First Line Comprehensive Care. Part I: Chronic Autoimmune Disease Management by Causes Rather than Symptomatic Consequences

Russell Jaffe, MD, PhD, CCN, NACB

This article addresses aspects of the human healing response in the context of what the evidence supports in the use of functional assays to improve diagnostic precision, patient-specific comprehensive case management, and outcomes monitoring.

Essential and innate to human life is our immune system, with a principal action in defense and repair. Both defense in response to foreign invaders and repair in response to daily wear and tear are the immune systems primary and required roles for maintenance of human life.

The fundamental approach to first line care articulated herein is based on patient-specific, comprehensive, functional, ex vivo tests and treatment plans. The roles of immune system dysfunction in good health and chronic ill health are explored. Advanced assays that provide comprehensive determination of an individual’s delayed type hypersensitivity (DTH)/delayed allergy reactions are used as examples of how to get to the cause of many chronic “treatment-resistant” issues.

While largely previously overlooked, functional immune responses provide examples of novel, “leap frog” technologies that improve diagnostic precision, enhance patient satisfaction, and lower total cost of care, particularly for high cost, high morbidity and mortality conditions ranging from obesity and diabetes to autism and neural tube defects. Getting to the causes is more likely to be sensitive, specific, predictive, and reliable than the current generation of largely static or physical chemical measurements now routinely performed in medical practices.

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 rehabilitate immune responses and, thereby, restore healthy tolerance and achieve sustainable remissions based on correctly cumulative repair deficits in chronic illnesses are described herein. Let us start with an understanding of the nature 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- to 18-hour interval.7 We can thus use transit time measurements as an overall, noninvasive, cost-effective, clinical assessment of digestive health.7

When healthy, any foreign immunoreactants (foreign antigen invaders) that gain entry are promptly identified, engulfed, and recycled by our ample supply of dendritic (phagocytic) surveillance cells.4-7 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 (from prions and viruses to mycoplasm and nanobacter bacteria)
2. Inhaled pollen or aerosallergens (either in lungs or swallowed and in the gut)
Immune dysfunction pathologies. When this occurs for a short time, it is easily remediated. In contrast, when burdened by maldigested antigens or parasites, our immune defenses are less able to neutralize infections or 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 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

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

1. Opsonins (nature’s antibiotics) and protective nutrients that inhibit pathogens produced by an abundance of healthy probiotic microflora. This includes flora on all body surfaces, from skin to mucosa.
2. Adequate mucin production that traps and retains digestive remnants until they can be digested.
3. Sufficient intestinal mucosal secretory IgA (sIgA) production to neutralize and inhibit pathogens and parasites.
4. Dendritic cells such as mucosal macrophages and fibroblasts with the capacity to trap and recycle digestive remnants and infectious agents as equally foreign if they reach the intestinal or respiratory mucosa.
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.

Only when the above five primary defenses are disabled or persistently overloaded do we chronically defer repair and thus become susceptible to delayed allergic responses. Indeed, the most overworked (distressed, “shock”) organ or system in the body is the most vulnerable to inflammation, ie, swelling, discomfort, and mononuclear (lymphocytic) cell infiltrates. Symptoms are specific for the particular distressed organ(s) and system(s) in the body.

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

1. Amino acids, di- and tri-peptides
2. Lipids and glycerides
3. Simple sugars
4. Nutrients including antioxidants, minerals, and metabolic cofactors

Malfunctions, 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. In fact, maldigestion (incomplete breakdown of food ingested) and dysbiosis (unhealthy composition of microorganisms in the intestine) can generate inflammation means cumulative repair deficits. Recognizing the cause or meaning of inflammation as accumulated deficits in repair opens for use by the comprehensive care clinician safer and more effective therapies that would otherwise be unavailable. This is an example in current medical care of the use of words (e.g., inflammation) whose true meaning is opposite to the general, common parlance understanding of the word.

