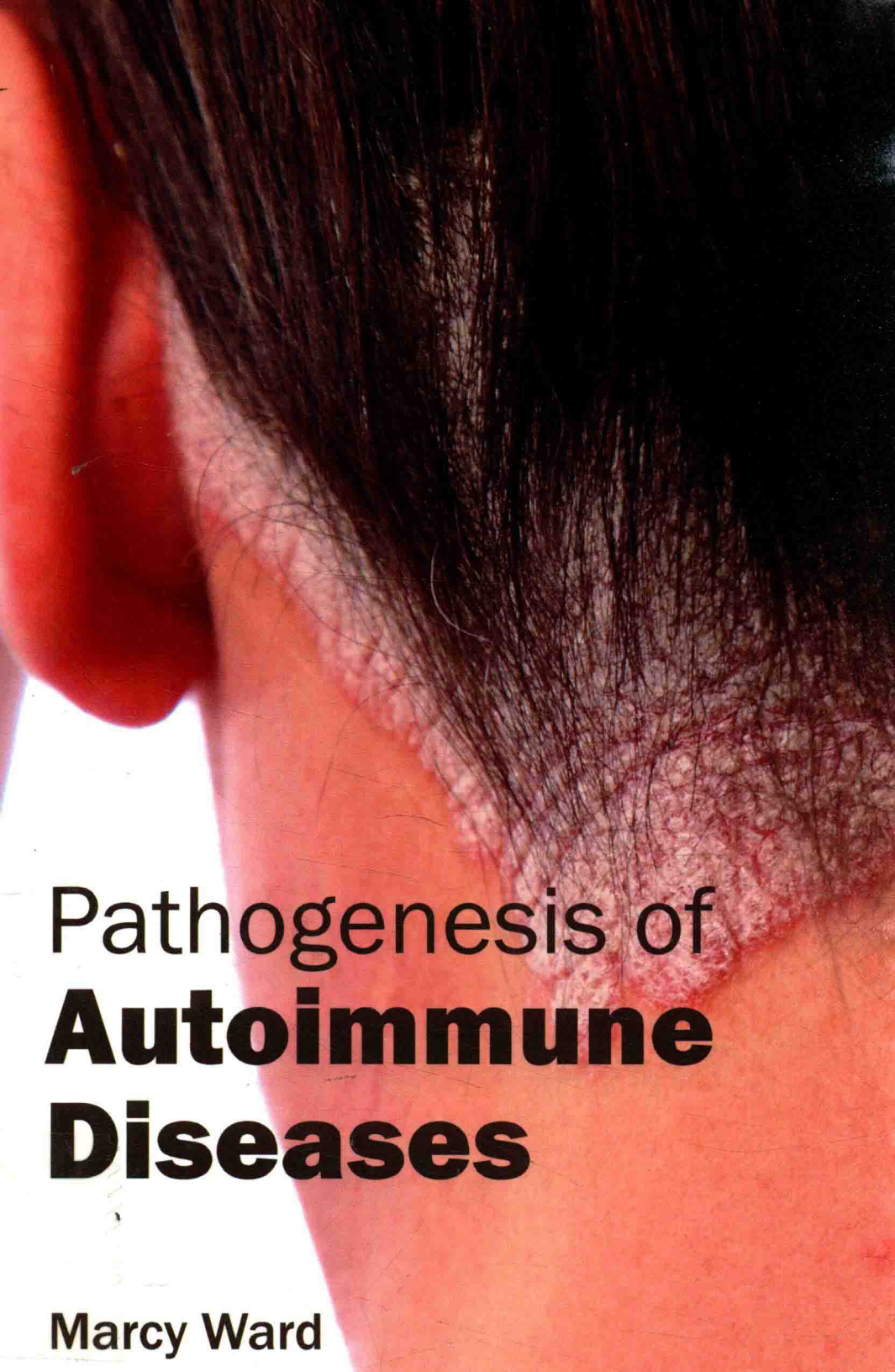

# Pathogenesis of **Autoimmune Diseases**

Marcy Ward

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Edited by **Marcy Ward**

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# Preface

This book was inspired by the evolution of our times; to answer the curiosity of inquisitive minds. Many developments have occurred across the globe in the recent past which has transformed the progress in the field.

