Oxidative coagulopathy
A proposed pathogenetic mechanism for environmental illness

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Abstract Freshly prepared, unstained peripheral blood smears from 46 of 50 patients with chronic environmental illness showed clear microscopic evidence of advanced oxidative injury to all elements of circulating blood. As observed with high-resolution (15,000×) phase-contrast and darkfield microscopy, morphologic patterns of oxidative injury to blood components have been designated oxidative coagulopathy, a state of circulating blood comprising: structural abnormalities involving erythrocytes and granulocytes and zones of congealed plasma in its early stages; fibrin clot and thread formation with platelet entrapment in the intermediate stages; and micro clot and microplaque formation in late stages. Moderate to advanced changes of oxidative coagulopathy were seen in only two of 15 healthy control subjects. Oxidative coagulopathy begins with oxidative activation of plasma enzymes and leads to oxidative permutations of plasma lipids, proteins, and sugars, and is not merely confined to oxidative activation of recognized coagulation pathways. It is proposed that oxidative coagulopathy represents one of the core pathogenetic mechanisms of homeostatic dysregulation seen in environmental illness and leads to oxidative injury to intracellular matrix, cell membranes, and intracellular organelles such as mitochondria. The observed cellular and plasma changes shed considerable light on many aspects of the macroecologic toxicants and their cellular targets, as well as the microecologic oxidants and their molecular targets. Oxidative coagulopathy is a powerful explanation of the production of symptom-complexes characteristically encountered in environmental illness.

Introduction
While clinical patterns of environmental illness are quite well recognized and established among physicians who practice environmental medicine[1-8] this subject remains controversial[9-12].

The primary reason for this is the nonlinear dynamics of clinical disease caused by ecologic factors[13]. Thus, unlike chemical toxicity, chemical sensitivity in most cases is not dose-related, and the range of susceptibility of environmentally sensitive persons to ecologic chemicals is so wide as to make the traditional approaches for establishing cause-and-effect relationships exceedingly difficult.

Moreover, the lack of morphologic or biochemical abnormalities in the results of commonly performed laboratory tests in environmental illness has further hampered progress in understanding clinical ecologic illness.

During nearly two decades of the author’s clinical work, he has investigated redox dysregulation in patients with environmental illness with biochemical
tests and high-resolution, phase-contrast microscopic studies. Specifically, he has focused on the following:

- the fundamental oxygen order of human biology[14];
- spontaneity of oxidation in nature and its impact on pathogenesis of illness[15];
- oxidative injury to elements of circulating blood called oxidative coagulopathy[16];
- oxidative injury to intracellular matrix, cell membranes, and mitochondria previously designated AA oxidopathy[17];
- clinical consequences of anoxia, acidosis, and accumulation of toxic organic acids[18];
- oxidative regression to primordial cellular ecology (ORPEC) that favors proliferation of anaerobes under primordial conditions[18]; and
- clinical entities caused by, or associated with, oxidative coagulopathy, AA oxidopathy, and the ORPEC state[19-22].

In this paper, morphologic evidence of accelerated oxidative injury to circulating blood in environmental illness is presented as an extension of the previous studies.

Patients and clinical diagnostic criteria for environmental illness
There were 31 females and 19 males in the study. The ages ranged from 15-67 years for females (average, 42.5) and from 17-61 years for males (average, 40.5). For this study, the following clinical criteria for the diagnosis of environmental illness were used:

- no history of organic or psychiatric illness before the onset of environmental illness;
- persistence of symptoms for a minimum of 12 months; and
- a clear pattern of clinical symptomatology characteristic of environmental illness elicited by a physician experienced in the diagnosis and management of environmental illness.

A total of 33 patients also met diagnostic criteria of chronic fatigue syndrome (21), fibromyalgia (12), or both.