Haptens are small molecules that bind to the body’s own proteins, distort their structure, and render then immunoreactive. Examples of haptens include: xenobiotic chemicals, toxic minerals, and food colorings.
appreciable quantities of immune reactive and health-diminishing digestive remnants and pathogen products. These immune reactive digestive remnants can penetrate the intestinal mucosal barrier, particularly if it is more permeable due to cumulative repair deficits. 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 because of compromise and impairment in innate immune defense and repair mechanisms.

Sources of Exposure to Immune Reactants

While 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.

This healthy resilience (homeostasis) is lost when maldigestion and dysbiosis persist. This suggests the central importance of the role digestion plays in health and well being. The consequences of this “epidemic of epidermics digestive disturbances” (as Don Donaldson used to opine) are both subtle and profound.

These consequences 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
2. Hospitable to chronic infection
3. Open to autoimmune or immune dysfunction conditions
4. More at risk of inflammatory cardiovascular diseases linked to elevated C-reactive protein (CRP) and increased homocysteine. 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.
5. Also more at risk of cancers related to loss of innate immune reactive surveillance due to reduced NK and cytotoxic T cell functions.

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

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. Although extensive, our immune system capacity is finite. 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.

Too often, repair becomes chronically deferred, particularly in distressed tissues or organs. This means that there is reduced synthesis of collagen, elastin, and basement membrane structural proteins. When this occurs, our organs become more permeable. This is clinically referred to as “leaky tissue” pathology.

Since structural proteins are also important in cell communication and orientation, these important functions are impaired. Table 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. 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 systematically and comprehensively.
2. Facilitate rehabilitation and repair of immune system mechanisms.
3. Show that the cumulative repair deficit in our body that leads to increased and altered permeability/intestinal uptake (leaky gut) 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.

### 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 (Fig. 1).

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 the following.

### Humoral Responses (Type II; B cell; Reactive or protective antibodies)

Reactive or provocative antibodies. These may be mucosally associated IgA, recent IgM, or systemic memory IgG. It is important clinically to know whether 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, blocking, helpful IgG response. In contrast, there are also reactive, symptom provoking IgG antibodies. These Type II DTH (B lymphocyte) responses can be specifically differentiated by functional autologous LRAs 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 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. However, other reactive antibodies (IgA or IgM), immune complexes, and T lymphocyte responses (any or all of which may provoke symptoms and persist pathology) are not measured or assessed by ELISA IgG (EIA) assays.

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 are likely to reappear.113,114

Further, antibody tests do not tell us about the important other mechanisms of immune defense reaction noted below.

### Immune Complexes (IC)

Immune complexes are IgM anti-IgG/antigen complexes. IC form as efforts by the body to protect itself from reactive (complement fixing) IgG antibodies. IC do not form in response to neutralizing (beneficial) IgG antibodies. Only functional assays that detect IC directly, such as ex vivo lymphocyte response assays or Raji cell assays detect these Type III DTH “delayed allergy” responses.112,115

### Cell-mediated Responses (Type IV; T cell; Th1/Th2; CD3, CD4, CD8, etc)

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
Comprehensive care of autoimmune diseases

allergy mechanisms) can give us information on all these sources of immune reactions. This will be explored in more detail later in this article, particularly 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 that results in further immune dysregulation and dysfunction132,133 and in further depletion of protective reserves and resilience factors.134,135

Clinically, this depletion of reserves and essential protective nutritive can contribute to:

1. Easy fatigability or chronic fatigue (CFIDS)136,137
2. Hospitality to recurrent infections (colds, flu, ear infections, chronic viral syndromes, etc.).127,138
3. Chronic inflammatory (repair deficit) conditions and autoimmune syndromes (see Table 1).139,140
4. Repair deficits that predispose to muscle (fibromyalgia)141 and visceral (endometriosis) 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.109,109 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 1000 autoimmune, immune dysfunction, and inflammatory cardiovascular diseases or syndromes.143

If we can identify the items to which an individual reacts through all three of the 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 nutrients143,144
2. Competent detoxification mechanisms,145 and
3. Distress adaptation146,147 so that necessary repair is not blocked or inhibited when the defense burden is lifted. This also means that posttraumatic stress disorder (PTSD) is recognized and the individual’s neuroimmunohormonal responses are rehabilitated.108-110

Decrease in defense burden also 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.148,149 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 (such as hemolytic Escherichia 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 also 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 fatigue93 as well as in type 1 and type 2 diabetes support 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.\textsuperscript{108-110}

When we concurrently address the causes of these problems, our immune defense and repair system can reset itself to a tolerant, nonreactive 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 essential and conditionally essential 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.