Autoimmune Disorders refers to a heterogeneous and multifaceted group of diseases which can affect virtually any organ system of the human body. This book intends to present currently accessible manifestations by providing an etiopathogenetic overview of both systemic and organ detailed autoimmune diseases, comorbidities of autoimmune disorders, growth as well as new findings in the thrilling fields of osteoimmunology and immunology of pregnancy.

This book was developed from a mere concept to drafts to chapters and finally compiled together as a complete text to benefit the readers across all nations. To ensure the quality of the content we instilled two significant steps in our procedure. The first was to appoint an editorial team that would verify the data and statistics provided in the book and also select the most appropriate and valuable contributions from the plentiful contributions we received from authors worldwide. The next step was to appoint an expert of the topic as the Editor-in-Chief, who would head the project and finally make the necessary amendments and modifications to make the text reader-friendly. I was then commissioned to examine all the material to present the topics in the most comprehensible and productive format.

I would like to take this opportunity to thank all the contributing authors who were supportive enough to contribute their time and knowledge to this project. I also wish to convey my regards to my family who have been extremely supportive during the entire project.

**Editor**

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# Part 1

# Pathogenesis of Systemic Autoimmune Disorders: Genetic and Enviromental Contributors

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# Autoimmune Diseases: The Role of Environment and Gene Interactions

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## 1. Introduction

Data from epidemiological studies indicate global increase in the incidence and prevalence of numerous autoimmune diseases (AD) as seen in the United States (Jacobson et al.1997). According to estimate from the US National Institute of Health (NIH) the prevalence of AD is in the range of 23.5 billion. From 1996 to date at least 237,203 cases per year of AD are diagnosed in the US; and of this, 42,137 are new cases of primary glomerulonephritis, multiple sclerosis, polymyositis/dermatomyositis and systemic lupus erythematosus (SLE). Early in 1996 alone 6,722,573 women and 1,789,273 men suffered from varieties of diseases that had components of autoimmunity. Currently up to 150 autoimmune based diseases have been identified and approximately 40 more are awaiting confirmation. Similarly the incidence of several autoallergic diseases, type 1 insulin dependent diabetes mellitus (IDDM), rheumatoid arthritis, and Graves' disease, hyperthyroidism included are on the increase. Of the 1.2 million new cases of AD diagnosed every 5 years, at least one or more cases will include these autoimmune disease components. (Jacobson et al.1997)

The global incidence and prevalence for each AD is currently lacking and that calls for improvement on data collection and reporting. Nearly 10% of developed world's population suffer from AD and contribute significantly to chronic diseases and mortality. Women are three times more likely to be at risk than men in acquiring these diseases with non-Caucasians at higher risk. We are also seeing global prevalence of allergic respiratory diseases on the increase for the past 20-30 years. Over 15 million people in US suffer from asthma alone; approximately 50 million are diagnosed with some form of allergic diseases (Smith et al, 1997). Presently the direct annual health care cost for AD in US is in excess of $100 billion US dollars as compared to $57 billion for cancer. Hospitalization alone takes over half the cost of the direct expenditures. Almost 20% of the population classified as 'high-cost patients' consume more than 80% of the resources. Consequently the cost to public health from clinical management of these conditions is on the increase. All indications point to future better

management of asthmatics through research and interventional efforts directed at communities, hospitalizations and high-cost patients in order to decrease health care resource use and provide cost savings. This calls for rigorous investigations into the role of environmental xenobiotics/substances and/or pollutants that are risk factors in the development of autoimmune diseases. In this chapter we intend to survey the public health concerns imposed by pollutants of the air, water and the food chain with concentration on typical examples of the effects of mercury on health to demonstrate the likelihood of dangers imposed through environmental and genetic disturbances in health.

## 2. Environmental chemicals and autoimmune diseases

Many scientists concur that several species within mammals to amphibians, birds, reptiles, and fish so far under monitoring systems are close to total extinction; well over 30,000 plant and animal species are estimated to be lost each year, a morbidity rate generally agreed to be much faster than at any time. Loss of species seems to be explained in most cases through the global weather changes as well as pollutional activities of man. But industrial activities seem to play major role in this problem; the latest data emanating from the industrial front estimate that at least 85,000 possible pollutants are currently being released into the environment through industrial activities alone http://www.epa.gov/glnpo/lmmb/substs.html (FDA/EPA).