Peripheral blood morphology examined with high-resolution phase-contrast and darkfield microscopy
Freshly prepared, unstained peripheral blood smears of patients were examined with a high-resolution (15,000×) microscope with phase-contrast and darkfield optics (American Biologics, Chula Vista, CA). The procedural details of such microscopy have been described[18]. The peripheral blood morphology with such microscopy is distinctly different from that studied with ordinary bright-light microscopy. The following brief comments about peripheral blood
morphology in healthy subjects are included here to provide a frame of reference for presenting features and degrees of oxidative coagulopathy in environmental illness. Erythrocytes appear as pliable round cells that readily change their shape to ovoid, triangular, dumbbell, or irregular outlines to squeeze past other erythrocytes in densely populated fields. Such cells resume their regular rounded contour as soon as they find open space (Plate 1). Most granulocytes were observed to show amoeboid movements, their locomotion provided by streaming of their granules into little protrusions of cytoplasm which grew in size to become the “legs” of the cells. Such cells continuously changed their configurations as they appeared to explore their microenvironment. Not uncommonly, active phagocytosis of bacteria and cellular debris by some cells is observed. Lymphocytic details seen included fine cytoplasmic granules and finer detail of the nuclear chromatin. The platelets appear as dark round-to-ovoid poorly circumscribed bodies with poorly visualized granules. Some fields show clumping. However, platelet agglutination and degranulation is only infrequently seen. There is little tendency toward plasma congealing in their vicinity. Indeed even when smears are allowed to stand for 15-30 minutes, platelets remain discrete and do not cause congealing of fields of plasma that surround them in the central portions of the smears. The peripheral parts of the smear commonly show cellular damage as a processing artifact.

Plate 1. Illustrates peripheral blood morphology of a healthy control subject as seen in freshly prepared, unstained smears with a high-resolution phase-contrast (15,000×) microscope. Note the smooth outline of erythrocytes and irregular shape of four polymorphonuclear cells included in the field. The plasma fields (open spaces between cells) are free of any zones of congealing, microclots or microplaques.
Morphologic patterns of oxidative coagulopathy

In previous studies of peripheral blood morphology in clinical entities characterized by accelerated oxidative stress, the author and his colleague, Omar Ali, have described the following salient morphologic features of oxidative coagulopathy:

- erythrocyte and leukocyte membrane deformities;
- diaphanous congealing of plasma;
- platelet aggregation and lysis;
- filamentous coagulum (fibrin needles);
- lumpy coagulum;
- microclots; and
- microplaques[17,18].

In the present study, the following observations were made in environmentally sensitive patients.

Erythrocytic morphology in environmental illness
The most common abnormalities observed in environmental illness involved erythrocytes and consisted of lack of erythrocyte membrane plasticity, irregularities of its outlines, and clumping. Many erythrocytes showed surface wrinkling, teardrop deformity, sharp angulations, and spike formations. In later stages, zones of plasma congealing were seen around many erythrocytes. In more advanced cases, an increasing number of erythrocytes showed shrinkage and filamentous outgrowths extending from their membranes, such filamentous outgrowths covering the entire surface of cells to produce a Medusa-like appearance. Other cells appeared as ghost outlines. Zones of congealed plasma surrounded many cells.

Granulocytic morphology in environmental illness
The earliest changes involving granulocytes were clumping and loss of locomotion, with cells lying limp in pools of plasma with absence of granular streaming and amoeboid cytoplasmic protrusions. In later stages, granulocyte cytoplasm showed vacuolation, zones of increased density, and disintegrating membranes. Congealed plasma surrounded ruptured cells. Clear evidence of granulocytic phagocytic dysfunction was observed in the majority of smears. Even when actively motile, phagocytic leukocytes failed to actively engulf and digest primordial life forms (yeast-like organisms).

