Understanding Autoimmune Disease – a review article for the layman

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A B S T R A C T

This article introduces a number of Autoimmune Diseases and inflammatory myopathies. It includes a definition of autoimmune diseases as well as a short explanation of immunity and its composition, as individuals affected by autoimmune disorders have compromised immune systems due various influences, namely, environmental factors, viruses/bacterium, and/or genetic factors.

Each factor is discussed briefly in this introduction. There is insufficient research which has been done on these disorders as they stem from numerous factors, and may be a combination of the above mentioned components. Risk factors as to autoimmune compromised individuals are pointed out as these all play a role in future studies targeting solutions for autoimmune diseases.

Various causes and possible solutions are discussed as per previous studies in this article as an introduction to further investigation on this subject.

This article includes Systemic Lupus Erythematosus, Acute Anterior Uveitis, Reactive Arthritis, Autoimmune Hepatitis, Sjögren’s Syndrome, Diabetes Mellitus Type 1, 21-Hydroxylase Deficiency, Scleroderma, Dermatomyositis, Autoimmune Thyroiditis, Rheumatoid Arthritis, Multiple Sclerosis, Graves’ Disease, Polyarteritis Nodosa, Autoimmune Pancreatitis and HIV.

For each autoimmune disorder, clinical features, incidence and prevalence rates, diagnosis, age of onset and prognosis are mentioned. Conclusions have not been drawn as yet due to the fact that this research needs to further be investigated and tested.

A Brief overview of the Immune System

Autoimmune disease is a condition which is triggered by the immune system initiating an attack on self-molecules due to the deterioration of immunologic tolerance to auto-reactive immune cells. [1] Smith and Germolec state that “autoimmune disorders affect approximately 3% of the North American and European populations, >75% of those affected being women.”

The initiation of attacks against the body’s self-molecules in autoimmune diseases, in most cases is unknown, but a number of studies suggest that they are strongly associated with factors such as genetics, infections and/or environment. [1]

One definition of the immune system is that it is an intricate set of cellular, chemical and soluble protein mechanisms, intended to shield the body against alien substances such as infections and tumour cells, without attacking self-molecules. Antigens are those molecules (self or alien molecules) which evoke specific immune responses in the body. Immune cells are situated throughout the entire body. Organs such as the spleen, thymus, skin and gut contain immune cells tactically placed in order to screen the entry of alien substances. Optimum functioning of the immune system occurs when the immune cells and cell products work together with each other in a sequential and harmonious manner.

The distinction between self-molecules and alien substances occurs through intricate mechanisms that are dependent on certain recognition molecules present on the surface of immune competent cells, specifically, T and B lymphocytes. There are non-specific effector mechanisms which complement the T and B lymphocytes to serve as the first line of defence against possible pathogens. These cells can be leukocytes such as macrophages, natural killer cells and polymorphonuclear leukocytes. There are also soluble mediators such as cytokines which play a role in the body’s defence structure. [1]

A small percentage of T and B lymphocytes form a normal part of the immune cell pool. Tolerance is preserved by the controlled interactions of various cell types and soluble mediators. However, in certain environments, tolerance can be broken and this results in an autoimmune pathogen. The development of autoimmune diseases are highly dependent on genetics, yet other factors such as viruses, bacterium or chemical exposure play as contributors to changes in self-reactivity. [1]

There are various symptoms and disorders which are encompassed in autoimmune diseases. They vary from organ specific to systemic, and include, insulin dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis and multiple sclerosis to name but a few. The most common areas in the body which are targeted...
by autoimmune diseases are the thyroid gland, stomach, adrenal glands and pancreas. Systemic autoimmune diseases most commonly include the skin, joints and muscle tissue. [1]

Extensive technical development in addition to the completion of the sequencing of the human genome in 2005, have recently permitted the identification of new genetic risk variants in numerous autoimmune disorders. It is widely accepted that the pathogenesis of autoimmune diseases is multifactorial, where the genetic, infectious and environmental factors play a role in determining the onset and progression of the disease. Despite this, the ability to quantify the environmental influences of autoimmune diseases is extremely difficult. Various evidences suggest that genetic factors are a major determinant of autoimmune disease susceptibility as well as progression. Different autoimmune diseases often co-exist within family members which points out, that common genes underlie multiple autoimmune diseases, and several diseases may share similar pathogenic pathways. This concept is additionally supported by various sets of evidence demonstrating variable prevalence degrees of autoimmune diseases in different geographical areas. [2]

