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Review

Sensitivity-related illness: The escalating pandemic of allergy, food intolerance and chemical sensitivity☆,☆☆

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ABSTRACT

The prevalence of allergic-related diseases, food intolerance, and chemical sensitivities in both the pediatric and adult population has increased dramatically over the last two decades, with escalating rates of associated morbidity. Conditions of acquired allergy, food intolerance and chemical hypersensitivity are frequently the direct sequelae of a toxicant induced loss of tolerance (TILT) in response to a significant initiating toxic exposure. Following the primary toxicant insult, the individuals become sensitive to low levels of diverse and unrelated triggers in their environment such as commonly encountered chemical, inhalant or food antigens. Among sensitized individuals, exposure to assorted inciting stimuli may precipitate diverse clinical and/or immune sequelae as may be evidenced by clinical symptoms as well as varied lymphocyte, antibody, or cytokine responses in some cases. Recently recognized as a mechanism of disease development, TILT and resultant sensitivity-related illness (SRI) may involve various organ systems and evoke wide-ranging physical or neuropsychological manifestations. With escalating rates of toxicant exposure and bioaccumulation in the population-at-large, an increasing proportion of contemporary illness is the direct result of TILT and ensuing SRI. Avoidance of triggers will preclude symptoms, and desensitization immunotherapy or immune suppression may ameliorate symptomatology in some cases. Resolution of SRI generally occurs on a gradual basis following the elimination of bioaccumulated toxicity and avoidance of further initiating adverse environmental exposures. As has usually been the case throughout medical history whenever new evidence regarding disease mechanisms emerges, resistance to the translation of knowledge abounds.

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1. Introduction

The incidence and prevalence of allergic-related diseases including asthma, (Lau et al., 2002) atopic dermatitis, (Kiyohara et al., 2008) hay fever, (Sih and Mion, 2010) food allergy, (Cochrane et al., 2009) atopic conjunctivitis, (Isolauri et al., 2009) and eosinophilic esophagitis (Nantes Castillejo et al., 2009) has escalated considerably in the last two decades. There has been increasing recognition, however, that not all sensitivities, including many types of food intolerance and chemical hypersensitivity reactions, are related to the classically understood concept of 'allergic' phenomenon involving immunoglobulin(Ig)-E antibody-mediated allergic responses (Gelincik et al., 2008; Miller and Ashford, 2000; Sicherer and Sampson, 2009). Food intolerance, for example, can precipitate a variety of outcomes, including headache, that are unrelated to atopic disease (Millichap and Yee, 2003). Despite discussion in the scientific literature of various hypotheses and theories, many consider the source etiology for escalating allergy, intolerance and sensitivities to be an enigma.

In this paper, a brief overview of the public health problem of sensitivities is initially presented to highlight the issue of allergy, food intolerance and environmental sensitivity. This is followed by the specific objective of this work: to present a review of the available research literature examining the etiology and pathogenesis of sensitivities and sensitivity reactions and to then examine interventions that can be used within clinical settings to address sensitivity problems. Finally, four brief case studies illustrating the pathway to sensitivity-related illness and strategies to advance recovery will be discussed.

2. Methodology

This review was prepared by assessing available medical and scientific literature from MEDLINE/PubMed, as well as by reviewing numerous books, toxicology and allergy journals, conference proceedings, government publications, and environmental health periodicals. References cited in identified publications were also examined for additional relevant writings. Searching techniques included key word searches with terms related to allergy, chemical sensitivity, food intolerance and environmental illness. A primary observation, however, was that limited scientific literature is available on the etiology of these disorders, on the pathogenetic mechanisms involved, as well as the general management of sensitivity-related illness and the associated clinical manifestations.

Available publications were reviewed and incorporation of data was confined to information deemed to be of clinical significance. The author's professional observations and experience as an environmental health physician were also incorporated into the discussion of management strategies. The format of a traditional integrated review was chosen as such reviews play a pivotal role in scientific research and professional practice in emerging medical issues with limited primary study and uncharted clinical territory (Dijkers, 2009). Brief case histories were included to illustrate the clinical importance of this issue and to highlight the potential benefit achievable with directed clinical interventions.

3. Description of terms

With overlap and ambiguity in commonly encountered vernacular, clarification of language is in order. Intolerance is a broad term describing any type of adverse reaction occurring in response to a specific trigger. Allergy commonly refers to conditions or reactions associated with an IgE antibody-mediated immunologic response following antigenic exposure. Antigen or incitant simply refers to material that, when introduced into the human body, is capable of initiating an immune response. Hypersensitivity or sensitivity are broad terms referring to situations where adverse reactions (including IgE responses) occur in association with exposure to low concentrations of antigenic stimuli such as foods, inhalants, or chemicals that are well-tolerated by the majority of people (Cullen, 1987).

Sensitivity-related illness (SRI), therefore, refers to adverse clinical states elicited by exposure to low-dose diverse environmental triggers, including inhalants (such as pollens), chemicals (such as synthetic perfumes), foodstuffs (such as gluten), biological compounds (such as molds), or electrical stimuli (Rea et al., 1991) (such as electromagnetic radiation). Between individuals with SRI, there may be marked variation in the nature of the clinical or immune response and sensitivity reactions may be apparent from early in life, or may present as acquired problems where no pre-existing difficulty was apparently evident.

4. Prevalence of sensitivity-related illness

Sensitivity to various compounds in our environment and our foods has become a ubiquitous phenomenon. The burden of disease related to atopic allergic illness is widespread and rising steadily, particularly in some jurisdictions. Estimates suggest that allergies affect as many as 40 to 50 million American people (University of Maryland Medical Centre, 2010). In Scotland, allergic disorders now affect about one in three of the population at some time in their lives, (Anandan et al., 2009) with over 4% of all primary care consultations in that country relating to allergy (Anandan et al., 2009). In 2005–2006, serum IgE antibodies to peanuts were detectable in an unprecedented 9% of American children, (Branum and Lukacs, 2009) with food allergy remaining a leading cause of life-threatening anaphylactic episodes (Papageorgiou, 2002). With at least 6–8% of the American pediatric population diagnosed with food intolerance, (Gupta et al., 2008) millions of families and educational institutions struggle to keep children safe by precluding exposure to inciting foods.

Not all such intolerance, however, is related to atopic illness. About 20% of the American population changes their diet in response to

perceived adverse food reactions (Mansueto et al., 2006) as unprecedented numbers of individuals without atopic illness in both the pediatric and adult age groups note a variety of unpleasant symptoms following the ingestion of specific foodstuffs. Furthermore, escalating proportions of the general population throughout much of the world complain of previously non-existent and inexplicable symptoms in different organ systems triggered by low levels of assorted environmental exposures, (Miller and Ashford, 2000; Sears, 2007) sometimes resulting in disability and chronic impairment (Miller and Ashford, 2000; Sears, 2007; Kreutzer et al., 1999; Miller, 1995). Many gathering places such as churches, offices and schools have begun to display signs declaring their building as a 'scent-free zone' to alert people that chemically sensitive individuals in their environment may seriously react to assorted common chemical agents.

Often referred to as 'multiple chemical sensitivity,' the incidence of hyper-reactivity to diverse chemical triggers continues to escalate in all age groups including children (Fukuyama et al., 2008) and has become a significant public health challenge (Miller, 1995; Pall, 2009; Rea, 1992; Sorg, 1999). It is estimated that about 3–4% of the American population suffers from severe forms of chemical sensitivity with about 15–30% of the general population exhibiting milder forms of chemical hypersensitivity (Miller and Ashford, 2000; Sorg, 1999). Similar studies in a range of other countries including Canada and various European countries also suggest a notable and increasing prevalence of this condition (Miller and Ashford, 2000; Joffres et al., 2001; Berg et al., 2008; Hausteiner et al., 2005; Johansson et al., 2005). What accounts for the swelling pandemic of allergy, abnormal hypersensitivity, and responses of intolerance to common agents that are well-tolerated by the population-at-large? Are the growing numbers of adults and children worldwide with SRI, now numbered in many millions, all suffering from psychiatric illness as some skeptics claim?

5. Etiology of chronic illness

In response to a considerable volume of emerging scientific data, the Centers for Disease Control recently concluded that the source of virtually all illness represents the complex interaction of a fixed genome with a modifiable environment (Office of Genomics and Disease Prevention: Centers for Disease Control and Prevention, 2000) (Fig. 1) Rather than primarily genetic in origin, expanding research continues to demonstrate that chronic illness is generally the consequence of various environmental factors acting in concert with a vulnerable genomic profile, often by epigenetic mechanisms which regulate or modify gene expression.

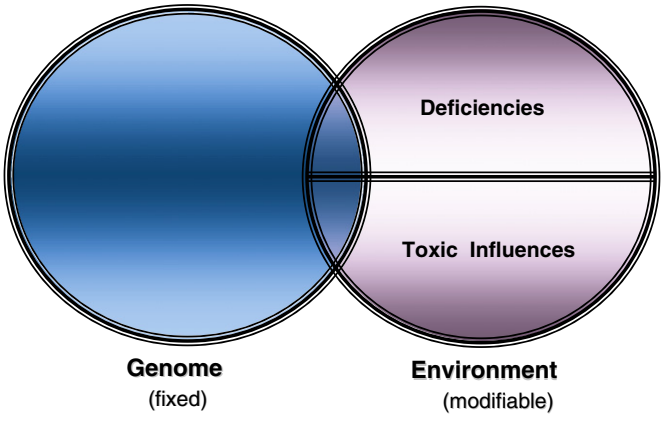

Fig. 1. Emerging model of disease etiology.
Genuis, 2010a.

What new environmental determinants might account for such a precipitous rise in the incidence and prevalence of SRI? The clinical practice of 'environmental health sciences' or 'environmental medicine' involves exploring and addressing disordered determinants within the modifiable environmental sphere. Broadly speaking, environmental determinants fall into two categories: i) deficiency of required elements for normal physiology; and ii) toxic influences which obstruct normal physiology — such as chemical or infectious determinants. Our genes have not changed in recent years, but our environment has. Evidence continues to suggest that specific environmental determinants are perhaps acting in concert with genetic predisposition to result in SRI (D'Amato et al., 2005; Genuis, 2008a).

6. Origins of sensitivity-related illness

Several determinants and mechanisms have been implicated in the escalating prevalence of SRI. Etiological variables discussed in the literature as contributing to sensitivity states include microbial deprivation as described in the hygiene hypothesis, (Bjorksten, 2009; Kalliomaki and Isolauri, 2002) nutritional transition and other factors resulting in arginine deficiency states, (Maarsingh et al., 2008, 2009; Meurs et al., 2003) environmental pollution with exposure to gaseous and particulate components of air contamination, (D'Amato et al., 2005) dissemination and widespread consumption of genetically modified foods, (Yum et al., 2005) climate change and meteorological features, (D'Amato and Cecchi, 2008) as well as psychological determinants (Montoro et al., 2009) and genetic factors (van den Oord and Sheikh, 2009). It is unlikely, however, that the rise in SRI is primarily related to new genetic determinants as it is improbable that a sudden deterioration has occurred in the gene pool causing a ubiquitous propensity to sensitivity states. Furthermore, the marked disparity in geographic distribution of sensitivity-related health problems, including diseases such as asthma, points to environmental variables other than genomic variance (Gold and Wright, 2005).

Several scientists and clinicians throughout the world have observed and studied specific events which appear to suggest a credible explanation for the emergence and rapid escalation in SRI. Following the 9/11 tragedy and recent warfare as occurred in the Gulf War, a significant percentage of previously well individuals working in theaters with toxicant exposures were noted to subsequently develop sensitivity conditions, allergic states and undiagnosed illnesses that were non-existent prior to the exposures (Bell et al., 1997; Fukuda et al., 1998; Fiedler et al., 1996, 2004; Reid et al., 2002). Severe health problems and previously non-existent sensitivities were also documented in various survivors of the 1984 Bhopal industrial catastrophe in India where about a half million people were exposed to various toxins released by a pesticide plant (Nemery, 1996). Several case series and reports in the scientific literature have described a similar phenomenon of individuals developing previously non-existent sensitivities following exposure to toxic insults (Cone and Sult, 1992; Welch and Sokas, 1992; Simon et al., 1990; Tabershaw and Cooper, 1966). It has also been noted that toxicant exposed persons are considerably more likely to develop sensitivity-related health problems such as asthma (Gauderman et al., 2005). In a recent book, Pall cites two dozen separate studies illustrating toxicant exposure as a prelude to development of SRI (Pall, 2007).

