Reversibility of Chronic Disease and Hypersensitivity

The Effects of Environmental Pollutants on the Organ Systems

VOLUME 2

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REVERSIBILITY OF CHRONIC DEGENERATIVE DISEASE AND HYPERSENSITIVITY

Reversibility of Chronic Degenerative Disease and Hypersensitivity,
Volume 1: Regulating Mechanisms of Chemical Sensitivity

Reversibility of Chronic Disease and Hypersensitivity,
Volume 2: The Effects of Environmental Pollutants on the Organ System

Reversibility of Chronic Disease and Hypersensitivity,
Volume 3: Clinical Environmental Manifestations
of the Neurocardiovascular Systems

Reversibility of Chronic Disease and Hypersensitivity,
Volume 4: The Environmental Aspects of Chemical Sensitivity

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Preface

The clinical aspects of the diagnosis and treatment of chemical sensitivity and chronic degenerative disease presented in this book are now complete. This book is for people interested in the origin of the clinical aspects of chemical sensitivity and chronic degenerative disease. The clinical aspects of chemical sensitivity are growing in leaps and bounds and need to be known and considered in every case of chronic degenerative disease.

In treating chronic degenerative disease, health-care providers must consider every aspect of chemical sensitivity. In this way, they will be able to help more patients obtain health and prevent advanced disease. Also, considering the aspects of chemical sensitivity will help each clinician to direct research for the prevention of advanced irreversible end stage disease. Modern technology has contributed to the advancement of chemical sensitivity, and it should be brought to bear on the solution of the problem.

William J. Rea, MD, FACS, FAAEM

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William J. Rea, MD, FACS, FAAEM, is a thoracic, cardiovascular, and general surgeon with an added interest in the environmental aspects of health and disease. He currently serves as the director of the Environmental Health Center–Dallas (EHC–Dallas), a highly specialized Dallas-based medical facility that he founded in 1974.

Dr. Rea was awarded the Jonathan Forman Gold Medal Award in 1987 for outstanding research in environmental medicine, the Herbert J. Rinkle Award in 1993 for outstanding teaching, and the 1998 Service Award, all by the American Academy of Environmental Medicine. He was named Outstanding Alumnus by Otterbein College in 1991. Other awards include the Mountain Valley Water Hall of Fame in 1987 for research in water and health, the Special Achievement Award by Otterbein College in 1991, the Distinguished Pioneers in Alternative Medicine Award by the Foundation for the Advancement of Innovative Medicine Education Fund in 1994, the Gold Star Award by the International Biographical Center in 1997, the Five Hundred Leaders of Influence Award in 1997, *Who's Who in the South and Southwest* in 1997, the Twentieth Century Award for Achievement in 1997, the Dor W. Brown, Jr., M.D. Lectureship Award by the Pan American Allergy Society, and the O. Spurgeon English Humanitarian Award by Temple University in 2002. Dr. Rea is the author of five medical textbooks, *Chemical Sensitivity (Volumes 1–4)* and *Reversibility of Chronic Degenerative Disease and Hypersensitivity, Volume 1: Regulating Mechanisms of Chemical Sensitivity*, and coauthor of *Your Home, Your Health and Well-Being*. He also published the popular *how to* book on building less polluted homes, *Optimum Environments for Optimum Health and Creativity*. He has also published more than 150 peer-reviewed research papers related to the topic of thoracic and cardiovascular surgery as well as that of environmental medicine.

Dr. Rea currently serves on the board and is president of the American Environmental Health Foundation. He is vice president of the American Board of Environmental Medicine and previously served on the board of the American Academy of Environmental Medicine. He previously held the position of chief of surgery at Brookhaven Medical Center and chief of cardiovascular surgery at Dallas Veteran's Hospital. He is also a past president of the American Academy of Environmental Medicine and the Pan American Allergy Society. He has served on the Science Advisory Board for the U.S. Environmental Protection Agency; on the Research Committee for the American Academy of Otolaryngic Allergy; and on the Committee on Aspects of Cardiovascular, Endocrine and Autoimmune Diseases of the American College of Allergists, as well as on the Committee on Immunotoxicology for the Office of Technology Assessment and on the panel on Chemical Sensitivity of the National Academy of Sciences. He was previously adjunct professor with the University of Oklahoma Health Science Center College of Public Health. Dr. Rea is a fellow of the American College of Surgeons, the American Academy of Environmental Medicine, the American College of Allergists, the American College of Preventive Medicine, the American College of Nutrition, and the Royal Society of Medicine.

Dr. Rea graduated from Otterbein College in Westerville, Ohio, and Ohio State University College of Medicine in Columbus, Ohio. He then completed a rotating internship at Parkland Memorial Hospital in Dallas, Texas. He held a general surgery residency from 1963 to 1967 and a cardiovascular surgery fellowship and residency from 1967 to 1969 with the University of Texas Southwestern Medical Center system, which includes Parkland Memorial Hospital, Baylor Medical Center, Veteran's Hospital, and Children's Medical Center. He was also part of the team that treated Governor Connelly when President Kennedy was assassinated.

From 1969 to 1972, Dr. Rea was assistant professor of cardiovascular surgery at the University of Texas Southwestern Medical Center; from 1984 to 1985, he held the position of adjunct professor of environmental sciences and mathematics at the University of Texas, while from 1972 to 1982 he served as clinical associate professor of thoracic surgery at the University of Texas Southwestern Medical Center. Dr. Rea held the First World Professorial Chair of Environmental Medicine at the University of Surrey, Guildford, England, from 1988 to 1998. He also served as adjunct professor of psychology and guest lecturer at North Texas State University.

Kalpana D. Patel, MD, FAAP, FAAEM, is a pediatrician with an added interest in the environmental aspects of health and disease. She founded the Environmental Health Center–Buffalo (EHC–Buffalo) in 1985, a specialized Buffalo-based medical facility. Dr. Patel was awarded the Jonathan Forman Gold Medal Award in 2006 for outstanding research in environmental medicine and the Herbert J. Rinkle Award in 2008 for outstanding teaching by the American Academy of Environmental Medicine. She was a recipient of the prestigious Hind Rattan Award granted by the NRI Welfare Society of India, an organization under the umbrella of the Government of India. She is a coauthor of the medical textbook, *Reversibility of Chronic Degenerative Disease and Hypersensitivity, Volume 1: Regulating Mechanisms of Chemical Sensitivity.* Dr. Patel has published many peer-reviewed research papers related to the topic of environmental medicine. She currently serves on the board and is president of the Environmental Health Foundation of New York. She has also served as president of the American Board of Environmental Medicine and on the board of the American Academy of Environmental Medicine. She previously held the position of director of child health in Erie County Department of Health and of chief of pediatrics at Deaconess Hospital, Buffalo, New York. She is a fellow of the American Academy of Environmental Medicine.

Dr. Patel graduated from St. Xavier's College with honors in the state of Gujarat, India, and also with honors from B. J. Medical College, Gujarat University, Ahmadabad, India. She then completed a rotating internship at Bexar County Hospital in San Antonio, Texas. She held a pediatric residency from 1969 to 1972. Dr. Patel has served as an assistant professor of pediatrics at the State University of New York at Buffalo since 1973.

1 Integument

I. INTRODUCTION

This, along with subsequent chapters, is dedicated to the understanding of the clinical aspects of homeostasis and dyshomeostasis and thus the clinical aspects of the mechanisms of chemical sensitivity and chronic degenerative disease.

The skin comes into contact with many toxic as well as nontoxic agents. It, along with the olfactory, neuromusculoskeletal, respiratory, gastrointestinal, and genitourinary areas of the body, is where entering pollutants directly affect the individual, causing chemical sensitivity and chronic degenerative disease. Fortunately, the skin has a good lipid barrier and is, therefore, not highly permeable, though, on occasion, it can become highly permeable to pollutants via toxic penetrators or raw areas. However, some chemicals (particularly if associated with solvents) can affect the skin, either directly or by penetrating it and producing systemic effects. Nerve gases, carbon tetrachloride, pesticides, and other solvents are known to be absorbed through the skin and clearly induce or exacerbate some cases of chemical sensitivity.[1] The biggest polluters of outdoor air in the United States are oil and natural gas extraction, metal mining, electric power generation, chemical production, and pesticide spraying. Indoors, they are natural gas stoves and heat, fireplaces, pesticide, and formaldehyde.[2] Organic chemical contaminants (see *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*[3]) in water have recently been shown to be absorbed through the skin[4] (Tables 1.1 and 1.2). Many patients with chemical sensitivity report that their illness exacerbates when they soak in a bathtub filled with unfiltered, chlorinated water. Pollutant entry causing nerve and immunological dysfunction results in symptoms of itching, pain, and fatigue after such an exposure.

Skin ailments constitute about 34% of all occupational diseases but appear less in the general population of individuals with chemical sensitivity. These ailments are probably higher for the total number of problems that are environmentally triggered. The skin is both a target organ for pollutant injury and a conduit through which some pollutants enter the body. There is a high incidence of skin involvement in patients with chemical sensitivity; therefore, this chapter devotes a brief discussion to the physiological involvement of the skin and the mechanisms of action of various chemicals involved in the onset and expression of chemical sensitivity. In addition, the commonly seen skin conditions that result from chemical exposure including autoimmune contact dermatitis, acute skin reactions, adult acne, urticaria, eczema, psoriasis, boils, and skin aging are given specific attention. This chapter is not intended to be all encompassing for skin toxicity, but it does give the clinician a perspective on the breadth and width of problems that can occur with chemical sensitivity and chronic degenerative disease.

II. STRUCTURE AND FUNCTION OF SKIN

A diagrammatic representation of the structure of the skin is shown in Figure 1.1. The skin contains three main layers: an outer layer of epithelial tissue, the *epidermis*; a loose connective tissue layer, the *dermis*; and an inner layer of variable thickness containing adipose tissue and connective tissue.[5] The epidermis contains a number of cell types including keratinocytes, melanocytes, Langerhans cells, and Merkel cells. Most numerous are the keratinocytes, which serve to produce keratin in the process of keratinization or cornification.[6]

TABLE 1.1
Estimated Dose and Contribution per Exposure for Skin Absorption versus Ingestion

		Dose (mg/kg)					
		Case 1[a]		Case 2[b]		Case 3[c]	
Compound	Concentration (mg/L)	Dermal	Oral	Dermal	Oral	Dermal	Oral
Toluene	0.005	0.0002	0.0001	0.0004	0.005	0.002	0.0002
	0.10	0.005	0.003	0.008	0.0095	0.033	0.0045
	0.5	0.02	0.0014	0.04	0.048	0.17	0.023
Ethylbenzene	0.005	0.0003	0.0001	0.0004	0.0005	0.002	0.0002
	0.10	0.005	0.003	0.008	0.0095	0.036	0.0045
	0.5	0.03	0.014	0.04	0.048	0.18	0.023
Styrene	0.005	0.0002	0.0001	0.002	0.0005	0.001	0.0002
	0.10	0.003	0.003	0.005	0.0095	0.023	0.0045
	0.5	0.02	0.02	0.02	0.048	0.11	0.023
		Relative Contribution (%)					
Toluene	0.005	67	33	44	56	91	9
	0.10	63	37	46	54	89	11
	0.5	59	41	45	55	89	11
Ethylbenzene	0.005	75	25	44	56	91	9
	0.10	63	37	46	54	89	11
	0.5	68	32	45	55	89	11
Styrene	0.005	67	33	29	71	83	17
	0.10	50	50	35	65	84	16
	0.5	59	41	29	71	83	17

Source: Reproduced from Brown, H.S. et al., *Am. J. Public Health*, 74(5), 479, 1984. With permission.

[a] 70 kg adult bathing 15 min, 80% immersed (skin absorption); 2 L water consumed per day (ingestion).

[b] 10.5 kg infant bathed 15 min, 75% immersed (skin absorption); 1 L water consumed per day (ingestion).

[c] 21.9 kg child swimming 1 h, 90% immersed (skin absorption); 1 L water consumer per day (ingestion).

The epidermis is divided into several layers based on the behavior of the keratinocytes. The *basal layer* consists of germinative cells, which are extremely active metabolically, divide rapidly, and display many mitotic figures and label with thymidine. Above this layer are two differentiated layers of viable cells, the *spinous* or *prickle cell layer* and the *granular cell layer.* The outer layer, the *stratum corneum*, consists of a multicellular membrane of dried, flattened keratinocytes, which have no metabolic activity and represent the nonviable end product of the synthetic activity of the lower layers. This layer is the main barrier site in the skin for water, electrolytes, most other chemicals, microorganisms, and electrical resistance. The epidermis also provides some mechanical resistance to stretching.[6] Damage to the epidermis can allow many toxic substances to penetrate the body easily. These substances include solvents, pesticides, petroleum products, bacteria, and viruses, which can cause chemical sensitivity.

Keratinization begins with the synthesis of fibrous prekeratins in the basal layer: aggregated filaments run the length of the cell by the time it reaches the spinous layer. In the granular layer, protein granules are formed that contribute to the process. In the stratum corneum, the cells are cornified and filled with a filamentous network of keratins embedded in a matrix containing mucus and lipids surrounded by a highly chemically resistant thickened cell envelope. Between the cornified cells is an intercellular material that contains ceramides that appear to contribute to the permeability barrier. These structural components are closely related, and the complex multicomponent system results in the effectiveness of the barrier.[7,8] Retinoids have been shown to profoundly alter

TABLE 1.2
Compounds and Recommended Dermal Absorption Fractions

Compound	Dermal Absorption Fraction (ABS_d)
Arsenic	0.03
Benzo(a)pyrene	0.13
Cadmium	0.001
Chlordane	0.04
DDT	0.03
Lindane	0.04
PAHs	0.13
Pentachlorophenol	0.25
Semivolatile organic compounds	0.1

Nonresidential (Outdoor Industrial Worker) Exposure Scenario

Under the industrial scenario, the department has chosen to protect the full-time adult worker whose daily activities are related to outdoor maintenance. Since adult workers will have only their arms, hands, and face exposed, the skin surface area is reduced to 3300 cm^2 with an adherence factor of 0.2 mg soil per cm^2. The department proposes to use USEPA's default value of 225 days/year for the exposure frequency and 25 years for exposure duration. Outdoor worker scenarios are for both carcinogens and noncarcinogens and based on adult-only exposures.

Source: Reproduced from USEPA, Supplemental Guidance for Developing Soil Screening Levels for Superfund Sites, Final, 2002. With permission.

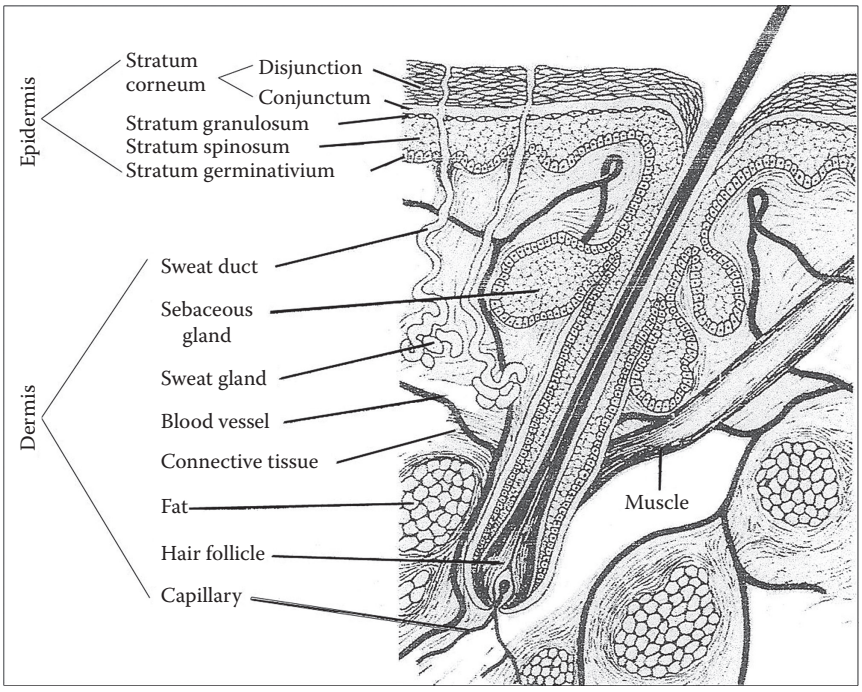


FIGURE 1.1 Diagram of a cross section of human skin. (Reproduced from Emmett, E.A., Chapter 15: Toxic responses of the skin, in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, eds. M.O. Amdur, J. Doull, and C.D. Klaassen, 4th edn., Pergamon Press, New York, 1991, p. 465. With permission.)

the differentiation pattern of human epidermal keratinocytes, but the underlying biochemical basis for this change is unknown.[9] The water content of stratum corneum varies from around 10% to 70%, depending particularly on external environmental conditions. The chemical composition and structure are significantly different in certain skin diseases such as psoriasis.

The epidermis contains a constantly renewing cell population. In the human, the transit time from mitosis within the viable epidermis is about 12–14 days and within the stratum corneum about 15 days, for a total of about 28 days. In psoriasis, however, it may be as short as 4 days. These times are shorter for certain experimental animal species, most of which have a much thinner epidermis than humans.[10]

Roughly, 5%–10% of the epidermal cells are Langerhans cells. These are mesenchyme-derived dendritic cells that form a network in the viable dermis. They are responsible for antigen recognition and processing.[10]

Melanocytes are dendritic cells derived from the neural crest that are responsible for the synthesis of melanin in a specialized organelle called the *melanosome*. These organelles are transferred to keratinocytes, where they are aggregated and destroyed by phagolysosomes in Caucasians but not in Negroids or Australoids. A number of morphologic differences exist between the races both in the production and lysis of melanosomes and in the degree and type of melanization. The role, if any, that pigmentation plays in modifying chemical damage in the skin is still contentious, although melanin has a major role in protection against ultraviolet (UV) radiation. Melanin is both an oxygen scavenger and a sunscreen. It may also function to remove the mutagenic and carcinogenic toxic oxygen from the surrounding keratinocytes and Langerhans cells.[11] These substances appear to be less relevant in chemical sensitivity, since no matter the amount of pigment, they appear to afford no advantage in the retardation, development, or propagation of chemical sensitivity.

The epidermis is separated from and attached to the dermis by a basal lamina. The epidermal–dermal junction has a characteristically ridged shape. The underlying dermis consists of loose connective tissue, which envelopes the body in a strong, flexible envelope. The dermis contains collagen, reticulin, and elastin fibers, glycosaminoglycan ground substance, and a variety of scattered cells including the predominant fibroblast, as well as macrophages, mast cells, and lymphocytes. The dermis actively determines wound repair, resulting in a balance between macrophage and fibroblast function. The ground substance provides a slow diffusion medium for constituent fluids.[11] It appears to be involved in chemical sensitivity.

The dermis has substantial vascular plexuses, unlike the epidermis, which is avascular. Thus, if bleeding is produced, the dermis must have been penetrated. The dermal blood supply is substantially greater than required for its metabolic activity; thus, dermal vessels can play an important role in thermoregulation by controlling the dissipation of heat to the surface,[12] and thus a role in chemical sensitivity.