### 2.1 Chemicals and substances of public health concern

These pollutants cover the heavy metals like thallium, aluminium, cadmium, lead, gold and mercury as well as pesticides, herbicides, preservatives, dyes, plastics, bisphenol A and rubber products. The Environmental Working Group indicated from studies in 2005 that a cocktail of 287 pollutants are measured in new born US fetal cord blood (http://www.ewg.org/reports/bodyburden2/execsumm.php). Perfluorooctanoic acid (*PFOA or* C8), and perfluorooctanoate, a synthetic but stable perfluorinated carboxylic acid and fluorosurfactant PFOA's were included in the findings as well as pesticides, dioxins, flame retardants. Recently another concern has been brought to the limelight by the internal Florida Department of Environmental Protection (DEP) Workgroup. It is stated that the current update of the American Chemical Society's Abstract Service reveals that as of August 2007 over 98% of the commercially available compounds are not under regulatory practices as they should be. This amounts to about 15 million out of over 32 million substances commonly referred to as Emerging Substances of Concern, or ESOC that have been registered for regulation (Chemical Abstract Service [CAS] website): http://www.cas.org/cgi-bin/cas/regreport.pl.

Much uncertainty surrounds the outcome from releases of these substances into the environment. No information about the pharmacokinetics or pharmacodynamics interactions among life forms on these substances are available. No available information on transport and toxicological effects are on record. Within two years between 2005 and 2007 over 5 million new chemicals have been reported to be registered and 5 million more chemicals became commercially available. Currently CAS informs that within each week more than 50 new substances or additions to existing substances to the database is the norm; http://www.cas.org/index.html. Apparently the ratio of unregulated to regulated chemicals keeps growing exponentially. The ESOC chemicals fall under various categories of organic groups encompassing from flame retardants (PBDEs), pharmaceuticals to endocrine-modulating chemicals (EMCs), nanoparticles to biological metabolites as well as newly discovered Industrial chemicals and toxins. They are constantly being discharged into

the environment where they find their way into our water bodies posing an unknown level of risk to life forms including humans, animals, and plants.
Regulatory Agencies are therefore challenged to find answers to solve what may be an unknown outcome of these ESOC substances being continually released into the biosphere. In the absence of detail knowledge on the environmental outcome and without effective regulation no useful assessment can be made on the environmental risk posed. Thus vast majority of ESOC substances have to be non-traditionally managed by other means such as prevention and effects-based environmental assessment methods. That effort is even more tasking and presents difficulties in monitoring the trends of the etiology of diseases now becoming prevalent in the environment under such practices. ESOC substances are now recognized to be of global concern; among these are included polybromina -teddiphenyl ethers (PBDEs), perfluorooctanoic acid (PFOA), siloxanes, perfluorooctanesulfonate (PFOS) and hexa- bromocyclododecanes (HBCDs). PBDEs and HBCDs come under flame-retardant chemicals that are moderately long-lived and volatile; readily released to the atmosphere because they do not strongly bind to substrates. Once in the atmosphere they are globally transported and readily bioaccumulate in biological tissues.

### 2.1.1 Nanoparticles

Human activities now have added sources of environmental contaminants. Human-originated nanomaterials are naturally man-made structures that differ in size range from 1 to 100 nanometers (nm). They are commonly used in drug delivery nanotherapeutic pharmaceuticals, cosmetics, personal care products, energy storage products, fabrics, lubricants and equipments like golf balls. The use of nanomaterials has been on the increase and now it is ubiquitous. Their minuscule sizes allow traversing not only biological membranes but also the blood/brain barrier (BBB) and display physical and chemical properties different from parental compounds. Examples are gold or silver metals known to be inducers of autoimmunity but also possess magnetic properties.
The intrinsic stereospecificity of these substances allow these molecules to play significant toxicological role in the environment (Donaldson et al 2004) and are therefore of public health concern. Carbon black displays enhanced severe effect than titanium dioxide (Renwick et al 2004), while the nanoparticle sizes of both chemicals are inducers of increased lung inflammation and destruction of the epithelial linings than their larger size. Adsorptions onto the surface of nanoparticles may play synergistic role in the reactivity; in vitro studies with fractions of diesel exhaust particles showed effects on cells (Xia et al 2004). Atmospheric nanoparticles may be complex enough to form interactions with organics and metals capable of higher levels of toxicity; metallic iron potentiates the effect of carbon black nanoparticles resulting in enhanced reactivity displayed as oxidative stress (Wilson et al 2002). Conversely other combinations with pullulan (polysaccharide polymer of maltotriose units, also known as α-1,4- ;α-1,6-glucan) and dextran tend to reduce toxicity of the respective nanoparticles (Gupta and Gupta 2005, Berry et al 2003).
Some nanoscale materials may be catalytic or behave as semiconductors, properties that can only increase the likelihood that nanomaterial could produce unanticipated toxicological effects. Nonbiodegradable ceramics, metals and metal oxides within nanomaterials are quite environmentally stable and persistent (EPA, 2007) and therefore undergo bioaccumulation in the food chain (Biswas and Wu, 2005). They are currently implicated in the induction of acute and chronic biological toxicity (Oberdörster, 2004a and 2004b; Lovern and Klaper, 2005; Lam et al., 2004; Shvedovaet al., 2005; Fortner et al., 2005) of unknown physiological mechanisms and hence consequences.

