**hyperimmune** - Having large quantities of specific antibodies in the serum from repeated immunizations or infections.

**hyperimmune adjective** Referring to an immune state characterized by an abundance of one or more immunoglobulins, due to repeated exposure to one or a limited palette of microorganisms. - McGraw-Hill Concise Dictionary of Modern Medicine


“In autoimmune disorders, the immune system produces antibodies to an endogenous antigen (autoantigen). The following hypersensitivity reactions may be involved:

- Type II: Antibody-coated cells, like any similarly coated foreign particle, activate the complement system, resulting in tissue injury.
- Type III: The mechanism of injury involves deposition of antibody-antigen complexes.
- Type IV: Injury is T-cell-mediated.

Several mechanisms may account for the body’s attack on itself. Autoantigens may become immunogenic if they are altered in some way. Alternatively, antibodies to a foreign antigen may cross-react with an unaltered antigen (eg, antibodies to streptococcal M protein may cross-react with human heart muscle). Or antigens normally sequestered from the immune system can become exposed and cause an autoimmune reaction (eg, systemic release of melanin-containing uveal cells after eye trauma triggers sympathetic ophthalmia).

**Autoantigens may be altered chemically, physically, or biologically:**

- **Chemical:** Certain chemicals can bind with body proteins, making them immunogenic, as occurs in drug-induced hemolytic anemia.
- **Physical:** For example, ultraviolet light induces keratinocyte apoptosis and subsequent altered immunogenicity of autoantigens, resulting in photosensitivity, as can occur in cutaneous lupus erythematosus.
- **Biologic:** For example, in animal models, persistent infection with an RNA virus that combines with host tissues alters autoantigens biologically, resulting in an autoimmune disorder resembling SLE.”
Overall, autoimmune diseases are common, affecting more than 23.5 million Americans. Autoimmune diseases have been found in virtually every organ system in the body and are a leading cause of death and disability. The population of the U.S. is about 319 million which means autoimmune diseases have been diagnosed in 7.37% of the population.

The National Institutes of Health estimates up to 23.5 million Americans suffer from autoimmune disease and that the prevalence is rising. American Autoimmune Related Diseases Association says that 50 million Americans suffer from autoimmune disease. This increases the rate of autoimmune to 15.67%. Autoimmune diseases affect around 5% of the world population, particularly people from developed countries (this is likely 10%).
Between 2001 and 2009, the incidence of type 1 diabetes increased by 23%, according to The American Diabetes Association. Celiac disease, which causes the body's immune system to attack the small intestine, is also on the rise, according to the U.S. National Institutes of Health and the University of Chicago Celiac Disease Center. In the United States, 1 in 133 people are affected by celiac disease.

Autoimmune diseases can be classified into two groups: organ-specific or systemic. Organ-specific is when the immune response specifically reacts against autoantigens located in a specific organ. Some examples of organ-specific autoimmune disorders are diabetes mellitus type 1, multiple sclerosis (MS), primary biliary cirrhosis, Hashimoto's thyroiditis, and Grave’s disease, among others. Systemic autoimmune disorders include RA, SLE, Sjögren’s syndrome, and psoriasis and are characterized by a multi-organ attack arising from the systemic distribution of the autoantigens. - Javierre BM, Esteller M, Ballestar E. Epigenetic connections between autoimmune disorders and haematological malignancies. *Trends Immunol* 29(12):616-623, 2008).

Wikipedia’s definition of Epigenetics, DNA methylation, and Histones:

“Epigenetics is the study, in the field of genetics, of cellular and physiological phenotypic trait variations that are caused by external or environmental factors that switch genes on and off and affect how cells read genes instead of being caused by changes in the DNA sequence.”

“DNA methylation is a process by which methyl groups are added to DNA. Methylation modifies the function of the DNA. When located in a gene promoter, DNA methylation typically acts to repress gene transcription.”

“In biology, histones are highly alkaline proteins found in eukaryotic cell nuclei that package and order the DNA into structural units called nucleosomes. They are the chief protein components of chromatin, acting as spools around which DNA winds, and playing a role in gene regulation.”

DNA methylation and histone modifications are the main epigenetic processes that are currently undergoing study.

Virginia T. Ladd, President and Executive Director of the American Autoimmune Related Diseases Association (AARDA): "With the rapid increase in autoimmune diseases, it clearly suggests that environmental factors are at play due to the significant increase in these diseases. Genes do not change in such a short period of time."