Patients with chemical sensitivity and chronic degenerative disease are usually hypothermic. Their core temperature may run from 89°F to 97°F. They often have cold hands and feet. They may also be cold over the entire body. It is thought that this coldness is not only a temperature deregulation in the central mechanism but also a deregulation of the peripheral vessels.

The dermis has a plexus of lymphatics, which drain to the regional lymph nodes and the thoracic duct. Of course, these appear to be involved in chemical sensitivity and chronic degenerative disease. These lymphatics respond well to lymphatic massage and appear to be opened by this process allowing the patient not only to feel better but also to function better.

The dermis has abundant sensory and sensorimotor nerves,[12] which also respond to pollutant entry and injury. This entry often signals the onset of toxicity resulting in itching, pain, and fatigue. The toxicity exposure can travel up the spinal cord to the brain disturbing the central homeostatic mechanism or result in a regional spinal reflex for the pain and itching. The peripheral sensory nerves can be involved in the initial development of chemical sensitivity and chronic degenerative disease before the immune system is involved. In some patients, neural sensitization can account for the onset of chemical sensitivity. However, the initial sensitization in the individual with chemical sensitivity usually comes from the olfactory and respiratory nerves or the

gastrointestinal mucosa nerves. Less frequently, this initial sensitization comes via the urogenital system. Not only are the sensory nerves involved in chemical sensitivity but also the autonomic nervous system is involved.

There are a number of epithelial structures known collectively as the *epidermal appendages*, which are extensions of modified epidermal cells into the dermis. These include the eccrine sweat glands, apocrine sweat glands, hair follicles, and sebaceous glands.

The eccrine sweat glands have a secretory portion located in the hypodermis immediately below the dermis and have a coiled duct leading to the epidermal surface. They are located over the entire body surface and produce sweat, a dilute aqueous solution whose function is evaporative cooling in thermoregulation and elimination of toxics. Eccrine sweating is produced by thermal, emotional, and gustatory stimuli, and the glands are under parasympathetic cholinergic control. However, there is controversy, and the anatomists like Netter[13] say it is postsynaptic sympathetic control.

Apocrine glands, which have no known function, are confined to the axillary areas, genitalia, and nipples. Their secretion is emptied into the pilary (hair) canal. Initially odorless, sweat acquires odor through bacterial decomposition[12] and toxic overload. Often, the patient with chemical sensitivity has a very pungent odor emanating from these glands. This sweat is stimulated by both the sympathetic nervous system and the central nervous system. Usually, the sweating is suppressed or damaged with pollutant overload. We often have to retrain our patients with chemical sensitivity and chronic degenerative disease to sweat. Once this is accomplished, the detoxification systems seem to work better and the patient improves significantly. Initially, when starting to sweat again, the patient often exudes strong noxious odors.

Secondary to this neurosensitization, or almost simultaneously, the immune system becomes involved. This involvement occurs either indirectly with the neural sensitization occurring and then nerve impulses trigger the mast cells, lymphocytes, and glia cells or directly by pollutant entry and injury of this immune system through the innate immune system.

Hair follicles are located over the entire body surface. Each follicle appears to have the potential to be a terminal hair, as in the scalp or the pubic region after puberty. Before puberty, the hair is vellus or lanugo. The deepest portion of the hair follicle is the germinal matrix, one of the most metabolically active tissues in the body, which is surrounded by a highly vascularized connective tissue. Often the patient with toxicity presents with hair loss probably due to damage in this area. The uppermost cells from the proliferating germinal follicle are pushed up into the external root sheath of the hair follicle, differentiate, become keratinized, and form the hair that protrudes from the canal.

The keratin of hair and of nail, though similar, is immunologically distinct from that of the stratum corneum, has a higher cystine content, and may have an additional matrix protein with a high sulfur content that serves to cross-link filament bundles.[12] When an individual is in a state of chemical sensitivity or chronic degenerative disease, his or her nails can develop holes or wedges, horizontal and vertical ridges, white and black spots, or other abnormalities. We analyze these types of hair and nails for toxic metals and minerals in order to evaluate part of the toxic total body pollutant load. To get as recent a picture of toxic load as possible, we clip the hair to be analyzed as close to the scalp as possible.

Sebaceous glands are associated with hair follicles except for the palms, soles, and dorsum of the foot. Sebaceous gland cells accumulate lipids, and as they break down, they discharge a holocrine secretion, sebum, into the pilary canal. These glands are under hormonal control. Sebum is expelled partly by the contraction of the small arrector pili muscles. Lipids on the surface of the skin vary in quantity, depending on both the amount of sebum and the numbers of desquamating epidermal cells, which also contribute lipids. In areas where sebaceous glands are active and abundant, such as the scalp, forehead, and upper back, up to 90% of the surface lipids may originate from sebum.[12] Many oily layers can trap solvents and the fat can collect chemicals seen in the chemical sensitivity. Many patients with chemical sensitivity have oily skin, but the skin of others is very dry and scaly.

There are substantial differences in the skin from one region of the body to another. The thickness of the epidermis varies greatly; whereas it is about 0.06 mm over much of the body, on the

palms and soles the epidermis may be several millimeters thick. The distribution and activity of the appendages, the vascular and nerve supply, and other characteristics also vary markedly. These structural differences are matched by functional differences—for example, marked variations in percutaneous absorption occur.[12]

The skin is one of the body's largest organs and represents about 10% of body weight. It is an important contributor to the function, metabolism, and integrity of the whole organism,[12] and the physician should not disregard it in the overall toxicity of the patient with chemical sensitivity and chronic degenerative disease.

III. POLLUTANT INJURY TO THE PHYSIOLOGY OF THE SKIN

The skin of the individual with chemical sensitivity and chronic degenerative disease is an important interface between the internal organs and environmental pollutants.[14] In some individuals with chemical sensitivity, however, the skin, consisting of the oily layer, epidermis, dermis, and appendages, as well as blood vessels and neuronal components, can be damaged or deregulated by pollutant entry and injury. Once damage occurs, chemical sensitivity will be initiated or exacerbated.

Chemical injury to the skin is influenced by a large number of environmental factors that alter the interface. These include variations in heat and humidity, friction, pressure, trauma, abrasion, wind, vibration, UV and visible radiations, electrical current, and coincident effects of infestations or infection. There are morphologic, physiologic, and biochemical protective and homeostatic mechanisms in the skin; these include the epidermal barrier, eccrine sweating, phagocytic cells and processes, metabolic detoxification, specific immunologic processes, and protective mechanisms, such as melanin pigmentation, which protect against UV radiation. These may vary on a genetic or phenotypic basis and may be influenced by systemic or local nutrition or disease or by the effects of other toxic substances. For example, individuals with atopy (characterized in part by infantile and adolescent eczema, hay fever, and asthma) seem particularly prone to develop irritant dermatitis. The actual expression or degree of expression of a toxic effect may thus be the result of a markedly complex set of local and general factors.

The oily layer of the skin of the individual with chemical sensitivity can be damaged by contact with solvents in bathing water or by contact with chemicals contained in a variety of common products used in the home or workplace. For example, bleaches, detergents, dishwashing liquids, floor cleaners and waxes, furniture polishes, metal cleaners, oven cleaners, pesticides, shampoos, soaps, toilet cleaners, window cleaners, and scouring pads are household contact irritants. Allergic contact sensitizers are perfumes, cosmetics, preservatives (e.g., parabens), rubber products (mercaptan, thorium), medications (neomycin, benzocaine, mercury), leather (formaldehyde, dichromate, polychlorinated biphenyl [PCB]), chromes, resins, and nickel. Once the oily layer of the skin has been damaged, superabsorption of these and other toxic substances may follow. Often, the patient with chemical sensitivity and chronic degenerative disease has extremely dry skin, which results in graded dysfunction. Some have excess oils when the skin appears to be struggling to overcome the chemical sensitivity. Their skin may have an excess in oil, keeping their hair darker than normal and collecting oil in their clothes.

Metals known to cause skin reactions include aluminum (Al), antimony (Sb), arsenic (As), beryllium (Be), boron (Bo), cadmium (Cd), chromium (Cr), cobalt (Co), copper (Cu), gold (Au), mercury (Hg), nickel (Ni), palladium (Pd), platinum (Pt), selenium (Se), silica (Si), silver (Ag), tellurium (Te), thallium (TI), zinc (Zn), and zirconium (Zr). These are found to be elevated in many patients with chemical sensitivity by both hair and intracellular blood analysis. They are particularly emphasized coming from metal implants. Most patients with metal in their body have an area around the implant that is saturated with metals.[15] Some of these may be found in the hair and/or skin. Challenge tests with chelates will often cause all or many of the heavy metals to be found in the urine.

Toxic chemicals known to produce skin reactions include alcohol, balsam of Peru, benzocaine, butyric acid, cephalosporin, chloramphenicol, chlorproma diethyltoluamide, epoxy resin,

gentamicin, lindane, mechlorethamine, menthol, neomycin, nickel, parabens, penicillin, plastic additives, propylene glycol, polysorbate, salicylic acid, sodium sulfate, sulfur dioxide, and streptomycin. Even compounds that are generally considered well tolerated, such as sodium benzoate, ascorbic acid, and acetic acid, are known to cause skin reactions in selected patients. Often, the reaction to ascorbic acid depends on sensitivity to the food source from which it is made, whether it is corn, tapioca, potato, or beets. This sensitivity would also be in addition to its chemical property.

In addition to their ability to damage the oily layer of the skin, toxic chemicals and metals can also damage the epidermis, which is a stratified cellular layer that is constantly evolving and forming the stratum corneum, which functions as a protective barrier. Although this barrier is supposed to guard the individual from absorption of harmful substances, it may be ineffective in some patients with chemical sensitivity. This is particularly so in patients exposed to solvents like hexane, xylene, toluene, and benzene.

The dermis, which also may be damaged in some patients with chemical sensitivity, lies underneath the epidermis and is composed of connective tissue, fibroblasts, collagen, and elastic fibers. It houses the appendages that include the sweat glands, pilosebaceous units, and apocrine glands. In some patients with chemical sensitivity, all of these often function abnormally. Hence, these individuals are vulnerable to pollutant exposure, and pollutant injury to these appendages can have significant effects. As shown in other chapters, the cold nature of the individuals with chemical sensitivity, as manifested by cold skin, is well documented. Their ability to sweat can be delayed or suppressed, and often their skin is dry. This inability to sweat easily may be one of the main reasons that chemicals remain in the body of patients with chemical sensitivity, further increasing their susceptibility to chemical exposure.

Not only can pollutants damage the oily layer of the skin or the epidermis or the dermis separately, but also all of these layers may be simultaneously injured. Often a large subset of patients with chemical sensitivity is seen with simultaneous damage occurring in various layers of the skin.

Body and skin temperatures are controlled by the rate of blood flow and the radiation of heat through small vessels. Although sweating may offer a defense against chemical injury by diluting xenobiotics, it may also increase the state of hydration of the barrier, which will then enhance the absorption of other toxic agents. Most patients with chemical sensitivity do not sweat. The need to sweat emphasizes a significant path to detoxification when the patient can do so.

Two types of skin are involved in chemical sensitivity. One is the glabrous and the other is the hairy skin. The glabrous skin of the palms and soles has a thick stratum corneum with sweat glands and encapsulated nerve endings, but no hair follicles or sebaceous glands. Many individuals with chemical sensitivity experience pain when they stand on their bare feet, and often the glabrous skin is found to be involved in their discomfort. The hairy type of skin has relatively thin stratum corneum with hair follicles and sebaceous and sweat glands, but no encapsulated nerve endings. It is prone to greater absorption and sensitization of anything it contacts. The individuals with chemical sensitivity that we have seen frequently experience this kind of excessive absorption.

As a target organ, the skin of the individual with chemical sensitivity is capable of responding in a variety of pathologic patterns that may involve specific cellular and structural components.[14] The cellular elements of mesenchymal origin are involved in wound healing and play an important role in both the development and maintenance of the fibrous structures. For the person with chemical sensitivity, these elements also provide a second-line defense against injury by chemical stimuli, physical agents, and microorganisms. Pollutant injury may retard healing in some individuals with chemical sensitivity.

The ground substance in the dermis transfers nutrients and metabolites to and from structures within its surroundings and is strongly influenced by vitamin C, which is depleted in 20%, and possibly more, individuals with chemical sensitivity. Nutrient deficiency (see the nutrition section in *Reversibility of Chronic Disease and Hypersensitivity: Treatment Options of Chemical Sensitivity*[16]), as seen in patients with chemical sensitivity, can adversely affect the function in not only these areas but also any area of the body.

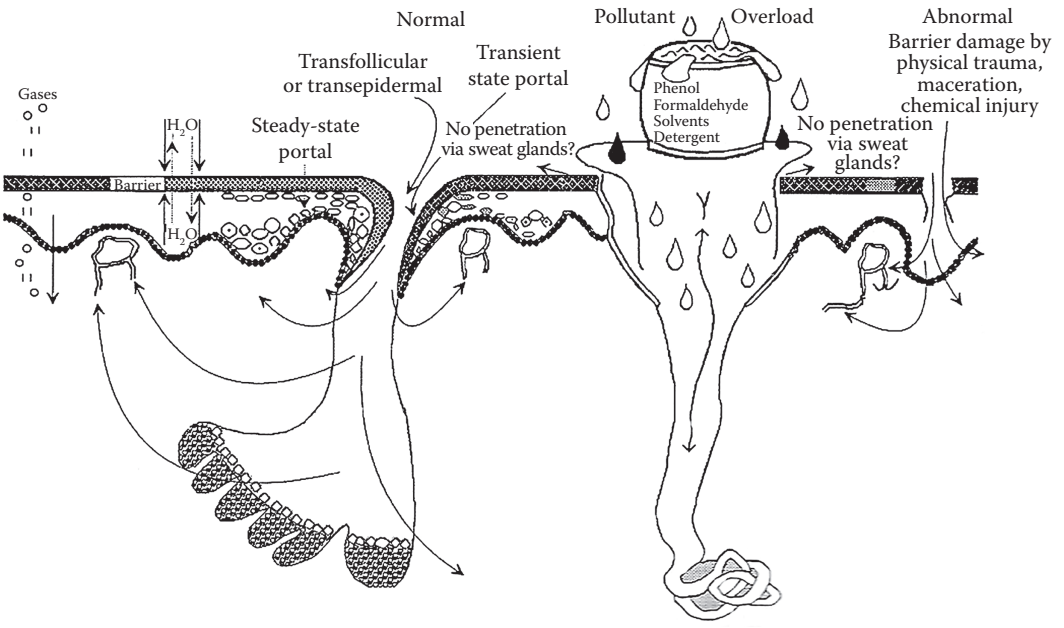


FIGURE 1.2 Routes of and factors that enhance percutaneous absorption of toxic chemicals and other microbials after pollutant injury in the chemically sensitive individual. Absorption depends on the properties of the skin, the substance(s) to be absorbed, and the environment (vehicle). Absorption is enhanced by the following factors: (1) the breaking barrier, (2) increasing hydration, (3) increasing temperature, (4) the location or site on the body surface, (5) reservoir capabilities, (6) blood flow, and (7) many chemical factors including concentration, molecular size, pH, state of ionization, lipid solubility, and biotransformation systems. (From Rea, W.J., *Chemical Sensitivity*, Vol. 3: *Clinical Manifestations of Pollutant Overload*, Lewis Publishers, Boca Raton, FL, 1996, p. 1696. With permission.)

The skin has two routes of absorption that can be potentially damaged in the individual with chemical sensitivity—transfollicular and transepidermal (Figure 1.2). Frequently, the chemical will first pass through the pilosebaceous route and through the epidermis. The facial hair of the beards of patients with chemical sensitivity is prone to trapping pollutants. Then the patient absorbs the chemicals through the skin. Normal skin without a beard offers the best protection against compounds of strong polar nonelectrolytes. It offers poor protection against lipid-soluble substances (solvents), low-molecular-weight compounds, and nonelectrolytes.

Several factors enhance the absorption of chemicals through the skin and are seen to be active in a subset of patients with chemical sensitivity (Table 1.3). These factors are body site (thin skin, face,

TABLE 1.3
Factors Enhancing the Absorption of Chemicals through the Skin

Body site	Thin skin, face, genitalia, and folds
Integrity of skin	Damage by trauma, inflammation, dehydration
Occlusion	Wearing dry-cleaned clothing (tetrachloroethylene contaminated), wearing clothing contaminated with pesticides, making contact with plastic wrapping
Vehicle	Urea, chlorpyrifos, ointment bases
Chemical factors	Solubility, pH concentration
Skin-burning chemicals	Alkyl mercury, cement, chromic acid, ethylene oxide, hydrofluoric acid, white phosphorus

Source: EHC–Dallas, 2010.

genitalia, and folds); integrity of skin damaged by trauma, inflammation, or dehydration; occlusion (wrapping with plastic, wearing dry-cleaned clothes [tetrachloroethylene]); vehicle (urea, chlorpyrifos, and ointment bases); and chemical factors (e.g., solubility, pH, and concentration). In addition, certain chemicals burn the skin. These include, but are not limited to, alkyl mercury compounds, cement, chromic acid, ethylene oxide, hydrofluoric acid, white phosphorus, and probably many more. Some chemicals cause a burning sensation but do not actively burn the skin. This symptom seems to have a poor prognosis in the patient with chemical sensitivity. Most likely, sensory nerve damage has occurred.

Toxic chemicals are more readily absorbed when in contact with intertriginous areas of the body (groin, inframammary, axillary, perianal) in contrast to the glabrous skin. Toxic chemicals produce varied effects on the skin, for example, increased melanin has been produced by arsenics,[17] busulfan,[17] tar,[17] and photochemical agents.[17] Storer et al.[18] applied many elements in coal tar that are commonly used in the treatment of skin lesions to the skin of volunteers and then demonstrated the presence of these elements in peripheral blood samples taken from the volunteers. Individuals with chemical sensitivity who have undergone minute exposures of toxic substances experience problems that suggest, in some cases, that superabsorption has occurred. In other cases, however, these problems are probably sensitization reactions.

There are many recently described conditions to toxic chemicals. Rantanen[19] described the cause of the sofa–chair dermatitis epidemic as sensitivity to dimethyl fumarate. Kovacic and Somanathan[20] showed that oxidative stress and electron transfer of many chemicals caused dermatitis.

De Groot et al.[21] found that for short-term use of topicals with formaldehyde levels 200–300 ppm in them is for normal skin. These levels are not safe for long-term use and may be able to induce chemical sensitivity.

According to Nedorost,[22] when contact dermatitis involves the hands and feet only, rubber chemicals and chromates are the most common allergens.