Autoimmune diseases are pathological conditions identified by abnormal autoimmune responses and characterized by auto-antibodies and T-cell responses to self-molecules by immune system reactivity. [2][3]

Autoimmunity is defined as the development of immune system reactivity in the form of auto-antibodies and T-cell responses to self-structures. This has fascinated researchers since the original theoretical description thereof in 1901. Autoimmunity is a necessary process of the immune regulatory networks in the body which need to sustain the body’s health. It is yet unknown fully why autoimmunity sometimes progresses to pathologic states which are generally characterized by tissue destruction, mediated by humoral-cellular self-reactive progression. There are many known autoimmune diseases ranging from tissue specific disorders to systemic disorders. The onset of an autoimmune disease can be from childhood or from adulthood.

There are possibly multiple “autoimmunity genes” which increase the risk of developing an autoimmune disease. Other factors such as environmental influences may also contribute to a particular autoimmune disease that may develop within an individual. It is strongly supported that autoimmune diseases are multifactorial diseases resulting from the interaction between the specific “autoimmunity genes” and environmental factors. [2]

Occupational exposures such as silica or silicon dioxide (SiO2); solvents such as vinyl chloride; pesticides and ultraviolet radiation are also known to be associated with the development of autoimmune disease. [2]

The Definition of Autoimmune Disease.

This definition includes a variety of diseases which can be described by the irregular functioning of the immune system that causes an individual’s immune system to generate antibodies which attack their own body tissues. The development of autoimmune disease occurs as a result of an overactive immune response to body material and tissues present in the body. This means that the body attacks its own cells. The immune system confuses a specific part of the body as a pathogen and attacks it. This could be restricted to specific organs (e.g. in autoimmune thyroiditis) or it could involve a specific tissue in various places (e.g. Good pasture’s disease which may have an effect on the basement membrane in both the lungs and kidneys). Immunosuppression, which is a disease medication that decreases the immune response, is typically the treatment of an autoimmune disease. [3]

An individual’s immune system protects one from disease and infection. If a person has an autoimmune disease, their immune system inaccurately attacks healthy cells in their body. These diseases tend be genetic. Women, in particular, African-American, Hispanic-American, and Native-American women - have a higher risk for certain autoimmune disorders. There are currently more than eighty various kinds of autoimmune diseases, and many of them have alike symptoms. This makes it difficult for a person’s general practitioner to know if they really have one of these diseases, and if so, which one. Obtaining a diagnosis may be frustrating and stressful. In many people, the first symptoms are being fatigued, having muscle aches and developing a low grade fever. These diseases may also have cycles of flare-ups, when they get worse, and remissions, when they recede. The diseases do not usually go away, but symptoms can be treated. [4]

In certain cases, the antibodies may not be directed at a specific tissue or organ; for example, antiphospholipid antibodies can react with substances such as phospholipids that are the normal components of blood platelets and the outermost layer of cells (cell membranes), which can lead to the formation of blood clots within the blood vessels as in thrombosis. [5]

Immune tolerance is defined as specific non-reactivity of the immune system to a particular antigen, which is capable under other circumstances of inducing an immune response. The administration of antigens either at high or low dose and infection with certain viruses during critical early stages of immunological development may also aid in inducing tolerance. [6]

Central tolerance occurs during lymphocyte development and functions in the thymus and bone marrow. Here, T and B lymphocytes that recognize self-antigens are deleted before they develop into fully immunocompetent cells, preventing autoimmunity. This process is most active in foetal life, but continues throughout life as immature lymphocytes are generated.

Positive selection occurs first when naive T-cells are exposed to antigens in the thymus. T-cells which have receptors with sufficient affinity for self-MHC molecules are selected. Other cells that do not show sufficient affinity to self-antigens will undergo a deletion process known as death by neglect which involves apoptosis of the cells. The positive selection is a
classic example of the importance of some degree of auto-reactiveness. This does not occur in B-cells. [7]

Immunity

There are various defence mechanisms that guard an individual from micro-organisms and potentially harmful material. Some of these mechanisms, such as physical barriers like the skin, phagocytic cells and certain chemical matter and enzymes, are active before contact with alien materials. These natural immune devices are not enhanced by prior exposure to alien substances. They do also not discriminate between most alien materials. [8]

Additional defence mechanisms, collectively known as adaptive immunity, contain components which are able to identify various structures present in foreign materials. The defence mechanism that is generated is thus able to eliminate precisely the alien material, additionally, succeeding exposure leads to a more proficient and effective immune response.