**Nutritional status will have a direct influence on the expression of genes. Folate has been extensively studied for its effect on DNA methylation because folate carries and delivers the methyl group for the reactions. Other methyl donor nutrients include methionine, choline, betaine, and vitamin B-12. Vitamin D plays is a natural immune modulator and has been implicated in the pathophysiology of autoimmune diseases, including systemic lupus erythematosus. Vitamin C and calcium is critical with viral infections.**
The most widely accepted environmental conditions that trigger autoimmunity through epigenetic mechanisms are drugs, pollutants, viruses and other pathogens, sex hormones, radiation, heavy metals, and stress induced hormones.

**DRUGS:**

The medications that most commonly induce drug-induced autoimmune syndromes are 5-azacytidine, procainamide, hydralazine, quinidine, isoniazid, methyldopa, minocycline, chlorpromazine, and phenytoin.

**ADDITIVES IN FOOD AND COSMETICS:**

Tetramethylpentadecane (TMPD /Pristane)

TMPD in crude oils is a common constituent of mineral oil, a byproduct of the fractional distillation of petroleum. “Medicinal (pharmaceutical or food grade) mineral oils, which are free of aromatic and unsaturated compounds, are used as laxatives, protective coatings for foods, and in cosmetics. For instance, canned sardines contain up to 370 mg/kg and white bread up to 550 mg/kg of mineral oil. **Dietary exposure to mineral oil is estimated at 9–45 grams per year, some of which is absorbed through the intestine.** Intestinal absorption of dietary mineral oil is thought to be responsible for the formation of “lipogranulomas” (follicular lipidosis) seen in the liver, spleen, lymph nodes, and other organs of most individuals living in developed countries” ([http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746238](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746238)).

**POLLUTION:**

**Air pollution in autoimmune rheumatic diseases: a review.**  
Farhat SC, Silva CA, Orione MA, Campos LM, Sallum AM, Braga AL.

“Oxidative stress and inflammation induced by inhaled pollutants may result in acute and chronic disorders in the respiratory system, as well as contribute to a state of systemic inflammation and autoimmunity. This paper reviews the mechanisms of air contaminants influencing the immune response and autoimmunity, and it focuses on studies of inhaled pollutants triggering and/or exacerbating rheumatic diseases in cities around the world. Remarkably, environmental factors contribute to the onset of autoimmune diseases, especially smoking and occupational exposure to silica in rheumatoid arthritis and systemic lupus erythematosus. Other diseases such as scleroderma may be triggered by the inhalation of chemical solvents, herbicides and silica. Likewise, primary vasculitis associated with anti-neutrophil cytoplasmic antibody (ANCA) may be triggered by silica exposure. Only few studies showed that air pollutants could trigger or exacerbate juvenile idiopathic arthritis and systemic lupus erythematosus. In contrast, no studies of tropospheric pollution triggering inflammatory myopathies and spondyloarthropathies were carried out. In conclusion, air pollution is one of the environmental factors involved in systemic inflammation and autoimmunity.”
FOOD ALLERGIES AND SENSITIVITIES:

Mark Hyman, MD says: “Autoimmune conditions are connected by one central biochemical process: A runaway immune response also known as systemic inflammation that results in your body attacking its own tissues.” AND “Hidden allergens, infections, environmental toxins, an inflammatory diet, and stress are the real causes of these inflammatory conditions.”

“It is important to be able to distinguish among food allergy, intolerance, and autoimmune disease in the management of these disorders. The role of food in the development of autoimmune disease may be exemplified by celiac disease, a food-induced enteropathy, requiring exposure to prolamins in wheat, rye, and barley. Various wheat and soy protein sources, including the soy protein isolates used to make infant formulas, have been related to juvenile or insulin-dependent diabetes mellitus (IDDM), a common chronic disease of childhood.” - Can J Physiol Pharmacol. 1997 Apr;75(4):241-54. Adverse reactions to food constituents: allergy, intolerance, and autoimmunity. Kitts D1, Yuan Y, Joneja J, Scott F, Szilagyi A, Amiot J, Zarkadas M.

“There is growing evidence that increased intestinal permeability plays a pathogenic role in various autoimmune diseases including CD and T1D.” AND “The classical paradigm of autoimmune pathogenesis involving specific gene makeup and exposure to environmental triggers has been recently challenged by the addition of a third element, the loss of intestinal barrier function.” (CD/Celiac Disease, T1D/Type 1 Diabetes) - Ann N Y Acad Sci. 2009 May; 1165: 195–205. doi: 10.1111/j.1749-6632.2009.04037.x Tight Junctions, Intestinal Permeability, and Autoimmunity Celiac Disease and Type 1 Diabetes Paradigms

“When someone has leaky gut (often referred to as increased intestinal permeability), the “net” in your digestive tract gets damaged, which causes even bigger holes to develop in your net, so things that normally can’t pass through, are now be able to. Some of the things that can now pass through include proteins like gluten, bad bacteria and undigested foods particles. Toxic waste can also leak from the inside of your intestinal wall into your bloodstream causing an immune reaction.” - Dr. Axe

ANTIBIOTICS, CANDIDA, PARASITES:

Juvenile rheumatoid arthritis afflicts 300,000 American children. Twenty-five years ago this disease was so rare that public health officials did not keep any statistics on it. There has been a 4-fold increase in asthma, and bowel disorders in children are much more common now than they were 50 years ago.