Metal working fluorides (MMFs) are complex mixtures of chemicals. Many contain biocides and aromatic chemicals in waters and oils. Reduced penetration was found in the oil mixtures and increased in water, which would allow for enhanced systemic and dermal reactions.[23]

Sensitizers to the skin like cinnamaldehyde induce upregulation of CD-86, CD-54, IL-8, or IL-1-B in human myeloid cells and peripheral monocytes–derived dendritic cells.[24] Fukuyama et al.[25] found that 2,4-D was a respiratory allergen while BRP and furathiocarb are contact allergens. White et al.[26] found that individuals with atopic chemical dermatitis and sensitivity to fragrances have an abnormal tolerance of dietary haptens. Haptens may occur with food protein tolerance by binding to the soluble protein to alter its configuration and immunogenic profile.

This tolerance breaks down in patients with chemical sensitivity. With fragrance overload and food sensitivity, the total pollutant load increases in these patients. They then become more sensitive to more and more foods. Furthermore, skin exposure to weak and moderate allergens induces interferon-gamma (IFNγ) production by lymph node cells of DC4+ T cell–depleted mice.[27]

The skin has a versatile group of defenses against penetration by chemical agents, fluid loss from the body, thermal stress, solar radiation effects, physical trauma, and against infection by microbial agents. In individuals with chemical sensitivity, these defenses may be inherently weak or defective, making these individuals vulnerable to pollutant exposure. In addition, these defenses may be weakened or damaged as a result of an exposure itself. These skin defenses are characterized on the basis of morphological, physiological, and biochemical processes.

Morphologically, the intact stratum corneum provides a significant defense against penetration by chemical agents and against body water loss. It is a physical barrier to invasion by microorganisms, and its surface lipids provide some bacteriostatic protection. The intact skin is infected with difficulty. Pigment components of the melanocytes found among the lowest layers of the epidermis are an important defense against UV radiation, which causes fragmentation and destruction of the elastic tissue fibers. UV- and chemical-induced aging of the skin, actinic keratosis, and skin cancer physiologically effect long-chain ($C_{16–18}$) fatty acids derived from sebaceous secretions, which have bacteriostatic

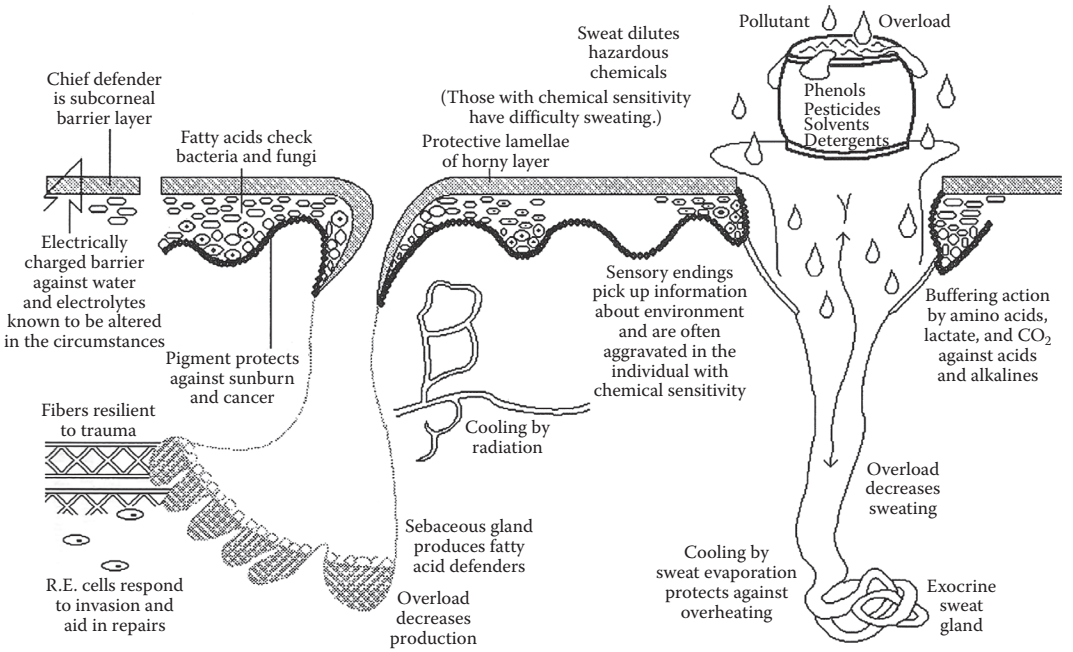


FIGURE 1.3 Natural defenses of intact skin that can be damaged by pollutant overload in individuals with chemical sensitivity. (From Rea, W.J., *Chemical Sensitivity*, Vol. 3: *Clinical Manifestations of Pollutant Overload*, Lewis Publishers, Boca Raton, FL, 1996, p. 1700. With permission.)

properties on a limited group of organisms (Figure 1.3). Odd-numbered carbon-chain fatty acids such as $C_{9,11,13}$ secreted by the sebaceous glands have fungistatic properties.[14] These are often deficient in the patient with chemical sensitivity, making some more prone to *Candida albicans* and TOE infections.

Elastic and collagen fibers provide the skin with physical resiliency and/or a fibrous barrier against trauma. They also provide support for the blood, nerves, and appendages. At times, these fibers are damaged in some patients with chemical sensitivity, resulting in burning and itching skin.

IV. MECHANISMS OF ACTION OF TOXIC CHEMICALS

The mechanisms of actions of toxic chemicals on the skin of individuals with chemical sensitivity are diverse. However, immune and nonimmune, usually neural sensitization, response are involved as shown in Chapters 2 and 4 of *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*.[28]

Xenobiotics, including small molecular weight compounds, are capable of any of the four immunologic reactions described in Chapter 3 of *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*.[29] In type I, circulating antibodies produced through mediators of B cells localize in the skin. When an incitant is reintroduced, it causes a release of vasoactive amines, such as histamine from basophils or mast cells that, in turn, induce a wheal and flare reaction or urticaria. Haptens, such as hexavalent chromium or sesquiterpene, form. These are then conjugated with either covalently or noncovalently bound epidermal protein, and this conjugate, in turn, is processed in Langerhans' cells or macrophages that then migrate via the afferent lymphatics into the paracortex of the draining lymph node. There, these cells interdigitate with the many T cells exposed to the antigens. The T cells then present the clonal expansion and migrate to the skin. When the skin is reexposed to a hapten, a complete antigen is formed by conjugation and reacts with the T cell. Cytokines are then released. Following the release of cytokines, there is a reaction in the epidermis characterized by an infiltrate of mononuclear cells

and microvesicle formation with edema. The response may be followed by an inflammatory reaction in the dermis, as seen in a subset of individuals with chemical sensitivity. These are the eczematous characteristics of allergic dermatitis.

A primary target cell of toxic chemicals is the T-lymphocyte, specifically the T suppressor cells, which are low in a subset of individuals with chemical sensitivity[30] (see Chapter 3 of *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*,[29] and *Reversibility of Chronic Disease and Hypersensitivity: Treatment Options of Chemical Sensitivity*[31]). These lymphocytes can be damaged and destroyed by free radicals produced by the chemicals. Subsequent production of massive amounts of antibodies may occur, as seen in the rapeseed oil-aniline disaster in Spain,[32] or the lymphocytes may just become sensitized with excess antibody production. With either outcome, extreme sensitivity reactions may follow.

The mast cells can be triggered by the direct stimulus of a chemical such as DDT, either by a neurological impulse or an immune reaction or both. The consequence is lipid peroxidation of the cell membrane and mitochondria, which can result in leakage or inhibition of function with impairment of the electron transport system and functional ATP. After degranulation of the mast cell, inflammatory mediators are released, with subsequent clinical sequelae of vascular spasm and, eventually, inflammation. Mast cells can be destroyed and/or sensitized. This sequence has been observed in individuals with chemical sensitivity.

The mast cells can also be triggered by the peripheral sensory, spinal sensory, and afferent autonomic nerves that have their protein kinase phosphorylated. This process can increase their sensitivity up to 1000 times.[33] This process can trigger the mast cells nonimmunologically resulting in a similar chain of events as the direct triggering just described.

Increased total body pollutant load can cause increased vascular permeability with subsequent edema, bruising, petechiae, and purpura in a large subset of individuals with chemical sensitivity. Vascular spasm with blanching or cyanosis can also occur, resulting in Raynaud's phenomena in a large subset of individuals with chemical sensitivity. This vascular spasm then results in further lipid peroxidation by free radicals with damage to more cell membranes. Peroxidation requires large amounts of oxygen, thereby reducing the availability of oxygen to cells and tissues for metabolism. This deprivation of oxygen results in a state of localized tissue hypoxia, which results in further vascular spasm followed by cellular edema. This sequence of events explains why some individuals with chemical sensitivity respond to oxygen supplementation. In addition, this condition of oxygen depletion compromises functional cellular competence and is further stressed by the requirement of supplemental oxygen in the formation of cytochrome P-450 oxidase. Inflammatory vasculitis occurs. Other inflammatory mediators are released via the phospholipid–fatty acid cycle with formation of free radicals, induction of lipid peroxides, peroxidation of cell membranes, and formation of prostaglandins and leukotrienes, leading finally to thrombosis. Some of the mast cell modulators include substances such as cyclic AMP, prostaglandins, phosphodiesterase inhibitor, and calcium channel blockers. Benign mast cell disease can occur. Meggs et al.[34] have devised a serological indicator (oligoclonal IgG) for diagnosing benign mast cell disease (mastocytosis) versus malignant mast cell tumors.

Hypersensitivity reactions are common to chemicals involving both the innate and adaptive immune systems.[35]

It has been shown that contact dermatitis is mediated by hapten-specific CD_8 T cells and downregulated by CD_4 T cells. Weak and moderate contact allergens can induce them.[27,36] These reactions in contact dermatitis are the delayed type of hypersensitivity reactions that are mediated by hapten-specific T cells. During the sensitization phases, CD_4 and CD_8 are activated in the draining lymph nodes by presentation of haptenated peptides by the skin dendritic cells. Inflammation occurs.[36]

In response to the upregulated sensitizers, some genes appear to be involved. These include HNOX-1 and NQa1 genes.[37]

Monoterpene hydroperoxides (i.e., limonene and pinene) formed by autoxidation of common fragrance terpenes are strong dermatitis allergens. These now can be detected by mass spectrometry.[38] Breath analysis of our patients with chemical sensitivity has detected these in 30%.

4,4′-Diaminodiphenylmethane and isocyanates, usually from industrial exposures, are sensitizers.[39]

Enzyme detoxification systems involved in toxic chemical overload of the skin in patients with chemical sensitivity include cytochrome P-450 oxidase, superoxide dismutase, aryl hydrocarbon hydrolase, gamma glutamyl transpeptidase, lipoxygenase, epidermal cyclooxygenase, epoxide hydrolase, ornithine decarboxylase, and uroporphyrinogen decarboxylase (see Chapter 4[40] of *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*).

Enzyme detoxification nutrients in the skin include glutathione; glutathione peroxidase; vitamins E, C, D, F, β-carotene, and A; L-cysteine; methionine; selenium; chromium; zinc; copper; manganese; magnesium; and potassium. Each, or all of these, may be depleted by direct toxic effects or overutilization of the detoxifying mechanisms of systemic malnutrition, thus causing or propagating the skin disease. The experiences of the EHC-Dallas have encompassed the full spectrum of skin pathology described in the textbook of medicine. When infection and parasitic organisms have been excluded, most entities in this spectrum can often find their etiology in nutritional imbalance with food and chemical overload.

Sensitization of the peripheral sensory nerves is one of the major areas of sensitization for toxics to affect any skin. Many receptors including the vanilloid, muscarinic, GABA, and sodium–lithium–potassium–calcium–magnesium channels can be involved and triggered by pesticide, solvent, or formaldehyde exposure. These toxics trigger capsaicin and other receptors that release glutamate–aspartate substances. These aid normal neurological function, but when in excess, they act as very toxic excitotoxins. These substances then help excess Ca^{++} to enter the cell and its mitochondria resulting in loss of energy, excess oxidized chemicals, and a decrease in ATP. This entry will clinically cause itching, pain, and fatigue. If phosphorylation to the protein kinase occurs, sensitivity of the peripheral and autonomic nerves and receptors can increase 1000 times rendering that area of the skin or the whole skin hypersensitive. (See neuromuscular, cardiovascular, gastrointestinal, and respiratory chapters for more information.) Other processes that can trigger hypersensitivity can be the release of prostaglandin E_2, tumor necrosis factor alpha (TNF-α), interleukin-1 β, and membrane-derived cAMP.

Neurological triggering of the immune and other systems may occur. Mast cells, glia cells, and lymphocytes and nodes can be stimulated neurologically resulting in access to the immune system.

Pickard et al.[41] felt that dissimilar sensitizing potencies of chemicals like 2,4-dinitrachlorobenzene and 2,4-dinitrothiocyanobenzene in the outer epidermal biochemical redox barrier were part of the innate immune defense mechanism that defend against sensitization.

A. Biotransformation

The skin, and particularly the epidermis, is an actively metabolizing organ that is capable of significant biotransformation of xenobiotics.[42] A number of studies have addressed the presence of an aryl hydrocarbon hydroxylase (AHH) activity in the skin (shown in later chapters); benzo(a)pyrene metabolites including epoxide may be formed in the skin. This activity is inducible.[43] Most of the enzymes are present in the lower epidermis rather than the dermis. The total AHH activity of skin toward benzo(a)pyrene is about 2% of that of the liver.

Metabolic transformation may affect topically applied drugs as well as air or contact deposited chemicals. For example, it has been estimated that from 16% to 21% of a dose of glyceryl trinitrate applied to monkeys is biotransformed by the skin.[44] This principle applies to a myriad of other chemicals that deposit in individuals with chemical sensitivity.

In addition to metabolic transformation, substances in the superficial layers of the skin are subject to photochemical reactions if they absorb UV light or visible radiation.

Biotransformation in other organs is also important in the production of toxic effects in the skin. An example of how a number of processes may be involved is porphyria cutanea tarda, which

is characterized by blistering and fragility of the skin, photosensitivity, changes in pigment, and excessive hirsutism. An epidemic of this disease occurred among several thousand people in southeastern Turkey in the late 1950s when, during a famine, wheat treated with hexachlorobenzene was eaten rather than planted.[45]

Hexachlorobenzene produces excessive accumulation of uroporphyrins and coporphyrins in liver as a result of interference with porphyrin metabolism.[46] Consequently, porphyrins accumulate in various tissues including the skin. These substances rendered the skin photosensitive as a result of intense absorption of porphyrins and the 400 nm, SORET band, with subsequent photo activation and damage to cell membranes and/or cell constituents.[47] We see many patients with chemical sensitivity who have sun sensitivity and have to keep their skin covered.

V. TOXIC SKIN REACTIONS

There are many other toxic reactions of the skin. They will now be discussed.

A. Irritant Responses

By the term *cutaneous irritant*, we generally refer to an agent that produces a local cutaneous inflammatory response (dermatitis) by direct action on skin without the involvement of an immunologic mechanism. In this sense, *irritation* is not used to describe noninflammatory reactions such as subjective sensations (itch, burning, etc.) or more subtle biochemical or histologic changes such as epidermal thickening, although these could represent variations of the same effect. Irritation of the skin is important, and it is commonly thought to account for about 60%–80% of the burden of clinically recognized human contact dermatitis, although this figure no doubt varies from location to location. Most of the remaining contact dermatitis represents allergic contact dermatitis. Contact dermatitis is manifest by signs of erythema (redness) and edema in experimental test animals. In humans, more varied responses are seen, and erythema and edema frequently progress to vesiculation, scaling, and thickening of the epidermis. Histologically, the hallmark is spongiosis or intracellular edema of the epidermis.[48]

It is useful to distinguish two reasonably distinct types of cutaneous irritation, acute irritation and cumulative irritation, and two related conditions, corrosion and phtotoxicity.[49,50]

1. Acute Irritation

A local, reversible inflammatory response of normal living skin to direct injury caused by a single application of a toxic substance, without the involvement of an immunologic mechanism. Acute irritation is produced by a relatively large number of substances of varying chemical types, many of which are highly chemically active such as relatively strong solvent acids and bases. However, no demonstrably reliable method for assessing irritancy based on chemical structure has been advanced.

2. Cumulative Irritation

Reversible irritation resulting from repeated or continued exposures to materials that do not in themselves cause acute irritation.

3. Corrosion

Direct chemical action on normal living skin that results in its disintegration and irreversible alteration at the site of contact; corrosion is manifested by ulceration and necrosis with subsequent scar formation.

4. Phototoxicity (Photoirritation)

Irritation resulting from light-induced molecular changes in the structure of chemicals or light applied to the skin.

VI. DERMAL VASCULAR RESPONSE TO POLLUTANT INJURY

The effects of toxic chemicals upon the skin of individuals with chemical sensitivity are becoming very well known. The early characteristic clinical signs and symptoms of toxic exposure can appear in various forms. A vascular syndrome of acne, petechiae (Figure 1.4), spontaneous bruising, or purpura as well as cold sensitivity and edema (periorbital, feet, and hands) and peripheral arterial spasm are seen in many patients with chemical sensitivity[51] (Table 1.4).

At the EHC-Dallas, where we have seen 4000 cases presenting with this vast array of symptoms (see vascular chapter, small vessel vasculitis), we have described this vascular syndrome. Correlating with our observations, 52% of 226 workers exposed to 2,4,5-trichlorophenoxyacetic acid (2-5-5T, a herbicide) had a residual mean duration of chloracne of 26 years.[52] Until evidence to the contrary can be compiled, we had the EHC-Dallas consider adult onset acne to result, in part, from overexposure to toxic chemicals (especially the chlorinated ones). Chemicals proven

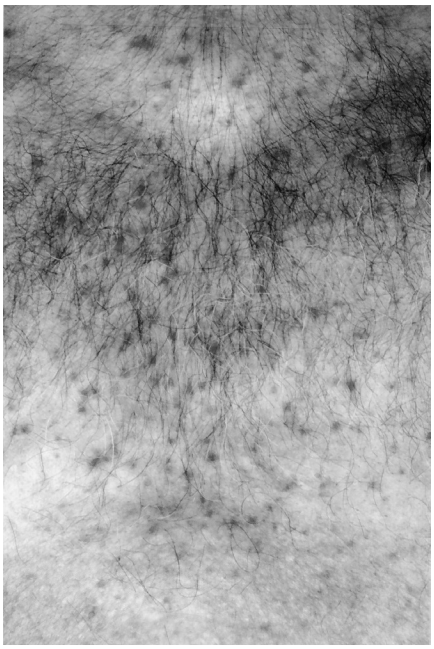
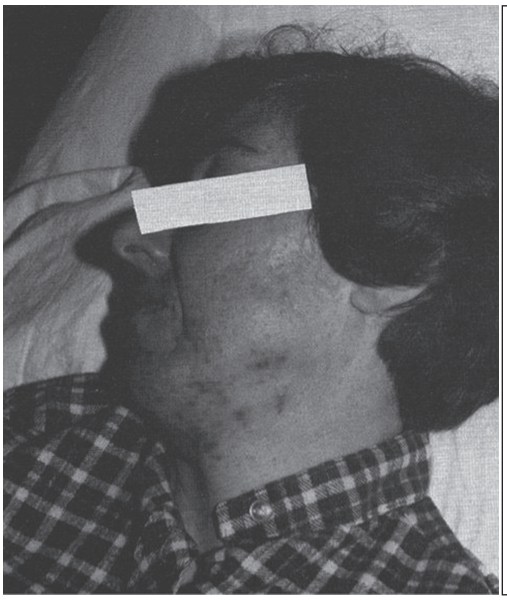


FIGURE 1.4 Dermal petechiae. A 57-year-old white male with exposure to ambient pesticide. Pyrethroid for 1 h. Note the multiple petechiae. Biopsy showed perivascular lymphocytic infiltrate. (From EHC-Dallas, 2010.)