Interestingly, leukocytes in such situations were observed to approach clusters of primordial organisms, shrink back, and move away. (For illustrated details of such altered predator-prey dynamics of granulocytic phagocytes and microbes in peripheral smears, see[18].)
Lymphocytic morphology in environmental illness
The dominant morphologic alteration of lymphocytes involved enlargement and lymphoblastic transformation. In mild to moderate degrees of oxidopathy, lymphocyte nuclei lost their normal intense basophilic appearance and exhibited pale blue staining. Cytoplasmic vacuolation was an uncommon feature. In most advanced stages, up to 90 per cent of lymphocytes in most smears showed abnormal cytologic characteristics with a majority of cells in lymphoblastic transformation.

Platelet morphology in environmental illness
The earliest changes involving platelets were platelet clumping and loss of membrane detail. Enlarged platelets were seen frequently. With increasing intensity of coagulopathy, degranulation and lysis were common. Zones of congealed plasma, the beginning of soft clots, were pronounced, and often extended to erythrocytes and leukocytes in the vicinity. Fibrin deposits occurred both as fibrin needles and amorphous masses surrounding lysed platelets and other corpuscles.

Plasma morphology in environmental illness
Zones of congealed plasma in close vicinity of platelets, erythrocytes, granulocytes, and lymphocytes, as described in the preceding paragraphs, were encountered in all cases. Such zones of plasma solidification were also commonly observed surrounding microbes (coccal and bacillary microbes as well as primordial life forms described fully previously[18]); this phenomenon was most pronounced in the vicinity of the latter. Congealed plasma also surrounded microcrystals encountered in oxidative coagulopathy (presumably composed of oxalates, urates, cholesterol and other substances precipitated by acidosis associated with oxidative coagulopathy). While congealed areas were small and discrete in mild cases, large and confluent areas of plasma consolidation were seen in nearly every microscopic field in advanced cases.

Micro clot and microplaque formation in the circulating blood in environmental illness
In earlier descriptions of oxidative coagulopathy in ischemic coronary artery disease, a micro clot was defined as a discrete zone of clotting of plasma components with entrapped blood corpuscles, with or without visible fibrin crystals. Microclots seen in this study ranged from 20-150microns or larger. Microclots were observed as loose ("soft") with poorly delineated edges or as firm ("hard") with rather circumscribed boundaries. A microplaque in that report was defined as a compacted micro clot with a clearly definable inner structure composed of fibrin needles, amorphous masses, and discrete layers of thrombotic material. The morphology of microclots and microplaques is illustrated in Plates 2-6.
Plate 2.
Shows radiating zones of congealed plasma (an early change of oxidative coagulopathy) spreading from the periphery of erythrocytes.

Plate 3.
Shows three irregularly shaped soft microclots composed of plasma coagulums with trapped agglutinated and lysed platelets. Some erythrocytes show crenated membranes.
Plate 4. Illustrates a transitional stage between a micro clot and a soft microplaque, and shows early changes of compaction. Some erythrocytes stick to the periphery of the micro clot.

Plate 5. Shows a well-formed, hard microplaque with a layered structure (created by compaction of a soft microplaque).
Plate 6.
Shows multiple well-formed microplaques in the center field and many dark shrunken erythrocytes. Faintly visible zones of congealed plasma are seen between 3 and 4 o’clock positions.

Semiquantitative assessment of abnormal peripheral blood morphology in environmental illness
In Table I, semiquantitative data for microscopic features observed in freshly prepared peripheral blood smears of 50 patients with environmental illness are compared with similar data for 15 apparently healthy subjects. Microscopy was performed within five minutes of the preparation of smears. The semiquantitative assessment of cellular and plasma abnormalities was done by examination of a minimum of 100 microscopic fields in each case.

The scale of scoring abnormalities was as follows:

- 0 = abnormal feature absent;
- 1+ = abnormal features present in less than one in ten microscopic fields;
- 2+ = abnormal features present in at least one in five fields;
- 3+ = abnormal features present in about one-half of fields; and
- 4+ = abnormal features present in nearly all fields.