The immune system is made up of a number of organs and various cell types. All the cells of the immune system originate and develop from pluripotent stem cells in the bone marrow. These cells include tissue cells as well as leucocytes, and they also give rise to erythrocytes. The production of leucocytes occurs through two main differentiation pathways.

The first is the lymphoid lineage which produces T and B lymphocytes, the second is the myeloid pathway which gives rise to mononuclear and polynuclear leucocytes, platelets and mast cells.

The blood platelets are involved in clotting and inflammations, whereas the mast cells are similar to basophils, except that they are found in body tissue. [8]

Lymphocytes make up 20% of the total white blood cell count present in adults. Mature lymphoid cells may survive as memory cells for many years. The small lymphocytes are agranular and are made up of T and B cells. The larger lymphocytes are granular and contain cytoplasmic granules. These lymphocytes are able to kill certain tumour and virally infected cells. This is called natural killing. Cells coated with immunoglobulin can also be destroyed by these lymphocytes. This is called antibody dependent cell-mediated cytotoxicity.

Immune System Composition.

Connective tissue is defined as a basic type of tissue which originates in the mesoderm, and provides structural and metabolic support to all other tissues and organs within the body. Connective tissue, as well as playing a mechanical structural role, facilitates the exchange of nutrients, metabolites and waste products between the body’s tissues and circulatory system. Blood and lymphatic vessels are components of connective tissue. Some of the support cells of which connective tissue is composed, produce an extracellular matrix. This extracellular matrix is the central component of connective tissue. An organic material by the name of ground substance embedded with a variety of fibres makes up the extracellular matrix. Connective tissues, also known as supporting tissue may present in various forms and with diverse physical properties. Connective tissues act as a type of biological packing material between the cells and tissues/organisms of the body. It also provides tough physical support in the dermis of the skin comprises the tough capsules of organs such as the liver or spleen and furthermore is a source of flexible strength in ligaments and tendons throughout the body. Highly specialised forms of connective tissue include cartilage and bone, both of which are major components of the skeleton. Connective tissues have essential metabolic roles such as the storage of fat and the regulation of bodily temperature especially in the foetus. The immune system contributes to the defence against pathogenic microorganisms once the cells enter the connective tissue. Where tissue damage is concerned, it is largely the function of connective tissue to initiate the process of repair within these tissues.

Inter cellular matrix in the framework of the body

Collagen is the main fibre found within connective tissue as well as being the most abundant protein within the human body. The most prominent function of collagen is to provide tensile strength. Collagen is secreted into the extracellular matrix as tropocollagen which comprises of 3 polypeptide chains (alpha chains) which are combined together to form a helical structure.

Elastin is a structural protein of importance that is organized as fibres and/or discontinuous sheets in the extracellular matrix specifically in the skin, lungs and blood vessels where it manages the stretching and elastic recoil of the tissues. Elastin is manufactured by fibroblasts in a precursor form recognised as tropoelastin which undergoes polymerisation in the extracellular tissue matrix. A layer of elastin in the form of fibres necessitates the attendance of microfibrils of the structural glycoprotein fibrillin which become included around and within the elastic fibres. [9]

Cells of Connective Tissue:

Connective tissue cells are derived from precursor cells in primitive connective tissue and are divided up into several varieties, each with diverse roles. A main shared role is synthesis and maintenance of extracellular matrix matter.

1. The most common support cell is the fibroblast which is responsible for secreting the extracellular matrix in the majority of bodily tissues.
2. Chondrocytes are responsible for secreting the extracellular matrix in cartilage, and osteocytes are responsible for secreting the extracellular matrix in bone.
3. Myofibroblasts have a contractile function and also have a role to play in the secretion of the extracellular matrix.
4. A group of highly adapted support cells are in control of the storage and metabolism of fat. These are known as adipocytes and may jointly comprise adipose tissue.

Connective tissue is largely made up of cells with defence and immune functions. These cells include the mast cells, tissue macrophages, white blood cells and antibody-secreting plasma cells. A number of these cells migrate into connective tissue and remain static, performing their resident purpose. Other
immune cells migrate through the connective tissue to various other parts of the body to perform different functions.