TABLE 1.4
Environmentally Triggered Vascular Response of the Skin Seen in over 1000 Patients with Chemical Sensitivity

Acne—usually chloracne adult onset
Spontaneous bruising
Petechiae
Purpura
Peripheral arterial spasm—Raynaud's phenomena
Peripheral and periorbital edema

Source: EHC–Dallas, 1976–2000.



Causes of chloracne:

- Polyhalogenated dibenzofurans
  - Polychlorodibenzofurans (PCDFs), especially tri-tetra-(TCDFs), penta-(PCDFs), and hexachlorodibenzofuran
  - Polybromodibenzofurans (PBDFs), especially tetrabomodibenzofurans (TBDF)
- Polychlorinated dibenzodioxins
- 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
- Hexachlorodibenzo-*p*-dioxin
- Polychloronaphthalenes (PCNs)
- Polyhalogenated biphenyls
  - Polychlorobiphenyls (PCBs)
  - Polybromobiphenyls (PBBs)
- 3,4,3',4'-Tetrachloroazoxybenzene (TCAOB)
- 3,3',4,4'-Tetrachlorozaobenzene (TCAB)
- Tetrachloroethane
- Trichloroethane
- Trichloroethylene
- Dichloroethane

FIGURE 1.5 Chloracne in a 40-year-old white male exposed to chlorinated hydrocarbons. (From EHC-Dallas, 1976; Rea, W.J., *Chemical Sensitivity*, Vol. 3: *Clinical Manifestations of Pollutant Overload*, Lewis Publishers, Boca Raton, FL, 1996, p. 1703. Updated data from the EHC-Dallas, 2010. With permission.)

to cause chloracne are chloronaphthalene,[53] PCBs,[54] polychlorinated dibenzofurans,[52] chlorophenols,[52] and chlorobenzene.[52] Also, chloracne has been observed in many soldiers returning from Vietnam who were sprayed with *Agent Orange*.[55] (See Figure 1.5.) Spontaneous bruises, purpura, and petechiae are present in many of the patients with chemical sensitivity and chronic degenerative disease whose illness is environmentally triggered. These symptoms signify vasculitis.

Skin pathologies in humans have recently been associated with a number of different toxic chemicals. Gases of pemphigus vulgaris were linked to known nonoccupational chronic pentachlorophenol (PCP) exposures.[56] There was a rough correlation between the serum PCP levels and the clinical course and titer of antibodies. Cole et al.[57] presented a patient who developed chloracne after exposure to PCP pressure-treated lumber. The authors presumed his difficulty was through percutaneous absorption of dioxins and furans, which are known to be contaminants of technical grade PCP.

Some pollutant injury related to the vascular tree manifests as signs and symptoms of the skin. For example, erythema occurs in some patients exposed to toxic chemicals. Usually, it is nontender and nonirritating. However, occasionally, it burns similar to sunburn. A diffuse erythema, or flushing, and heat intolerance are seen in a smaller group of patients with chemical sensitivity. Pruritus, stinging, and burning are often common manifestations of chemical intolerance. One of the cardinal signs of chemical sensitivity is a yellow hue to the skin (see Figure 1.6) without jaundice or massive ingestion of β-carotene. The most common offender for the production of the yellow tone is phenol. However, many other chemicals can trigger the yellow color. At the EHC-Dallas, the most common offenders from chemical exposure of the skin are formaldehyde, phenol, aromatic hydrocarbons (e.g., pesticides, PCB, PBB), and chlorine.

Systemic vascular manifestations have been demonstrated by many groups including our own.[58,59] Results of large and small end-organ responses were observed in the heart, veins of the legs, and large blood vessels with resultant arrhythmias, phlebitis, and spastic vascular phenomena.[60,61] (See the cardiovascular chapter.) Some important triggering agents were pesticides, phenols, formaldehyde, chlorine, and petroleum alcohol.[62] Skin yellowing accompanied by itching and changes in the immune system is exemplified in the following patient who was challenged with phenol (see Figure 1.7).

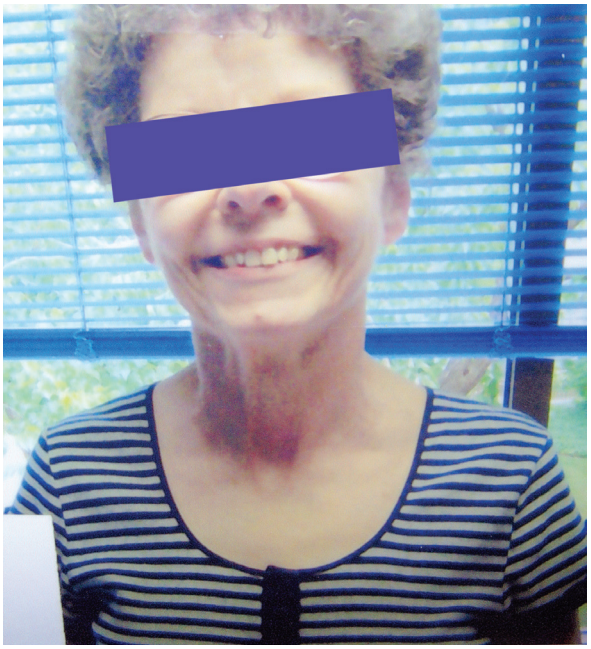


FIGURE 1.6 A 55-year-old white female. Chemical yellow syndrome. (From EHC–Dallas, 2012.)

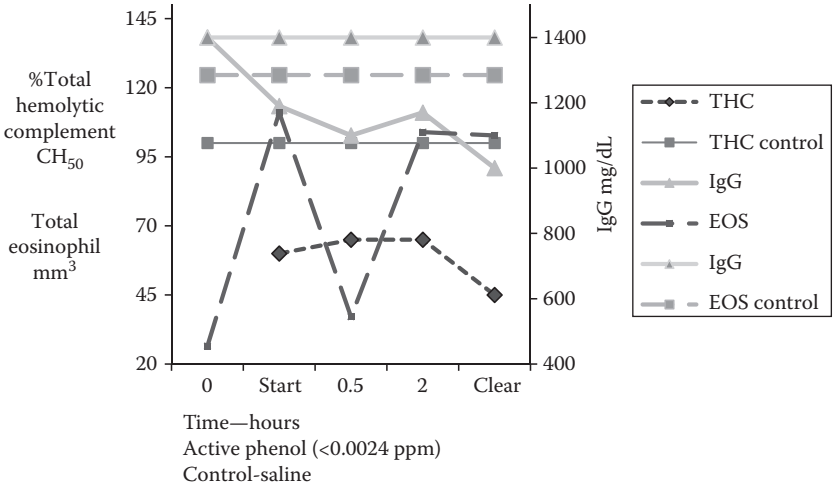


FIGURE 1.7 A 26-year-old white female. Double-blind inhaled challenge after 4 days deadaptation in the ECU with the total load reduced. Symptoms reproduced on challenge included generalized itching; cough; arrhythmia; urgency; hot, sweaty palms with flushing of hands; yellow skin; and edema. (From EHC-Dallas, 1979; Rea, W.J., *Chemical Sensitivity*, Vol. 3: *Clinical Manifestations of Pollutant Overload*, Lewis Publishers, Boca Raton, FL, 1996, p. 1705. With permission.)

CASE STUDY

Five weeks after exposure to a phenol spill in her workplace, a 26-year-old white female was admitted to the ECU. She had experienced a rapid downhill course characterized by weakness, fatigue, nausea, loss of appetite, mild peripheral and periorbital edema, and the severe yellow color to her skin. Her physical exam showed positive findings limited to periorbital edema and 2+ nonpitting edema of the feet and a severe yellow color to her skin with normal color sclera. This patient was fasted for 5 days in the ECU, during which time her color gradually returned to normal, and her edema cleared. Double-blind, inhaled challenge of <0.0034 ppm of phenol reproduced the edema and yellow-colored skin. In addition, her eosinophil count and her complement became abnormal after the challenge. Inhaled challenges with petroleum-derived ethanol (<0.50 ppm) and saline were negative.

A. Urticaria

Urticaria, which is also discussed in the vascular chapter, can be caused by any number of foods and chemicals, including formaldehyde.[63] It can be cleared with fasting. The efficacy of diet therapy was evidenced by Okamoto et al.,[64] who used this treatment with a 28-year-old woman with chronic urticaria that had previously responded only to systemic administration of glucocorticosteroids. This patient's rashes began to decrease on the third therapeutic day of fasting and completely disappeared on the 11th day. Although milder than the previous ones, the rashes returned 3 days of eating after her therapy terminated. The overall response to fasting therapy with this patient certainly implies a causal relationship between intake of certain foods with or without chemical contamination and the onset of the urticaria. The sequence of response to this patient would be individual organic food challenges and then a rotary diet with elimination of the offending foods.

The type of eruption described by Okamoto et al.[64] was formerly classified as chronic idiopathic urticaria. At the EHC-Dallas, we have seen the underlying food and chemical sensitivities in chronic idiopathic urticaria. We have treated 500 patients with urticaria resulting from multiple triggering agents. In addition to avoidance, intradermal neutralization (desensitization) injection therapy is usually necessary for full clearing of symptoms. In patients with refractory urticaria, toxic volatile chemicals, such as xylene, are often found in their blood. Rigid avoidance of these chemicals is often essential for recovery to occur.

At the EHC-Dallas, we followed a small, prospective series of 35 patients with urticaria ranging in age from 21 to 90 years, with a mean age of 41 years; 88% were female. Foods played a large role in triggering urticaria as shown in Table 1.5. The average patient was sensitive to 15 foods by oral

TABLE 1.5
Comparison of Food Sensitivity by Oral and Intradermal Challenge in 35 Patients with Urticaria

	Oral Challenge		Intradermal Challenge	
	No. of Patients Tested	No. of Foods to Which Patient Was Sensitive	No. of Patients Tested	No. of Foods to Which Patient Was Sensitive
Total	35	160	35	775
Average	1	15	—	22

Source: EHC–Dallas, 1986–2010.

challenge and 22 by intradermal challenge. Often, elimination of these positive foods combined with subcutaneous injection of the offending foods neutralizing (desensitization) doses markedly decreased the urticaria. However, since the patients were all chemically sensitive, reduction of the total load of toxic chemicals was necessary. An abundance of toxic chemicals was found in these patients' blood (Table 1.6). Both inhaled and intradermal challenge tests confirmed the sensitivity (Tables 1.7 and 1.8). IgEs were elevated in 50% of the patients. Complements were changed in 46%, and T cells were changed 52% (Table 1.9).

It is clear from the series that urticaria has had multifactorial etiologies. We suggest that if urticaria appears, multiple factors should be sought and defined. The following is a case report of recurrent intractable urticaria triggered by xylene.

TABLE 1.6
Frequency of Toxic Chemicals in 35 Patients with Urticaria

	No. of Patients	No. of Positive	Frequency (%)
Pesticides			
Aldrin	32	4	12.5
α-BHC	32	10	31.3
β-BHC	32	18	56.3
DDD	32	2	0.0
DDE	32	30	93.8
Dieldrin	32	20	62.5
Endosulfan I	32	2	6.3
Heptachlor	32	2	6.3
Heptachlor epoxide	32	24	75.0
HCB	32	28	87.5
trans-Nonachlor	32	10	31.3
Volatile chlorinated hydrocarbons			
Dichloromethane	26	8	30.8
Chloroform	24	12	50.0
1,1,1-Trichloroethylane	16	8	50.0
Trichloroethylene	26	14	53.8
Tetrachloroethylene	26	22	84.6
Dichlorobenzene	20	4	20.0
Volatile aromatic hydrocarbons			
Benzene	26	14	53.8
Toluene	26	24	92.3
Ethylbenzene	26	8	30.8
Xylenes	26	18	69.2
Styrene	26	4	15.4
Trimethylbenzene	26	10	38.5

Source: EHC–Dallas, 1986–2010.

TABLE 1.7
Intradermal and Inhalant Challenge of Chemicals in 35 Patients with Urticaria after 4 Days of Deadaptation in the ECU with the Total Load Reduced

	Intradermal Challenge			Inhalant Double-Blind Challenge		
Chemicals	**No. of Tested**	**No. of Positive**	**%**	**No. of Tested**	**No. of Positive**	**%**
Molds	35	35	100.0	—	—	—
Cigarette smoke	29	24	82.8	—	—	—
Orris root	25	20	80.0	—	—	—
Ethanol	25	20	80.0	5	4	80.0
Formaldehyde	20	20	100.0	9	7	77.8
Newsprint	27	18	66.7	—	—	—
Perfume	24	15	62.5	—	—	—
Phenol	16	11	68.8	9	8	88.9
Chlorine	8	4	50.0	8	8	100.0
Pesticides	—	—	—	8	7	87.5
Placebo	—	—	—	30	+2	+6

Source: EHC–Dallas, 1986–2010.
Notes: Ages = 21–90 years; Gender = 17 females, 18 males.

TABLE 1.8
Terpenes Intradermal Test in 25 Patients with Urticaria

Terpenes	**No. of Patients**	**No. of Positive**	**%**
Pine	24	17	70.8
Tree	24	15	62.5
Grass	24	20	83.3
Ragweed	25	20	80.0
Mt. Cedar	24	20	83.3
Mesquite	19	14	73.3
Sage	10	9	90.0

Source: EHC–Dallas, 1986–2010.

TABLE 1.9
Frequency of Abnormal Immune Parameters in 36 Patients with Urticaria

Immune Parameters	No. of Patients Tested	No. above Normal	No. below Normal	No. Abnormal	%
WBC	35	3	5	8	22.9
Lym (%)	30	2	6	8	26.7
Lym C	33	0	11	11	33.3
T_{11}	36	5	6	11	30.6
T_{11} C	36	4	15	19	52.8
T_4 (%)	20	6	1	7	35.0
T_4 C	20	2	5	7	35.0
T_8 (%)	20	0	3	3	15.0
T_8 C	20	2	2	4	20.0
T_4/T_8	20	2	1	3	15.0
Bly (%)	33	7	5	12	36.4
Bly C	33	6	4	10	30.3

Frequency of Abnormal Immune Antibodies in 35 Patients with Urticaria

Immune Antibodies	No. of Patients Tested	No. above Normal	No. below Normal	No. Abnormal	%
IgA	17	0	0	0	0.0
IgE	35	10	8	18	51.0
IgG	24	2	0	2	8.3
IgM	18	3	0	3	16.7

Frequency of Abnormal Complements in 21 Patients with Urticaria

Complements	No. of Patients Tested	No. above Normal	No. below Normal	No. Abnormal	%
CH_{100}	21	1	4	5	23.8
C_{1q}	8	0	0	0	0.0
C_2	5	0	2	2	40.0
C_3	15	0	3	3	20.0
C_4	15	4	3	7	46.7
C_5	9	2	0	2	22.2

Source: EHC–Dallas, 1986–2010.

CASE STUDY

This 46-year-old white male worked at a plant where he used xylene as an extracting solvent. He had worked there for 7 years without problems. He suddenly developed urticaria that covered his entire body and was refractory to medication. He was admitted to the ECU and fasted for 5 days. His urticaria cleared. He was then challenged intradermally with pollen, dust, molds, weeds, trees, and grasses. He was found to be sensitive to some of these at strong dilutions. Both oral and intradermal challenges showed him to be sensitive to some foods. His hives, however, did not return during these tests. He then underwent double-blind inhaled challenge with several toxic chemicals to which he did not react. However, when he was challenged with an ambient dose of xylene, his urticaria was reproduced (Table 1.10). He was kept away from xylene compounds in the workplace and at home for 4 months, after which time he had no recurrence of his urticaria.

TABLE 1.10
A 46-Year-Old White Male: Inhaled Double-Blind Challenge after 5 Days of Deadaptation with the Total Load Reduced in the ECU

Incitant	Dose (ppm)	Reaction
Formaldehyde	<0.20	—
Phenol	<0.0020	—
Ethanol petroleum-derived	<0.50	—
Chlorine	<0.33	—
Insecticide 2,4-DNP	<0.0034	—
Xylene	Ambient	Urticaria severe 3 days
Saline 1	—	—
Saline 2	—	—
Saline 3	—	—

Sources: EHC–Dallas, 1986; Rea, W.J., *Chemical Sensitivity*, Vol. 3, CRC Press, Boca Raton, FL, 1996, p. 1709. Reproduced with permission.

VII. ITCHING, STINGING, AND BURNING

Itching seems to be one of the early signs of noncontact chemical sensitivity, in approximately half of the patients with chemical sensitivity. It usually occurs in the contact patients but also in the noncontact ones. Patients describe this as a creepy-crawling feeling as if there were a small insect crawling on their arms and legs. Often scratching exacerbates the problem. Withdrawal from the chemically contaminated environment usually relieves the itching, and reexposure will trigger it again. This sign should not be ignored or suppressed by medication because it can be used as a sentinel for the early diagnosis of a pollutant exposure in the patient with chemical sensitivity. A sudden stinging may also occur and is often misinterpreted as an insect bite. Usually, petechiae occur at this spot.

Burning of the skin is seen in a large subset of patients with chemical sensitivity. The skin is tender to touch and difficult to clear. However, definition of triggering agents can be done, which will aid in diagnosis.

VIII. AUTOIMMUNE CONTACT DERMATITIS

Cosmetics, metals (e.g., nickel), plants, medications, fabrics, and many of their chemicals have now been shown to produce cutaneous manifestations. For example, dihydroxybiphenyl methane bisphenol F gives contact dermatitis.[65] Individuals with heavy exposure to these substances are office workers, electroplaters, auto welders, carpenters, and sheet metal workers. Nickel is found in hand tools, bracelets, and steel prosthesis, including heart valves and other metal prosthesis. In some individuals, problems associated with contact with these have been found.[66] The most sensitizing epoxy resins are those with a molecular weight of 340. Preservatives such asquaternium-15, IMID 20, parabens, formaldehyde, and glutaraldehyde may be sensitizers found in numerous topical preparations.