Studies on workers occupationally exposed to various toxicants, for example, have revealed an increased prevalence of SRI, (Zibrowski and Robertson, 2006; Yu et al., 2004) with significant differences between exposed versus non-exposed employees within the same occupation (Zibrowski and Robertson, 2006). Dental employees exposed to mercury during amalgam removal, for instance, were noted to develop higher rates of symptoms suggestive of SRI (Moen et al., 2008). Many papers also report on sensitivity issues

commencing after exposure to contaminated air in building settings (Welch and Sokas, 1992; Simon et al., 1990; Gordon, 1987; Ashford and Miller, 1998; Lax and Henneberger, 1995; Miller and Mitzel, 1995). Furthermore, the epidemiological escalation of SRI in the general population appears to have mirrored the rising prevalence of exposure by the population-at-large to adverse agents in the environment. Finally, it has also been observed that SRI can be induced in animals by exposure to toxic insults (Rogers et al., 1999; Overstreet et al., 1996; Sorg and Hochstatter, 1999).

These observations have provoked intense analysis of common etiological determinants and processes involved in patients with SRI. A mechanism of toxicant induced loss of tolerance (TILT), (Miller, 1997) first proposed by Claudia Miller in a 1996 paper in *Toxicology*, (Miller, 1996) is discussed to explain the pandemic of allergic and sensitivity-related phenomena, a problem having an increasing and profound impact on individual and public health.

7. Pathway to development of sensitivity-related illness

The pathway to clinical conditions resulting from allergy and sensitivity appears to involve three successive stages (as displayed in Fig. 2): i) exposure to a primary toxicant; ii) initiation of a state of hypersensitivity (or diminished tolerance resulting from the toxic insult referred to as TILT); and iii) triggering of diverse clinical reactions by exposure to low levels of assorted antigens — this may be referred to as 'MATES' (minute assorted triggers evoke symptoms). Accordingly, the overall process or mechanism of SRI involves the stages of 'exposure,' 'initiation' and 'triggering.'

7.1. Initiation of SRI

Any major exposure or toxicant insult that is foreign to the body has the potential alone or in combination with other toxic stressors to induce or initiate a hypersensitivity state. The primary toxicant insult or combination of insults may originate from various sources: i) adverse chemical exposure — single major exposure or chronic low-dose chemical exposure; (Miller and Ashford, 2000) ii) insertion of foreign material into the body such as an implant; (Brautbar et al., 1995; Miller and Prihoda, 1999a) iii) biological exposure such as an infection with mold or associated mycotoxins; (Steyn et al., 2009) or iv) major electrical or nuclear exposure (Barnes, 2001). Although SRI can result from a single toxic insult, it appears that the path to SRI is determined by the total load or the total body burden of accumulated exposures — the greater the total burden, the more likely a state of diminished tolerance and hypersensitivity ensues. Exposures contributing to the initiation of SRI may commence at any time during the life cycle including the gestational phase through vertical transmission (Jedrychowski et al., 2006).

Exposure to primary toxicants may occur through ingestion, inhalation, dermal exposure, olfactory intake, vertical transmission as well as through injection or implantation as typically occurs with dental work, injection, and surgical implantation. Adverse chemical exposures and mold exposure appear to be the most common routes

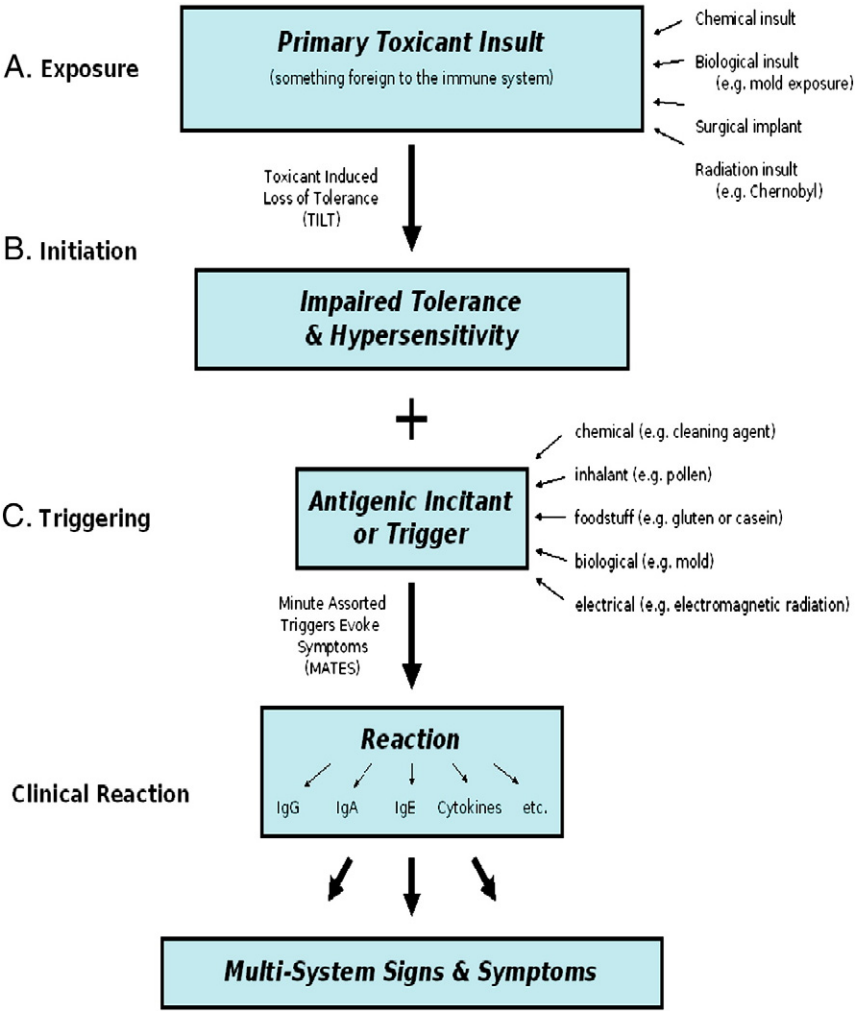

Fig. 2. Pathway to sensitivity-related illness.

of initiation. Rather than one specific type of chemical exposure, many different kinds of chemical agents have been implicated. As well as molds and their mycotoxin metabolites, (Lee, 2003; Pestka et al., 2008; Mahmoudi and Gershwin, 2000; Hintikka, 2004) various types of pesticides, (Ziem and McTamney, 1997) solvents, (Yu et al., 2004) hydrogen sulfide, (Kilburn, 2003) and some toxic metals such as mercury (Stejskal and Stejskal, 2006; Stejskal et al., 1999) have been noted to instigate SRI. Initiation may develop after a single high-level exposure or insidiously after months or years of low-level exposure (Miller, 1999). Initiating events, for example, may include exposures in situations such as a pesticide exposure, a gas leak in an apartment, employment in an auto body shop, close proximity to a gas well blow-out, indoor air contamination following renovation; clerical work with off-gassing from new office equipment, and so on. Medication used during gestation such as with maternal antibiotic use can also act as an initiating agent for subsequent postnatal SRI (Jedrychowski et al., 2006).

In response to an accumulated toxicant threshold, a state of impaired tolerance is initiated, which may develop within days of a serious primary exposure (Miller and Ashford, 2000). The degree of impaired tolerance or hypersensitivity often parallels the intensity of the total body burden of bioaccumulated toxicants. Furthermore, the level of hypersensitivity is not fixed: if the body burden of toxicants is diminished, the hypersensitivity slowly beings to wane and individuals react to lesser degrees; if the body burden continues to accumulate, the hypersensitivity response worsens with more pronounced symptoms and sensitivity to an increasingly wider array of inciting compounds (Rea, 1997). A clinical outcome ensues whereby minute exposures to assorted triggers evoke diverse signs and symptoms (Miller, 1997).

7.2. Triggering of SRI

Following the initiation phase, the exposed individual becomes hyper-reactive to low levels of a wide spectrum of chemical, inhalant, food or even electrical exposures that are not bothersome to healthy people. Specific incitants are not necessarily chemically related to the primary initiating exposure (Sorg et al., 1998) — for example, a soldier initially exposed to chemical weapons which initiated the TILT state may subsequently become sensitive to specific perfumes or cleaning agents absent from the war theater. Between individuals, there will be variance in specific triggers — the exact nature of which presumably depends on various determinants including the nature of the total load of exposures and the unique genomic background of that individual.

Possible incitants include a wide array of chemicals such as automobile exhaust, flavoring agents in foods, assorted perfumes, petrochemicals, air fresheners, off-gassed household materials from carpets or paint, newsprint odors, synthetic chemicals from clothing, fillers in medications, and many more. Incitants also include an array of foods as well as the additives within the foodstuffs. Germs such as bacteria or molds in the environment can evoke reactions, as can inhalants such as pollens. Some types of electromagnetic radiation as found with certain types of artificial lighting may also induce cytokine disturbances and trigger SRI (Kalinina et al., 1999).

Although the assorted triggers evoking symptoms may vary considerably between individuals, it has repeatedly been demonstrated that certain triggers such as gluten, corn, casein, soy, monosodium glutamate (MSG), perfumes and cleaners are common inciting stimuli for many individuals with SRI. The number of diverse triggering stimuli in any one individual is often proportionate to the body burden of toxicants in that person; individuals with a heavy underlying total load will invariably have multiple triggers. Various publications are available which provide lists and tables of common triggers (Sears, 2007).

Triggering responses can occur at incitant levels below olfactory-threshold concentration, levels where the individual might not smell or sense the trigger (Miller and Ashford, 2000). The specific incitants triggering the reactions usually include compounds that the individual is frequently exposed to within their life — sensitivity tends to develop to agents that the body frequently encounters. Accordingly, the circle of intolerance (Miller and Ashford, 2000) can change if individuals stay away from some compounds for a while or are exposed to new ones, and the circle will expand and contract depending on the ongoing severity of the initiating underlying burden of toxicants. The end result is that there are common compounds that most sensitive people react to which appears to be based on the frequency of previous exposure to these given antigens in their environment — i.e. sensitized individuals usually become sensitive to antigens that are ubiquitous in their environment such as pollens, or compounds that they are frequently exposed to in their diet such as MSG, gluten and casein.

Some toxic compounds act to initiate TILT, but these same compounds may also subsequently act as triggers for reactions. For example, cleaning solutions or biological compounds such as molds can intensify the underlying toxicant load as well as provoking sensitivity reactions. Pharmaceutical products, compounds that are inherently foreign to the human body, can also add to the total burden of foreign compounds while some drugs and fillers or excipients within their preparations such as corn starch, lactose or gluten frequently act as incitants in susceptible hosts. As many chronically ill people are on several pharmaceuticals, these agents are often a source of ongoing stimulus (Miller and Prihoda, 1999b).

It has also been observed that some SRI patients with recurrent psychiatric manifestations appear to experience exacerbation of illness during seasons of high inhalant exposure from common environmental incitants such as snow mold, pollens and weeds (Randolph and Moss, 1980). A recent study, for example, confirmed a significant positive association between allergy scores and anxiety scores (Postolache et al., 2008). Some mental health providers have casually referred to seasons of high inhalant exposure as 'bipolar season,' because of anecdotal observation of increased admission rates to psychiatric facilities in such time periods.

8. Clinical manifestations of sensitivity-related illness

Manifestations of SRI are diverse and may involve many organ systems (Ashford and Miller, 1998). Although delayed reactions are reported, signs and symptoms usually occur within minutes to an hour following incitant exposure. The reactions range from mild (slight headache, sneezing, minor heartburn) to severe (incapacitating arthritis, panic attacks, migraines, depression, bloody diarrhea, and so on.) (Miller and Ashford, 2000) The severity of morbidity may or may not relate to the intensity of the initiating toxic burden as well as the dose of subsequent incitants encountered. Various authors report that the most common symptoms associated with SRI include fatigue, muscle aches, memory and concentration difficulties, anxiety, gastrointestinal problems and headache (Sorg, 1999; Gibson and Vogel, 2009). There are, however, many other multisystem signs and symptoms that may be the direct result of SRI.

Gastrointestinal complaints including bloating, indigestion, heartburn, constipation, and loose stools are routine in patients with SRI. Health challenges associated with malabsorption and consequent nutritional deficiencies resulting from GI inflammation are common with SRI (Genuis and Bouchard, 2010). Dermatologic symptoms may include itchy skin, acne and dryness, while musculoskeletal complaints frequently involve joint discomfort, muscle aches and back pain (Ashford and Miller, 1998). Common neuropsychological symptoms include inexplicable panic attacks, depression, brain fog, disproportionate anger or irritability, pronounced vulnerability to stress, as well as disordered thoughts and behavior (Miller and Ashford, 2000; Pall, 2007). Central nervous system involvement with resultant neuropsychological symptomatology often leads to a clinical diagnosis of generalized anxiety, phobias or depression with somatisation disorders.

Sensitivity reactions can also affect metabolic indices such as lipid status, autonomic nervous system functions such as blood pressure control or thermoregulation, and inflammation at various sites including vasculitis (Rea, 1992). The author has also noted that many patients with SRI will experience dark circles under their eyes on an intermittent or chronic basis.