From Claude Bernard to Ivan Pavlov; from Hans Selye to Rene Dubos, from David Felton to Bruce McEwan this message has been well documented yet remains largely unapplied in practice. The human and economic costs are growing substantially; the lag from scientific documentation to integration in practice is increasingly troublesome, particularly as scientific evidence continues to grow geometrically. This means that the doubling of scientific knowledge occurs at increasingly shorter intervals.

**Clinical 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.\textsuperscript{3,106-110,160}

### Meaning of positive LRA by ELISA/ACT Results

**Immune Recognition**\textsuperscript{161}

All of the delayed allergy pathways can be programmed into lymphocyte subsets for reaction. Only a functional LRA measures all pathways. Further, beneficial (neutralizing, blocking) IgG antibodies are not measured because they do not trigger lymphocytes to respond nor do they provoke symptoms.

**Contaminant Recognition**\textsuperscript{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.

### Cross Reaction with an Identical Antigen or Reactive Epitope\textsuperscript{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:

1. Gut pathogens may contain a structure (antigen) identical to one found in a food. Improving intestinal microbial ecology with probiotics, an alkaline way diet, and substituting for foods that cause delayed allergic reactions can displace pathogens and shorten digestive transit so pathogens are less able to proliferate.
2. Related food family antigen or reactive epitope, for example, common antigens in the nightshade family may induce reactions from a food eaten to another member of the food family that has not been eaten.
3. An individual’s tissue antigens may cross react with a tested substance. This only occurs when repair deficits have exposed tissue antigens that are designed to be hidden. Stimulating repair can rebuild the blood–tissue barrier to healthy, low permeability and stop this autoantigen exposure.

A positive result on lymphocyte blastogenic\textsuperscript{c} or mitogenic\textsuperscript{d} response assays, for example, LRA by ELISA/ACT, can be due to one of three causes. These include immune recognition of:

1. An antigen specific to the compound tested,\textsuperscript{161}
2. An identical antigen from another source, such as a pathogen that sheds the same antigenic structure,\textsuperscript{164}
3. A nonspecific reactivity due to generalized lymphocyte response, usually due to not following the preparation instructions and being exposed to something that preactivated the lymphocytes before they reached the lab.\textsuperscript{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 1-ounce blood draw. This is the amount of blood the bone marrow produces in about 1 hour.

For accurate results certain substances need to be avoided for a few days. Steroid medications need to be avoided for 4 days.\textsuperscript{166} A “steroid bridge” is available to help in this interim if needed.\textsuperscript{165} Aspirin and antihistamines also stabilize lymphocyte membranes and reduce reactivity.\textsuperscript{167-169} Aspirin and

\textsuperscript{c}This means that a colony of cells would form over several weeks of observation of the lymphocytes in vivo or in cell culture.

\textsuperscript{d}A mitogen is a substance that lymphocytes have been programmed or have learned to react to upon exposure, such as an antigen, hapten, or reactive epitope.
antihistamines need to be avoided for 2 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 cooled between 4 and 10°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.\(^\text{170}\)

An entire LRA assay can be performed on only 40 \(\mu\)L of CRP. The sample is incubated at 35 ± 2°C for 3 hours. This is long enough to measure the initial response when a lymphocyte recognizes a substance it has been preprogrammed 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 whether enzyme activation has occurred.\(^\text{171}\)

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.\(^\text{172}\) 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, 6 months are needed to reset strong reactions while intermediate or moderate reactions can be reset in 3 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.”\(^\text{173}\) 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.\(^\text{174,175}\) However, there is no such universally agreed upon standard for determining delayed hypersensitivity reactions.\(^\text{176}\) 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, then, is the current clinical “gold standard.”\(^\text{177}\)