Children exposed to antibiotics may be at greater risk for juvenile arthritis: In a nested case–control study of 153 children with juvenile arthritis and 1,530 matched controls, researchers found that exposure to antibiotics during childhood significantly increased the risk for developing JIA (adjusted odds ratio = 2.6) in a dose-dependent manner. Compared with those with no exposure, the odds ratio for developing JIA was 3.1 for children exposed to one or two courses of antibiotics, and for those exposed to three to five courses the odds ratio was 3.8. - http://emedicine.medscape.com/article/1007276-overview
“Antibiotics damage the bowel environment in two ways. The first is by destroying beneficial bacteria. The small intestine and large intestine host over hundreds of different kinds of beneficial bacteria. These bacteria are vital for healthy metabolism and immune response within the intestines. Through their enzyme secretions, bacteria transform metabolic and microbial wastes before they are discharged by the body. These wastes include cellular debris, hormones, chemical wastes, bile, pus, viral toxins, bacterial toxins, etc. For example, the body creates bile not only as a lubricant to flush wastes out of the liver, but also, by its cold and bitter nature, to detoxify many of the poisons accumulating in the liver. Bile however is extremely caustic to large intestine epithelium. When bile enters the small intestine via the common bile duct, beneficial bacteria break the bile salts down into a less caustic compound, making it safe by the time it reaches the large intestine. **Antibiotics destroy these bacteria and thus allow bile salts to enter and damage the large intestine.**” - Jeremy E. Kaslow, MD, FACP, FACAAI, Physician and Surgeon, Board Certified Internal Medicine

“Chronic infestation with *Entamoeba histolytica*, another **common protozoan parasite**, has **been associated with autoimmune phenomena**, including the appearance of antibodies to colonic epithelial cells and the development of ulcerative colitis after cure of amebic colitis. Extra-intestinal autoimmune reactions to intestinal amebiasis include a case of antiphospholipid antibody syndrome with deep vein thrombosis and pulmonary embolism and development of symmetrical polyarthritis very similar to rheumatoid arthritis (RA). Singh et al. measured amoebic antibody levels in 41 Indian patients with a primary diagnosis of RA, 35 age- and sex-matched healthy volunteers, 162 hospital inpatients and 26 patients with other arthritides. Amebic antibodies were elevated in 39% of RA patients and 0-11% of the various control groups. Only two patients with RA had experienced recent diarrheal disease. These authors suggest that an excessive and prolonged antibody response to *Entamoeba histolytica* or other enteric organisms may contribute to joint inflammation in RA.”

- Intestinal Protozoan Infestation and Systemic Illness, Leo Galland M.D., Foundation for Integrated Medicine, New York, N.Y.

“Some investigations show that various **protozoa and helminthes are connected with the main immune-mediated intestinal conditions including celiac disease (CD), inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS)**. Celiac disease is a digestive and autoimmune disorder that can damage the small intestine and characterized by a multitude gastrointestinal (GI) and extra GI symptoms. IBD (including ulcerative colitis and Crohn’s disease) is a group of inflammatory conditions of the small intestine and colon. The etiology of IBD is unknown, but it may be related to instability in the intestinal microflora that leading to an immoderate inflammatory response to commensal microbiota. Irritable bowel syndrome (IBS) is a common, long-term condition of the digestive system. Bloating, diarrhoea and/or constipation are nonspecific symptoms of IBS. Various studies have shown that some intestinal parasites can effect on immune system of infected hosts and in some cases, they are able to modify and change the host’s immune responses, particularly in autoimmune disorders like celiac disease and IBD.” - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4403024/
“Chronic Fatigue Syndrome; Crohn’s Disease; Fibromyalgia; Irritable Bowel Syndrome; Lupus; Multiple Sclerosis, Numbness in the hands; Rheumatoid Arthritis; and Ulcerative colitis: what do these have in common? They all respond to dietary intervention and anti-yeast treatment.” AND “In the intestinal tract, there is Candida, which tries to invade the intestinal wall, and the immune system responds with inflammation. The problem is that the Candida suppresses the immune system’s offensive weapons, so the Candida stays and the inflammation is prolonged. This prolonged inflammation is called ulcerative colitis if it occurs in the large intestine and it is called Crohn’s disease if it occurs in the small intestine. These disorders are prolonged inflammation resulting from the immune system’s inability to clear Candida.”