Discussion
Environmental toxicants profoundly influence the physiologic processes of humans[23-26]. The critical aspects of toxicant-cell dynamics are the following:
<table>
<thead>
<tr>
<th>Morphologic characteristic</th>
<th>Patient score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Control score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rouleaux</td>
<td>2.8</td>
<td>0.4</td>
</tr>
<tr>
<td>RBC crenation/spikes</td>
<td>3.2</td>
<td>0.6</td>
</tr>
<tr>
<td>RBC membrane rupture</td>
<td>2.2</td>
<td>0.2</td>
</tr>
<tr>
<td>RBC lysis</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Diminished WBC granules streaming</td>
<td>2.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Diminished WBC motility</td>
<td>3.2</td>
<td>0.8</td>
</tr>
<tr>
<td>WBC membrane rupture</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>WBC lysis</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Lymphocyte enlargement</td>
<td>3.7</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoblastic transformation</td>
<td>2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Platelet agglutination</td>
<td>3.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Platelet lysis</td>
<td>2.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Congealed plasma</td>
<td>4.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Filamentous coagulum</td>
<td>3.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Lumpy coagulum</td>
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<td>0.5</td>
</tr>
<tr>
<td>Microclots per 20 fields</td>
<td>18</td>
<td>2.4</td>
</tr>
<tr>
<td>Microplaques per 20 fields</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Bacteria</td>
<td>1+</td>
<td>Rare</td>
</tr>
<tr>
<td>Crystals per 20 fields</td>
<td>6</td>
<td>1.1</td>
</tr>
<tr>
<td>Oxidative coagulopathy</td>
<td>2.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Overall score</td>
<td></td>
<td></td>
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</table>

**Note:** <sup>a</sup> See scale of scores in text

Semiquantitative scores of morphologic abnormalities observed in oxidative coagulopathy in 50 patients with environmental illness

- exposure to toxicant (concentration and route of entry);
- uptake;
- transport;
- storage;
- direct toxicity;
- metabolism of toxicant (including Phase-I involving oxidation, reduction, or hydrolysis and phase II involving various conjugation reactions);
- secondary and tertiary tissue responses; and
- excretion.

All of the above are complex issues. For instance, uptake of the toxicant by the cells involves complex dynamics between the cell membrane and the xenobiotics, including:

- passive diffusion through spores or relevant spaces of lipid-protein-sugar bilayers;
- facilitated transport that requires water-soluble substances “carried” by fat-soluble moieties; and
- lipophility of the toxicant.
Moreover, each of the above elements is profoundly influenced by the concentration and tension of oxygen, pH, temperature, humidity, light, and the availability (as well as lack) of redox-active nutrients. While many advances in our understanding of the above factors have been made in plant and animal models[26-28], little, if any, progress has been made in this field as regards human ecologic illness. The primary reason is that plant and animal ecotoxicity experiments are designed to culminate in sacrifice of the living organisms, which, of course, cannot be planned for human subjects. To such difficulties must be added the previously noted lack of biochemical and morphologic abnormalities in the traditional diagnostic laboratory tests in clinical environmental illness. It is in this context that the changes of oxidative coagulopathy observed in the present study not only open up the possibility of an expedient laboratory method of assessing the degree of oxidative stress in environmental illness but also provide valuable insight into the pathogenesis of its symptom-complexes.

To provide a framework for considering the role of oxidative coagulopathy in the pathogenesis of symptom-complexes of environmental illness, brief comments about the following aspects of human redox regulation seem necessary: spontaneity of oxidation and disease; clotting-unclotting dysequilibrium in environmental illness; redox dynamics of oxidative coagulopathy; primary pathologic processes triggered or perpetuated by oxidative coagulopathy; and oxidative injury to matrix, membranes, and mitochondria.