### 2.1.2 Particulate matter

Nanoparticles compare with particle pollution or particulate matter (PM), a group of complex mixture of extremely small air-borne particles and liquid droplets in air suspensions. There are a number of components covering acids (nitrates and sulfates, organic chemicals, metals, soil or dust and sulfates, organic chemicals, metals, soil or dust or mold spores). Particles less than 10 micrometers in diameter ($PM_{10}$) pose an even worse health concern because of their inhalation properties that allow for accumulation in the respiratory system; they are found in all types of combustion (motor vehicles, power plants, wood burning, etc.) and some industrial processes. Severe health risks are posed among fine particles less than 2.5 micrometers in diameter ($PM_{2.5}$). Fine particles easily lodge and penetrate deeply into the bronchial tree and into the deepest alveolar areas of the lung upon inhalation. Coarse particles measuring between 2.5 and 10 micrometers are derived from crushing or grinding operations, and dust from paved or unpaved roads.

Properties of PM link them to a variety of significant health problems starting from offensive asthma to early mortality of exposed patients who suffer from cardiac and bronchial diseases. Exposures to PM result in high rate of respiratory symptoms involving irritation of the airways, coughing, or difficulty breathing, decline in lung functions, aggravated asthma, and development of chronic bronchitis, irregular heartbeat and nonfatal heart attacks. Individuals with a variety of health issues particularly those with prior heart or lung diseases tend to suffer premature deaths on exposure to PM. Children and older adults are the most likely to be affected by particle pollution exposure but healthy individuals are found to experience temporary symptoms from exposure to elevated levels www.epa.gov/asthma; and plays esthetic role by significantly effecting visibility impairment in the nation's cities and national parks. To protect public health and welfare, EPA has continually issued National Ambient Air Quality Standards (NAAQS) since 1971 for six criteria pollutants among which are particulate matter and Sulfur Dioxide ($SO_2$), Ozone ($O_3$), Nitrogen Dioxide ($NO_2$), Lead (Pb), and Carbon Monoxide (CO). The NAAQS from EPA has undergone revisions in 1987 and 1997 and again in September 2006 and it is helpful to familiarize oneself; there is an urgent need for studies to unravel the pharmacokinetics and pharmacodynamics of these particles to help disclose the role played in disease pathogenesis especially concerning the autoimmune state- asthma being one of the priorities.

## 3. Autoimmune diseases: etiologies and mechanisms

All indications show that tissue burdens of PBDE in life forms including humans are doubling in every two to five years. Human breast milk has been found to contain as much as 419 ng/g lipid weight of PBDE (Schecter et al., 2003). The question then arises whether these molecules contribute to what we measure in the increases in the incidence of ADs. These substances are known to interfere with the reproductive and developmental stages of mammals as well as in birds and invertebrates (McKernan *et al.*, 2006, Wollenberger 2005); they are carcinogenic, endocrine-modulating, and have neurotoxicological effects (Birnbaum, 2005). Autoimmune diseases present a major affront to the health of Americans as well as of global concern. Vast arrays of diseases come under auto-allergic/-immunity; these cover maladies that may present as localized to be organ specific or systemically distributed to the extremities to involve all organ systems typically noted in systemic lupus erythematosus (SLE). In health the Immune System guards us against invasion of foreign