Machine cutting fluids commonly contain antimicrobials; therefore, most have preservatives such as orthophenylphenol, *p*-chloro-meta-xylenol, and formaldehyde-releasing agents.[67] Ethylene diamine dihydrochloride is a stabilizer found in many creams. Glyceryl monothioglycolate (a constituent of acid permanent waves) is a common sensitizer used by beauticians and their clients. Photosensitivity and chronic actinic dermatitis from musk ambrette and aftershave lotion occur.[68,69] Contact urticaria has resulted from orthophenylphenate, a preservative used in plaster

cast material.[70] Extreme sensitivities of phenolic and thiazide compounds have occurred in metal-working biocides.[71] Rats exposed to methyl mercury chloride have impaired cutaneous sensitivity.[72] This response is similar to that seen in individuals with mercury-driven Minamata disease reported in Japan.[73,74] 12-*O*-Tetradecanoylphorbol-13 acetate (TPA) induces permeability.[75] Contact dermatitis due to maleic hydrazide (MH) in workers handling flue-cured tobacco occurs.[76] Pyrethroids have been associated with skin sensory effects characterized by transient itching/tingling sensations.[77]

IX. ACUTE SKIN REACTIONS FROM POLLUTANT EXPOSURE

The most recognized reaction to pollutant exposure is necrolysis. Erythema multiforme (Stevens–Johnson type) and severe drug reactions also commonly result from toxic chemical exposures. These well-known entities will not be discussed further here, since they are well described in dermatology texts.

The following case illustrates how chronic and then acute exposure can trigger an acute and definitive reaction.

CASE STUDY

This 56-year-old, white female engineer had numerous exposures to chlorinated solvents and pesticides from living on military bases all her life. She then retired to an environmentally clean area in Wyoming. She also had taken a recent trip to South America. She did well until she was exposed to pyrethroid pesticides, and then, upon returning home, she ate some mushrooms, which she had grown. These were contaminated with Candida zeylanoides. Mycotoxin levels of her urine showed ochratoxin 25 ppb. An erythematous rash developed on her arms, legs, and torso (see Figures 1.8 and 1.9). Her breath analysis showed high levels of pyrethroid pesticides, cyclopropane, ethylene, and acetone.

She was treated with an avoidance regimen (less-polluted spring water, organic food, and good air) and intravenous and oral supplementation of vitamin C, glutathione, taurine, multivitamin, and multiminerals for 2 weeks. She also did daily saunas for one half hour per day, six times per week for 2 months.

She took a course of nystatin, ¼ teaspoon (200 mg), four times per day for 1 month and fluconazole for 1 week. Her skin gradually cleared.

At the end of her treatment, her skin was completely clear. Her urine mycotoxins were nondetectable. She had recovered completely.

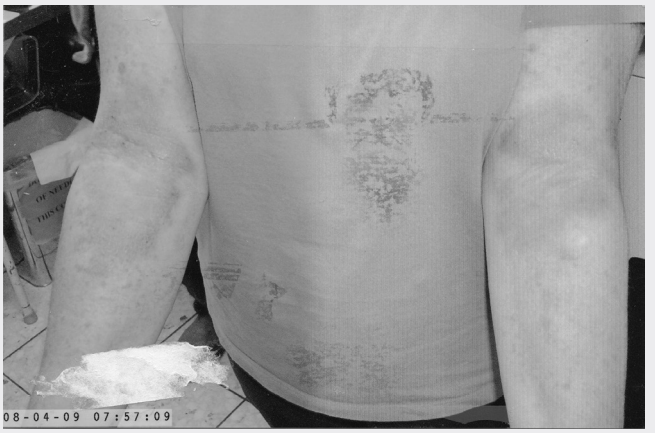


FIGURE 1.8 Rash from exposure to pyrethroid pesticides and mycotoxins. (From EHC–Dallas, 2009.)

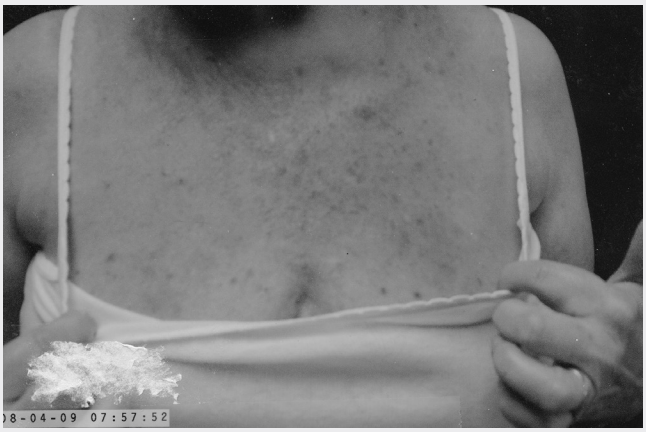


FIGURE 1.9 A 56-year-old white female after a trip to South America, where she was exposed to pyrethroid pesticide and mycotoxins. (From EHC–Dallas, 2009.)

Environmental disasters resulting from chemically contaminated food have revealed well-defined clinical facets, as well as potential mechanisms of some dimensions of the problem of chemical sensitivity. One example of such an event comes from Japan and Taiwan where rice cooking oil was contaminated with PCB (a breakdown product of DDT) and polychlorinated dibenzofurans.[78] Those exposed to, and affected by, this contamination presented with acute symptoms—swelling of the upper eyelids, hypersecretion of the meibomian glands, chloracne, and conjunctival pigmentation. Follow-up of these patients a year later revealed that 54% were still ill[79] and that they had clearly developed chemical sensitivity. Two groups of patients evolved. One group had slowly decreasing PCB levels, while the other group remained constant.[80] Similar types of responses, characterized by faster clearing and no clearing, respectively, have been seen in other patients with skin disorders and chemical sensitivity. Among the patients with chemical sensitivity seen at the EHC-Dallas, we have observed a group who are slow to clear both PCBs and chlorinated pesticides such as lindane, aldrin, dieldrin, chlordane, heptachlor, benzene hexachloride, and hexachlorobenzene.[81] Also, some patients with chemical sensitivity are slow to clear benzene, toluene, xylene, trimethylbenzene, and chlorinated solvents, as is evidenced by studies at the EHC-Dallas.[82] However, we have been able to accelerate their clearance by rigid environmental control measures, vitamin and mineral supplementation, and physical therapy in conjunction with heat depuration and administration of a tolerance moderator such as transfer factor and autogenous lymphocytic factor.

Another large incidence of acute skin and systemic problems resulting from toxic chemical overexposure is the aforementioned Turkish epidemic in which over 3000 people were damaged by eating grain contaminated with hexachlorobenzene used as a fungicide. These patients initially developed hirsutism, pigmentation, weakness, porphyrinuria (porphyria cutanea tarda), and bullae. Two years of follow-up showed chronic effects. Neurologic, orthopedic, and dermatologic abnormalities were still present. In addition, the chemical sensitivity problem persisted. Neurological symptoms included weakness (66%), paresthesias (54%), neuritis (62%), myotonia (49%), and cogwheeling (29%). Orthopedic symptoms were small stature (44%), small hands (64%), painless arthritis (67%), residual scarring of blisters (85%–90%), pinched fascia (scleroderma-like features) (42%), and enlarged thyroid (32%, of which 59% were females).[83] HCB levels were as high as 2.8 ppm in human milk, averaging 290 ppb. This finding was 140 times the supposedly safe level allowed in cow's milk.

Sixty-four percent of the patients seen in the years 1981–1984 at the EHC-Dallas had hexachlorobenzene in their blood. Many of their initial symptoms were similar to the acute symptoms found in the Turks. However, it should be noted that other pesticides (chlorinated compounds, organophosphates, carbamates, pyrethroids, etc.), herbicides (e.g., hexachlorobenzene), and solvents (e.g., xylene, toluene, styrene) were found in the blood of most of our patients. These findings might have been the case in the Turkish experience, but concurrent tests were not available at that time to measure as many parameters as we were able to gauge.

A third example of acute toxic chemical contamination of food was the Spanish disaster involving 18,000 people who ingested contaminated rapeseed oil containing denatured aniline.[84] Long-term chemical sensitivity again resulted. Antinuclear antibody titers were positive (1/140 to 1/320) in a high percentage of patients who were affected by this contamination. We have seen similar autoimmune changes in our patients with chemical sensitivity. At the EHC-Dallas, 17% of our outpatients with chemical sensitivity and 51% of our inpatients with chemical sensitivity have positive low levels of autoantibodies, suggesting a similar damaging of self-recognition in the immune system. A number of drugs and chemicals are known to produce positive ANA titers and to induce systemic lupus erythematosus (SLE)-like syndromes. The long-term follow-up over a 20-year period revealed no progression of autoimmune disease in our patients receiving proper treatment. However, those who did not have definition and removal of the triggering agents continued to worsen.

Other chemicals are known to cause acute autoantibody reactions, as well as other responses. For example, seven patients with SLE who had exacerbations of their cutaneous lesions after taking a variety of medications not usually associated with induction of SLE were seen by Pereyo.[85] These medications contained tartrazine, which is a derivative of aniline, and hydrazine derivative (isoniazid, hydralazine, phenylhydrazine, acetylphenylhydrazine, sulfanilic acid, *p*-sulfophenyl hydrazine, sulfanilamide, aniline).[86,87] Also, saccharine, which is a coal tar derivative, can cause a photosensitization reaction.

Not only are there acute, localized cutaneous manifestations of chemical sensitivity, but also these often reflect an underlying systemic biochemical, neurological, and immunological pathology. For example, Rozman et al.[88] demonstrated that decreased thyroid hormone levels in hexachlorobenzene induced porphyria in the female Sprague-Dawley rats, whereas Phoon et al.[89] showed five patients with liver involvement with erythema multiforme major after exposure to trichloroethylene for 2–5 weeks. Another example of systemic manifestation was shown by Doss et al.,[90] who found a chronic hepatic disorder induced by long-term industrial exposure to vinyl chloride in 34 workers.

Contact periorbital leukoderma has been seen due to contact with rubber swim goggles. Probably this condition resulted from the breakdown products of neoprene and its glue components.[91] Several patients have been seen at the EHC-Dallas with blisters and contact dermatitis from floating on inner tubes. Isoprene rings and aldehydes are the basis for terpenoids, which are discussed in the volumes of the book *Chemical Sensitivity*.[92] As our study has shown throughout this book, most patients with chemical sensitivity are sensitive to terpenes upon challenge.

Tumorigenic activity of some chemicals such as TPA,[93] phorbol-12-myristate-13 acetate (PMA), benzopyrene, 7,12-dimethylbenzanthracene,[94] and hexachlorobenzene has been observed to trigger hepatocarcinogenicity, as well as purpura, in rats.[83,95,96] Some of these chemicals may well trigger tumors in humans.

When patients with known contact allergy to phenol-formaldehyde resins were tested with 3-dihydroxydiphenylmethanes, 16 reacted.[97] At least nine of these patients experienced acute reactions to 1-dihydroxydiphenyl methanes (HPM), and all reacted to 2,4(1)-HPM. Three reacted

simultaneously to 2,4(1)-HPM and 4,4(1)-HPM, and one of these reacted to all three HPMs. Maibach[98] found no evidence of photoirritation and photosensitization with a glyphosate herbicide in 346 volunteers.

Animal studies have shown DNA polymerase activity in *N*-hexadecane-induced hyperkeratotic epidermis.[99] Mice were injected with equivalent to human clinical doses of cisplatin, melphalan, and mitoxantrone.[100] Only the melphalan was ulcerogenic when injected undiluted.

X. ECZEMA

Acute and chronic eczema has been known for ages. The specific immune and nonimmune mechanisms involved in it, however, are now only being defined. At the EHC-Dallas, studies of over 200 patients with eczema and chemical sensitivity revealed that usually a combination of foods and chemicals triggered this condition. However, the chemical overload seems to predominate. Figure 1.10 shows a case of severe eczema triggered by inhalants, foods, and chemicals. The most common foods and other substances triggering eczema were wheat, corn, cane sugar, beef, pork, cow's milk, and Candida albicans. At the EHC-Dallas, a prospective series of 33 patients with eczema and chemical sensitivity (7 males and 26 females), ranging in age from 40 to 70 years, revealed the approximate ratio most often seen in overt, unmasked chemical sensitivity. In 10 of these patients studied for the presence of chlorinated pesticides, one or more were identified in all, while one or more volatile aromatic hydrocarbons were identified in seven others (Table 1.11). All 33 patients had their chemical sensitivity provoked by intradermal and/or inhaled challenge of ambient doses of toxic chemicals (Table 1.12). In addition, mold provocation appeared to play a significant role in their eczema. All of these patients were triggered by one or more terpenes (Table 1.13). Various immune parameters, including the gamma globulins, complements, and T- and B-lymphocytes, were altered in this group of patients (Table 1.14). It is clear from studies by us and others, including Little,[101] Randolph,[102] Monro,[103] Maberly,[104] Zhang,[105] Runow,[106] and Friedrickson,[107] that eczema is frequently present in individuals with chemical sensitivity. It can be treated with meticulous definition and avoidance of the triggering agents, intradermal injection therapy, nutrient supplementation, and tolerance mediators such as transfer factor. Occasionally, heat depuration and physical therapy are used. These help if the patient's skin can tolerate the heat. Rogers[108] reported a case exemplifying environmental triggers in atopic dermatitis.

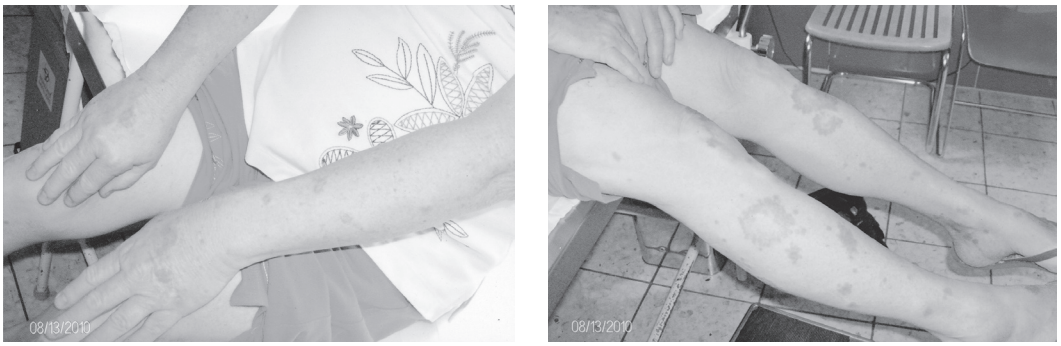


FIGURE 1.10 Eczema triggered by inhalants, foods, and chemicals. (From EHC–Dallas, 2000.)

TABLE 1.11
Frequency of Toxic Chemicals in Patients with Eczema

	No. of Patients	No. of Positive	Frequency (%)
Pesticides			
Aldrin	20	0	0.0
α-BHC	20	2	10.0
β-BHC	20	10	50.0
DDD	20	0	0.0
DDE	20	20	100.0
Dieldrin	20	8	40.0
Endosulfan I	20	2	10.0
Heptachlor	20	0	0.0
Heptachlor epoxide	20	16	80.0
HCB	20	16	80.0
trans-Nonachlor	20	10	50.0
Volatile chlorinated hydrocarbons			
Dichloromethane	21	6	28.6
Chloroform	21	11	55.0
1,1,1-Trichloroethylane	21	11	55.0
Trichloroethylene	21	9	42.9
Tetrachloroethylene	21	15	71.4
Dichlorobenzene	21	3	14.3
Volatile aromatic hydrocarbons			
Benzene	21	3	14.3
Toluene	21	18	85.7
Ethylbenzene	21	6	28.6
Xylenes	21	15	71.4
Styrene	21	3	14.3
Trimethylbenzene	21	6	28.6

Source: EHC–Dallas, 1988–2010.

TABLE 1.12
Intradermal and Inhalant Challenge of Chemicals in 33 Patients with Eczema after 4 Days of Deadaptation in the ECU with the Total Load Decreased

	Intradermal Test				Double-Blind Inhalant Test		
Chemicals	No. of Tested	No. of Positive	%	Dosage (ppm)	No. of Tested	No. of Positive	%
Molds	33	33	100.0		—	—	—
Cigarette smoke	25	18	72.0		—	—	—
Orris root	21	17	81.0		—	—	—
Ethanol	23	16	69.6	<0.50	1	0.0	0.0
Formaldehyde	17	17	100.0	<0.20	1	0.0	0.0
Newsprint	18	12	66.7		—	—	—
Perfume	17	12	70.6		—	—	—
Phenol	15	9	60.0	<0.002	1	1.0	100.0
Chlorine	9	5	55.6	<0.33	2	0.0	0.0
Pesticides (2,4-DNP)	—	—	—	<0.0034	2	1.0	50.0
Placebo	—	—	—		6	1.0	16.7

Source: EHC–Dallas, 1988–2010.

TABLE 1.13
Terpenes Intradermal Test in 27 Patients with Eczema

Terpenes	No. of Patients	No. of Positive	%
Pine	26	15	57.7
Tree	26	21	80.8
Grass	27	19	70.4
Ragweed	26	19	73.1
Mt. Cedar	25	19	76.0
Mesquite	24	17	70.8
Sage	17	15	88.2

Source: EHC–Dallas, 1988–2010.

TABLE 1.14
Frequency of Abnormal Immune Parameters in 23 Patients with Eczema

Immune Parameters	No. Patients Tested	No. above Normal	No. below Normal	No. Abnormal	%
WBC	23	1	4	5	22.7
Lym%	17	2	4	6	35.3
Lym C	22	0	6	6	27.3
$T_{11\%}$	23	5	6	11	47.8
T_{11} C	23	2	10	12	55.2
$T_{4\%}$	12	2	2	4	33.3
T_4 C	12	1	5	6	50.0
$T_{8\%}$	12	0	3	3	25.0
T_8 C	12	0	5	5	41.7
T_4/T_8	12	1	0	1	8.3
Bly%	18	5	3	8	44.4
Bly C	18	5	3	8	44.4
CMI	7	0	2	2	28.6

Frequency of Abnormal Immune Antibodies in 29 Patients with Eczema

Immune Antibodies	No. Patients Tested	No. above Normal	No. below Normal	No. Abnormal	%
IgA	12	0	4	4	33.3
IgE	29	12	5	17	58.6
IgG	14	0	0	0	0.0
IgM	11	1	0	1	9.1

Frequency of Abnormal Complements in 17 Patients with Eczema

Complement	No. Patients Tested	No. above Normal	No. below Normal	No. Abnormal	%
CH_{100}	17	0	5	5	29.4
C_{1q}	4	0	0	0	0.0
C_2	2	1	0	1	50.0
C_3	7	0	1	1	14.3
C_4	7	1	1	2	28.6
C_5	5	1	0	1	20.0

Source: EHC–Dallas, 1988–2010.

CASE STUDY

A 38-year-old white female with 10 years of atopic dermatitis and nasal congestion and 5 years of depression and fatigue was evaluated by Dr. Sherry Rogers.[108] She was found to be sensitive to pollen, dust, and mold by intradermal challenge. In addition, she had zinc, chromium, and manganese deficiencies. She was treated with intradermal neutralization (desensitization) injections for the inhalants. Her nutrient deficiencies were remedied with vitamin and mineral supplementation and institution of a macrobiotic diet. Within 5 months, all of her symptoms cleared. She later returned for reevaluation after her palms had turned purple for 2 weeks. Eczema that had cleared with her first course of treatment had returned on her neck. This area of skin also was purple, as was the skin and the liver area of her abdomen. She brought a bag to her doctor containing her bed sheets and showed that they were purple where she had laid on them. This patient worked as a hairdresser, and she revealed that the dye of a permanent wave solution she had used on her patrons over the course of the preceding 18 years was purple. Following a second course of treatment that included reduction of her total body load of pollutants and continued implementation of a macrobiotic diet, this patient's symptoms diminished. After 2 weeks, she was free of symptoms. She continued the macrobiotic diet and has done well for several years.