The clinical response is highly individual, likely dependent on genomic status and how the specific toxicant burden affects the immune response. The signs and symptoms are often most intense within the first 24–48 h with a lingering response for several days or even longer in some patients, even if the exposure is minute and quickly terminated (Randolph, 1978). Accordingly, a patient experiencing migraine headache in response to a specific antigen may have chronic unremitting migraines if exposed to that antigen every 2–3 days. Consequently, patients with SRI often live with chronic symptoms and are routinely given a diagnosis of chronic disease. Some degree of fluctuation in symptoms is very common and may depend on the intensity of the triggering exposure. In some cases, it appears that the sensitivity response may have the potential to intensify upon further or repeated exposure to incitants.

Specific incitants may trigger specific symptoms so, for example, gluten may evoke gastrointestinal bloating, nightshades may trigger joint inflammation, and perfume may trigger headache all within the same person. If individuals with SRI are exposed to a multiplicity of triggers, they may not notice response to individual agents as their body is overwhelmed and in a constant state of reaction (Miller and Ashford, 2000). The mechanism of clinical symptoms in many cases relates to inflammation as well as the ensuing consumption of energy and nutrients related to the inflammatory processes. Furthermore, the body is also engaged in an ongoing endogenous effort to detoxify the underlying toxicant load — a process which also consumes energy and depletes nutrients. This constellation of disordered biology contributes to ongoing fatigue, the most consistent finding in SRI (Ashford and Miller, 1998).

The manifestations of exposure do not necessarily correlate with the route of exposure — for example, dermatological manifestations can result from respiratory exposure. A study looking at patients with atopic eczema and dermatitis who were exposed to exhaust from vehicles for 30 min were noted to have significant elevation in skin wheal responses as well as certain serological changes when compared to non-exposed controls (Kimata, 2004a).

If left untreated, ongoing sensitivity-related inflammation may result in inflammatory disorders with the potential to develop permanent sequelae. With musculoskeletal problems, for example, SRI patients often present with aches and pains characteristics of arthralgia and myalgia; left unmanaged, the ongoing inflammation may lead to persistent symptoms with arthritis and myositis if left untreated. With sustained inflammation over extended periods, permanent damage in the form of fibrosis and scarring may ensue.

9. Proposed pathophysiological mechanism to development of sensitivities

In order to provide a compelling case to explain the unique pathway to SRI — the development of TILT, consequent MATES, and the diverse clinical sequelae — a consistent pathophysiological model must be provided and supported by evidence. Although the exact biochemical and pathophysiologic mechanism for each type of sensitivity response remains an enigma, various general and specific theories have been proposed to explain the sensitivity phenomenon.

Thus far, there has been no specific genetic profile identified that predisposes to SRI (De Luca et al., 2010). Emerging evidence has allowed various hypotheses to unfold, however, including theories related to neural sensitization (Sorg, 1999). In a recent publication, Pall details an intriguing model suggesting that SRI is centered on a cycle involving chronically elevated levels of nitric oxide and its oxidant product peroxynitrite with resulting neural sensitization (Pall, 2007). Pall suggests that signs and symptoms of SRI are generated by elevated levels of various compounds including nitric oxide, varied inflammatory cytokines, oxidative stress, NMDA (*N*-methyl-D-aspartate) and other agents acting at the local level of individual cells to effect tissue change (Pall, 2009).

Mechanisms proposed also include a sensitization of the nervous system pathway leading from the olfactory system to the limbic system in the brain, (Bell et al., 1992) neurogenic inflammation, (Bascom, 1992) cholinergic system supersensivity, (Overstreet et al., 1996) and a variety of psychogenic theories (Staudenmayer et al., 1993). In an effort to distinguish allergy from chemical sensitivity, it has been hypothesized that while IgE mediated reactions involve protein antigens binding IgE antibody found on mast cells with the resultant discharge of inflammatory mediators, chemical sensitivity might result from low molecular weight chemical compounds binding to chemoreceptors on sensory nerve C-fibers leading to the release of inflammatory mediators (Meggs, 1999). With evidence that various antibodies and cytokines are frequently released in association with sensitivity reactions, immunologic involvement is evident for at least some types of sensitivity reactions. The fact that treatment with corticosteroids and pro-inflammatory cytokine modifiers has been successful in many patients with SRI, also suggests immune system involvement. Accordingly, much attention has been directed towards immunogenic mechanisms to explain the TILT and MATES phenomena.

9.1. Toxicant induced autoimmunity

It has been confirmed that exposure to adverse exogenous agents has the ability to induce a toxicant induced loss of tolerance to endogenous tissue with a resultant state of autoimmunity. Autoimmunity — the failure of an organism to recognize its own constituent parts as self — results in an immune response against its own cells and tissues. Emerging evidence confirms that toxic environmental factors such as infection, implants and xenobiotics have potential to initiate the pathogenesis of immune intolerance of self or autoimmunity (Brautbar et al., 1995; Vojdani, 2008). Specific autoimmune processes have been linked to exposures such as asbestos, (Brown et al., 2005) tricholorethylene, (Gilbert et al., 2006) various pharmaceutical agents, (Brown et al., 2005; Rubin and Kretz-Rommel, 1999) dioxins, (Ishimaru et al., 2009) breast implants, (Brautbar et al., 1995) and assorted heavy metals (Brown et al., 2005).

Following toxicant exposure and prior to onset of clinical autoimmunity, emerging evidence confirms that auto-antibodies directed against various human tissue antigens can often be detected (Notkins, 2007). This process of toxicant exposure inducing autoimmunity may explain the clusters of autoimmune illness that accompany adverse exposures in population groups (Dahlgren et al., 2007a; Kuroda et al., 2004) and likely explains why industrial regions, particularly in Northern Europe and North America, exhibit the highest rates of most autoimmune diseases.

9.2. Toxicant induced loss of tolerance to exogenous stimuli

As well as the autoimmune pathological reaction to endogenous triggers, it is surmised that a variant of this immunologic response to toxicant overload may account for the hypersensitivity to assorted exogenous antigens. It is hypothesized that exogenous exposures initiate a hyper-sensitive immune state, whereby the immune system becomes dysregulated with impaired tolerance to minute exposures of both endogenous as well as foreign antigens. Mechanisms of immunogenic pathogenesis on the development of TILT continue to unfold including the idea that some cytokines released in association with exposure events (Duramad et al., 2007) may directly induce a sensitization effect on the immune system, (Anisman and Merali, 1999) through an induced immune system dysregulation (Rowat,

1998). The consequent response to low-dose stimuli and resulting inflammation may be triggered by a reflex mechanism which initiates an inflammatory immune reaction, (Tracey, 2009) perhaps through varied immune cells and their byproducts.

The support for this perspective includes the finding of assorted antibodies, including IgE in atopy, IgE and IgG in some types of food intolerance, (Tay et al., 2007; Bernardi et al., 2008; Anthoni et al., 2009) as well as cytokine changes in response to some chemical triggers (Duramad et al., 2007). Urban air particulate matter, for example, has been associated with a pro-inflammatory cytokine response in some individuals (Jalava et al., 2008, 2009) and bacterial contamination of indoor air has been found to stimulate cytokine release in vivo (Hirvonen et al., 2005). As assorted cytokines are immuno-modulating agents involved in inflammation as well as cell-to-cell signaling, it is possible that various stimuli may trigger a host of varied cytokines or a 'cytokine storm' which may result in dysregulated cell signaling, biochemical disruption and inflammation with resulting clinical manifestations (Tracey, 2007; Czura and Tracey, 2005).

In fact, some cytokines act as messengers between the immune system and the central nervous system with the potential to induce various neuropsychological manifestations (Leonard and Song, 1999). Furthermore, inflammatory cytokines have been found in the nasal passages and lungs of individuals exposed to some toxicants, (Hirvonen et al., 1997, 1999) which might explain various respiratory and other common symptoms in SRI. Recognizing that some pro-inflammatory cytokines cross the placental barrier and affect brain development, further research into toxicants and SRI continues to explore the clinical outcome of elevated cytokine levels in-utero (Ellman et al., 2010). In review, it appears that pro-inflammatory cytokine release may be involved in both initiation of the TILT state as well as resulting MATES. The constellation of clinical sequelae associated with dysregulated cytokine release is the subject of ongoing research.

There is also suspicion that adipokines (Hsueh et al., 2009) — cytokines released from adipose tissue (MacDougald and Burant, 2007) — may be involved in hypersensitivity reactions. Adipose tissue is an active endocrine organ that discharges several bioactive mediators that influence homeostasis and inflammation (Lau et al., 2005) and serves as an active participant in regulating certain physiological processes. Adipose tissue is also a main storage site for lipophilic toxicants and houses much of the toxicant burden within the body. As release of adipokines can be involved in the process of inflammation (Fantuzzi, 2005) as well as being implicated in disease development, (Fantuzzi, 2005) it is hypothesized that contaminated adipose tissue may be involved in impaired tolerance and hypersensitivity.

Although the sensitivity state may, in part, reflect immune dysregulation, it is unclear to what degree a toxicant induced disordered immune status is responsible for the totality of the hyper-reactive phenomena. Although it has been noted, for example, that various environmental triggers can induce a hyper-reactive microglial state in the brain with consequent inflammation and neurotoxicity; (Block et al., 2007) the mechanism of such a reaction, however, is not well understood. More clarity will be brought to this issue as further study and emerging research endeavor to explain the pathophysiological mechanisms by which environmental toxicants induce a sensitivity response.

10. Biomarkers for sensitivity-related illness

It would be ideal to have a single characteristic of SRI that could be objectively measured as an indicator of the pathogenic process associated with this condition. The ideal biomarker for SRI would help link specific levels of certain environmental exposures to TILT and subsequent disease outcomes. Such a marker might be an immunological biomarker, indicating impaired tolerance and immune dysregulation. In SRI reactions, there have been various reports of atypical laboratory findings, (Rea, 1997) but thus far there is no single marker or pathologic finding that is pathognomonic for SRI.

Ongoing study, nonetheless, continues to explore immunogenic markers associated with chemical sensitivity responses. In searching for a consistent indicator of SRI, it has been noted that some patients will have cytokine changes, antibody responses, assorted autoimmune markers, (Vojdani, 2008) as well as general inflammatory marker changes (Rea, 1997). In addition to high values for IgE, patients with atopic disease demonstrate elevations in selected neurotropins upon exposure to antigens such as automobile exhaust (Kimata, 2004a). IgA responses may be found in some sensitivity reactions (Cabrera-Chavez and de la Barca, 2009) and IgG antibodies have been found to be useful markers with some types of food intolerance (Tay et al., 2007; Bernardi et al., 2008; Anthoni et al., 2009) and the associated inflammation (Wilders-Truschnig et al., 2008). Research is also demonstrating that antigen-specific serum IgE, IgG, IgG4, and IgA response levels may vary significantly between each specific antigen tested in patients with multiple sensitivities (Ciprandi et al., 2009).

A recent study demonstrated that some chemical triggers evoke changes in IgE and Th2 cytokines while others elicit a Th1 cytokine response with no elevation of serum IgE (Fukuyama et al., 2008). Some mold exposures can induce immune dysregulation (Terr, 2009) through IgE changes as well as other non-IgE immune mechanisms (Edmondson et al., 2005). These findings further the hypothesis that diverse triggers elicit different immunological responses — which might in turn account for the diverse clinical manifestations. There is increasing evidence however, that metabolic parameters suggesting accelerated lipid oxidation, increased nitric oxide production and glutathione depletion in combination with increased plasma inflammatory cytokines are commonly found in individuals with SRI (De Luca et al., 2010).

There are limitations, however, with using serologic immune indicators as markers of sensitivity. Serologic markers may be inconsistent as cytokine levels measured in peripheral blood on a single occasion, for example, can change rapidly and only represent a brief or transient snapshot of cytokine activity (Duramad et al., 2007). Furthermore, it is misguided to rely on current methods including IgE and IgG testing for food sensitivity to comprehensively diagnose food incitants. Although such testing may benefit some individuals, some food antigens elicit cytokine release, which may not be detected on antibody based testing.

Attempt has also been made to identify other types of pathognomonic findings in order to confirm the diagnosis of SRI. Patients with chemical sensitivity have been noted, for example, to demonstrate elevations in specific neuropeptides when exposed to certain volatile organic toxicants, a response not observed in normal subjects (Kimata, 2004b). It is uncertain, however, whether this represents a secondary reaction to an immune system response. Secretions and biopsies in those with SRI have also shown evidence of tissue response. A study of the nasal pathology of individuals experiencing sensitivity syndromes, for example, revealed defects in tight junctions between cells, desquamation of the respiratory epithelium, glandular hyperplasia, lymphocytic infiltrates, and peripheral nerve fiber proliferation, suggesting a model for a relationship between the chronic inflammation seen in these conditions and an individual's sensitivity to chemicals (Meggs, 1997). Such findings of inflammatory change, however, are not necessarily limited to sensitivity responses.