substances including harmful bacteria, viruses, and parasites quite well without any perturbation. At times, however this machinery loses control and begins to attack even the self itself. Hypersensitivity responses resulting from direct attack of body components by antibodies or immune cells instead of attacking foreign substances alone generally come under autoimmunity or autoallergic responses. Autoimmune state becomes apparent with rise of demonstrable presence of autoantibodies or complexes of these with body substances or the presence of cells, T lymphocytes that attack self-constituents. Minor and harmless autoimmune states exist in normal persons in general; it is part component of the defense system as envisaged by Jerne's hypothesis (<http://www.enotes.com/microbiology encyclopedia/). In the disease state, however, autoimmunity becomes defined when the benign state results rather in pathology; it sets in motion homeostatic deterioration. The process is dependent on both genetic influences and environmental triggers.

For the past decades it has been conclusively demonstrated that alleles of the major histocompatibility complex (*MHC*) contribute to the susceptibility to autoimmunity but relatively recently there is an unparalleled discovery of novel genes in molecular pathways implicated in autoimmunity. Some of the variants identified clearly participate in the modulation of T-lymphocyte (T-cell) activation and do contribute to many different forms of human autoimmunity. Other genes tend to have restricted roles, with susceptibility apparently confined to one autoimmune condition or to a specific ethnic group. To gain insight into the initiation mechanisms of autoimmune diseases requires identification of the genetic determinants underlying disease pathogenesis and this implicates new biochemical pathways. The Autoimmune state may be either the direct originator of disease itself or arise as a secondary disease from perturbations from other chronic diseases. Direct autoimmune states are phenotypically demonstrated in patients that have antibodies in the active disease phase: examples are represented by idiopathic thrombocytopenia (ITP), Grave's disease and myasthenia gravis, pemphigus vulgaris and bullous pemphigoid, diseases that can be transferred among species through antibody transfers.

Disease transfer through T lymphocytes exchanges have not conclusively been demonstrated to lead to pathology but with the aid of cytokines may rather alleviate or exacerbate disease state. Indirect cause of autoimmunity has been defined by Rose and Bona, 1993 as when disease can be induced in an animal model. SLE is well represented by several genetically determined mouse models which, while not exactly clinical replica of the human disease do very closely replicate pathological and serological characteristics clinically seen to occur. Hashimoto's thyroiditis and multiple sclerosis can be reproduced by immunizing animals with an antigen analogous to the putative autoantigen of the human disease. Absence of direct and indirect evidence with markers describing the state of autoimmunity become circumstantial: positive family histories for disease, presence of certain MHC class II alleles are examples.

Currently it takes a great effort to assess accurately the initiation levels of these diseases in humans; the very initiating factors are difficult to focus on and in which stage/s or area of the metabolic processes gets initially disturbed becomes challenging to screen and allow for therapeutic management. Majority of ADs such as multiple sclerosis (MS), insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and thyroiditis one finds representative spectrum of autoimmune diseases that appear to have etiological background in dysregulated immune system. Enough supporting evidence exist to confirm the autoimmune nature of many of these disorders but still it is gravely challenging to decipher their precise etiology and/or the initiating factors. Of late a small fraction of the T cells, the regulatory T cells are among the focal area of studies and have become recognized as

particularly crucial for control of autoreactive immune responses. Normally the processing of a self antigen by the antigen presenting cells (APC) allow binding of processed antigenic fragments to the MHC molecules within the APC followed by display of these MHC-peptide complexes on APC's membrane surface for presentation to the appropriate T cells; this eventually terminates in activation of antigen-specific T cells. These T cells are then capable of attacking the self tissues expressing that particular self antigen. The process is believed to be the critical steps in the initiation of anti-self T cell responses.