- Dr. Bruce Semon, Board Certified Child, Adolescent and Adult Psychiatrist, Ph.D. in Nutrition

BACTERIA, MYCOPLASMA, VIRUSES:

Mycoplasma is a genus of bacteria that lack a cell wall around their cell membrane. Without a cell wall, they are unaffected by most antibiotics such as penicillin or other antibiotics that target cell walls. They are the smallest free-living organisms with a pliable membrane which allows them to take different shapes. They are difficult to identify even under a high powered electron microscope. Mycoplasmas can also be very hard to culture in the laboratory and are often missed as pathogenic causes of diseases for this reason.

Mycoplasmas were observed to have a fungi-like structure (Mycology is the study of fungi - hence "Myco") and it also had a flowing plasma-like structure without a cell wall - hence "plasma". The first strains were isolated from cattle with arthritis and pleuro-pneumonia in 1898 at the Pasteur Institute. The first human strain was isolated in 1932 from an abscessed wound. The first connection between mycoplasmas and rheumatoid diseases was made in 1939 by Drs. Swift and Brown.

They are still looking at the inactivation of mycoplasmas in vaccinations.

http://www.bjmp.org/content/bacterial-infections-and-pathogenesis-autoimmune-conditions
BRITISH JOURNAL OF MEDICAL PRACTITIONERS

“Bacterial infections are associated with many autoimmune diseases involving chronic inflammation and demyelination. The possible mechanisms of bacterial involvement as aetiological agents or in the exacerbation of these diseases have been investigated intensively. This review focuses the role of bacterial infections in the pathogenesis of autoimmune, inflammatory and demyelinating diseases. Possible modes of pathogenic action of bacteria are discussed, viz. the role of cytokines, Toll-like receptor signalling, the interaction of heat shock proteins with the immune system, and the role of nitric oxide. An auto-regulatory loop might exist in the interaction of bacteria with the host and in pathogenic signal processing. These studies reveal potential therapeutic targets.”
Rheumatoid arthritis is caused by a Proteus urinary tract infection.

“Genetic, molecular and biological studies indicate that rheumatoid arthritis (RA), a severe arthritic disorder affecting approximately 1% of the population in developed countries, is caused by an upper urinary tract infection by the microbe, Proteus mirabilis. Elevated levels of specific antibodies against Proteus bacteria have been reported from 16 different countries. The pathogenetic mechanism involves six stages triggered by cross-reactive autoantibodies evoked by Proteus infection. The causative amino acid sequences of Proteus namely, ESRRAL and IRRET, contain arginine doublets which can be acted upon by peptidyl arginine deiminase thereby explaining the early appearance of anti-citrullinated protein antibodies in patients with RA. Consequently, RA patients should be treated early with anti-Proteus antibiotics as well as biological agents to avoid irreversible joint damages.”


Autoimmune rheumatic diseases are generally considered as a multifactorial aetiology, mainly genetic susceptibility combined with environmental triggers of which bacteria are considered one of the most prominent. Among the rheumatic diseases where bacterial agents are more clearly involved as triggers are: reactive arthritis (ReA), rheumatic fever (RF) and Lyme disease.

The role of bacterial infections in inducing other seronegative spondyloarthritis and antiphospholipid antibody syndrome has been hypothesized but is still not proven. The classic form of ReA is associated with the presence of HLA-B27 and is triggered by the urethritis or enteritis causing pathogens Chlamydia trachomatis and the enterobacteria Salmonella, Shigella, and Yersinia, respectively. But several other pathogens such as Brucella, Leptospira, Mycobacteria, Neisseria, Staphylococcus and Streptococcus have also been reported to cause ReA.

RF is due to an autoimmune reaction triggered by an untreated throat infection by Streptococcus pyogenes in susceptible individuals. Carditis is the most serious manifestation of RF and HLA-DR7 is predominantly observed in the development of valvular lesions. Lyme disease is a tick-transmitted disease caused by the spirochete Borrelia burgdorferi. Knowledge is limited about how this spirochete interacts with human tissues and cells. Some data report that Borrelia burgdorferi can manipulate resident cells towards a pro- but also anti-inflammatory reaction and persist over a long period of time inside the human body or even inside human cells.