**The role of T-Lymphocytes.**

T cells have a variety of effector and regulatory functions. Both T and B cells are derived from stem cells within the bone marrow. Immature T lymphocytes travel from the bone marrow to the thymus where they grow into mature T lymphocytes. This development includes proliferation, rearrangement of TCR genes and acquisition of the surface receptors and accessory molecules of mature T cells. T cells with the ability to react with self-antigens are then removed by apoptosis, creating a state of self-tolerance. Mature T cells then inhabit the secondary lymphoid tissues and from there constantly recirculate via the bloodstream in the pursuit of antigens.

**The role of B-lymphocytes.**

B lymphocytes originate in the bone marrow and also become fully matured there. Stimulated B cells develop into plasma cells that synthesise significant amounts of antibody (immunoglobulin). *Immunoglobulins* fall into five different basic classes, namely, IgG, IgA, IgD, IgM, and IgE, all of which are secreted and circulate in the blood. Surface immunoglobulin is the antigen receptor for B lymphocytes and when it attaches to an antigen the B cell is activated, usually with the help of a TH cell responding to the same antigen.

Once the B cell is activated, it undergoes mitotic division to manufacture a replica of cells which are able to synthesise immunoglobulin of the same antigen specificity. Most of the B cells of such a clone mature into plasma cells. When an antigen is encountered for the first time, this is described as the primary immune response. A few cells from the same clone mature to become memory B cells, which are circulating lymphocytes that are able to respond quickly to any subsequent challenge with the same antigen. Antibody production during this secondary immune response occurs much more rapidly, is of much greater magnitude and produces IgG. This phenomenon explains the lifetime immunity that follows many common infections; it is also the general principle on which vaccination is used. [9]

**The function of Lymphocytes.**

The immune factor of the body’s defence system is embodied in the lymphocytes, antibodies and lymphokines. The T lymphocytes have specific cell-membrane-associated antigen binding receptors. The direct T-cell receptor binding to target antigens, results in two different types of effector actions. Cytotoxic killing of the target is one type, the other type being the release of lymphokines that regulate the migration and useful capabilities of other inflammatory cells. [10]

The group of B-lymphocytes and plasma cells produce immunoglobulin’s with a large variety of antibody-combining sites which interact with a target. Complexes of antibodies with antigens attach preferentially to inflammatory cells of the phagocytic system by the steady region sites of the immunoglobulin (Ig) molecules, and they can activate the humoral complement system. [10]

Lymphocytes not only assemble the specific inflammatory reactions to the antigenic stimulus, but also focus non-specific inflammatory responses on the target. This provides bodies with the ability to adapt and enlarge reactions designed to get rid of deleterious causes with efficiency and without delay. Immunity is also involved in the elimination of old or damaged cells within the body and in the demolition of abnormal or mutant cells which occur within the body. This last function is known as immune surveillance, and constitutes as a major defence against cancer. It has, on the other hand, become apparent that immune responses are not always advantageous and may result in severe damage to the body. [11]

**The role of APC (Antigen presenting cells)**

Numerous parts of the immune system may be involved in autoimmune pathology. Antigens are taken up by antigen-presenting cells (APCs) such as dendritic cells (DCs) and processed into peptides which are loaded onto the major histocompatibility complex (MHC) molecules for presentation to T cells via clonotypic T cell receptors (TCRs). Cytolytic T cells (Tc, activated by MHC Class I on APC) can directly damage a target, while T helper cells (Th, activated by MHC class II) release cytokines that can have direct effects or can activate macrophages, monocytes and B cells. B cells themselves have surface receptors that can bind to surface antigens. Upon receiving signals from Th cells, the B cell secretes antibodies specific for the antigens. An antibody may bind to its specific target alone or may bind to and activate macrophages simultaneously via the Fc receptor. [12]

**Antigen Presenting Cells (APCs) fall into two categories: professional or non-professional.**

**Professional APCs**

Professional APCs are very efficient at internalizing antigens, either by phagocytosis or by receptor-mediated endocytosis, and then displaying a section of the antigen, bound to a class II MHC molecule, on their membrane. The T cell recognizes and interacts with the antigen-class II MHC molecule complex on the membrane of the antigen-presenting cell. An additional co-stimulatory signal is then produced by the antigen-presenting cell, leading to activation of the T cell. The expression of co-stimulatory molecules is a defining feature of professional APCs.