Patients with some types of sensitivities may display changes in markers of brain function. Recent study has demonstrated alteration in PET (positron emission tomography) scans, (Hillert et al., 2007; Heuser and Wu, 2001) SPECT (single photon emission computerized tomography), (Simon et al., 1994; Fincher et al., 1997a,b) as well as EEG (electroencephalography) studies (Bell et al., 1999; Fernandez et al., 1999). Objective clinical signs are also being investigated including signs of autonomic nervous system dysfunction — such as distortions of heart rate variability and pupillary response (25th

Annual International Symposium, 2007). In review, research continues to explore physiological change associated with SRI, but thus far no consensus has yet been achieved on the identification of a single objective clinical feature, serological biomarker, pathological finding, or other investigative test to conclusively establish the diagnosis of SRI.

11. Clinical approach to sensitivity-related illness

Thus far, most of the management of SRI has focused on symptom control through use of assorted pharmaceutical preparations. For example, those with headaches may be treated with analgesics, those with serious intestinal or airway inflammation may be treated with bronchodilators; and those with joint problems may receive assorted anti-inflammatory therapies. All of these interventions, however, only temporarily conceal symptoms and fail to deal with the etiology of the problem or to achieve long-term resolution of illness.

There is limited information in the scientific literature about interventions or therapy to deal with and correct the problem of SRI. Accordingly, the author's clinical experience will be incorporated along with the literature into this aspect of the discussion. In order to address SRI, it is necessary to consider interventions to mitigate sensitivity reactions as well as the three-stage process to overcome SRI (Fig. 3).

11.1. Mitigation of sensitivity response

After a reaction has been triggered, efforts to blunt the inflammatory response and the consequent signs and symptoms can be employed. Ingesting of alkalinizing agents to mitigate tissue acidosis that often accompanies inflammation may diminish the intensity of the reaction (Ashford and Miller, 1998; Rea, 1997). Anti-inflammatory medications may alleviate musculoskeletal symptoms associated with the inflammatory response. Various allergy medications are also useful in controlling the signs and symptoms associated with atopic reactions.

High glycemic loads from various ingested foods including refined sugar, white flour products, white rice, or high-fructose corn syrup may provoke the release of insulin and insulin-like growth factor thus promoting dysregulation of pro-inflammatory cytokines — resulting in inflammation (Duvnjak and Duvnjak, 2009) and aggravating SRI. Accordingly, avoidance of high-glycemic foods is indicated. Furthermore, vigorous physical exercise appears to diminish pro-inflammatory cytokines and may be of some help in mitigating the intensity of a sensitivity response (Colbert et al., 2004). Allergic and sensitivity reactions are sometimes ameliorated or completely resolved by high dose vitamin C (Cathcart, 1986). Such efforts, however, will not preclude the clinical reaction but may ameliorate the severity and duration of the unpleasant symptoms associated with the sensitivity response.

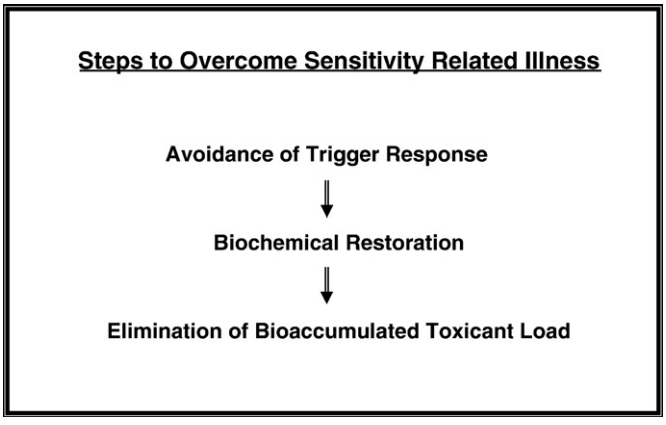

Fig. 3. Steps in overcoming sensitivity-related illness.

By generalized immune suppression, steroids and immunosuppressant medications may blunt symptoms associated with SRI and then preclude the adverse hyperactive immune response. This is why steroids have such broad indication as a treatment for numerous apparently unrelated conditions such as asthma, ulcerative colitis, temporal arteritis, scleroderma and rheumatoid arthritis, each involving different organ systems. Recently there has been the expanding use of biologic response modifiers such as agents that attempt to suppress pro-inflammatory cytokines including tumor necrosis factor (TNF) (Staren et al., 1989; Blonski and Lichtenstein, 2006). Such cytokine modifying medications appear to recognize, attach to, and block the action of pro-inflammatory cytokines — thus reducing the inflammatory response associated with SRI. A serious challenge with these pharmaceutical approaches, however, is the risk of serious side effects such as infection or malignancy resulting from generalized drug-induced immune compromise (Bongartz et al., 2006).

Neutralization of the SRI reaction by injection of a miniscule dose of the offending incitant (if identified) has been used with reported success by some physicians to 'turn off' the reaction by blunting the ongoing immune system response to the incitants (Rea, 1997).

11.2. Step I: avoidance of trigger response

Once the imitation phase has occurred and a state of TILT has developed in the patient, there are two approaches which appear to completely prevent the elicitation of a clinical reaction: A) avoidance of triggers; and B) desensitization. Avoidance of incitants — selected foods, chemicals, inhalants, biologic agents, and electrical stimuli (in electrically sensitive individuals) — will preclude a triggering response and prevent the onset of resulting clinical sequelae. Avoidance of triggers is the hallmark of intervention at this stage. Patients generally improve and achieve a relatively normal baseline after a period of a few days to weeks if they avoid exposure to inciting triggers, providing that permanent damage has not already occurred (Ziem, 1992; Spergel et al., 2005). When incitants are completely eliminated, symptoms will often substantially subside or completely resolve within 6 weeks. Various reports in the literature confirm restoration from disabling chronic conditions including autism (Genuis and Bouchard, 2010) and schizophrenia (De Santis et al., 1997) (with resolution of changes in the frontal cortex as measured by SPECT scanning (De Santis et al., 1997)) by avoidance of incitants which trigger a sensitivity reaction.

There are a few challenges, however, with endeavoring to avoid triggers:

i) Complete avoidance of triggers can be difficult as there is no comprehensive testing to identify the diverse and assorted triggers that may be eliciting reactions. There are, however, common food triggers (Table 1) and chemical antigens that constitute the majority of incitants. A detailed list of common triggers including food, chemical, electrical, inhalant and biological incitants can be found in table 6 of the recently released Government of Canada document on environmental sensitivities (Sears, 2007).
ii) As incitants can change depending on frequency of exposure and status of the total toxicant load, previously tolerated compounds may become new incitants and thus be overlooked.
iii) Although patients may eliminate food triggers, symptoms may persist if exposed to unsuspected inhalant triggers such as pollens or chemical triggers such as fragrances, synthetic clothing materials, skin cream ingredients, and automobile exhaust.
iv) Avoidance of all potential food and chemical triggers can be difficult and socially isolating, however, particularly for those with limited self-discipline and those accustomed to habitual eating-out — a practical problem that makes it difficult to assist some adolescents and young adults experiencing SRI.

Table 1
Common food incitants.

1. Gluten
2. Casein
3. Corn and corn products
4. Soy
5. Monosodium glutamate
6. Artificial sweeteners
7. Food dyes
8. Caffeine
9. Nuts
10. Nightshades
11. Yeast
12. Eggs

v) There may be aggravation of symptoms due to withdrawal effect in the first week to 10 days of avoidance, often causing discouragement and disbelief. Thereafter, however, symptoms usually abate and patients improve.
vi) Some patients with SRI are inclined to cut back but not completely eliminate incitants. Just as a child with allergies to peanuts may have a severe reaction even to miniscule exposures to the incitant, fractional exposure to other incitants can also trigger a response. Complete elimination of triggers is required for optimal results.
vii) If triggers are inadvertently encountered, or the patient fails to persist with avoidance, symptoms return and the process must be re-commenced to be successful.

In addition to avoidance, there are other therapies aimed at precluding the adverse immune response associated with exposure in susceptible individuals. Allergy injections have been used to provide a low dose of antigen with the observation that low-dose exposure to some inhalant antigens may induce a state of desensitization whereby the immune response to specific antigens is blunted. In the same way, there is increasing exploration of therapy using micro-doses of specific inciting antigens to suppress the immune response to food and chemical antigens that are triggering food intolerance and chemical sensitivities (Sicherer and Sampson, 2009; Rea, 1997; Nowak-Wegrzyn and Sicherer, 2008). This may be referred to as desensitization immunotherapy.

Desensitization immunotherapy is typically achieved by injecting or sublingually applying micro-doses of the trigger which, by uncertain mechanisms, may turn off or preclude a hypersensitivity response to that incitant. This technique has now been successfully applied to diminish the allergic reaction to some medications (Helms et al., 2008) as well as to diminish the severe sensitivity response some individuals experience with peanut exposure (Clark et al., 2009). Using oral desensitization therapies, it is also possible to suppress the adverse serological change representing the immune hyper-reaction to the stimulus (Jones et al., 2009). Homeopathic therapies also endeavor to introduce a diminutive dose of like antigens which may, in some cases, suppress immune hyperactivity.

In addition, there has been observation that some individuals with conditions such as fibromyalgia and Crohn's disease, sometimes linked with hypersensitivity immune reactions, may clinically respond to ongoing treatment with daily low-dose naltrexone (Younger and Mackey, 2009; Smith et al., 2007; Gironi et al., 2008; Brown and Panksepp, 2009; Zagon et al., 2009; Shannon et al., 2009; Desjardins et al., 2009; Kariv et al., 2006) — an agent which has demonstrated efficacy at diminishing inflammatory reactions in animal studies (Block et al., 2007). It has also been recently noted that treatment with low-dose lipoic acid has the potential to be an immuno-modulating agent to prevent some types of sensitivity response in animals (Ma et al., 2010). The mechanisms of action appear to include reductions of mast cell numbers, histamine release, and serum IgE, as well as attenuation of the cytokine response, the Th2-type immune response, and an amended ratio of CD4(+) to CD8 (+) T cells (Ma et al., 2010). Some patients, however, may risk developing insulin dysregulation and frequent hypoglycemia attacks with use of lipoic acid (Uchigata et al., 2009).

There has also been emerging research relating to interleukin-17 (IL-17) — a pro-inflammatory cytokine group integral to many inflammatory states potentially linked in some cases to SRI, including rheumatoid arthritis, multiple sclerosis, asthma and systemic lupus erythematosus (Dong, 2009; Kawaguchi et al., 2009; Mok et al., 2010; Segal, 2010). Vitamin A deficiency has been associated with enhanced production of IL-17, which activates various immune cells to produce a series of pro-inflammatory cytokines (Kim, 2008; Cha et al., 2010). Securing vitamin A sufficiency may facilitate desensitization by promoting immune tolerance and suppressing inappropriate inflammation associated with IL-17 (Cha et al., 2010; Schambach et al., 2007). Finally, use of other agents such as resveratrol and curcumin may also have a desensitizing immune regulatory role through the IL-17 mechanism (Petro, 2010; Xie et al., 2009).

Mitigation interventions such as immunosuppressive agents, biologics, and vitamin C can also be used on an ongoing or intermittent basis to suppress the trigger response. Although all of these methods of intervention provide significant clinical benefit and amelioration of symptoms to many patients, they do not address the cause of the problem and often do not provide a sustained answer to the challenge of sensitivity.

11.3. Step II: remediation of disordered biochemistry

Many patients with SRI have nutritional depletion of selected nutrients for two common reasons: i) the gastrointestinal tract often demonstrates maldigestion and/or malabsorption as a result of inflammation resulting from incitant exposure; and ii) over-utilization of nutrients as a result of chronic inflammation. As nutrients are the basic molecules required for innate human physiology, nutritional repletion is required for optimal health restoration.

Lack of adequate uptake of required nutrients into the body as a result of GI inflammation with SRI often results in varied clinical signs and symptoms. When SRI triggers are avoided, however, GI dysfunction usually subsides and it is possible to correct underlying biochemical deficiencies with resulting clinical improvement (Genuis and Bouchard, 2010). Celiac disease is a common example of malabsorptive difficulty which results from a sensitivity to a specific food incitant (Freeman, 2010) — which often results in biochemical irregularities (Genuis and Bouchard, 2010). Nutritional status testing is invaluable in diagnosing specific deficiencies and in directing the restoration of optimal nutrient status (Bralley and Lord, 2005).

Repletion of specific nutrients such as vitamin D also appear to diminish the sensitivity response to some antigens (Kreindler et al., 2010). Furthermore, biochemical restoration will improve excretory pathways, facilitating intrinsic detoxification to diminish the total body burden. Remediation of disordered biochemistry will allow the body to facilitate repair and often results in significant clinical improvement (Genuis and Bouchard, 2010; Genuis and Lobo, 2010).

