowered nor is substantial repair allowed in most cases. Further comprehensive repair and rehabilitation of digestive functions depends upon substantial reduction in immunoreactive burden and

systematic repair, detoxification diet, targeted supplements, and a healing actions plan.

6) Careful "best efforts" to substitute for the reactive burdens on the immune system, coupled with a better diet (Alkaline Way Guide), targeted supplementation, and healing actions are sufficient to achieve sustained remissions. In some cases, repair requires repeat tests at six months to determine which items have been reset and which new reactants are acquired before digestion and intestinal permeability are reset to a fully healthy state.

7) Both prompt and long term remissions from inflammatory (repair deficit), autoimmune and immune dysfunction conditions have been documented for over a decade.

8) Suffering can be reduced, practice evidence base enhanced, and care delivered more cost effectively by addressing the patient specific causes of chronic disease rather than reacting to and suppressing their symptoms.

Clinical Consequences of Increased Permeability

Organ System/Condition

Common Sign

Digestive Tract:

"Leaky Gut Syndrome" that can express itself as

"Silent Maldigestion" (48)	Bloating / Gas / Belching
Gastritis (49)	Heartburn
Irritable Bowel Syndromes [IBS] (50)	Cramps
Regional Enteritis [Crohn's Disease] (51)	Constipation / Diarrhea
Ulcerative Colitis [UC] (52)	Mucous / Frequent Stool
Celiac Enteropathy (51,53)	Duodenal Atrophy

Nervous System:

'Blood-Brain Barrier Permeability' (54)

Migraine Headaches (55,56)	CNS Pain
Multiple Sclerosis [MS] (57,58)	MRI Plaque Demyelination

Endocrine System:

Thyroiditis	Energy Dysregulation
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[blood-thyroid barrier permeable] (59,60)	Cold Intolerance
Insulin resistance/ diabetes (61-64)	Energy Dysrhythmia
Endometriosis (65,66)	Abdominal or Pelvic Pain
Other Endocrinopathies (67)	Poor Tissue Healing
Cardiovascular System:	
Autoimmune Cardiomyopathies (68,69)	Poor Cardiac Ejection
Inflammatory Vascular Syndromes (70,71)	Endothelial Dysfunction
Arteriosclerotic Vascular Diseases	
[ASHD] (72,73)	Vascular Insufficiency
Coronary Artery Diseases [CAD] (74-76)	Angina; Coronary Spasm
Respiratory System:	
Asthma (77,78)	Expiratory Resistance
Autoimmune Bronchitis (79,80)	Recurrent Lung Irritation
Chronic Sinusitis (81,82)	Sinus Swelling/Tenderness
Liver:	
Autoimmune hepatitis (83-85)	Impaired Liver Function
Cholangitis (86,87)	Impaired Bile Function
Spleen and Immune Systems:	
Sjogren's syndrome (88,89)	Dry Eyes/Mouth; Big Spleen
Lupus [SLE] (90,91)	"Myriad Symptoms"
Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) (92-94)	
	Unexplained Fatigue/Easy Fatigue
Musculoskeletal System:	
Fibromyalgia [FM] (95-97)	Muscle Pain
Joints:	
Arthritides (98,99)	Joint Pain/Swelling
Connective Tissue Syndromes (100)	"Myriad Symptoms"

Genitourinary:

Glomerulonephritis (101)

Impaired Kidney

Function

Interstitial Cystitis (102,103)

Painful Urination

Skin:

Eczema (104,105)

Scaly Rash

Psoriasis (106,107)

Painful Rash

RESOURCE GUIDE

1) LRA by ELISA / ACT[™] tests are available from ELISA / ACT Biotechnologies, 14 Pidgeon Hill #300, Sterling, VA 20165; Phone: (800) 553-5472; Fax: (703)450-2981; Email: clientservices@ELISA ACT.com.

2) The Health Studies Collegium Alkaline Way[™] Guide is available. Write to: 14 Pidgeon Hill #310, Sterling, VA 20165; Phone: (800)328-7372 Fax: (703)450-2998.

3) PERQUE[™] Supplements are available from PERQUE, 14 Pidgeon Hill, #180, Sterling, VA 20165; Phone: (800)525-7372; Fax: (703)450-2995; Email: clientservices@PERQUE.com; Website: www.PERQUE.org.

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