Genome wide studies indicate that costimulatory signals examplified by CTLA4 or PD1 and the modulators of T-cell receptor signaling (LYP, encoded by *PTPN22*), somehow must be confirmatory key checkpoint for human autoimmunity as happens in the T-cell during the period of T-cell receptor training to eliminate self-antigen carrying T cells in the thymus. This notion of the crypticity of self antigenic determinants (Sercarz et al., 1993; Moudgil and Sercarz, 2005) takes strength from the premise that rely on potentially immunogenic regions (determinants/epitopes) within a self antigen that are processed and presented by the MHC molecule to T cells at different levels of immunogenecity. This means that certain 'dominant self' epitopes are well processed and presented, whereas others, the (cryptic or recessive self) (Sercarz et al., 1993) ones are poorly or never processed and presented. Thus this type of staging of determinants (dominance/crypticity) in turn plays a critical role in thymus gradation of the T cell repertoire: the T cells specific for dominant self epitopes are tolerized with ease while those purportly aimed at cryptic self epitopes evade tolerance induction and become part of the mature T cell repertoire (Gammon and Sercarz, 1989; Cibotti et al., 1992; Sinha et al., 2004).

T cells that evade tolerance induction are capable of being activated in the periphery under certain stressful inflammatory circumstances such as occur during infection; this has the consequence of enhanced processing and presentation of once latent (cryptic) determinants (Lehmann et al., 1992; Lanzavecchia, 1995). These activated T cells at times are capable of escaping appropriate constraint from regulatory T cells and permitted to execute their effector function of initiating autoimmune damage. The unveiling of previously cryptic determinants leading to activation of self-reactive T cells that escaped tolerance induction during thymic selection, owing to the crypticity of self determinants is considered a primary cornerstone of a theory of autoimmunity (Moudgil and Sercarz, 2005). The idea of determinant hierarchy provides a vital link between the thymic selection of potentially autoreactive T cells and the subsequent activation of these T cells in the periphery under conditions that facilitate the revelation of previously cryptic determinants. Peripheral ongoing immune tolerance of the mature immune system also attracts attention as another source of autoimmune initiation. This idea is supported by variations seen in the expressions of "self-antigen" in the thymus (e.g., insulin in T1D); in this instance T-cells are selected for survival according to the affinity of their cell surface receptors for self-antigen. This may represent a major key step in the genesis of autoimmune disease.

Other means of autoimmune genesis stem from APCs. These cells play crucial role in antigen processing and presentation to the T-helper (Th) cells. Dendritic cells for example are key cells in the initiation and perpetuation of immune responses. Highly polymorphic genes within the *MHC*, with links to autoimmune inductions, encode proteins to which antigens bind and presented directly to T-cells by APCs. Another source of autoimmune initiation focus on the cell surface marker CD4-positive Th cells; they are the conductors of the adaptive immune response and many genes with an established role in autoimmune disease have their expression in this cell type.

Autoimmune diseases present specific issues that need attention. Drugs used to manage known chronic and acute diseases are implicated in triggering and are therefore thought to be indirect causes of various autoimmune diseases following administration. Many of the prescription drugs commonly used for highly prevalent diseases come under this category: these inexhaustively include drugs like Alferon N, Allopurinol, Atenolol, Atorvastatin, captopril, Penicillin, Carbamazepine, chlorpromazine, Chlorthalidone, cimetidine, Ethosuximide, gold salts, griseofulvin, Hydralazine, Interleukins, Infergen, Interferons, Interferon Alfa, Hydrochlorothiazide, Intron A, Isoniazid, Levodopa, Lithium, Lovastatin, Mesantoin, Methimazole, Methyldopa, Methylsergide, Metoprolol, Minocycline, Minoxidil, Ophthalmic timolol, Nitrofurantoin, Oral contraceptives, Quinidine, Phenytoin, PegIntron, P-aminobenzoic, Penicillamine, Perphenazine, Trimethadione, Pravostatin, Phenylbutazone, Procainamide, Valproic acid, Propylthiouracil, Simvastatin, sulfasalazine, sulfonamides, streptomycin, Sulfonamide antimicrobials, Tetracyclines, Tiotropium Bromide inhaler and Tumor Necrosis factor.

The concern here can well be summarized with the incidence and/or prevalence of asthma, one of the most common chronic diseases of childhood estimated to affect 6 million children. More than 22 million Americans are diagnosed with asthma, and approximately 50 million of individuals are diagnosed with some form of allergic diseases. Presently in US the annual direct health care cost for AD in general is in excess of $100 billion US dollars as compared to $57 billion for cancer. Hospitalization alone takes over half the cost of the direct expenditures. "High- cost patients" that form about 20% of the population spend more than 80% of the resources. As a result, the cost to public health from clinical management of these conditions is on the increase.