11.4. Step III: elimination of bioaccumulated toxicant load

In order to achieve resolution of SRI, it is necessary to eliminate the underlying toxicant load and to avoid further exposure. A detailed environmental assessment is required in order to identify the sources and nature of previous exposures and to intervene to prevent ongoing exposures (Marshall et al., 2002; Genuis, 2008b). Although expensive and fraught with challenges, toxicant testing can be invaluable for comprehensive assessment in patients with SRI (Genuis, 2006a,b). A main problem is that many accrued toxicants are sequestered in tissues and their actual level of contamination is often not reflected or

even detectable in blood or urine testing (Genuis, 2010b). Specialized toxicant mobilization interventions and laboratory techniques may be required to determine the actual nature and extent of the bioaccumulated body burden of adverse toxicants.

The ultimate way to address the SRI problem is, nonetheless, to unload the body burden of initiating toxicants through detoxification techniques (Genuis, 2010b,c). As the total burden of toxicants diminishes, the intensity of the TILT response also diminishes, leading to gradual amelioration of SRI. Persistent presence of bioaccumulative toxic compounds, or ongoing toxicant exposure usually results in continuous impaired tolerance with ongoing SRI. Escalating bioaccumulation of xenobiotics or further major exposures will lead to a further deterioration of impaired tolerance, with heightened sensitivity and consequent symptoms. It appears impossible to recover health and avoid SRI if the individual continues to maintain a heavy burden of toxicants or ongoing toxicant exposure.

Numerous researchers have observed that removal of the underlying toxicant burden by avoidance of further contamination and detoxification therapies results in abatement of SRI (Ashford and Miller, 1998; Rea, 1997; Randolph and Moss, 1980; Hobbs, 2003). Diminution of mercury load through amalgam removal, for example, appears to diminish immune dysregulation (Sterzl et al., 2006). When the total load is adequately addressed, individuals are able to tolerate previous incitants without adverse response. Individuals previously experiencing pronounced chemical sensitivity are able to re-engage in society without fear of ongoing illness and those with food triggers are able to become less guarded about their dietary intake (Hobbs, 2003).

The science of active detoxification is a relatively new discipline within clinical medicine, with limited scientific literature available (Genuis, 2010b,c; Schnare et al., 1982; Kilburn et al., 1989; Dahlgren et al., 2007b; Cohn et al., 1978; Tretjak et al., 1990; Shields et al., 1989). As the reality and sequelae of toxicant bioaccumulation continues to unfold in the emerging scientific and public health literature, however, this field will continue to attract more clinical attention as scientists endeavor to address the swelling pandemic of those suffering from the consequences of toxicant bioaccumulation.

In review, the preferred management and potential restoration of health and freedom from SRI involves three phases i) avoidance of a trigger response; ii) restoration of optimal biochemical status; and iii) removal of the total body burden of primary initiating toxicants. Environmental Health Sciences, the field of medicine often dealing with SRI, involves assessment and correction of modifiable environmental factors (Fig. 1) in order to maximize health within the context of a given fixed genome. With this approach, there is enormous potential to reverse what is often considered to be chronic disease. A series of brief case studies with differing clinical presentations is offered for consideration to demonstrate the potential outcome of interventions designed to remove triggers and to eliminate initiating toxic burdens.

11.5. Case study #1: Crohn's disease

An 11 year old boy with a 2 year history of severe Crohn's disease, arthritic hip joints and severe bone compromise (T-score: minus 6.2 at lumbar spine on bone densitometry) was referred to a physician trained in Environmental Medicine. The child averaged 7 watery bowel movements per day. For 2 years, the boy had been cared for at a pediatric gastrointestinal clinic and had been initially treated with Prednisone for 2 months followed by Azathioprine (Imuran®) and Sulfasalazine (Azulfidine®) for over a year with no improvement. Naproxen (Naprosyn®) was used for joint pain with minimal relief. The family consulted assorted complementary and alternative medicine (CAM) practitioners including a naturopath, an acupuncturist, a homeopath, a hypnotherapist, a chiropractor, and others with no substantial improvement. Prior to age 9, the child had been well with no medical or surgical health problems.

Within 3 weeks of eliminating common chemical and food triggers, the child's diarrhea completely settled and the mother commented “he is doing awesome,” “he eats like a pig,” “his joint pain is gone,” “he is able to play and attend gym class at school,” and “he has gained 7 pounds.” CRP levels went from 66.9 mg/L (normal <8.0). prior to trigger avoidance to 12.2 mg/L 6 weeks after commencement of trigger avoidance. On searching for an initiating event, mold testing results were strongly positive in the child's bedroom. Urine mycotoxin testing revealed considerable Ochratoxin and Trichothecenes. When the source of mold was removed and the child received treatment to eliminate mycotoxins, SRI settled appreciably over the next year.

11.6. Case study #2: chronic migraine headaches

A 23 year old single personal trainer presented to a physician trained in environmental medicine with a 12 year history of daily migraine headaches, fatigue, constipation and psoriasis. The patient also complained of frequent bloating, excessive gas and abdominal discomfort. She described her life as one of near constant suffering and pain. Previous investigations by a neurologist revealed a normal MRI, CT scan and EEG. Various medications including Ketorolac (Toradol®), Topiramate (Topamax®), Rizatriptan (Maxalt®), and Naratriptan (Amerge®) were tried in order to deal with the headaches. With unsatisfactory results, she reported that her physician stated: “there is nothing that can be done” and “you just need to deal with it.” She consulted a number of CAM practitioners including a chiropractor, a massage therapist, a Chinese herbalist, an acupuncturist, a naturopath and consumed numerous supplements.

Within 2 weeks of elimination of common triggers, the headaches were gone, energy levels increased, bowel habit improved and GI symptoms abated. By 4 weeks, the patient stated “I feel great!” Testing for initiating toxicants revealed considerable lead and mercury on both serologic and toxic metal challenge testing. Detoxification of mercury and lead was commenced. The patient remained symptomatically well over the next 6 months and detoxification of metals was successful as evidenced by declining levels on toxic metal challenge testing.

11.7. Case study #3: polyarticular juvenile rheumatoid arthritis

A 10 year old girl with a 5 year history of worsening Polyarticular Juvenile Rheumatoid Arthritis presented to a physician trained in Environmental Medicine. Over the last 4 years, the patient had been cared for at a specialty pediatric clinic and had received various therapies including Naproxen (Naprosyn®), Methotrexate (Trexall®), and Prednisone. With ongoing discomfort, swollen joints, and persistent inability to play, the parents were frustrated with the lack of response. As a result, they chose to consult a number of CAM practitioners — all to no avail. At the time of presentation for environmental medicine assessment, the child also complained of fatigue, recurrent abdominal pain, intermittent dermatological problems, as well as the multi-joint discomfort.

Within 4 weeks of eliminating common chemical and food triggers, joint pain and swelling were near gone and gastrointestinal symptomatology had cleared. On investigating for an initiating event, laboratory investigations revealed a very high urinary level of Aflatoxin and Ochratoxin, and mold testing in her bedroom was positive. CRP slowly declined from 40.8 mg/L to 6.7 mg/L over the next year after inconsistent elimination of common triggers. Mold remediation was performed and the child has continued to be well and pain free 18 months hence.

11.8. Case study #4: animal allergy

A 44 year health worker initially presented to his family doctor with a worsening problem of wheezing, intractable itchy eyes and

throat, as well as nighttime shortness of breath. After assessment to rule out any underlying cardiac or respiratory condition, the physician provided a diagnosis of adult-onset allergies and asthma. Allergy testing revealed a marked reaction to cats and it was recommended that he should remove his pets. The patient and his wife objected to getting rid of three indoor house cats, claiming he had lived with cats all of his life. Reluctant to part with the animals he tried various medications including a Salbutamol (Ventolin®) inhaler, various eye drops, and antihistamines. The problem persisted, and rather than taking steroid medication, he decided to part with his cats. After extensive house cleaning and removal of the animals, the symptoms subsided in part.

Through environmental medicine assessment, he was found to have bioaccumulated mercury, likely resulting from the 15 amalgam fillings in his teeth, four of which were replaced 5 years previously. In line with findings reported in the medical literature, safe removal of all amalgam fillings was undertaken as well as detoxification therapy for bioaccumulated mercury (Lindh et al., 2002; Wojcik et al., 2006; Genuis, 2008c). Eighteen months after completion of mercury detoxification, he was able to have cats again without any symptoms whatsoever.

12. Concluding thoughts

Sensitivity-related illness appears to be a toxigenic condition with three successive components — toxicant exposure, impaired tolerance and hypersensitivity reactions. This mechanism of illness accounts for a considerable proportion of contemporary clinical disease presenting to physicians in various specialty fields. As a result of escalating exposures in the environment commencing in the pre-natal period (Genuis, 2009) and continuing throughout life, increasing numbers of individuals in the population are bioaccumulating varied toxicants (Centers for Disease Control, Department of Health and Human Services, 2009). The health sequelae of toxicant exposure can be related directly to toxic damage, (Genuis, 2006a) as well as indirectly to problems resulting from SRI.

The topic of SRI, however, remains the focus of intense debate as some authors steadfastly dismiss emerging evidence related to this mechanism of illness (Staudenmayer, 2001; Das-Munshi et al., 2006; Graveling et al., 1999). Based on dated understanding and writings about SRI, and disregard for recent laboratory and animal evidence, some researchers conclude that SRI does not exist or is a psychogenic confabulation. Despite the fact that SRI has now been repeatedly documented in demographically diverse groups in many countries following documented toxicant exposures, (Miller and Ashford, 2000) and despite the introduction of government policy in relation to SRI in some jurisdictions (Sears, 2007) there are many reasons why skepticism and resistance prevail within the medical and scientific community.

Reasons for lethargic knowledge translation and reluctance to recognize SRI include:

i) As healthy people do not react to triggers even at high concentration, it is hard for many health providers to believe that some people react at seemingly insignificant doses to otherwise non-toxic compounds such as certain foods.
ii) Some skeptics do not accept that such a diverse group of triggers can elicit such profound yet varied and dissimilar clinical responses.
iii) Details of the underlying pathophysiological dynamic are not yet understood completely and there are no consistent biochemical markers that act as diagnostic for all types of sensitivities.
iv) As neuropsychological symptoms such as depression, anxiety and panic are common pathophysiological responses in SRI patients, symptoms associated with this illness are often dismissed as psychogenic.
v) Clinical reactions with SRI may be delayed, and thus may not be correlated with any precipitating exposure.
vi) The intensity of the sensitivity response may fluctuate depending on antigen dose or change in total toxicant load, thus appearing inconsistent to observers.
vii) Hypersensitivity responses may be blunted or not reproducible if the sensitive individual has been away from a specific incitant for some time.
viii) Some clinicians are only comfortable with recognized and rigid definitions of what constitutes allergy, disregarding sensitivity reactions that do not meet traditional criteria.
ix) Scientists with questionable integrity are sometimes hired by those facing liability charges to publicly discredit any toxicant-disease link. (Michaels, 2008).
x) Industry-affiliated peer reviewers for some scientific journals have been alleged to suppress or obstruct publication of information relating to adverse outcomes associated with toxicant exposure (Genuis, 2010c).

It is noteworthy, however, that other various common disorders have also met cynicism, disbelief and resistance in the past, particularly those diseases that affect women. Menopause, premenstrual syndrome, and chronic fatigue syndrome were initially dismissed as non-entities. Post-traumatic stress disorder, ulcerative colitis, migraine headaches, ulcer disease, asthma, Parkinson's disease, multiple sclerosis and various other conditions are among the disease states previously considered psychogenic (Pall, 2007; Marshall, 2002). Practitioners dealing with patients afflicted with such health issues have historically been labeled as 'quacks' or 'alternative practitioners' engaged in organized junk science. Despite resistance from the prevailing medical community each time, however, these health problems have subsequently been confirmed to be credible physiologically-based disorders rather than psychologically-based confabulations.

Lethargy in achieving consensus on emerging information, no matter how compelling the evidence, has always been the rule as history consistently demonstrates that medical knowledge translation is notoriously slow (Doherty, 2005; Rogers, 1995; Genuis and Genuis, 2006). Furthermore, as patients with SRI consume an inordinate amount of health care services, (Buchwald and Garrity, 1994) and issues related to insurance, liability, employment, human rights, and compensation have the potential to be colossal in relation to toxicant exposure, there is serious concern that vested interests may be obstructing evolution of knowledge translation by the common ploy of introducing doubt (Michaels, 2008). SRI is beginning to receive increasing attention, nonetheless, in governmental policy and courts in various jurisdictions.

In Canada, for example, the Canadian Human Rights Commission has published a position paper recognizing disability that may result from chemical sensitivity (Sears, 2007) and the Office of Disability Policy at the United States Department of Housing and Urban Development considers chemical sensitivity to be a disability under their legislation (Development, 1991). Recently, Swedish authorities have officially acknowledged electrosensitivity as a functional impairment (Johansson, 2006). Legal decisions have also begun to reflect the impact of sensitivities as a court in Spain, for example, recently awarded full disability for chemical sensitivities to an individual developing SRI following an environmental accident (Valverde, 2010).