This study exemplifies what we have always known. When the body cannot properly metabolize and detoxify chemicals, it stores them. When it is sufficiently unloaded however, it can begin to depurate old, stored pollutants and dispose of them.

XI. PSORIASIS

Psoriasis is a genetically determined, chronic, epidermal proliferative disease of unpredictable cause. There is increased prevalence of psoriasis in individuals with HLA antigen BW17, B13, and BW37. Clearly, environmental triggers are able to trip these genetic time bombs. We have seen yeast triggers as well as food and some toxic chemicals. The basic alteration involves an accelerated cell cycle and an increased number of dividing cells, culminating in rapid epidermal cell accumulation. Cellular turnover is increased sevenfold, and the transit time from the basal layer to the top of the stratum corneum is 3–4 days, rather than the usual 28 days.

Rogers[109] has reported several cases of psoriasis that were triggered by composite battery of inhaled molds, yeast, foods, and chemicals. We have seen several causes of psoriasis in our patients at the EHC-Dallas also. This problem seems to result from a combination of the genetic time bomb and environmental triggers.

CASE STUDY

A 75-year-old white female presented with a history of losing hair and skin with psoriasis, chronic fatigue, and hormonal imbalance. Her physical exam showed the lesions of psoriasis. Laboratory tests showed positive ANA at 1/320 (C = 0) and thyroid antibody at 14 (C ≤ 2). Levels of progesterone and estrogen were also low. She had multiple food and chemical sensitivities. She was treated with environmental control and antigen injections for molds, foods, and chemicals. She was also given hormone supplementation. She has done well. (See Figure 1.11.)

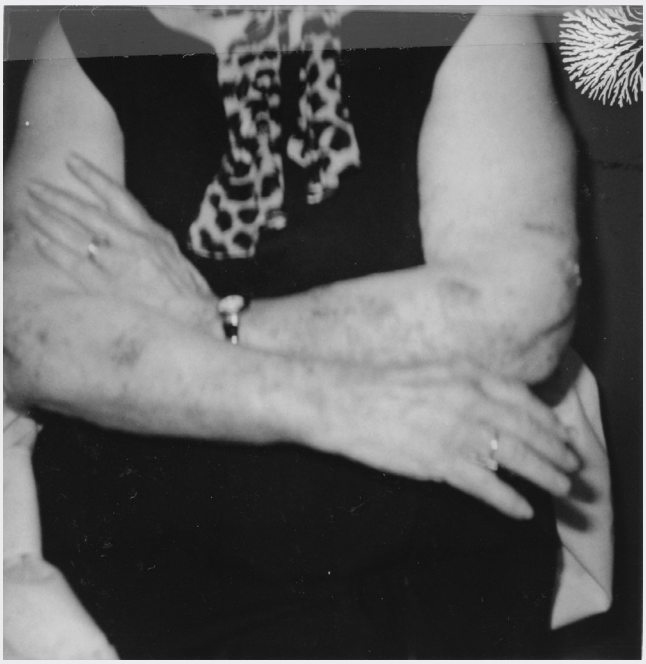


FIGURE 1.11 A 75-year-old white female with long history of psoriasis that was environmentally triggered. (From EHC–Dallas, 2009.)

XII. BOILS

Some patients with chemical sensitivity develop recurrent boils. Some of these patients with boils seen at the EHC-Dallas have had the hyper-IgE syndrome with an IgE of 2000 IU/mL or above. However, others have normal IgE but disturbed low killing capacity for bacteria and fungus. The triggering agents in these cases and in those cases with the low IgEs are usually multifactorial, being due to biological inhalants, foods, and chemicals. Studies on some of these patients show impaired killing as well as impaired phagocytosis. A select group of these patients can be cleared on an avoidance program with reduction of pollutants in air, food, and water, along with injection neutralization (desensitization) program for inhalants and foods. A second group responds to transfer or autogenous lymphocytic factor. The hyper-IgE group is the most difficult to treat, and they respond only partially to all of the aforementioned measures.

XIII. HYPER-IgE SYNDROME

The syndrome of IgE supersensitivity is extremely difficult to manage. In this supersensitivity syndrome, the IgE is over 1000 u/L (control = 140 u/L), whereas the average patient with allergies is 140–500 IgE/u. This syndrome appears to involve a hyperactivity of the mast cells or other neurological or immune cells or their sensitive receptors, which release histamine. The patients become sensitive early in life and continue to have problems most of their life. They usually have a widespread sensitivity triggering where eczema as well as other symptomatology occurs (see Figure 1.12). Their IgE will run anywhere from over 1,000 to 60,000 u/L as shown in Table 1.15. Medication treatment appears to be less than satisfactory. These patients are rapid sensitizers, and

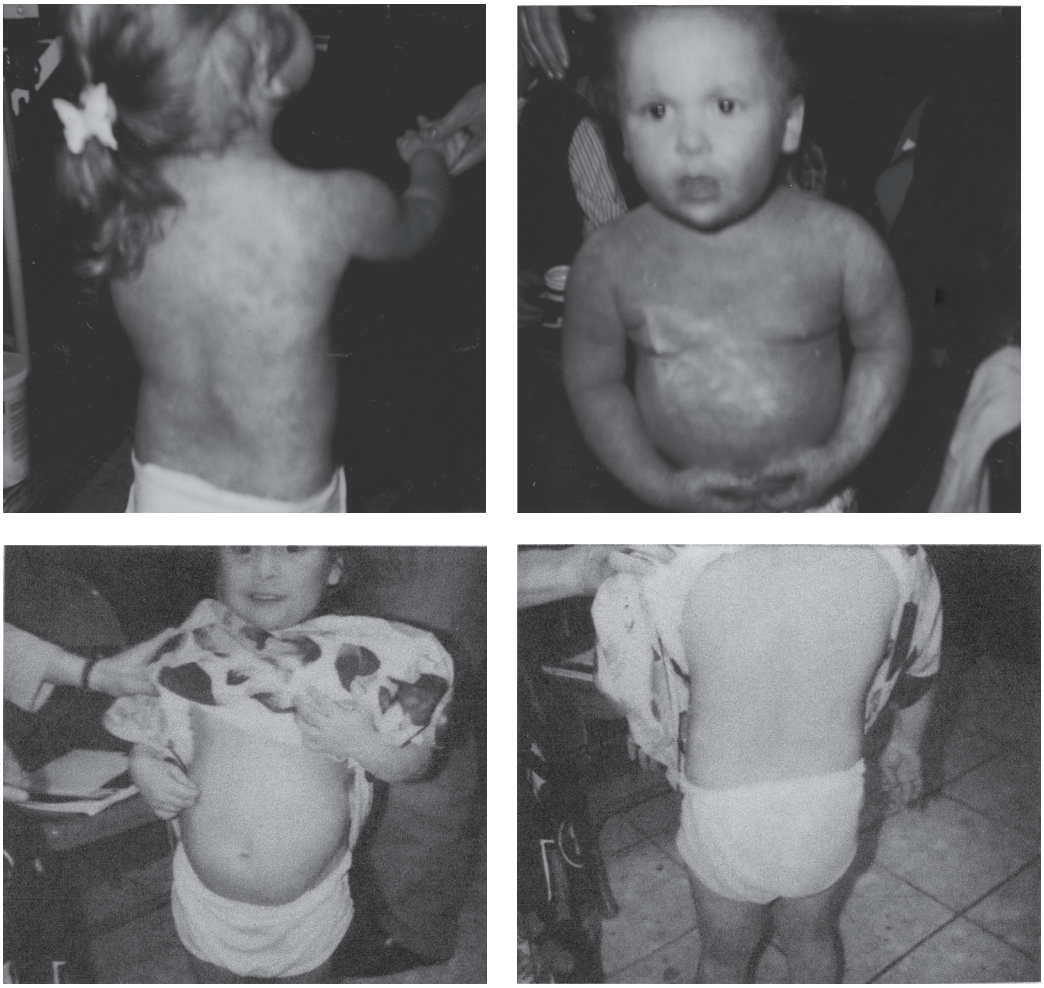


FIGURE 1.12 Hyper-IgE syndrome (IgE 10,000). A 2-year-old white female—avoidance of food, mold, and chemicals. Injection neutralization (desensitization) for foods, molds, and chemicals. (From EHC–Dallas, 2008.)

they frequently acquire additional new triggering agents. Neutralization for food and chemical sensitivities appears to help these patients as do nutrition supplementation and decrease in the total body pollutant load.

XIV. AGING OF THE SKIN

With the elimination of as many toxic chemicals as possible, the environmentally triggered disease process becomes manageable. In addition, maintenance of health and retardation of aging in the properly treated individual with chemical sensitivity may now be possible using ecological principles (see *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*[3]). It is common to see skin texture improve acutely (and a consequent reduction of the signs of aging) in an environmental unit, where there is a decrease in the patient's chemical and food load. Subsequent toxic chemical challenge, in contrast, causes an increase in the aging processes and a resultant alteration in the appearance of the skin.

TABLE 1.15
Hyper-IgE Syndrome

Patient	IgE (ku/L)	Patient	Age	Sex	Inhalants Test	Food Test	Symptoms
1	2,761–1,533	M.S.	65	F	+	42 skin	EX, ARS, GI
2	48,653–43,044	F.R.	20	F	+	1 oral	EX—severe total body; GI upset
3	3,444	T.F.	25	M	+		EX, ARS, GI, fatigue, ANSD, vasculitis
4	7,094	M.L.	7	M	+	75 skin and oral	TBS, ARS, ANSD, vasculitis, fatigue
5	41,338–3,983	F.B	13	F	+	12 skin and oral	EX, anaphylaxis, ARS
6	3,800–2,234	A.E.	9	M	+	71 skin and oral	Anaphylaxis, dermatitis, ARS, GI upset
7	5,832–4,832	B.G.	2	M	+	1 skin and oral	Autism, IBS
8	4,184	R.C.	45	F	+	19 skin and oral	Dermatitis, EX, ARS, asthma
9	338–4,289	E.R	6	M	+	43 skin and oral	Urticaria, dermatitis, angioedema, aortic stenosis
10	2,403–17,059	M.P	40	M	+	12 skin and 20 oral	Eczema, dermatitis
11	2,000–19,000	K.O.	30	F	+	30 skin and 30 oral	Eczema, dermatitis
12	3,000	W.S.	5	M	+	20 skin and oral	Eczema
13	10,000	F.B.	2	F	+	40 skin and oral	Eczema
14	3,000	J.S.	2	M	+	20 skin and oral	Eczema

Source: EHC–Dallas, 2010.

These observations are compatible with those made by Weidruch and Walford[110] who observed the retardation of aging and disease with dietary restrictions in rats. This underfeeding phenomenon of age retardation was also found in studies by McCarter et al.[111] and others.[112–117] McCarter et al.[111] also found that underfeeding allowed peripheral tissue to become sensitive to T_3 in spite of no reduction of minimal oxygen consumption.

These findings are compatible with the recognized role that both genetic and environmental factors play in the aging process. Aging is characterized by a reduced ability to maintain homeostasis after cumulative exposure to stressful conditions, and it appears to be accelerated in individuals with chemical sensitivity whose cells are continuously exposed to a bevy of exogenous and endogenous stressors like toxic chemicals, ionizing (UV) and nonionizing radiation, bacteria, and viruses in an already pollutant overloaded individual. The main targets are found among simple cellular components, such as amino acids, nucleotides, and lipids, and high-molecular-weight structures like cellular membranes and cytoskeletons. Finally, functional damage to cellular elements, for example, mitochondria, endoplasmic reticulum, plasma membranes, and nucleus, are brought about. As a result, cells have developed a variety of defense and repair mechanisms to neutralize these damages and to maintain homeostasis. Unfortunately, however, these may already be damaged in the individual with chemical sensitivity, thus accelerating the aging process. The most important cellular defense systems appear to be DNA repair mechanisms, antioxidant defense mechanisms (either enzymatic or nonenzymatic), production of heat shock and other stress proteins, and poly (adenosine diphosphate [ADP]-ribose) polymerase activation[118] (Figure 1.13).

In order to remove or overcome lesions induced in their DNA, cells of prokaryotes and eukaryotes are equipped with certain mechanisms of repair: photo activities, excision repair, and postreplication repair.[119–132]

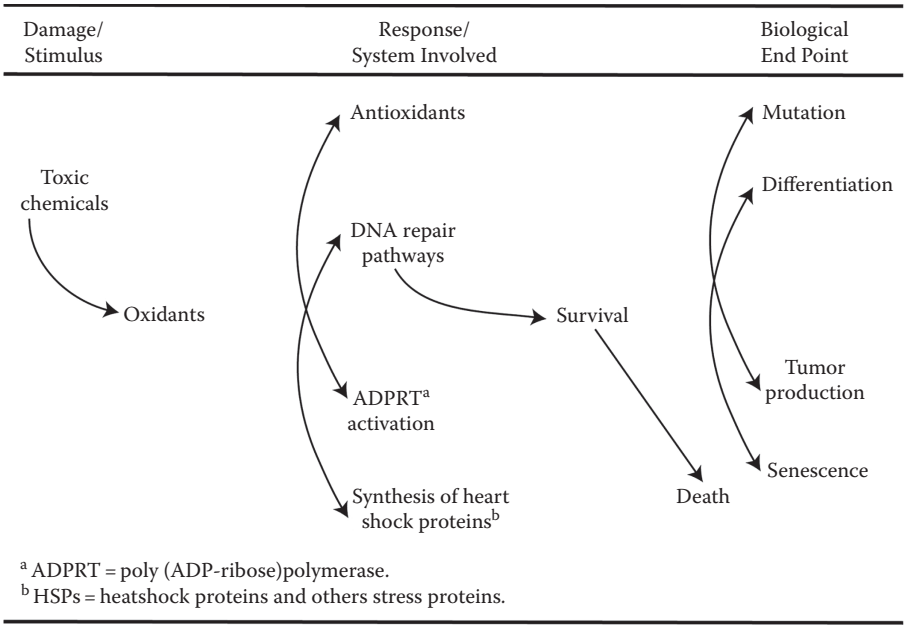


FIGURE 1.13 The network of cellular defense systems seen in the individual with chemical sensitivity. (From Rea, W.J., *Chemical Sensitivity*, Vol. 3: *Clinical Manifestations of Pollutant Overload*, Lewis Publishers, Boca Raton, FL, 1996, p. 1719. With permission.)

Antioxidant defenses are discussed in *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*[133] and will not be elaborated on here. Comments made previously are applicable to the skin.

Heat shock proteins (HSPs) are generated by heat and chemical exposure to protect the cell from toxic exposures and may in the long run cause an acceleration of aging.[119,134–138]

Poly (ADP-ribose) synthetic is an abundant and ubiquitous enzyme that cleaves the bond of NAD^+ and the *N*-glycosidic bond between nicotinamide and ribose rings and then transfers ADP ribosyl.[139–144]

Part of NAD^+ transfers either to chromatin proteins or to another ADP-ribose molecule. This sequencing is described as a cellular defense system that is interconnected and constitutes a network. The proteins and sugars forming the network must be considered together because a single agent can activate multiple pathways. For example, oxidants, besides being counteracted by the enzymatic and nonenzymatic antioxidants, induce HSPs, damage DNA bases (which are excised and substituted by DNA repair enzymes), and cause DNA single-strand breaks (which, in turn, activate ADPRT or ADP-ribosyltransferase). It is important to realize that the mechanisms that favor cell survival and the mechanisms that favor cell suicide are part of the same network. The network allows the survival of intact cells and, at the same time, the elimination of severely damaged cells, in order to avoid an excessive accumulation of mutated or transformed cells. The outcome depends upon the variety of factors described in this book. Excess chemical overload in the individual with chemical sensitivity appears to accelerate aging, whereas reduction of the total body load appears to decrease it. Senescence has also been shown to suppress tumorigenic activity in many systems.[118,145–147]

Many toxic substances occur in soil remediation. In susceptible individuals, these substances cannot only accelerate aging but also they can cause chemical sensitivity. Toxic substances that occur in high concentrations/levels are identified in Table 1.16.

TABLE 1.16
Soil Remediation Standards for the Ingestion and Dermal Absorption Pathway

Chemical	Ingestion–Dermal (mg/kg) Unrestricted (Residential)	Ingestion–Dermal (mg/kg) Restricted (Outdoor Worker)
Acenaphthene	3,400[a]	37,000[a]
Acetone (2-propanone)	70,000[a,d]	1,000,000[a,d]
Acetophenone	6,100[a]	68,000[a]
Aluminum	78,000[a,d]	1,100,000[a,d]
Anthracene	17,000[a]	180,000[a]
Barium	16,000[a,d]	230,000[a,d]
Benzaldehyde	6,100[a]	68,000[a]
1,1′-Biphenyl	3,100[a]	34,000[a]
Bis(2,chloroisopropyl)ether	2,400[a]	27,000[a]
2-Butanone (methyl ethyl ketone) (MEK)	3,100[a,d]	44,000[a,d]
Caprolactam	31,000[a]	340,000[a]
Carbon disulfide	7,800[a,d]	110,000[a,d]
Chloroethane (ethyl chloride)	220[b,d]	1,100[b,d]
Chloroform	780[a,d]	11,000[a,d]
Cobalt	1,600[a,d]	23,000[a,d]
Copper	3,100[a,d]	45,000[a,d]
Cyanide	1,600[a,d]	23,000[a,d]
1,2-Dichlorobenzene (*o*-dichlorobenzene)	5,300[a]	59,000[a]
1,3-Dichlorobenzene (*m*-dichlorobenzene)	5,300[a]	59,000[a]
1,4-Dichlorobenzene (*p*-dichlorobenzene)	610[a,c]	6,800[a]
1,2-Dichloroethene (*cis*) (*c*-1,2-dichloroethylene)	780[a,d]	11,000[a,d]
1,2-Dichloroethene (*trans*) (*t*-1,2-dichloroethylene)	1,300[a,d]	19,000[a,d]
Diethyl phthalate	49,000[a]	550,000[a]
Di-*n*-butyl phthalate	6,100[a]	68,000[a]
Di-*n*-octyl phthalate	2,400[a]	27,000[a]
Endosulfan I and endosulfan II (alpha and beta)	470[a,d]	6,800[a,d]
Endosulfan sulfate	470[a,d]	6,800[a,d]
Ethylbenzene	7,800[a,d]	110,000[a,d]
Fluoranthene	2,300[a]	24,000[a]
Fluorene	2,300[a]	24,000[a]
Hexachlorocyclopentadiene	370[a]	4,100[a]
Manganese	11,000[a,d]	160,000[a,d]
Methyl acetate	78,000[a,d]	1,100,000[a,d]
2-Methylphenol (*o*-cresol)	310[a,c]	3,400[a,c]
Methyl *tert*-butyl ether (MTBE)	780[a,c,d]	11,000[a,c,d]
Naphthalene	2,400[a,c]	25,000[a,c]
Nickel (soluble salts)	1,600[a,d]	23,000[a,d]
Phenol	18,000[a]	210,000[a]
Pyrene	1,700[a]	18,000[a]
Styrene	16,000[a,d]	230,000[a,d]
Tertiary butyl alcohol (TBA)	1,400[a,c,d]	20,000[a,c,d]
Toluene	6,300[a,d]	91,000[a,d]
1,1,1-Trichloroethane	290[a,d]	4,200[a,d]
Trichlorofluoromethane	23,000[a,d]	340,000[a,d]

TABLE 1.16 (continued)
Soil Remediation Standards for the Ingestion and Dermal Absorption Pathway

Chemical	Ingestion–Dermal (mg/kg) Unrestricted (Residential)	Ingestion–Dermal (mg/kg) Restricted (Outdoor Worker)
1,1,2-Trichloro-1,2,2-trifluoroethane	2,300,000[a,d]	34,000,000[a,d]
Xylenes	12,000[a,d]	170,000[a,d]
Zinc	23,000[a,d]	340,000[a,d]

Source: Modified from The Official Web Site for The State of New Jersey, Ingestion-dermal exposure pathway soil remediation standards: Basis and background, June 2008, http://www.state.nj.us/dep/srp/regs/rs/bb_ingest_dermal.pdf, Accessed February 11, 2012. With permission.