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 5 years. Diagnoses of subjects included autoimmune conditions (rheumatoid diseases, multiple sclerosis, asthma, ulcerative colitis, eczema, psoriasis, lupus, thyroiditis, diabetes), and immune dysfunction conditions (fibromyalgia, and chronic fatigue).\(^\text{178}\)

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 tests 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 ± 14.5 \textit{before} and 26.4 ± 18.2 \textit{after} 6 to 30 months of following this healing program (\(p < 0.0001\)). 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.\(^\text{178}\)

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.”\(^\text{179}\) During the 3-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 were read as not reactive.\(^\text{179}\)

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.\(^\text{179}\)

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.\(^\text{180,181}\) This is in contrast to Type 1 (IgE) hypersensitivity reactions (not tested for with LRA assays) or a psychologically programmed (distress) response.\(^\text{182}\)

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.\(^\text{64}\) Similar results in both type 1 and type 2 diabetics are also supportive of this comprehensive care technology breakthrough.\(^\text{95}\) Clinical reports from a database of over 40,000 cases are further re-
Common conditions associated with each aspect of delayed allergy (hypersensitivity) are shown below. Only LRA by ELISA/ACT® functional, comprehensive, ex vivo assays reveal what provokes responses from all delayed allergy pathways.

<table>
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<tr>
<th>Type II Reactive Antibody (Only) [No protective antibody]</th>
<th>Type III Immune Complex IgM Anti-IgG/antigen</th>
<th>Type IV Cell Mediated T lymphocytes</th>
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For management of autoimmune and immune dysfunction problems, comprehensive and functional assays give more predictive basis for sustained clinical improvement and long-term remission.

Figure 2 Common clinical conditions associated with various delayed allergy-specific hypersensitivity mechanisms.

inforcement 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 dangers. 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 conditions108,109 (Fig. 2).

LRA by ELISA/ACT tests are useful tools for identifying the reactive substances of delayed hypersensitivity by providing a comprehensive “immunologic fingerprint” 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

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 Synthroid 0.125 mg/day for functional hypothyroidism; Dipentum 750 mg BID; cortisone/butyratene 2-5 times per week; and supplements, including a high-potency multivitamin, 2 g/day buffered ascorbate, 120,000 IU, 3 times per week beta carotene, 800 IU mixed natural tocopherols (vitamins E)/day, 500 mg/day quercetin complex, sialic acid 2 caps BID, and 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.

Progress was noted as follows: October, 1991: Obtained LRA by ELISA/ACT tests results and started recommended plan. January 1992: “85% better,” off cortisone; Dipentum reduced 50%; June 1992: Asymptomatic for 3 months.

The patient reported, “...last 6 months have been the best in last 10 years...my ELISA/ACT plan made the difference.” Sustained improvement has been maintained over the past decade.

Irritable Bowel Syndrome/Ulcerative Colitis Case Success

AA presented as a 35-year-old, 67.5-kg, white, married woman, blood pressure 132/68, with a 10-year history of irritable bowel syndrome (IBS) and ulcerative colitis (UC) established by biopsy and barium enema in December 1983. Until 1990, her IBS/UC remained clinically unresponsive to multiple therapies that included intensive management with azulfadene (0.5 gm QID); steroids with dosage based on symptoms; and a variety of antiinflammatory and cytokine blockers.

Annual sigmoidoscopies documented “cobblestone granuloma” from 8 to 25 cm in the colon. Patient reported 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 1 month.

Follow up LRA by ELISA/ACT in November 1991 showed a 54% decrease in reactive items (from 45 to 20). 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 of 343 items tested. The patient remains asymptomatic at 10 years follow up.