## 4. Global problems associated with asthma and COPD

Epidemiological data following the natural history of asthma reveal that in 1999 mortality rates from the disease declined in comparison to previous years. This was followed by a surge in recent decades in asthma prevalence also in the United States and other Western countries; data suggest this trend may also be reaching a plateau. The general trend of global asthma incidence is rising worldwide but looking at US data we see increased morbidity and mortality from asthma from 1980s -1990s with plateau in the 1990s. This finding is the reverse of what was seen in the 1978-1980 where an increase in mortality due to asthma was measured: from 1990-1999 mortality declined. Commencing from 1995 the rate of outpatient visits for asthma increased; whereas the rates of hospital admissions declined *from 19.5 per 10,000* of the population in 1995 to *15.7 in 1998* attributed to enhanced rates of dispensed steroid prescriptions for inhaled medications. This finding has been interpreted as due to the improved treatment of asthma responsible for these favorable developments.

The implication, if it holds supports explanations of certain changes in environmental chemicals releases. Recent increases in asthmatic conditions in the population may be linked to many causes the cardinal one being the amount and types of substances that are being released increasingly into the biosphere. Releases of substances most of which have an unknown effect and still others closely linked to inductions of asthmatic features in the ever increasing population with genetic predispositions present ominous threat to the very survival of several species including man himself.

Exposures to environmental factors early on in childhood play significant role in the risk in developing asthma. Clinicians have known for quite a while that asthma is not a single disease. Risk to asthma stems from early environmental factors as well as the presence of

susceptibility genes; subsequent disease induction and progression from inflammation as well as response to therapeutic agents plays big roles in disease etiology. It is a typical consequence of environmentally induced autoallergic disease known to be heterogeneous (Asosingh et al 2007, Dompeling et al, 2000, Dweik et al, 2001, Kharitonov and Barnes, 2001, Weiss, 2002, Pascual and Peters 2005, Salvato, 2001, Wu et al, 2000) existing in many forms. The immunologic profile of the asthmatic airways presents as proliferation and activation of helper T lymphocytes (CD4+) of the subtype $T_H2$ responsible for the allergic inflammation in atopic asthmatics. Upon stimulation these cells release a number of cytokines covering IL-4, agent for IgE synthesis, IL-5, essential for eosinophils' maturation, and IL-3 and granulocyte-macrophage colony-stimulating factor, GMCSF (Bolland and Ravetch 2000, Candore et al, 2002, Lang et al, 2010, Pollard et al 1997).

In allergic as well as nonallergic individuals we observe populations of eosinophils in the airways with increased levels in asthmatics with allergies http://www. clevelandclinicmeded .com/ medical pubs/disease management/allergy/ bronchial-asthma/that have higher rates of asthmatic attacks. These cells serve as the source of mediators that exert damaging effects on the airways. Ultimately, mediators lead to degranulation of effector/proinflammatory cells in the airways that release other mediators and oxidants, a common final pathway that culminates in chronic injury and inflammation commonly seen in asthma. Chronicity of the asthmatic condition has been confirmed by several parameters. Low pH and high output of reactive oxygen and nitrogen species (ROS) during asthmatic exacerbations are specific biomarkers in expired air reflecting altered airway redox problems (Clynes et al, 1988, Comhair et al, 2000, De Raeve et al, 1997, Dweik et al 2001). Superoxide, hydrogen peroxide, and hydroxyl radicals are among ROS agents that are responsible for the inflammatory changes in the asthmatic airway (Candore et al 2002, Bolland and Ravetch 2000, Pollard et al, 1997). These ROS originate from the lungs of asthmatic patients induced by activated inflammatory cells (ie, eosinophils, alveolar macrophages, and neutrophils) (Holgate et al, 2000).

Pathogenicity in asthma in particular is portrayed by overall interactions between neural mechanisms, inflammatory cell mediators such as leukotrienes and prostaglandins, and intrinsic abnormalities of the arachidonic acid pathway and smooth muscle; all these cells play significant roles in the initial as well as disease progression. Inflammation is the most likely etiological basis of airway hyperreactivity and variable airflow obstruction.