The prevalence of SRI in the form of allergies, food intolerance and chemical sensitivity continues to escalate and has become a serious public health problem throughout the world. As virtually all illness represents the interaction of a fixed genome with a modifiable environment, (Office of Genomics and Disease Prevention: Centers for Disease Control and Prevention, 2000) it is elucidating to consider that our genome has not changed, but our environment has. It is time for health professionals including medical students to become apprised

of the issue of environmental determinants and bioaccumulative toxicant exposure — the underlying etiology of much contemporary clinical illness. Much can be done to prevent disease and restore health for those afflicted with SRI. It is also imperative that governments begin to consider public policy related to toxicant exposure if they wish to address the ever-increasing expenditures associated with providing health care services to their populations.

Learning points

- Sensitivity-related illness — including allergy, food intolerance and chemical sensitivity — is generally the result of genetic predisposition combining with a toxicant burden resulting from environmental exposure.
- A signficant toxic burden on the human body which reaches beyond a threshold level appears to initiate a state of impaired tolerance and hypersensitivity in that individual. This may be referred to as a 'Toxicant Induced Loss of Tolerance' or 'TILT.'
- Individual patients with impaired tolerance and hypersensitivity begin to react to minute doses of diverse triggers in their environment which do not bother healthy individuals. This may be referred to as 'Minute Assorted Triggers Evoke Symptoms' or 'MATES.' The resulting clinical sequelae may vary with manifestations of myriad health conditions involving diverse organ systems.
- Sensitivity-related illness will generally abate if underlying toxicant burdens are identified and removed.

References

Anandan C, Gupta R, Simpson CR, Fischbacher C, Sheikh A. Epidemiology and disease burden from allergic disease in Scotland: analyses of national databases. J R Soc Med 2009;102(10):431–42 Oct.

Anisman H, Merali A. Anhedonic and anxiogenic effects of cytokine exposure. Cytokines, Stress, and Depression. New York: Kluwer Academic/Plenum Publishers; 1999.

25th Annual International Symposium on Man and His Environment in Health and Disease: The Autonomic Nervous System. Dallas: June 7–10, 2007.

Anthoni S, Savilahti E, Rautelin H, Kolho KL. Milk protein IgG and IgA: the association with milk-induced gastrointestinal symptoms in adults. World J Gastroenterol 2009;15(39):4915–8 Oct 21.

Ashford N, Miller C. Chemical exposures: low levels and high stakes. 2nd ed. New York: John Wiley and Sons; 1998.

Barnes JG. 'Sensitivity syndromes' related to radiation exposures. Med Hypotheses 2001;57(4):453–8 Oct.

Bascom R. Multiple chemical sensitivity: a respiratory disorder? Toxicol Ind Health 1992;8(4):221–8 Jul–Aug.

Bell IR, Miller CS, Schwartz GE. An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. Biol Psychiatry 1992;32(3):218–42 Aug 1.

Bell IR, Walsh M, Gross A, Gersmeyer J, Schwartz G, Kanof P. Cognitive dysfunction and disability in geriatric veterans with self-reported intolerance to environmental chemicals. J Chron Fatigue Syndr 1997;3(3):15–42.

Bell IR, Szarek MJ, Dicenso DR, Baldwin CM, Schwartz GE, Bootzin RR. Patterns of waking EEG spectral power in chemically intolerant individuals during repeated chemical exposures. Int J Neurosci 1999;97(1–2):41–59 Mar.

Berg ND, Linneberg A, Dirksen A, Elberling J. Prevalence of self-reported symptoms and consequences related to inhalation of airborne chemicals in a Danish general population. Int Arch Occup Environ Health 2008;81(7):881–7 Jul.

Bernardi D, Borghesan F, Faggian D, Bianchi FC, Favero E, Billeri L, et al. Time to reconsider the clinical value of immunoglobulin G4 to foods? Clin Chem Lab Med 2008;46(5):687–90.

Bjorksten B. The hygiene hypothesis: do we still believe in it? Nestle Nutr Workshop Ser 2009;64:11–22.

Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci 2007;8(1):57–69 Jan.

Blonski W, Lichtenstein GR. Safety of biologics in inflammatory bowel disease. Curr Treat Options Gastroenterol 2006;9(3):221–33 Jun.

Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295(19):2275–85 May 17.

Bralley JA, Lord RS. Laboratory evaluations in molecular medicine: nutrients, toxicants, and cell regulators. Norcross GA: The Institute for Advances in Molecular Medicine; 2005.

Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics 2009;124(6):1549–55 Dec.

Brautbar N, Campbell A, Vojdani A. Silicone breast implants and autoimmunity: causation, association, or myth? J Biomater Sci 1995;7(2):133–45.

Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. Med Hypotheses 2009;72(3):333–7 Mar.

Brown JM, Pfau JC, Pershouse MA, Holian A. Silica, apoptosis, and autoimmunity. J Immunotoxicol 2005;1(3):177–87 Jul 1.

Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 1994;154(18):2049–53 Sep 26.

Cabrera-Chavez F, de la Barca AM. Bovine milk intolerance in celiac disease is related to IgA reactivity to alpha- and beta-caseins. Nutrition 2009;25(6):715–6 Jun.

Cathcart III RF. The vitamin C treatment of allergy and the normally unprimed state of antibodies. Med Hypotheses 1986;21(3):307–21 Nov.

Centers for Disease Control, Department of Health and Human Services. Fourth National Report on Human Exposure to Environmental Chemicals. 2009. [Accessed Jan 18, 2009] Atlanta: Georgia. pp. 1–529. http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf 2009.

Cha HR, Chang SY, Chang JH, Kim JO, Yang JY, Kim CH, et al. Downregulation of Th17 cells in the small intestine by disruption of gut flora in the absence of retinoic acid. J Immunol 2010;184:6799–806.

Ciprandi G, De Amici M, Tosca MA, Negrini S, Puppo F, Marseglia GL. Immunoglobulin production pattern is allergen-specific in polysensitized patients. Int J Immunopathol Pharmacol 2009;22(3):809–17 Jul–Sep.

Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. Allergy 2009;64(8):1218–20 Aug.

Cochrane S, Beyer K, Clausen M, Wjst M, Hiller R, Nicoletti C, et al. Factors influencing the incidence and prevalence of food allergy. Allergy 2009;64(9):1246–55 Sep.

Cohn WJ, Boylan JJ, Blanke RV, Fariss MW, Howell JR, Guzelian PS. Treatment of chlordecone (Kepone) toxicity with cholestyramine. Results of a controlled clinical trial. N Engl J Med 1978;298(5):243–8 Feb 2.

Colbert LH, Visser M, Simonsick EM, Tracy RP, Newman AB, Kritchevsky SB, et al. Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2004;52(7):1098–104 Jul.

Cone JE, Sult TA. Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivities? Toxicol Ind Health 1992;8(4):29–39 Jul–Aug.

Cullen M. The worker with multiple chemical sensitivities: an overview. In: Cullen M, editor. Workers with multiple chemical sensitivities: occupation medicine — state of the art reviews, 2(4). Philadelphia: Hanley and Belfus; 1987. p. 655–62.

Czura CJ, Tracey KJ. Autonomic neural regulation of immunity. J Intern Med 2005;257(2):156–66 Feb.

Dahlgren J, Takhar H, Anderson-Mahoney P, Kotlerman J, Tarr J, Warshaw R. Cluster of systemic lupus erythematosus (SLE) associated with an oil field waste site: a cross sectional study. Environ Health 2007a;6:8.

Dahlgren J, Cecchini M, Takhar H, Paepke O. Persistent organic pollutants in 9/11 world trade center rescue workers: reduction following detoxification. Chemosphere 2007b;69(8):1320–5 Oct.

D'Amato G, Cecchi L. Effects of climate change on environmental factors in respiratory allergic diseases. Clin Exp Allergy 2008;38(8):1264–74 Aug.

D'Amato G, Liccardi G, D'Amato M, Holgate S. Environmental risk factors and allergic bronchial asthma. Clin Exp Allergy 2005;35(9):1113–24 Sep.

Das-Munshi J, Rubin GJ, Wessely S. Multiple chemical sensitivities: a systematic review of provocation studies. J Allergy Clin Immunol 2006;118(6):1257–64 Dec.

De Luca C, Scordo MG, Cesareo E, Pastore S, Mariani S, Maiani G, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. Toxicol Appl Pharmacol 2010 Apr 27.

De Santis A, Addolorato G, Romito A, Caputo S, Giordano A, Gambassi G, et al. Schizophrenic symptoms and SPECT abnormalities in a coeliac patient: regression after a gluten-free diet. J Intern Med 1997;242(5):421–3 Nov.

Desjardins S, Doyen C, Contejean Y, Kaye K, Paubel P. Treatment of a serious autistic disorder in a child with Naltrexone in an oral suspension form. Encephale 2009;35(2):168–72 Apr.

Development. DoHaU. Subsection 802(h) of the Fair Housing Act, 42 U.S.C. 3602(h), and the Department's implementing regulation, 24 C.F.R. 100.201. 1991.

Dijkers MP. The value of traditional reviews in the era of systematic reviewing. Am J Phys Med Rehabil 2009;88(5):423–30 May.

Doherty S. History of evidence-based medicine. Oranges, chloride of lime and leeches: barriers to teaching old dogs new tricks. Emerg Med Australas 2005;17(4):314–21 Aug.

Dong C. Differentiation and function of pro-inflammatory Th17 cells. Microbes Infect 2009;11:584–8.

Duramad P, Tager IB, Holland NT. Cytokines and other immunological biomarkers in children's environmental health studies. Toxicol Lett 2007;172(1–2):48–59 Jul 30.

Duvnjak L, Duvnjak M. The metabolic syndrome — an ongoing story. J Physiol Pharmacol 2009;60(Suppl 7):19–24 Dec.

Edmondson DA, Nordness ME, Zacharisen MC, Kurup VP, Fink JN. Allergy and "toxic mold syndrome". Ann Allergy Asthma Immunol 2005;94(2):234–9 Feb.

Ellman LM, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Kern DM, et al. Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. Schizophr Res 2010;121(1–3):46–54 Aug.

Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115(5):911–9 May, quiz 920.

Fernandez M, Bell IR, Schwartz GE. EEG sensitization during chemical exposure in women with and without chemical sensitivity of unknown etiology. Toxicol Ind Health 1999;15(3–4):305–12 Apr–Jun.