Colitis/ Bronchitis/Glossitis/Fibromyalgia/ Chronic Fatigue (CFIDS) Case Success

PR presented as a 60-year-old female with a 25-year history of chronic, treatment-resistant UC established by biopsy and repeated barium enemas, constipation with intermittent diarrhea, postprandial bloating, chronic fatigue immune dysfunction syndrome (CFIDS), fibromyalgia (FM), insomnia, bronchitis, and 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 1 month she reported marked reduction in constipation, relief from postprandial bloating, and more energy (“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, the “best I've felt in years;” sleeping well, no insomnia; regular bowel habits without bloating, constipation, or diarrhea; muscle aches and pain were “minimal;” and concentration and memory were “much better.”

She continues to be asymptomatic at 15 months follow up.

Fibromyalgia/CFIDS Case Success

JA, a 44-year-old woman with treatment-resistant fibromyalgia and CFIDS for 5 years, reports, “unbearable ” upper back, thigh and calf muscle pain; stiffness “all over,” especially in the morning and after being at rest; depression, acquired; constipation (since childhood); pruritis (especially knees and elbows); memory and concentration problems; sensitivity to
Fibromyalgia, My Journey to Wellness
mission from disabling fibromyalgia and CFIDS in her book, "Dying to Live: The Acid-Alkaline Way Guide," taking targeted supplements, and following healing actions. After 6 months, she reported ">75% reduction in back pain, stiffness is gone, and overall health is 90% better." Constipation resolved; she felt optimistic and 90% better. Diabetes/Insulin
Resistance Case Success
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 A1c) 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 5 months, he was reported to have fasting blood sugar in the 80-125 mg/dL range on only 6 U Humulin TID; 2-hour postprandial blood sugar in the 120-150 mg/dL range; and glycosylated protein (Hgb A1c) reduced to 5.1 mg/dL. In a community-based RCT we noted systematic improvements in these same markers in both type 1 and type 2 diabetics.190

Chronic Fatigue and Rhinitis Case Success
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 “perpetual colds and flu;” recurrent headaches (possibly due to sinusitis/rhinitis); and 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 1 month she reported sleep now gives rest and energy and rhinitis/sinusitis symptoms were gone. After 5 months, she was asymptomatic and off all medications.

Asthma Case Success
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) as well as NSAIDs periodically.189

LRA by ELISA/ACT tests were performed in August 2001. Reactions were noted to 12 of 377 substances tested. After 1 month, rhinitis was gone and asthma was less symptomatic. Inhaler use with exercise remained. Follow up at 6 months showed her to be symptom free. Repeat tests found her reacting to only 2 of the initial items. As often happens when persisting malnutrition, 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
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 A1c) 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 5 months, he was reported to have fasting blood sugar in the 80-125 mg/dL range on only 6 U Humulin TID; 2-hour postprandial blood sugar in the 120-150 mg/dL range; and glycosylated protein (Hgb A1c) reduced to 5.1 mg/dL. In a community-based RCT we noted systematic improvements in these same markers in both type 1 and type 2 diabetics.190

Thyroiditis Case Success
EO presented as a 35-year-old mother of three with an unremarkable presentation except for 18 kg (40 pound) excess over her lean target weight. She reports that she “always has to push myself to get through the day.” Observations include first morning basal temperatures that fluctuate between 96.7 and 97.3°F over a month of daily observations; thin, slow growing, coarse hair and nails; easy fatigue (possible CFIDS); high personal standards “rarely met;” loss of lateral margins of eyebrows; and marital distress.

While previous thyroid tests had been “OK,” measurement of free hormone and concurrent TSH had not previously been reported. Data include free T3 of 120 pg/dL; free T4 of 0.5 ng/dL; TSH of 12; TRF with a peak TSH of 92 μIU at 30 min; microsomal antibodies > 2048.1; anti-thyroid antibodies > 4096.1; cholesterol of 325 mg/dL; triglycerides of 280 mg/dL; 2-hour postprandial blood sugar 186 mg/dL; and 2-hour postprandial insulin 80 IU.

She was evaluated using LRA by ELISA/ACT tests and was found to react to 4 items and 1 food group 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, 2 grains of desiccated thyroid daily were initiated.