**Spontaneity of oxidation and disease**
In 1983, the author proposed that spontaneity of oxidation in nature is the core pathogenetic mechanism of the aging process and all diseases[15]. That one basic mechanism should be the basis of molecular injury in all diseases seems implausible at first blush. However, extensive review fails to provide any evidence to the contrary[15-19]. Specifically, in 1988, the author proposed that spontaneity of oxidation provides the molecular basis of environmental illness in the sense that all agents causing environmental illness are oxidizing in nature and that oxidizing injury once initiated perpetuates itself. (Spontaneity of oxidation, then, becomes the essential mechanism that flames the oxidative fires and perpetuates molecular injury.) In 1990, following the study of peripheral blood morphology of several hundred patients with chronic fatigue syndrome, the oxidative nature of the erythrocyte abnormalities observed in patients with chronic fatigue syndrome was established by demonstrating the reversibility of changes by ascorbic acid[18]. In 1991, the author established the oxidative nature of platelet aggregation and clot formation by the addition of ascorbic acid and ethylenediaminetetraacetic acid (EDTA) to platelet aggregates induced by oxidizing agents such as collagen, epinephrine, ADP, and ristocetin. Both ascorbic acid and EDTA can readily break up platelet aggregates formed by addition of various aggregating agents[19]. In 1995, accelerated oxidative molecular injury was recognized as the core pathogenetic
mechanism of chronic fatigue syndrome[20]. In 1997, oxidative coagulopathy was proposed as the core pathogenetic mechanism of ischemic coronary artery disease[10].

Abnormal coagulative phenomena within the circulating blood occur in diverse clinicopathologic entities such as eclampsia, anaphylaxis, localized and generalized Shwartzman reactions, hemorrhagic diathesis in clinical and experimental acute viral in fections, bacterial endotoxic shock and others[21]. However, until recently, intravascular clotting was regarded as a homeostatic dysregulation of interest only in life-threatening acute illnesses. The essential role of such homeostatic dysregulation in chronic illness has only recently been recognized[23-26].

Clotting-unclotting dysequilibrium (CUD) in environmental illness

Clotting-unclotting equilibrium (CUE) is, in the author’s view, the second most critical homeostatic requirement in health, the first being the redox equilibrium. The present study adds to the author’s previously published evidence for this view. Notable in those investigations are the studies documenting reversibility of the early changes of oxidative coagulopathy by antioxidants such as ascorbic acid[29,30] vitamin E, taurine and others[31]. Accelerated oxidative molecular injury, regardless of its origin, disrupts the CUE of health and causes CUD of disease[18]. It is noteworthy that all oxidants operant on the circulating blood contribute to oxidative coagulopathy.

Human external and internal ecosystems are under increasing oxidative stress. The oxidizing capacity of the planet earth is increasing[31,32]. The ozone layer is thinning and is oxidizing[33]. Global anoxia is increasing and is oxidizing[34]. Ever-increasing levels of fossil fuel burning are increasing oxidant stress. Industrial pollution is increasing, and most pollutants are oxidizing. Ten thousand years ago, the estimated average temperature of Earth was 50°F[35] and it has been steadily rising. From January to July 1998, average monthly temperatures consistently broke previous monthly records, with temperatures rising to 124°F in India, claiming 3,000 lives[36]. The greenhouse effect is oxidizing. All of the above natural and anthropogenic oxidizing elements contributing to the increasing oxidizing burden on human ecosystems have increased enormously in recent decades.

As for the various body organ ecosystems in environmental medicine, oxygen transport and utilization in chemical sensitivity is impaired, as evidenced by increased urinary excretion of toxic organic acids such as tartaric acid that inhibit the Krebs’ cycle[37]. Clinical evidence for that is furnished by the pervasive sense of “air hunger” among patients with environmental illness and clinical benefits of oxygenative therapies for such patients[18]. The bowel ecology disrupted by massive sugar overload and extended antibiotic use (which feeds yeast and primordial flora) is oxidizing[18]. Lactic acidosis and dehydration, almost invariably seen in advanced environmental illness, is
oxidizing by interfering with the Krebs’ cycle as well as hepatic enzyme detoxification pathways. This subject has been recently discussed at length[18].