Fiedler N, Kipen H, Natelson B, Ottenweller J. Chemical sensitivities and the Gulf War: Department of Veterans Affairs Research Center in basic and clinical science studies of environmental hazards. Regul Toxicol Pharmacol 1996;24(1 Pt 2): S129–38 Aug.
Fiedler N, Giardino N, Natelson B, Ottenweller JE, Weisel C, Lioy P, et al. Responses to controlled diesel vapor exposure among chemically sensitive Gulf War veterans. Psychosom Med 2004;66(4):588–98 Jul–Aug.
Fincher CE, Chang TS, Harrell EH, Kettelhut MC, Rea WJ, Johnson A, et al. Comparison of single photon emission computed tomography findings in cases of healthy adults and solvent-exposed adults: correction of previous results. Am J Ind Med 1997a;32 (6):693–4 Dec.
Fincher CE, Chang TS, Harrell EH, Kettelhut MC, Rea WJ, Johnson A, et al. Comparison of single photon emission computed tomography findings in cases of healthy adults and solvent-exposed adults. Am J Ind Med 1997b;31(1):4-14 Jan.
Freeman HJ. Celiac disease (gluten-sensitive enteropathy). Minerva Gastroenterol Dietol 2010;56(2):245–9 Jun.
Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. JAMA 1998;280 (11):981–8 Sep 16.
Fukuyama T, Ueda H, Hayashi K, Tajima Y, Shuto Y, Saito TR, et al. Detection of low-level environmental chemical allergy by a long-term sensitization method. Toxicol Lett 2008;180(1):1–8 Jul 30.
Gauderman WJ, Avol E, Lurmann F, Kuenzli N, Gilliland F, Peters J, et al. Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology 2005;16(6): 737–43 Nov.
Gelincik A, Buyukozturk S, Gul H, Isik E, Issever H, Ozseker F, et al. Confirmed prevalence of food allergy and non-allergic food hypersensitivity in a Mediterranean population. Clin Exp Allergy 2008;38(8):1333–41 Aug.
Genuis SJ. The chemical erosion of human health: adverse environmental exposure and in-utero pollution — determinants of congenital disorders and chronic disease. J Perinat Med 2006a;34:185–95.
Genuis SJ. Health issues and the environment — an emerging paradigm for providers of obstetrical and gynecological healthcare. Hum Reprod 2006b;21:2201–8.
Genuis SJ. Our genes are not our destiny: incorporating molecular medicine into clinical practice. J Eval Clin Pract 2008a;14(1):94-102 Feb.
Genuis SJ. Medical practice and community health care in the 21st century: a time of change. Public Health 2008b;122(7):671–80 Jul.
Genuis SJ. Toxic causes of mental illness are overlooked. Neurotoxicology 2008c;29(6): 1147–9 Nov.
Genuis SJ. Nowhere to hide: chemical toxicants and the unborn child. Reprod Toxicol (Elmsford, N.Y.) 2009;28(1):115–6 Jul.
Genuis SJ. Evolution in pediatric health care. Pediatr Int 2010a. doi:10.1111/j.1442-200X.2010.03106.x.
Genuis SJ. Elimination of persistent toxicants from the human body. Hum Exp Toxicol 2010b Apr 20.
Genuis SJ. Human detoxification of perfluorinated compounds. Public Health 2010;124 (7):367–75 Jul.
Genuis SJ, Bouchard TP. Celiac disease presenting as autism. J Child Neurol 2010;25: 114–9.
Genuis SK, Genuis SJ. Exploring the continuum: medical information to effective clinical practice: Paper 1. The translation of knowledge into clinical practice. J Eval Clin Pract 2006;12:49–62.
Genuis SJ, Lobo RA. Potential amelioration of morbidity in patients with chromosomal anomalies: relevance to Bardet–Biedl syndrome. Clin Genet 2010 Jun 21.
Gibson PR, Vogel VM. Sickness-related dysfunction in persons with self-reported multiple chemical sensitivity at four levels of severity. J Clin Nurs 2009;18(1): 72–81 Jan.
Gilbert KM, Pumford NR, Blossom SJ. Environmental contaminant trichloroethylene promotes autoimmune disease and inhibits T-cell apoptosis in MRL(+/+) mice. J Immunotoxicol 2006;3(4):263–7 Dec 1.
Gironi M, Martinelli-Boneschi F, Sacerdote P, Solaro C, Zaffaroni M, Cavarretta R, et al. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. Mult Scler (Houndmills, Basingstoke, England) 2008;14(8):1076–83 Sep.
Gold DR, Wright R. Population disparities in asthma. Annu Rev Public Health 2005;26: 89-113.
Gordon M. Reactions to chemical fumes in radiology departments. Radiography 1987;53(608):85–9 Mar–Apr.
Graveling RA, Pilkington A, George JP, Butler MP, Tannahill SN. A review of multiple chemical sensitivity. Occup Environ Med 1999;56(2):73–85 Feb.
Gupta RS, Kim JS, Barnathan JA, Amsden LB, Tummala LS, Holl JL. Food allergy knowledge, attitudes and beliefs: focus groups of parents, physicians and the general public. BMC Pediatr 2008;8:36.
Hausteiner C, Bornschein S, Hansen J, Zilker T, Forstl H. Self-reported chemical sensitivity in Germany: a population-based survey. Int J Hyg Environ Health 2005;208(4):271–8.
Helms DJ, Mosure DJ, Secor WE, Workowski KA. Management of trichomonas vaginalis in women with suspected metronidazole hypersensitivity. Am J Obstet Gynecol 2008;198(4):370 Apr, e371-377.
Heuser G, Wu JC. Deep subcortical (including limbic) hypermetabolism in patients with chemical intolerance: human PET studies. Ann NY Acad Sci 2001;933: 319–22 Mar.
Hillert L, Musabasic V, Berglund H, Ciumas C, Savic I. Odor processing in multiple chemical sensitivity. Hum Brain Mapp 2007;28(3):172–82 Mar.
Hintikka EL. The role of stachybotrys in the phenomenon known as sick building syndrome. Adv Appl Microbiol 2004;55:155–73.
Hirvonen MR, Nevalainen A, Makkonen N, Monkkonen J, Savolainen K. Induced production of nitric oxide, tumor necrosis factor, and interleukin-6 in RAW 264.7 macrophages by streptomycetes from indoor air of moldy houses. Arch Environ Health 1997;52(6):426–32 Nov–Dec.
Hirvonen MR, Ruotsalainen M, Roponen M, Hyvarinen A, Husman T, Kosma VM, et al. Nitric oxide and proinflammatory cytokines in nasal lavage fluid associated with symptoms and exposure to moldy building microbes. Am J Respir Crit Care Med 1999;160(6):1943–6 Dec.
Hirvonen MR, Huttunen K, Roponen M. Bacterial strains from moldy buildings are highly potent inducers of inflammatory and cytotoxic effects. Indoor Air 2005;15 (Suppl 9):65–70.
Hobbs A. The sick house survival guide. Gabriola Island, British Columbia: New Society Publishers; 2003.
Hsueh KC, Lin YJ, Lin HC, Lin CY. Serum leptin and adiponectin levels correlate with severity of allergic rhinitis. Pediatr Allergy Immunol 2009 Aug 30.
Ishimaru N, Takagi A, Kohashi M, Yamada A, Arakaki R, Kanno J, et al. Neonatal exposure to low-dose 2,3,7,8-tetrachlorodibenzo-p-dioxin causes autoimmunity due to the disruption of T cell tolerance. J Immunol 2009;182(10):6576–86 May 15.
Isolauri E, Kalliomaki M, Rautava S, Salminen S, Laitinen K. Obesity — extending the hygiene hypothesis. Nestle Nutr Workshop Ser 2009;64:75–89.
Jalava PI, Salonen RO, Pennanen AS, Happo MS, Penttinen P, Halinen AI, et al. Effects of solubility of urban air fine and coarse particles on cytotoxic and inflammatory responses in RAW 264.7 macrophage cell line. Toxicol Appl Pharmacol 2008;229 (2):146–60 Jun 1.
Jalava PI, Hirvonen MR, Sillanpaa M, Pennanen AS, Happo MS, Hillamo R, et al. Associations of urban air particulate composition with inflammatory and cytotoxic responses in RAW 246.7 cell line. Inhal Toxicol 2009;21(12):994-1006 Oct.
Jedrychowski W, Galas A, Whyatt R, Perera F. The prenatal use of antibiotics and the development of allergic disease in one year old infants. A preliminary study. Int J Occup Med Environ Health 2006;19(1):70–6.
Joffres MR, Williams T, Sabo B, Fox RA. Environmental sensitivities: prevalence of major symptoms in a referral center: the Nova Scotia Environmental Sensitivities Research Center Study. Environ Health Perspect 2001;109(2):161–5 Feb.
Johansson O. Electrohypersensitivity: state-of-the-art of a functional impairment. Electromagn Biol Med 2006;25(4):245–58.
Johansson A, Bramerson A, Millqvist E, Nordin S, Bende M. Prevalence and risk factors for self-reported odour intolerance: the Skovde population-based study. Int Arch Occup Environ Health 2005;78(7):559–64 Aug.
Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124(2):292–300 Aug, 300 e291–297.
Kalinina NH, Nikiforova ID, Syssoev KA, Sidorenko VA. Immunological aspects of osteoporosis in Chernobyl cleanup workers. Conference proceedings. International conference on the effects of low and very low doses of ionizing radiation on human health: June 16–18, 1999; 1999. 48.
Kalliomaki M, Isolauri E. Pandemic of atopic diseases—a lack of microbial exposure in early infancy? Curr Drug Targets 2002;2(3):193–9 Sep.
Kariv R, Tiomny E, Grenshpon R, Dekel R, Waisman G, Ringel Y, et al. Low-dose naltreoxone for the treatment of irritable bowel syndrome: a pilot study. Dig Dis Sci 2006;51(12):2128–33 Dec.
Kawaguchi M, Kokubu F, Fujita J, Huang SK, Hizawa N. Role of interleukin-17F in asthma. Inflamm Allergy Drug Targets 2009;8:383–9.
Kilburn KH. Effects of hydrogen sulfide on neurobehavioral function. South Med J 2003;96(7):639–46 Jul.
Kilburn KH, Warsaw RH, Shields MG. Neurobehavioral dysfunction in firemen exposed to polychlorinated biphenyls (PCBs): possible improvement after detoxification. Arch Environ Health 1989;44:345–50.
Kim CH. Regulation of FoxP3 regulatory T cells and Th17 cells by retinoids. Clin Dev Immunol 2008;2008:416910.
Kimata H. Exposure to road traffic enhances allergic skin wheal responses and increases plasma neuropeptides and neurotrophins in patients with atopic eczema/ dermatitis syndrome. Int J Hyg Environ Health 2004a;207(1):45–9 Jan.
Kimata H. Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity. Int J Hyg Environ Health 2004b;207(2):159–63 Feb.
Kiyohara C, Tanaka K, Miyake Y. Genetic susceptibility to atopic dermatitis. Allergol Int 2008;57(1):39–56 Mar.
Kreindler JL, Steele C, Nguyen N, Chan YR, Pilewski JM, Alcorn JF, et al. Vitamin D3 attenuates Th2 responses to Aspergillus fumigatus mounted by CD4+ T cells from cystic fibrosis patients with allergic bronchopulmonary aspergillosis. J Clin Invest 2010;120(9):3242–54 Sep 1.
Kreutzer R, Neutra RR, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population-based survey. Am J Epidemiol 1999;150(1):1-12 Jul 1.
Kuroda Y, Nacionales DC, Akaogi J, Reeves WH, Satoh M. Autoimmunity induced by adjuvant hydrocarbon oil components of vaccine. Biomed Pharmacother 2004;58 (5):325–37 Jun.
Lau S, Nickel R, Niggemann B, Gruber C, Sommerfeld C, Illi S, et al. The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS). Paediatr Respir Rev 2002;3(3):265–72 Sep.
Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol 2005;288(5): H2031–41 May.
Lax MB, Henneberger PK. Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. Arch Environ Health 1995;50(6):425–31 Nov–Dec.