Follow up at 6 months found her “more energetic and pleased with my nails and hair.” She had lost 10 kg (22 pounds) “without dieting.” Lab test results before and after the plan included free T3 430 pg/dL before, 380 pg/dL after; free T4 0.9 ng/dL before, 1.1 ng/dL after; TSH 5.2 IU before,
Comprehensive care of autoimmune diseases

4.4 IU after; microsomal antibodies 8:1 before, not detected after; anti-thyroid antibodies 8:1 before, not detected after; cholesterol 220 mg/dL before, 190 mg/dL after; triglycerides 150 mg/dL before, 145 mg/dL after; 2° PP glucose 108 mg/dL before, 94 mg/dL after; and 2° PP insulin 160 IU before, 150 IU after.

Further follow up at 1 year included repeat of LRA by ELISA/ACT tests. She was found reactive to only 2 of 343 items tested. She had now lost 18 kg (40 pounds) and was at her lean body weight. Basal morning temperatures were within the healthy range. Data observed after the plan are shown above.

These cases illustrate the applicability of this fundamental approach to the first line comprehensive care management of autoimmune, immune dysfunction, and chronic inflammatory/repair dysfunction syndromes.

Conclusions

Examples of integrative care philosophy and practice have been reviewed. The benefits of functional, comprehensive ex vivo tests in redressing the causes rather than responding to the symptoms proves well accepted by practitioners and patients alike. The economics of care are favorable. LRA by ELISA/ACT tests and clinical outcome plans have been used for over 20 years. Through a variety of clinical outcome studies and case examples, this “gold standard” of integrative care is now usual and customary, medically necessary, and appropriate for the management of autoimmune, immune dysfunction, and chronic inflammatory conditions.

Additional conclusions about first line comprehensive care approach are:

1. It is time to consider these and related functional, patient-specific, clinically actionable tests and treatment guides as first-line therapy for comprehensive care of chronic autoimmune, immune dysfunction, and inflammatory conditions. The evidence in support of these approaches is robust and growing.

2. Comprehensive, functional, ex vivo tests for all delayed immune pathways gives clinically predictive and useful information to guide therapy. Up to 420 LRA assays can be performed on just 1 ounce of whole blood. Some describe this as an “immunologic fingerprint,” others refer to this as “PCR-like amplification for functional immunology.” LRA tests are more comprehensive and less time consuming than provocative skin testing. LRA tests are more specific and functional than serum ELISA IgG tests in that LRA, being functional, measures reactive antibodies of all types (IgA, IgM, and IgG), distinguishing harmful, reactive antibodies that are detected from protective, neutralizing antibodies that are not detected. In addition, immune complexes and T cell direct immune reactions are also measured.

LRA assays, as cell response assays, were designed to detect only reactive, symptom-provoking antibodies. In contrast, serum ELISA IgG tests are fundamentally different, being static tests of physical chemistry. ELISA IgG tests are not functional. As a serum test, ELISA IgG measures presence or absence of antibody regardless of function. Both neutralizing, protective, beneficial as well as reactive, symptom-provoking, harmful antibodies are measured. The assay procedure cannot distinguish between them. This means unnecessarily avoiding items with a protective antibody response if an assumption is made that all antibodies are harmful! 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, CD4) responses are not detected due to intrinsic limitations of the ELISA IgG procedure.

3. People respond to a group of items that are specific to them rather than to their condition or disease state. Results of functional tests are usually specific for the individual rather than tied to the symptoms or diagnosis. In other words, the diagnosis no longer tells the practitioner what to do when integrative medicine is practiced.

4. 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.

5. 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 every 6 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.

6. Both prompt and long-term remissions from inflammatory (repair deficit), autoimmune, and immune dysfunction conditions have been documented for over a decade. It is a privilege to report on our several decades experience with integrative healthcare treatment guides, practice protocols, and evidence-based care.

7. 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. Our 50,000+ case database is helpful in developing case and condition management approaches to the chronically unwell.

Resources

LRA by ELISA/ACT™ tests and treatment plans are available from ELISA/ACT Biotechnologies, 14 Pidgeon Hill #300,
Supplemental Supportive Peer-reviewed References

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