Redox dynamics of oxidative coagulopathy in environmental illness

Not unexpectedly, erythrocytes were found to be more vulnerable to oxidative injury than other blood corpuscles since such cells transport oxygen, the most important oxidizer in the body. Furthermore, unlike the leukocyte cell membrane which is sturdy and uniquely equipped with enzymatic antioxidant defenses against oxidative stresses of microbial invaders, the erythrocyte membrane is more permeable to oxygen (to facilitate uptake and delivery of oxygen). Erythrocyte lysis leads to the release of free hemoglobin in plasma. Free hemoglobin has been considered a dangerous protein – a biological Fenton catalyst[38]. It rapidly quenches free radicals in a highly oxidizing environment and becomes oxidized, thus turning into a potent oxidant. It is readily degraded by H₂O₂ to release free iron, which initiates and propagates several free radical reactions[39,40]. Hemoglobin reacts with H₂O₂ to produce a protein-bound oxidizing species capable of causing lipid peroxidation[41]. Free hemoglobin also avidly binds with nitric oxide radicals and induces vasospasm, triggering yet other oxidizing events which, in turn, feed the oxidative fires of AA oxidopathy.

Not unexpectedly, granulocytes also play critical roles in the initiation and perpetuation of oxidative coagulopathy.[42,43]. In health, such cells produce bursts of oxidizing species for microbial killing as well as for oxidative neutralization of toxins. In oxidative coagulopathy, granulocytes are activated by increasing oxidant stress and, in turn, feed the oxidative flames by their own increased generation of toxic oxidative species that degrade other intracellular and extracellular molecular species, inflict peroxidative injury to cytoplasmic and organelle membranes, enhance polymorphonuclear leukocyte-endothelial adhesion, and increase microvascular permeability[44,45]. Evidently, all of those factors can initiate, perpetuate and intensify oxidative phenomena in environmental illness. Some oxidizing molecular species elaborated by granulocytes increase capillary permeability and enhance granulocyte-endothelial adhesiveness[46,47]. The cytoplasmic granules of human granulocytes are rich in many enzymes, including proteases such as elastase, which is capable of degrading proteins in intracellular as well as extracellular fluids[48]. Oxidative cell membrane injury may be expected to result in escape of proteases from granulocytes into the circulating blood. The destructive capacity of granulocytes represents an exaggerated physiologic response in which bursts of potent oxidative molecular species are produced during inflammatory and repair responses. Specifically, hydroxyl radicals (OH) derived from superoxide radicals (O₂⁻) produced by granulocytes are a major cause of cellular injury. Granulocytic myeloperoxidase generates hypochlorite
radicals when exposed to $\text{H}_2\text{O}_2$ following phagocytic activation\cite{49}. Hypochlorite, in turn, oxidizes protease inhibitors, thus leading to increased proteolytic tissue damage.

**Primary pathologic processes initiated or perpetuated by oxidative coagulopathy**

Oxidative coagulopathy initiates and perpetuates the following seven primary pathologic processes that feed upon each other and serve as core pathogenetic mechanisms for various symptom-complexes of environmental illness:

1. impaired perfusion;
2. increased free radical activity;
3. anoxia;
4. acidosis;
5. impaired enzymatic functions;
6. matrix, membrane, and mitochondria dysfunctions; and
7. autoimmune injury.

It is proposed that oxidative coagulopathy triggers *all* of the recognized symptom-complexes of environmental illness.

Oxidative coagulopathy impairs perfusion by the following mechanisms:

- increased viscosity and impaired rheology of the blood;
- vasospasm induced by increased free radical activity;
- occlusion of capillaries and arterioles by microclots and microplaques;
- diminished antithrombotic characteristics of the endothelium.

Clear evidence for all of those factors is vasodilation by intravenous infusion of EDTA, which arrests oxidative coagulopathy and increases perfusion\cite{50}.