Asthma usually persists into later childhood and adulthood from early childhood in the presence of the appropriate genetic background. Tolerance to allergens is a normal security that prevents such responses, but the specific immunological events that mediate tolerance in this setting are still under scrutiny. Despite the explosion of information about asthma, the nature of the basic pathogenesis has not been established. However, asthma clearly does not result from a single genetic abnormality, but is rather a complex multigenic disease with a strong environmental contribution. For example, asthmatic children and adults sensitive to inhalant allergens such as dust mites, mold spores, cat dander, etc portray such reactions right from childhood compared with adult-onset asthmatics. Local epithelial environment within the connective tissue is believed to be actively involved in regulation of events and the relation between the airway epithelium and the subepithelial mesenchyme is proposed to be a key determinant in the concept of *airway remodeling* (Davies et al, 2003; Weiss, 2002; Li and Wilson 1997, Pascual and Peters, 2005, Salvato 2001). Difficulties and/or problems underlying diagnosis and classification of these diseases are simply due to the fact that most of the ADs become apparent only at variable phases of several chronic stages of organic ailments. Some ADs present as auto allergies covering several fields of diseases: the

incidence of several of these diseases is also on the increase and covers type 1 insulin dependent diabetes mellitus (IDDM), rheumatoid arthritis, and Graves' disease, hyperthyroidism included. There is scarcity of information on the global incidence and prevalence for each AD. Some autoimmune/allergic diseases (AD) can be seen in cases of chronic obstructive pulmonary diseases (COPD). As such the incidence of these disorders has not been well defined. However, sharp global increases in the prevalence have been observed in the United States.

Etiological initiators of and pathogenesis of most ADs are obscure; they are presumed to be numerous with cigarette smoking a typical COPD-associated. Cigarette smoking is clearly the major risk factor for COPD but exposures to other noxious substances including dusts and chemicals found under occupational settings are known to contribute to the development of the disease (Pauwels et al, 2001).The attributable fraction contributing to COPD cases caused by occupational exposures is estimated to be in the range of less than 15% to as high as 31% among those who never smoked (Hnizdo et al, 2004). We find that minority groups have been historically overexposed to hazardous industrial substances and are candidates with increased risk for work-related airflow obstruction putting them highly in the AD group as well; making it necessary to improve on data collection and reporting. Estimation shows, however that nearly 10% of developed world's population suffer from AD and contribute significantly to chronic diseases and mortality. Women are three times more likely at risk than men in acquiring these diseases with non-Caucasians in the higher risk groups. The global prevalence of allergic respiratory diseases including COPD has been also on the increase for the past 20-30 years.

## 5. Mercury as environmental inducer of autoimmunity

Psychoneuroimmunological studies demonstrate in various ways that homeostatic regulation of the internal milieu links the soma with the neural pathways; stressors effects relate the two in bidirectional pathways. Current Naturopathic Medical view of diseases also links the involvement of the genes to autoimmune proneness. In this wise the authors concentrate on the metal mercury as a representative highly reactive toxic agent within the body as a means of gaining an insight into the problem of etiologies of autoimmune diseases. Mercury has a high affinity binding to *sulfhydryl* as well as to *hydroxyl, carboxyl,* and *phosphoryl* functional groups very commonly displayed on macromolecules, proteins and the genetic materials. It is widely distributed as an environmental and industrial pollutant. No known beneficial metabolomic effect is assigned to mercury in the physiology of humans, yet a 70 kg man is loaded with an equivalent of 13mg mercury (Pier, 1975) distributed in the skin, nails, hair, and kidneys. The net outcome of exposure to mercury is dose-dependent and at low concentrations mercury is the agent for the induction of several diseases that affect most systems of the body.

The central nervous system (CNS), the brain and the kidneys suffer most where Mercury Induced Autoimmunity (MeIA) can be particularly threatening in onset and severe among especially non-Caucasians that manifest *defined* major histocompatibility complex (MHC) haplotypes. Several data confirm that mercury is also associated with polyclonal cell stimulation. Mercury Induced Autoimmunity (MeIA) engages helper T lymphocytes in the induction of disease process in responder animals (Jiang YG, Möller G 1995, Horwitz and Stohl, 1993; Puck JM, Sneller MC. 1997) and in humans (Liossis et al 1996). It is suggested there is a genetic basis for airway hyperresponsiveness with linkage to chromosomes 5q, 11q (Li and