[a] Calculated values correspond to a noncancer hazard quotient of 1.

[b] Calculated values correspond to a cancer risk of 1 in 1,000,000.

[c] Calculated values based on DEP C-carcinogen policy that includes an additional safety factor of 10.

[d] No dermal absorption data available or standard based on ingestion data only.

XV. SUMMARY

In summary, the skin clearly may be the target organ for numerous toxic chemicals in the individual with chemical sensitivity. Damage from exposure to these chemicals can result either from direct contact with them or from systemic involvement. Precise definition and elimination of triggering agents through challenge testing in a controlled environment with the individual's total body pollutant load reduced will aid in the diagnosis and treatment of the individual who has developed chemical sensitivity with skin involvement.

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2 Ear, Nose, and Throat

I. INTRODUCTION

The field of environmental toxicology and chemical sensitivity has become quite important to the study of environmental health in human beings. Particularly, this field is germane in the area of ear, nose, and throat (ENT) physiology. The stability of the ecosystem in which we live is threatened by the nearly five million chemical compounds that have been synthesized worldwide. Many of these have real or potentially toxic effects on the environment as well as on life forms. Particularly, the ENT system is involved in a response to myriad exposures. Four major groups of chemicals—metallic elements, nonmetallic elements, organic compounds, and inorganic compounds—have certain agents within them that are known toxins to human beings. Some of these agents have as yet unknown effects, whereas others have been well characterized. They can be found in the workplace, home, and outdoors, and many are unseen and odorless but can have an effect on the ENT system. In the past, most agents have been described in terms of their carcinogenic potential or major toxic effects on organ systems. It is now likely that the important characterization of some of these agents referable to the upper digestive tract and other ENT areas should be at their receptor sites and identify the discrete and small effects on the sites and their cumulative effects, which can eventually develop into devastating chemical sensitivity and end-stage disease. The concept of threshold is an arbitrary one because today, these discrete effects have not been studied thoroughly. Susceptibility on an individual basis varies from low to high, depending on the patient's immunologic, neurologic, vascular, and other defense mechanisms and the existence of hereditary, congenital, or acquired (e.g., epigenetic) risk factors. The reactions depend on the numbers and virulence of environmental triggers versus the body's response mechanism, particularly of the ENT region. New attention must be given to more subtle effects on the upper aerodigestive tract (i.e., sinus, pharynx, larynx, ears, and upper esophagus) and the vestibular and hearing apparatus in view of the potential effects of certain toxic agents not only on these tissues but also on their distal effects.[1]

Patients presenting with symptoms related to the ears, nose, and throat are often in the beginning phase of chemical sensitivity or chronic degenerative disease. For example, an individual with symptoms of allergies or rhinitis is experiencing early periodic homeostatic dysfunction most likely from the environmentally triggered or genetic phenomenon. Additionally, the symptoms of vasomotor rhinitis may be one of the earlier symptoms of more advanced or even irreversible chronic degenerative disease if left untreated properly. With the onset of ENT symptoms, a patient treated chronically with medication in order to suppress symptoms is a formula leading to fixed-named irreversible disease either locally or distally. These entities are not only found locally (e.g., recurrent sinus symptoms, transient hearing loss, vertigo, and recurring laryngitis) but also resulting distally in vasculitis or arteriosclerosis including myocardial infarction, strokes, phlebitis, and angioedema. Such long-term problems have been stroke, recurrent bronchial and lung infections, dermatitis, and recurrent GI and GU disorders. The causes of ENT symptoms should be sought, found, and neutralized or eliminated in order to maintain good short- and long-term health.

Odor sensitivity to toxic substances (e.g., car exhaust, pesticides, formaldehyde, and natural gas) and nontoxic substances (e.g., perfume, newsprint, and pine terpene) is one of the primary symptoms of chemical sensitivity. It should not be ignored because, in addition to signaling the onset of chemical sensitivity, it can also be a forerunner of long-term chronic diseases and a harbinger of end-stage disease that can result in loss of hearing, balance, or memory or even death. Patients often consult the ENT surgeon for these early symptoms.

II. ENVIRONMENTAL TRIGGERING AGENTS AND THEIR INTERNAL RESPONSE MECHANISM

Environmental stressors are the triggering agents for the initiation of the internal (genetics) and external (epigenetic) mechanism of response of the body. As stated throughout these books, the environmental stressors (i.e., natural gas, pesticides, formaldehydes, alcohols, phenols, solvents, car and diesel exhaust, and over 60,000 chemicals plus 300,000 different mycotoxins) are legion. Some facts are known about a few environmental stressors and their mechanisms of response in the body. However, little is known about the combinations of toxics. Not only are the dynamics of biological inhalants and foods a problem for the early triggers of ENT disease but also are the myriads of chemicals and electromagnetic stimulation. The triggering of the body's genetic and epigenetic time bombs appears to be the mechanisms of response of the patient who is environmentally sensitive and has ENT-related illness. Usually, biological inhalants, foods, chemicals, and mycotoxins trigger chronic rhinosinusitis (CRS) and some hearing loss, laryngeal edema, loss of balance, upper dysphagia, and CRS. The entry of these environmental triggering agents usually results in an epigenetic response.

A. Epigenetic Mechanisms

The cells in a multicellular organism, such as the patient with ENT symptoms, have nominally identical DNA sequences (and therefore the same genetic instruction sets) yet maintain different terminal phenotypes and, therefore, different clinical responses to environmental stimuli. This nongenetic cellular memory, which records developmental and environmental cues (and alternative cell states in unicellular organisms), is the basis of epigenetics. This lack of the body's identifiable genetic determinants that fully explain the heritability of complex traits and the inability to pinpoint causative genetic effects in some complex diseases suggest possible epigenetic explanation for the missing data, that is, deafness from nerve failure due to natural gas or mold stimuli, pesticide-stimulated tinnitus, or formaldehyde-stimulated chronic laryngitis.

Epigenetics has become shorthand for many regulatory systems involving DNA methylation, histone modification, nucleosome location, or noncoding RNA (ncRNA). Epigenetics is heritable, self-perpetuating, and reversible.[2] These epigenetic states can act as sensors of environmental stress (molds and mycotoxins, toxic chemicals [pesticides, natural gas, formaldehyde, solvents, Pb, Cd, Hg, etc.]) and through the phenotype changes promote and potentially drive evolution[3] as well as abnormal clinical states in the ENT and other systems. These characteristics are present in the patient with chemical sensitivity who evolves from a state of simple rhinitis to one of end-stage disease such as hearing loss, Ménière's disease, brain dysfunction, chronic tinnitus, recurrent laryngeal edema, respiratory failure, heart failure, or ventricular fibrillation.

The cells in multicellular organs have nominally identical DNA sequences and therefore the same genetic instruction sets for response to environmental triggers, yet the organism maintains the terminal phenotypes for its individuality of response to environmental stressors. This nongenetic cellular memory, which records developmental and environmental cues, is the basis of epigenetic status. This type of nongenetic cellular memory appears to be florid in chemical sensitivity and chronic degenerative disease.

The lack of identified genetic determinants that fully explain the heritability of complex traits and the inability to pinpoint causative genetic effects in some complex diseases, such as chemical sensitivity, suggest possible epigenetic explanations for this missing information. There is a deprogramming of differentiated cells into pluripotent/totipotent states, which has led to *epigenetics* becoming shorthand for many regulatory systems involving DNA methylation, histone modification, nucleosome location, or ncRNA.

An epigenetic system should be heritable, self-perpetuating, and reversible,[2] which is what is seen in chemical sensitivity and many early chronic degenerative diseases. These criteria are observable

in patients with chemical sensitivity when they are challenged with environmental incitants like molds, algae, foods, some other biological inhalants, particulates, and chemicals. Whether histone modifications (and many ncRNAs) are epigenetic is debated, but general consensus is they are. Prions (infectious proteins) are clearly epigenetic, perpetuating themselves through altered folding states. These states can act as sensors of environmental stress and, through the phenotypic changes they promote, potentially drive evolution and individual function.[3]

Some people may suppress the activity of potentially deleterious DNA sequences; thus, epigenetics occurs. The activity of various populations of small ncRNAs[4] probably acts as tags for these deleterious sequences. These small RNAs (sRNAs) may also be involved in assessing parental compatibility at fertilization but also later in life as seen in some patients with chemical sensitivity. Similar RNAs are likely to be important determinants in paramutation, where homologous DNA sequences communicate in transit to establish heritable expression states,[5] which have been triggered by chemical and food exposure in patients with chemical sensitivity. Therefore, the traits for the development of chemical sensitivity may be predetermined but not the specific sensitivity to environmental triggering agents. These traits appear to occur through environmental toxins, bacteria, virus, mycotoxins, and internal excitotoxins, that is, excess glutamate and aspartate. Reprogramming is also critical for developmental phenomena such as imprinting in both plants and animals, as well as for cell differentiation, and is linked to the establishment of pluripotency in gametes and zygotes.

Adaptation to environmental changes and cell specialization in multicellular organisms require a complex orchestration of the transcriptional memory output of the genome. From the simplest prokaryote to the most sophisticated human neuron, cells have evolved forms of molecular memory of past stimuli that can often be transmitted through cell division. This principle is seen in the patient with chemical sensitivity after significant environmental exposure expressed through the ENT system. An example of the phenomenon is food and chemical sensitivity, which will trigger recurrent rhinosinusitis, pharyngitis, vertigo, sneezing, hoarseness, etc., after a massive exposure or a series of smaller exposures leading up to tipping the threshold of DNA methylation or other mechanisms. The maintenance of cell identity in multicellular organisms constitutes a classic example of such inheritable cellular memory: Starting from the same zygotic genome, subsets of progeny cells become engaged in distinct programs of gene expression that dictate their developmental trajectory and specific functions. These cells await the environmental triggers in order to express their chemical sensitivity response, which is often through phosphorylation of the protein kinase. Typically, cell identities are maintained for a lifetime, even when the differentiation signal was experienced only once, during embryonic development[6] or later in life. This is no trivial achievement, as a complex pattern of gene expression must be faithfully transmitted to each progeny cell upon division. This observation is emphasized when the symptoms of odor sensitivity of each cell division are seen in the patient with chemical sensitivity.

1. Epigenetic Signals

We use the term *epigenetics* to classify those processes that ensure inheritance and variation (*-genetic*) above and beyond (*epi-*) changes in the DNA sequence, which are seen in food, chemical, and electrical sensitivity. Unlike genetic alleles, epialleles do not differ in their DNA sequence; the epigenetic information resides in self-propagating molecular signatures that provide a memory of previously experienced stimuli, without irreversible changes in the genetic information. This principle allows for avoidance of toxics, neutralization of the chemical hypersensitivity, and precise nutrition replacement for therapy that will help the patient with chemical sensitivity. The nature of these molecular signatures and the manner by which they initiate, maintain, and reverse epigenetic states are clear. The ENT patient with chemical sensitivity and severe sensitivities fits our model of sensitivity proclaimed throughout this series of books on the mechanisms of chemical sensitivity.

According to Bonasio et al.,[2] three independent criteria should determine whether a certain molecular signal is indeed epigenetic: (1) the mechanism for propagation, that is, pathways that

explain how the molecular signature is faithfully reproduced after DNA replication/cell division; (2) evidence of transmission, that is, the demonstration of self-sustaining transmission to the progeny cells; and (3) the effect on gene expression, that is, a bona fide epigenetic signal should be sufficient to cause a transcriptional memory outcome reminiscent of that caused by the establishing stimulus.[3] Chemical sensitivity involving the ears, nose, and throat appears to meet these criteria. This situation becomes evident when triggering agents such as natural gas, pesticides, and phenol are defined, and their sensitivity and toxicity are propagated not only by themselves but also by other chemicals, foods, and molds and electromagnetic incitants. Here, they develop recurrent sinusitis, pharyngitis, balance irregularities, or hearing loss, faithfully carrying out the memory of the establishing stimulus.

According to Bonasio et al.,[2] epigenetic regulatory mechanisms are conservative in that no information is lost, and, given the appropriate signal, an epigenetic state can transition to a different one, as exemplified by the generation of induced pluripotent stem (iPS) cells from mouse embryonic fibroblasts (MEFs) by transient overexpression of cocktails of TFs.[7] Although embryonic stem (ES) cells and MEFs have very different gene expression profiles, H3K4me and H3K27me distribution, and DNA methylation patterns, MEF-derived iPS cells closely resemble ES cells, both at the transcriptional and epigenetic levels.[8] These observations not only demonstrate the plasticity of epigenetic signals but also confirm the interdependence between cell identity and epigenetic states. The patient with chemical sensitivity fits this picture in that once the hypersensitivity is triggered, many other environmental incitants can cause the same or similar symptoms. Often, in the patient with chemical sensitivity, organ involvement or symptoms can switch, even though the original symptoms usually stay, depending on the dose or combination of pollutants and triggering agents demonstrating plasticity. At times, the original symptoms are lost, and the symptoms of a new area of involvement occur. Then, the new hypersensitivity persists.

Epigenetic signals are responsible for the establishment, maintenance, and reversal of metastable transcriptional states that are fundamental for the cell's ability to remember past events such as exposure to environmental stressors like Pb, Cd, Hg, As, pesticides, solvents, natural gas, and formaldehyde. When chemical sensitivity develops, the cellular memory becomes superacute and hypersensitive, and the cell then releases histamine, serotonin, and other various substances, which will cause the patient with ENT involvement to develop symptoms.

As long as a transcriptional response is self-sustaining in the absence of the originating stimulus, it can be categorized as epigenetic. An example would be the patient who developed polio at a young age, which damaged the brain and peripheral nerves, but allowed relatively normal function. Then, after years of quiescence, this patient develops chemical sensitivity in response to a massive natural gas exposure. Chemical sensitivity is often triggered by physical trauma, a bacterial or viral infection, or an environmental agent, such as a pesticide or natural gas. It is then propagated by a myriad of other environmental agents (pollens, terpenes, newsprint, perfumes, molds, foods, etc.), the reaction, which is self-sustaining with reactions going on at times for days. This response condition, such as seen in patients with chemical sensitivity, can be achieved by self-propagating, transacting mechanisms, or by cis-acting molecular signatures physically associated with the DNA sequence that they regulate.

Self-propagating transcriptional states that are maintained through feedback loops and networks of transcription factors (TFs)[9] are the most common type of trans-epigenetic states. These are often the system of choice for cellular memory in simple organisms, such as prokaryotes and single-cell eukaryotes but also appear to occur in humans. If a TF activates its own transcription (or represses antagonistic networks), it yields an epigenetic state that is self-sustaining after the organisms' stimulus is removed. This state is often found in chemical sensitivity. However, it can be released as the total environmental and body load are reduced. Once the load is reduced enough, reactions become shorter and shorter until they disappear, but the memory of the incitants persists, and massive or constant low-level exposure may again activate the chemical sensitivity.

After each cell division, memory is inherited; TFs resumed their transfunction on regulatory DNA sequences. Some sRNAs can also act as trans-epigenetic signals.[2,10,11]

In contrast to trans-epigenetic signals, cis-epigenetic signals are physically associated and inherited along with the chromosome on which they act. For example, there can be a covalent modification of the DNA itself, such as DNA methylation, or as changes in histones, which constitute the protein backbone of chromatin. Histones can carry information in their primary sequence (histone variants), in posttranslational modifications often present on an N- and C-terminal tails, or in their position (remodeling) relative to the DNA sequence.[12–14] Cis-epigenetic information might also be encoded in chromatin through stable association of nonhistone proteins, higher-order chromatin structure, and nuclear localization.

It is often difficult to distinguish experimentally between trans- and cis-epigenetic signals. For example, initial observations implicated SWI/SN chromatin remodelers in transcriptional memory at the *Saccharomyces cerevisiae GALI* locus,[15] but cell fusion experiments rigorously demonstrated that the site of memory was in the cytosome,[16] a case of trans epigenetics. However, if two identical DNA sequences are differentially regulated in the same nucleus, cis-epigenetic mechanisms must be responsible. This is observed for monoallelic gene expression in diploid cell imprinting and X inactivation in mammals, wherein large portions of one X chromosome that are inheritable are silenced, while its homologue continues to transcribe in the same nucleus.[17] In fact, X chromosome inactivation involves many putative epigenetic signals and provides an excellent experimental and didactical model to study epigenetics.

If trans-acting transcriptional memory systems were readily available during evolution, why did the appearance of multicellularity expand the repertoire of cis-epigenetic signals? One possibility is that trans mechanisms were simply inadequate for tackling the increased complexity and number of transcriptional networks in a large multicellular organism. Epigenetic states that are encoded in cis need to be set only once, and many transcriptional patterns can be maintained by a relatively small number of common molecular pathways, without having to deploy trans-acting feedback loops for each gene network. Thus, there appears to be a basic mechanism for handling or not handling the environmental triggers observed in patients with chemical sensitivity who also have ENT involvement.

This condition of status of health appears to be involved in the patient with chemical and electrical sensitivity who encounters the toxic environment. This type of body realizes that it does not have the coping ability to handle the multitoxic load of chemicals and electromagnetic stimuli and thus becomes hypersensitive as a coping mechanism. This condition most likely occurs so that the body will not take in as many chemicals in the hypersensitive state as in the normal state.