Lee TG. Health symptoms caused by molds in a courthouse. Arch Environ Health 2003;58(7):442–6.
Leonard BE, Song C. Stress, depression, and the role of cytokines. Cytokines, stress, and depression. New York: Kluwer Academic:Plenum Publishers; 1999.
Lindh U, Hudecek R, Danersund A, Eriksson S, Lindvall A. Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviates symptoms and improves quality of life in patients with amalgam-associated ill health. Neuroendocrinol Lett 2002;23(5–6):459–82.
Ma X, He P, Sun P, Han P. Lipoic acid: an immunomodulator that attenuates glycinin-induced anaphylactic reactions in a rat model. J Agric Food Chem 2010;58(8):5086–92 Apr 28.
Maarsingh H, Zaagsma J, Meurs H. Arginine homeostasis in allergic asthma. Eur J Pharmacol 2008;585(2–3):375–84 May 13.
Maarsingh H, Bossenga BE, Bos IS, Volders HH, Zaagsma J, Meurs H. L-arginine deficiency causes airway hyperresponsiveness after the late asthmatic reaction. Eur Respir J 2009;34(1):191–9 Jul.
MacDougald OA, Burant CF. The rapidly expanding family of adipokines. Cell Metab 2007;6(3):159–61 Sep.
Mahmoudi M, Gershwin ME. Sick building syndrome. III. Stachybotrys chartarum. J Asthma 2000;37(2):191–8 Apr.
Mansueto P, Montalto G, Pacor ML, Esposito-Pellitteri M, Ditta V, Lo Bianco C, et al. Food allergy in gastroenterologic diseases: review of literature. World J Gastroenterol 2006;12(48):7744–52 Dec 28.
Marshall B. Helicobacter pioneers: firsthand accounts from the scientists who discovered helicobacters. Victoria, Australia: Blackwell; 2002.
Marshall L, Weir E, Abelsohn A, Sanborn MD. Identifying and managing adverse environmental health effects: 1. Taking an exposure history. CMAJ 2002;166:1049–55.
Meggs WJ. Hypothesis for induction and propagation of chemical sensitivity based on biopsy studies. Environ Health Perspect 1997;105(Suppl 2):473–8 Mar.
Meggs WJ. Mechanisms of allergy and chemical sensitivity. Toxicol Ind Health 1999;15(3–4):331–8 Apr–Jun.
Meurs H, Maarsingh H, Zaagsma J. Arginase and asthma: novel insights into nitric oxide homeostasis and airway hyperresponsiveness. Trends Pharmacol Sci 2003;24(9):450–5 Sep.
Michaels D. Doubt is their product: how industry's assault on science threatens your health. New York: Oxford University Press; 2008.
Miller CS. Multiple chemical sensitivity syndrome. J Occup Environ Med 1995;37(12):1323 Dec.
Miller CS. Chemical sensitivity: symptom, syndrome or mechanism for disease? Toxicology 1996;111(1–3):69–86 Jul 17.
Miller CS. Toxicant-induced loss of tolerance—an emerging theory of disease? Environ Health Perspect 1997;105(Suppl 2):445–53 Mar.
Miller CS. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abdiction. Toxicol Ind Health 1999;15(3–4):284–94 Apr–Jun.
Miller CS, Ashford NA. Multiple chemical intolerance and indoor air quality. Chapter 27. In: Spengler JD, Samet JM, McCarthy JF, editors. Indoor air quality handbook. New York: MacGraw-Hill; 2000.
Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health 1995;50(2):119–29 Mar–Apr.
Miller CS, Prihoda TJ. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. Toxicol Ind Health 1999a;15(3–4):386–97 Apr–Jun.
Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. Toxicol Ind Health 1999b;15:370–85.
Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. Pediatr Neurol 2003;28(1):9-15 Jan.
Moen B, Hollund B, Riise T. Neurological symptoms among dental assistants: a cross-sectional study. J Occup Med Toxicol (London, England) 2008;3:10.
Mok MY, Wu HJ, Lo Y, Lau CS. The Relation of Interleukin 17 (IL-17) and IL-23 to Th1/Th2 Cytokines and Disease Activity in Systemic Lupus Erythematosus. J Rheumatol 2010.
Montoro J, Mullol J, Jauregui I, Ferrer M, Bartra J, et al. Stress and allergy. J Investig Allergol Clin Immunol 2009;19(Suppl 1):40–7.
Nantes Castillejo O, Zozaya J, Jimenez-Perez F, Martinez-Penuela J, Borda F. Incidence and characteristics of eosinophilic esophagitis in adults. An Sist Sanit Navar 2009;32(2):227–34 May–Aug.
Nemery B. Late consequences of accidental exposure to inhaled irritants: RADS and the Bhopal disaster. Eur Respir J 1996;9(10):1973–6 Oct.
Notkins AL. New predictors of disease. Molecules called predictive autoantibodies appear in the blood years before people show symptoms of various disorders. Tests that detected these molecules could warn of the need to take preventive action. Sci Am 2007;296(3):72–9 Mar.
Nowak-Wegrzyn A, Sicherer SH. Immunotherapy for food and latex allergy. Clin Allergy Immunol 2008;21:429–46.
Office of Genomics and Disease Prevention: Centers for Disease Control and Prevention. Department of Health and Human S. Gene–Environment Interaction Fact Sheet. 2000.
Overstreet DH, Miller CS, Janowsky DS, Russell RW. Potential animal model of multiple chemical sensitivity with cholinergic supersensitivity. Toxicology 1996;111(1–3):119–34 Jul 17.
Pall ML. Explaining 'unexplained illness': disease paradigm for chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia; post-traumatic stress disorder, Gulf War syndrome and others. New York: Harrington Park Press; 2007.
Pall ML. Multiple chemical sensitivity: toxicological questions and mechanisms (part eight, chapter 92). In: Ballantyne B, Marrs TC, Syversen T, editors. General and applied toxicology. 3rd Edition. New Jersey: Wiley; 2009.
Papageorgiou PS. Clinical aspects of food allergy. Biochem Soc Trans 2002;30(Pt 6):901–6 Nov.
Pestka JJ, Yike I, Dearborn DG, Ward MD, Harkema JR. Stachybotrys chartarum, trichothecene mycotoxins, and damp building-related illness: new insights into a public health enigma. Toxicol Sci 2008;104(1):4-26 Jul.
Petro TM. Regulatory role of resveratrol on Th17 in autoimmune disease. Int Immunopharmacol 2010. Aug 12.
Postolache TT, Langenberg P, Zimmerman SA, Lapidus M, Komarow H, McDonald JS, et al. Changes in severity of allergy and anxiety symptoms are positively correlated in patients with recurrent mood disorders who are exposed to seasonal peaks of aeroallergens. Int J Child Health Hum Dev 2008;1(3):313–22.
Randolph TG. Specific adaptation. Ann Allergy 1978;40(5):333–45 May.
Randolph TG, Moss R. An alternative approach to allergies. New York: Lippincott & Crowell; 1980.
Rea WJ. Chemical sensitivity: (volume 1): tools of diagnosis and methods of treatment. Boca Raton: CRC Press; 1992.
Rea WJ. Chemical sensitivity: (volume 4): tools of diagnosis and methods of treatment. Boca Raton: Lewis Publishers; 1997.
Rea WJ, Pan Y, Fenyves EJ, Sujisawa I, Suyama N, Ross GH. Electromagnetic field sensitivity. J Bioelectricity 1991;10:241–56.
Reid S, Hotopf M, Hull L, Ismail K, Unwin C, Wessely S. Reported chemical sensitivities in a health survey of United Kingdom military personnel. Occup Environ Med 2002;59(3):196–8 Mar.
Rogers EM. Diffusion of innovations. New York: The Free Press; 1995.
Rogers WR, Miller CS, Bunegin L. A rat model of neurobehavioral sensitization to toluene. Toxicol Ind Health 1999;15(3–4):356–69 Apr–Jun.
Rowat SC. Integrated defense system overlaps as a disease model: with examples for multiple chemical sensitivity. Environ Health Perspect 1998;106(Suppl 1):85-109 Feb.
Rubin RL, Kretz-Rommel A. Initiation of autoimmunity by a reactive metabolite of a lupus-inducing drug in the thymus. Environ Health Perspect 1999;107(Suppl 5):803–6 Oct.
Schambach F, Schupp M, Lazar MA, Reiner SL. Activation of retinoic acid receptor-alpha favours regulatory T cell induction at the expense of IL-17-secreting T helper cell differentiation. Eur J Immunol 2007;37:2396–9.
Schnare DW, Denk G, Shields M, Brunton S. Evaluation of a detoxification regimen for fat stored xenobiotics. Med Hypothesis 1982;9:265–82.
Sears M. The medical perspective on environmental sensitivities. Government of Canada: Canadian Human Rights Commission; 2007 ([available at http://www.chrc-ccdp.ca/research_program_recherche/esensitivities_hypersensibilitee/toc_tdm-en.asp] accessed Oct 11/2009.).
Segal BM. Th17 cells in autoimmune demyelinating disease. Semin Immunopathol 2010;32:71–7.
Shannon A, Alkhouri N, Mayacy S, Kaplan B, Mahajan L. Low-dose naltrexone for treatment of duodenal Crohn's disease in a pediatric patient. Inflamm Bowel Dis 2010;16(9):1457 Sep.
Shields M, Beckman SL, Cassidy-Brinn G. Improvement in perception of transcutaneous nerve stimulation following detoxification in firefighters exposed to PCBs, PCDDs and PCDFs. Clin Ecol 1989;6:47–50.
Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010;125(Suppl 2):S116–25 Feb.
Sih T, Mion O. Allergic rhinitis in the child and associated comorbidities. Pediatr Allergy Immunol 2010 Aug 2.
Simon GE, Katon WJ, Sparks PJ. Allergic to life: psychological factors in environmental illness. Am J Psychiatry 1990;147(7):901–6 Jul.
Simon TR, Hickey DC, Fincher CE, Johnson AR, Ross GH, Rea WJ. Single photon emission computed tomography of the brain in patients with chemical sensitivities. Toxicol Ind Health 1994;10(4–5):573–7 Jul–Oct.
Smith JP, Stock H, Bingaman S, Mauger D, Rogosnitzky M, Zagon IS. Low-dose naltrexone therapy improves active Crohn's disease. Am J Gastroenterol 2007;102(4):820–8 Apr.
Sorg BA. Multiple chemical sensitivity: potential role for neural sensitization. Crit Rev Neurobiol 1999;13(3):283–316.
Sorg BA, Hochstatter T. Behavioral sensitization after repeated formaldehyde exposure in rats. Toxicol Ind Health 1999;15(3–4):346–55 Apr–Jun.
Sorg BA, Willis JR, See RE, Hopkins B, Westberg HH. Repeated low-level formaldehyde exposure produces cross-sensitization to cocaine: possible relevance to chemical sensitivity in humans. Neuropsychopharmacology 1998;18(5):385–94 May.
Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol 2005;95(4):336–43 Oct.
Staren ED, Essner R, Economou JS. Overview of biological response modifiers. Semin Surg Oncol 1989;5(6):379–84.
Staudenmayer H. Idiopathic environmental intolerances (IEI): myth and reality. Toxicol Lett 2001;120(1–3):333–42 Mar 31.
Staudenmayer H, Selner ME, Selner JC. Adult sequelae of childhood abuse presenting as environmental illness. Ann Allergy 1993;71(6):538–46 Dec.
Stejskal V, Stejskal J. Toxic metals as a key factor in disease. Forword. Neuro Endocrinol Lett 2006;27(Suppl 1):3–4 Dec.
Stejskal VD, Danersund A, Lindvall A, Hudecek R, Nordman V, Yaqob A, et al. Metal-specific lymphocytes: biomarkers of sensitivity in man. Neuro Endocrinol Lett 1999;20(5):289–98.

Sterzl I, Prochazkova J, Hrda P, Matucha P, Bartova J, Stejskal V. Removal of dental amalgam decreases anti-TPO and anti-Tg autoantibodies in patients with autoimmune thyroiditis. Neuro Endocrinol Lett 2006;27(Suppl 1):25–30 Dec.
Steyn PS, Gelderblom WC, Shephard GS, van Heerden FR. Mycotoxins with a special focus on aflatoxins, ochratoxins and fumonisins. (Part fourteen, chapter 146) In General and Applied Toxicology, 3rd Edition. Ballantyne B, Marrs TC, and Syversen T (Eds). New Jersey: Wiley.
Tabershaw IR, Cooper WC. Sequelae of acute organic phosphate poisoning. J Occup Med 1966;8(1):5-20 Jan.
Tay SS, Clark AT, Deighton J, King Y, Ewan PW. Patterns of immunoglobulin G responses to egg and peanut allergens are distinct: ovalbumin-specific immunoglobulin responses are ubiquitous, but peanut-specific immunoglobulin responses are up-regulated in peanut allergy. Clin Exp Allergy 2007;37(10):1512–8 Oct.
Terr AI. Sick building syndrome: is mould the cause? Med Mycol 2009;47(Suppl 1): S217–22.
Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 2007;117(2):289–96 Feb.
Tracey KJ. Reflex control of immunity. Nat Rev Immunol 2009;9(6):418–28 Jun.
Tretjak Z, Shields M, Beckman SL. PCB reduction and clinical improvement by detoxification: an unexploited approach. Hum Exp Toxicol 1990;9:235–44.
Uchigata Y, Hirata Y, Iwamoto Y. Drug-induced insulin autoimmune syndrome. Diab Res Clin Pract 2009;83(1):e19–20 Jan.
University of Maryland Medical Centre. http://www.umm.edu/allergies/stats.htm (accessed Jan 17, 2010). Allergies Health Guide.
Valverde C. A judge in Spain grants full disability for chemical sensitivities for environmental accident; 2010 [accessed August 12, 2010 at http://sacfs.asn.au/news/2010/07/07_03_spanish_court_case.htm].
van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. BMJ 2009;339:b2433.
Vojdani A. Antibodies as predictors of complex autoimmune diseases and cancer. Int J Immunopathol Pharmacol 2008;21(3):553–66 Jul–Sep.
Welch LS, Sokas R. Development of multiple chemical sensitivity after an outbreak of sick-building syndrome. Toxicol Ind Health 1992;8(4):47–50 Jul–Aug.
Wilders-Truschnig M, Mangge H, Lieners C, Gruber H, Mayer C, Marz W. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. Exp Clin Endocrinol Diab 2008;116(4):241–5 Apr.
Wojcik DP, Godfrey ME, Christie D, Haley BE. Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994–2006). Neuro Endocrinol Lett 2006;27(4):415–23 Aug.
Xie L, Li XK, Funeshima-Fuji N, Kimura H, Matsumoto Y, Isaka Y, et al. Amelioration of experimental autoimmune encephalomyelitis by curcumin treatment through inhibition of IL-17 production. Int Immunopharmacol 2009;9:575–81.
Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. Pain Med (Malden, Mass.) 2009;10(4):663–72 May–Jun.
Yu IT, Lee NL, Zhang XH, Chen WQ, Lam YT, Wong TW. Occupational exposure to mixtures of organic solvents increases the risk of neurological symptoms among printing workers in Hong Kong. J Occup Environ Med 2004;46(4):323–30 Apr.
Yum HY, Lee SY, Lee KE, Sohn MH, Kim KE. Genetically modified and wild soybeans: an immunologic comparison. Allergy Asthma Proc 2005;26(3):210–6 May–Jun.
Zagon IS, Rahn KA, Turel AP, McLaughlin PJ. Endogenous opioids regulate expression of experimental autoimmune encephalomyelitis: a new paradigm for the treatment of multiple sclerosis. Exp Biol Med (Maywood) 2009;234(11):1383–92 Nov.
Zibrowski EM, Robertson JM. Olfactory sensitivity in medical laboratory workers occupationally exposed to organic solvent mixtures. Occup Med (Oxford, England) 2006;56(1):51–4 Jan.
Ziem GE. Multiple chemical sensitivity: treatment and followup with avoidance and control of chemical exposures. Toxicol Ind Health 1992;8(4):73–86 Jul–Aug.
Ziem G, McTamney J. Profile of patients with chemical injury and sensitivity. Environ Health Perspect 1997;105(Suppl 2):417–36.