*Ingesting food and water contaminated with bacteria or viruses is a leading cause of enteritis.
A wide variety of bacterial infections have been associated with rheumatoid conditions. Rheumatic diseases might have a manifold aetiology with varying genetic susceptibility, but bacteria-related autoimmunity might be an important factor. **Mycoplasma infection**, e.g. by M. pneumoniae, M. salivarum, and M. fermentans, has been strongly associated with RA (rheumatoid arthritis). There is often systemic infection of more than one species. Mycoplasma antigens induce both cell-mediated and humoral immune responses.

We know that viruses have been associated with MS for about the last 60 years. **Almost two dozen viruses have been isolated from the brains of MS patients.** These include herpesviruses, paramyxoviruses, and retroviruses. Further, virus infections often precede MS exacerbations.

**HHV-6 may also be involved in MS** — specifically related to triggering relapses. Steve Simpson, PhD, and colleagues at the Universities of Tasmania and Melbourne have found that HHV-6 antibodies were associated with a higher risk of relapse. Also, antibody levels were nearly three times higher in women with progressive MS. These researchers suggest that tracking HHV-6 antibodies may help to predict the clinical course of MS.
Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family. It is one of the most common human viruses. EBV is found all over the world. Diagnosing EBV infection can be challenging since symptoms are similar to other illnesses. EBV infection can be confirmed with a blood test that detects antibodies. About 90% of adults have antibodies that show that they have a current or past EBV infection.

VACCINATIONS:

The most commonly reported reactions were injection site reactions (40%), fever (22%), allergic reactions (19%) and rash (10%). Only 7% of all the reported adverse events were categorised as serious. There were 2 reports of death, which were investigated by the TGA and no clear causal relationship with vaccination was found. Commun Dis Intell 2014;38(3):E232–E246. *

*WHAT IS SERIOUS? “In this report, an AEFI is defined as ‘serious’ if it meets one or more of the following criteria: (1) results in death (2) is life-threatening (3) requires inpatient hospitalisation or prolongation of existing hospitalisation (4) results in persistent or significant disability/incapacity (5) is a congenital anomaly/birth defect, or (6) is a medically important event or reaction.”

Since the implementation of the mass vaccination campaign against hepatitis B in France, the appearance of multiple sclerosis, sometimes occurring in the aftermath of vaccinations, led to the publication of epidemiological international studies. This was also justified by the sharp increase in the annual incidence of multiple sclerosis reported to the French health insurance in the mid-1990s. Almost 20 years later, a retrospective reflection can be sketched from these official data and also from the national pharmacovigilance agency. Statistical data from these latter sources seem to show a significant correlation between the number of hepatitis B vaccinations performed and the declaration to the pharmacovigilance of multiple sclerosis occurring between 1 and 2 years later. The application of the Hill's criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causa

Virus-induced autoimmunity may play a causal role in autism. To examine the etiologic link of viruses in this brain disorder, we conducted a serologic study of measles virus, mumps virus, and rubella virus. Viral antibodies were measured by enzyme-linked immunosorbent assay in the serum of autistic children, normal children, and siblings of autistic children. The level of measles antibody, but not mumps or rubella antibodies, was significantly higher in autistic children as compared with normal children (P = 0.003) or siblings of autistic children (P <or= 0.0001). Furthermore, immunoblotting of measles vaccine virus revealed that the antibody was directed against a protein of approximately 74 kd molecular weight. The antibody to this antigen was found in 83% of autistic children but not in normal children or siblings of autistic children. Thus autistic children have a hyperimmune response to measles virus, which in the absence of a wild type of measles infection might be a sign of an abnormal immune reaction to the vaccine strain or virus reactivation.

Vaccines, in several reports were found to be temporally followed by a new onset of autoimmune diseases. The same mechanisms that act in infectious invasion of the host, apply equally to the host response to vaccination. It has been accepted for diphtheria and tetanus toxoid, polio and measles vaccines and GBS. Also this theory has been accepted for MMR vaccination and development of autoimmune thrombocytopenia, MS has been associated with HBV vaccination. Occupational and other chemical exposures are considered as triggers for autoimmunity. A debate still exists about the role of silicone implants in induction of scleroderma like disease. Not only foreign chemicals and agents have been associated with induction of autoimmunity, but also an intrinsic hormonal exposure, such as estrogens. This might explain the sexual dimorphism in autoimmunity. Better understanding of these environmental risk factors will likely lead to explanation of the mechanisms of onset and progression of autoimmune diseases and may lead to effective preventive involvement in specific high-risk groups. So by diagnosing a new patient with autoimmune disease a wide anamnesis work should be done.