Most epigenetic states are established by transiently expressed or transiently activated factors that respond to environmental stimuli (e.g., pesticides and transient exposures to petrochemicals, including natural gas and formaldehyde), developmental cues, or internal events (e.g., the reactivation of a transposon and excess glutamate). These establishment signals converge on chromatin to shape the transcriptional landscape. They are then converted into cis-epigenetic signatures. Many chemical stimuli are not significant and, therefore, are transient. However, others produce symptoms that last from minutes to hours to years, with the ENT system having a lasting memory of the chemical insult.

TFs orchestrate lineage-specification programs and are leading candidates as establishment signals.[18] In addition to recruiting factors that modulate transcription transiently, TFs also influence cis-epigenetic states.

DNA methylation satisfies all three requirements: (1) because of the semiconservative nature of DNA replication, a DNA sequence carrying symmetrical methylation marks on both strands gives rise to two hemimethylated double strands, which can be restored to fully methylated status by maintenance methyltransferases[19]; (2) in vitro methylated DNA remains methylated after several rounds of DNA replication in vivo[20]; and (3) methylation regulates transcription. It appears that propagation of chemical sensitivity in the patient with involvement fits this model.

2. Histone

The case for histone posttranslational modifications is less clear, and each mark should be considered separately. Some modifications exhibit strong correlation with transcriptional states[2]; however, correlation does not imply causation, and experimental evidence for the epigenetic inheritance of histone modifications remains scarce, but few studies appear solid.

Propagation mechanisms (criterion 1) have been proposed for several histone modifications in the form of the same histone modifier/binder interactions involved in signal reinforcement and spreading. This model assumes that the information to reestablish chromatin domains is transferred from the parental nucleosomes containing such modifications to those deposited on the two daughter strands. However, it remains unclear whether and how parental histones (and their associated modifications) are reassembled after DNA replication in vivo. Alternatively, domains of histone modifications could be propagated via an intermediary (secondary) epigenetic signal. This appears to be the case for H3K9me in *Schizosaccharomyces pombe* heterochromatin, where S-phase-restricted transcription of repetitive sequences generates sRNAs that direct the reestablishment of H3K9me after replication.[21]

Whether or not histone posttranslational modifications are transmitted (criterion 2) remains largely unknown. This question can be addressed by artificially recruiting a histone modifier to chromatin using the GAL4/upstream activation sequence (UAS) system and then measuring the persistence of the resultant histone modification through cell division after terminating the expression of the histone modifier. The GAL4/UAS can also be used to demonstrate that histone modifications cause (not only correlate with) a transcriptional response (criterion 3).[22] To date, only short-term (4 days) transmission H3K27me3 in cultured human cells has been observed,[23,24] but doubts remain regarding incomplete repression of the GAL4-fused histone modifier. In addition, polycomb repressive complex 1 remains bound to chromatin (independently of histone modifications) during DNA replication in vitro,[25] and MLL (a trxG protein) appears to associate with mitotic chromosomes,[26] suggesting that some chromatin modifiers may also function directly as cis-epigenetic signals.

Some epigenetic information is also transmitted through meiosis and gamete formation in multicellular organisms, giving rise to transgenerational inheritance. Many epigenetic signals appear capable of meiotic transmission, including maternally deposited TFs and piRNAs,[27] RNAs involved in pair of mutation in mice,[28] histone modifications in sperm chromatin,[29] and DNA methylation in plants.[30] In observing thousands of patients with chemical sensitivity at the Environmental Health Center-Dallas (EHC–Dallas) over a 40-year period, we have seen many families of two to three generations who appear to pass their propensity for chemical sensitivity. However, often, the environmental triggering agents may be different. They appear to be the result of individual exposure, which makes their condition unique. The question of whether these tendencies are transmitted by meiosis or other mechanisms is unclear, but they appear to give epigenetic signals, probably by both mitosis and meiosis.

Reversible chromatin changes and antagonism between TFs provide the basis for cellular plasticity, which obviously occurs in chemical sensitivity. Opposing TF networks reinforced by feedback loops direct the specification of hematopoietic and embryonic lineages.[14,31] Histone modification profiles are also the result of a delicate balance between antagonistic pairs of histone-modifying enzymes—for example, histone acetyltransferase versus deacetylase and histone methyltransferase versus demethylase.[12]

Nonetheless, the forced transition between two metastable epigenetic states requires a considerable *activation energy*, as evidenced by the poor efficiency of epigenetic reprogramming by nuclear transfer or overexpression of pluripotency factors. Cells that fail to fully overcome this barrier are trapped in an intermediate state, probably because of a failure in resetting epigenetic signatures.[8] For example, improper silencing of DNA hypermethylation and histone hypoacetylation of the imprinted *Dlk1-Dio3* cluster correlates with the failure of many iPS cell lines to generate chimeras.[32] Thus, small-molecule inhibitors of histone modifiers and DNA methyltransferases that stimulate reprogramming may do so by facilitating the creation of an *epigenetic tabula rasa*.[33] Since the patient

with chemical sensitivity has an energy defect, he or she may not have enough activation energy. When this failure of energy occurs, there may be a failure in cell lines with an increase in the hypersensitivity when there is an improper silencing of the DNA hypermethylation and histone hyperacetylation. This type of condition is seen in the patient with chemical sensitivity when avoidance or intradermal neutralization of response occurs. At times, with these modalities, we get total regression of symptoms with an increase in energy. At other times, we achieve partial neutralization of the hypersensitive response. At still other times, no neutralization is achieved. However, when this neutralization of the hypersensitivity occurs, but the increase in energy does not occur acutely after a period of weeks to months to years, we may get total neutralization of the adverse response.

Cis-epigenetic states, such as those presumably encoded by histone posttranslational modifications and DNA methylation, can be reinforced locally or spread to adjacent areas to form larger chromatin domains. This spreading phenomenon is seen in the patient with food and chemical sensitivities (see *Reversibility of Chronic Degenerative Disease and Hypersensitivity: Regulating Mechanisms of Chemical Sensitivity*[34]) who neglects dealing with the problem sufficiently by maintaining a massive avoidance program, periodic injection neutralizations, and nutritional replacement. This condition is particularly true in the ENT patient with recurrent sinusitis who can spread the problem to the adjacent bronchi and lung and then to the cardiovascular system when the sinuses become overloaded with excess food antigens or environmental chemical causes. In addition, a spreading of more sensitivities occurs until the patient becomes universally sensitive to environmental triggering agents. Feedback loops exist, in which enzymes responsible for the installment of a histone modification also interact with factors that bind to it as well as those that have the cis-epigenetic state. The local reinforcement may be necessary, because histone modifications are not permanent and may be removed by dedicated enzymes or histone turnover. We frequently see this process with avoidance and intradermal provocation neutralization (desensitization therapy) of the incitants in the patient with chemical sensitivity. The patients with severe illness may become nutritionally depleted if they are unable to replace the nutrients rapidly enough to maintain the histone turnover. The patients with chemical sensitivity then react until the turnover is complete.

On the other hand, spreading in cis may be required to extend the reach of epigenetic regulation beyond the confined area in which establishment took place. Toxics can rapidly spread to other organs causing more than local or regional dyshomeostasis. Spreading of chromatin domains is the basis of classical epigenetic phenomena such as position-effect variegation in Drosophila and formation of silent domains in S. cerevisiae.[17] It was also observed for artificially established H3K27me3 domains in human cells.[23] Thus, this spreading phenomenon seen in the patient with chemical sensitivity who gets worse clinically is a widely observed condition with pollutant exposure resulting in more hypersensitivity.

Epigenetic states can also be reinforced by cross talk among histone modifications and DNA methylation.[44] This state apparently occurs in patients with food and chemical sensitivities when they are in areas of high pollution, including molds and mycotoxins as well as toxic chemicals. De novo DNA methyltransferase and associated factors bind to unmethylated DNA,[36] providing a molecular explanation for the anticorrelation between H3K4me and DNA methylation levels.[37] This interplay suggests that, when present, DNA methylation may serve as a reinforcing signal for preexisting but less stable epigenetic signatures such as histone modifications. Chemical sensitivity may occur acutely, but usually, it occurs gradually progressing from an early episodic exposure to subsequent mild unstable sensitizations to more stable long-term sensitization, which occurs from a more minute exposure.

3. Noncoding RNA

ncRNA is a functional RNA molecule that is not translated into a protein. ncRNA genes include highly abundant and functionally important RNAs such as transfer RNA (tRNA) and ribosomal RNA (rRNA), as well as RNAs such as snoRNAs; microRNAs, siRNAs, and piRNAs; and the long ncRNAs that include examples such as Xist and HOTAIR. The number of ncRNAs encoded within

the human genome is unknown; however, recent transcriptomic and bioinformatic studies suggest the existence of thousands of ncRNAs.[38–41] Since many of the newly identified ncRNAs have not been validated for their function, it is possible that many are nonfunctional.[42]

The expression of many thousands of genes is regulated by ncRNAs. This regulation can occur in trans or in cis forms. In the human nucleus, RNaseP is required for the normal and efficient transcription of various ncRNAs transcribed by RNA polymerase III.

A number of ncRNAs are embedded in the 5′ UTRs of protein-coding genes and influence their expression in various ways. For example, a riboswitch can directly bind a small target molecule. The binding of the target affects the gene's activity.

ncRNAs have been associated with many diseases such as cancer, autism, Alzheimer's, and hearing loss.

Variation within the seed region of mature miR-96 has been associated with autosomal dominant, progressive hearing loss in humans and mice. The homozygous mutant mice were profoundly deaf, showing no cochlear responses. Heterozygous mice and humans progressively lose the ability to hear.[43,45]

The transcription process affects chromatin structure, but it is often difficult to ascribe this effect to the physical passage of RNA polymerase II (RNAPII) or to the synthesis of ncRNAs. Noncoding regions of the genome are heavily transcribed, giving rise to a constellation of ncRNAs that often have regulatory functions.[46] Although early investigations focused on posttranscriptional gene silencing by microRNAs and other sRNAs, pioneering work in *S. pombe* and *Arabidopsis thaliana* established that sRNAs also affect epigenetic states.[10]

Small ncRNAs are well suited for a role in bridging chromatin modifiers with the genome,[2] but to fulfill this function, they must interact in sequence-specific fashion with chromatin. Bonasio et al.[2] envision three modes of sequence recognition: (1) RNA/RNA interactions with nation transcripts,[10] (2) RNA/single-stranded DNA (ssDNA) heteroduplex, and (3) RNA/double-stranded DNA (dsDNA) triplex.[10]

4. Nucleosome Location

Although the nucleosome is a very stable protein–DNA complex, it is not static and has been shown to undergo a number of different structural rearrangements including nucleosome sliding and DNA site exposure. Depending on the context, nucleosomes can inhibit or facilitate TF binding. Nucleosome positions are controlled by three major contributions: First, the intrinsic binding affinity of the histone octamer depends on the DNA sequence. Second, the nucleosome can be displaced or recruited by competitive or cooperative binding of other protein factors. Third, the nucleosome may be actively translocated by ATP-dependent remodeling complexes.[47]

Nucleosomes are the basic unit of DNA packaging consisting of DNA wound around a histone protein core. Nucleosomes are folded through a series of successively higher-order structures to form chromosomes. This compacts DNA and creates an added layer of regulatory control. Nucleosomes are thought to carry epigenetic inherited information in the form of covalent modifications of their core histones.

Nucleosomes reconstituted on to the 5S DNA positioning sequences were able to reposition themselves translationally onto an adjacent sequence when indicated thermally.[48] Repositioning did not require disruption of the histone octamer, but was consistent with nucleosomes being able to slide along the DNA in cis form.[49] Although nucleosomes are intrinsically noble, eukaryocytes have evolved a large family of ATP-dependent chromatin remodeling enzymes to alter chromatin structure, many of which do so by chromosome slides.

Epigenetic signals are also transmitted from cell to cell in a horizontal fashion.[4] We see this phenomenon in patients with chemical sensitivity when they undergo intradermal provocation testing. Here, the patient may go from one to many cells spreading information regionally, but often, the reaction spreads throughout the body. This phenomenon is at the basis of the inheritance of RNA interference in *Caenorhabditis elegans* and occurs in plants, both in the germ line and

in the soma.[50,51] Here, two sensitivity cases occur in which sequence information is transmitted across cells to silence transposable elements. As noted, genomic DNA is exchanged between these cells; the epigenetic information must be transmitted in trans. In fact, it takes the form of sRNAs that direct DNA methylation of genomic sequences, converting a trans-epigenetic signal into a cis-epigenetic state.[51]

5. Prions

According to Halfmann and Lindquist,[3] the epigenetic phenomenon passes all mechanisms because biological traits do not involve alterations of the coding sequence of DNA.

Halfmann and Lindquist[3] discuss an extreme case of epigenetic inheritance with a mechanism that is not based on heritable changes in nucleic acid. Instead, it is based on robust self-propagating changes in the folding of certain proteins known as prions.

Prions operate outside the canonical steps of molecular biology's central dogma. As protein variation in sequences downstream of stop codons that are silent in the absence of the prion.

Many prion phenotypes resulted from qualitative changes in protein function. Because function is dictated by structure, the refolding of a polypeptide into its prion form can dramatically alter the nonprion function and can even create gains of function. Thus, chemical sensitivity could occur as the individual becomes hypersensitive, although this condition has not been defined in this type of patient. Aside from the ability to template their own conformational changes through homotypic interactions, some prion conformers form new interactions with other proteins.

Prions respond to environmental extremes, which certainly occurs with many chemical exposures as well as exposure to bacteria and viruses. The way the proteins fold and interact with other proteins is very sensitive to environmental stress and the status of the protein-folding machinery. Abrupt changes in temperature, pH, and intracellular metabolites, which can occur from toxic chemicals, bacteria, and viruses, can have immediate consequences for protein folding and the regulation of protein chaperones and protein-remodeling factors. Not surprisingly then, environmental stresses also dramatically increase rates at which prions appear and disappear.[52] We do see a fluctuating phenomenon in some patients with chemical sensitivity who become sensitive to some chemical stimuli but then with avoidance or reduction of the total body load lose their sensitivity. The more extreme the stress, the greater the frequency of prion switching. In this way, prions connect to environmental stresses with an unusual type of phenotypic plasticity that could improve the organisms will to adapt to alternate environments. When organisms experience protein homeostatic stress, which will commonly occur when they are poorly adapted to their environment, increases in protein *folding* and prion formation will facilitate the exploration of alternative types. Halfmann and Lindquist[3] postulate that the accelerated appearance of prions in response to stress constitutes an evolved bet-hedging strategy: it allows a fraction of cells to try new responses, with reasonable frequency, which proves beneficial.[53,54] The self-sustaining nature of prions ensures that successful strategies are immediately heritable to subsequent generations. Prions, then, are a quasi-Lamarckian[55,56] mechanism that connects environmental stressors.

a. Prions Allow for the Sudden Appearance of Complex Traits

Complex evolutionary adaptations are the product of multiple interacting genetic loci.[57] A possible mechanism for the parent's complex adaptations is phenotypic capacitance. Phenotypic capacitance is a property of certain biological systems that allows for accumulation of genetic variation in silence forms, followed by its sudden stepwise release to create new phenotypes.[58] Because prions allow cells to switch between two distinct and heritable physiological states, they provide one of the clearest examples for the reversible expression of natural genetic variation. In contrast to other mechanisms for genetically encoded stochastic phenotypic variation, such as Hsp90-buffered protein folding and variably methylated CpG islands,[59] newly revealed prion-based phenotypes are immediately and robustly heritable. These traits can ultimately become hardwired by subsequent genetic changes, as demonstrated for phenotypes revealed by Sup35 prion formation.[60] This observation

provides experimental validation for the conjecture of the West-Eberhard[61] change that in some cases may be followers rather than leaders in evolution.[62] This observation shows that both respond (directly or indirectly) to changes in the extracellular environment.

Yeast prions are well positioned to alter the phenotypic effects of genetic variation. The approximately two dozen prion genetic proteins discovered to date in yeast are enriched for proteins with information-processing functions, including TFs, and are in a-binding proteins.[53,63] Some, such as Swil, Cyc8, and Sfpl, are globally acting transcriptional regulators of a large fraction of the yeast genome.[64–66] Others such as Puf2, Pu69, and Pub1 act posttranscriptionally on the stabilities of hundreds of functionally diverse MRNAs.[67] Because of the large number of regulatory targets of these proteins, reductions or alterations in their activities resulting from their conversion to prion confirmation can have large and complex phenotypic effects. Importantly, these effects also change the strength of the selective pressures that act on prion targets, resulting in these target sequences diverging at different rates when expressed under the prion versus nonprion states. As a consequence, prions revealed in phenotypes will tend to differ between genetic backgrounds.[60] Thus, prions create phenotypic diversity on two levels: within isogenic populations, they create distinct physiological states (prion versus nonprion), and within genetically diverse populations, they enhance the effects of genetic variation between lineages.

An array of regulatory strategies influences protein folding and may in the future prove to blur distinctions between prions and other epigenetic mechanisms for perpetuating phenotypes. Covalent modifications, including disulfide formation, phosphorylation, ubiquitination, and glycosylation, as well as protein–protein interactions (such as chaperone binding and prion templating), can all profoundly change protein-folding landscapes and/or the activity of folded proteins. All of these forms of regulation can therefore especially give rise to self-sustaining heritable—that is, epigenetic—states. In fact, examples of these types of heritable factors now include an autoactivatable kinase, an autoactivatable protease, and a prion that appears to result from the interaction of two separate proteins involved in glucose signaling.[62,68]

As opposed to DNA methylation (which is typically inherited), some histone modifications are known to be reset in each generation. This reprogramming entails erasure of DNA methylation and loss of histone modifications (as well as loss of histones and histone variants); here, we focus on demethylation of DNA. The loss of DNA methylation by E13.5 (the developmental point of reprogramming) is truly global; in mouse female PGCs, only 7% of Cp Gs remain methylated (versus 70%–80% and ES cells and somatic cells), and most promoters and genic and intergenic trends. Posen sequences are hypomethylated at this stage. A programming process likely occurs. In the patient with chemical sensitivity, the reprogramming is accomplished by avoidance of the total body load of pollutants and the specific pollutant involved along with intradermal neutralization (desensitization) and nutrient replacement.

The origins of prions are ancient. The propensity of proteins to misfold and aggregate is probably as ancient as protein-based life forms themselves. Indeed, most polypeptides have an inherent tendency to form self-templated amyloid structures.[69] Prion-forming proteins are unusual in having a conformational flexibility that allows access to the amyloid fold under physiological conditions.[63,70] This property derives in part from a greatly reduced amino acid complexity as compared with that of globular proteins.[63,71] Halfmann and Lindquist[3] suggest that primordial proteins would have had similarly simple sequences, resulting in an elevated tendency to form self-perpetuating structures. Further, early biological systems would have lacked elaborate protein-folding machinery whose primary modern role is the prevention of protein aggregation. Without strong control over the important final step in the processing of gene encoded information—protein folding—ancient polypeptides would have unencumbered access to self-perpetuating prion states.

Our increasing awareness of prion phenomena highlights the fact that protein folding is not always uniquely specified by an amino acid sequence but instead provides a rich substrate for epigenetic determination of the map between genotype and other types. Beyond their speculative