Oxidative coagulopathy, initially triggered by oxidative stress, is known to facilitate free radical generation by all known mechanisms operant in the circulating blood\cite{17}. Specifically, it causes lysis of erythrocytes and releases into the plasma free autoxidation of glucose, oxidatively damages plasma proteins, and accelerates activation of myriads of redox-active enzyme systems.

Oxidative coagulopathy causes anoxia, both by impaired perfusion and increased free radical activity. Anoxia, in turn, leads to yet greater free radical activity, as is amply demonstrated by reperfusion studies\cite{51,52}, and further fires the oxidative flames of coagulopathy. Thus, perfusion deficits, increased free radical activity, and anoxia feed upon each other, setting off reverberating cycles of coagulative stresses.

Oxidative coagulopathy causes acidosis by the following mechanisms:

- accumulation of lactic acid due to impaired tissue perfusion;
- accumulation of other organic acids due to accumulated oxyradicals; and
anoxia. Intracellular acidosis results in compensatory alkalosis in peripheral blood, which further impairs oxygen transport to tissues by shifting to the right the oxygen dissociation curve.

Oxidative coagulopathy, if allowed to persist, leads to autoimmune injury by all of the mechanisms that cause impaired tissue perfusion, increased free radical activity, anoxia, and acidosis.

**Clinical significance of oxidative coagulopathy in environmental illness**

The symptom-complexes of environmental illnesses have been delineated in numerous clinical studies[1-6,53-54]. One or more of the seven primary pathologic processes of oxidative coagulopathy listed above trigger or perpetuate almost all of the molecular mechanisms that underlie such symptom-complexes. Many of those mechanisms have been recently reviewed[55]. However, the precise initial molecular events that render patients exquisitely sensitive to minute amounts of chemicals that do not cause symptoms in subjects without chemical sensitivity have not been fully elucidated. Notwithstanding, the phenomenon of oxidative coagulopathy illuminates well the pathogenesis of the following symptom-complexes:

- Absorptive/digestive dysfunctions, including indigestion, malabsorption, abdominal bloating and cramps, and cycles of constipation and diarrhea.
- Activity disorders including easy fatiguability, diminished endurance, and, in advanced cases, disabling fatigue.
- Autonomic dysfunction, including temperature dysregulation, palpitations, cardiac arrhythmias, and vasculitis.
- Adrenal, thyroid, and pancreas functional disorders, including cold sensitivity, dry skin, rapid hyperglycemic-hypoglycemic shifts, and hyperadrenergic episodes. Clear laboratory evidence of such dysfunctions was seen in the majority of patients in this study.
- Allergic diathesis, asthma, bronchospastic episodes, and air hunger.
- Arthralgia, myalgia, and soft tissue pain syndromes.
- Amenorrhea, PMS, lack of libido, and related dysregulation of sex hormones, pituitary-hypothalamus axis, and the limbic system. The common disorders of mood, memory and mentation in environmental illness are also included in this category.

It is noteworthy that accelerated oxidative injury (which triggers, and is fed by, oxidative coagulopathy) is the common denominator in all pathophysiologic derangements that underlie the pathogenesis of clinical symptom-complexes in environmental illness. Why some symptom-complexes predominate in some patients while other symptoms predominate in others, is in the author’s view, is a matter of genetic predisposition.
Conclusion
Occurrence and intensity of oxidative coagulopathy in 50 chemically-sensitive patients are described. Such coagulopathy is recognized as the core homeostatic dysregulation in environmental illness. It is triggered by oxidative stressors operant in our internal and external environments. Seven major pathologic processes triggered and perpetuated by oxidative coagulopathy are highlighted and are shown to cause all of the established symptom-complexes of environmental illness. High-resolution phase-contrast microscopy is identified as a useful laboratory method for assessing the degree of oxidative stress in environmental illness as well as for monitoring the efficacy of therapies employed in the recently described model of integrative medicine.[56,57].

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