There are three main types of professional antigen-presenting cells:
- Dendritic cells, which have the widest range of antigen presentation, and are probably the most important antigen presenting cells. Activated dendritic cells are especially potent T<sub>H</sub> cell activators because, as part of their composition, they express co-stimulatory molecules such as B7.
- Macrophages, which are also CD4+ and are therefore also susceptible to infection by HIV.
- B-cells, which express and secrete a specific antibody, can internalize the antigen, which bind to its BCR and present it incorporated to MHC II molecule, but are inefficient antigen presenting cells for most other antigens.
Non-professional APCs
A non-professional APC does not constitutively express the Major Histocompatibility Complex class II proteins required for interaction with naive T cells; these are only expressed once the non-professional antigen presenting cells are stimulated by certain cytokines such as IFN-γ. Non-professional APCs include:

- Fibroblasts (skin)
- Thymic epithelial cells
- Thyroid epithelial cells
- Glial cells (brain)
- Pancreatic beta cells
- Vascular endothelial cells

Genetic Risk Factors
The pathogenic methods underlying idiopathic inflammatory myopathies (primarily characterized by chronic inflammation of human skeletal muscle tissue) are unclear, yet family studies and candidate gene approaches propose there is a genetic constituent to these disorders. The development of this disease cannot solely be explained by genetic factors and is supported with exposure to certain environments as well. Genetic risk factors are currently being investigated clinically, and may provide valuable insights into the pathogenesis of thereof. [13]

A transmission disequilibrium testing approach assesses the same genes but analyses them within a specific family by comparing affected and unaffected members. It is a powerful method of confirming genetic risk factors for the disease in an independent way. There are even methods allowing accommodation for a missing parent. This approach demonstrates associations of human leukocyte antigen genes, T-cell receptor genes, cytokine and cytokine receptor genes, immunoglobulin genes and immunoglobulin Fc receptor genes for various autoimmune diseases. Of all these associations, HLA allele associations show the strongest associations and, in many cases are considered as primary susceptibility factors for many autoimmune disorders. Further clarification of the autoimmunity genetics is currently being addressed using complete genome scans in multi-case families as well as with single members in large cohort studies. [13]

Traditional family studies are difficult to perform due to the rarity of idiopathic inflammatory myositis. There are reports on inclusion of body myopathy in siblings as well as multiple kindred’s who show various inheritance patterns. The ability to evaluate the relationship between possible environmental agents and idiopathic inflammatory myositis has been difficult. Often there has been literature on patients who do not meet the accepted diagnostic criteria for this disorder. Most of the controlled epidemiologic studies in the past have failed to disclose a clear environmental source for any of these diseases. Despite numerous problems, various environmental exposures which include infectious as well as non-infectious agents are implicated as possible etiologic agents for the idiopathic inflammatory myositis. Further examinations are needed to establish more comprehensible links and to identify instruments whereby environmental agents may cause myositis.

A primary autoimmune disease is the term used for diseases originating from a reactive immune system which are mainly composed of an excess of T-cell activity. Secondary autoimmune diseases usually develop from a completely normal immune system [8].

There are diverse causes of autoimmune diseases, namely genetic causes, defects in the immune system, hormonal causes and environmental causes. Patients with the same antidouble-stranded DNA who have systemic lupus erythematosus (SLE) may differ vastly from each other regarding symptoms. Where one patient may develop CNS damage and renal failure, another patient may develop auto-antibodies being deposited on the skin or joints. [9]

Many animal studies have been performed in order to test which antibody response will result from which antigen with its related epitopes. In autoimmune diseases, the immune system damages the normal components of an individual. [8]

Role of Environmental Factors.
Environmental factors may have various roles in promoting, causing or modifying autoimmune diseases. If, and when specific environmental factors contribute to autoimmune diseases, they may well determine the onset of illness, the nature of initial manifestations, or be a determining factor on whether an autoimmune disease contained within an individual might occur at all. [14]

Environmental factors are one of the most important initiators determining the time and type of autoimmune disease when one is manifested. The type of disease in an individual, in an autoimmune prone family, can be determined by a specific combination of various infectious agents, chemicals, drugs and even vaccines. [15]

Toxic Metal Exposure - A predicted 25% of individuals have some form of heavy metal poisoning. Studies have shown that exposure to toxic metals such as mercury, cadmium, lead, arsenic, aluminium, nickel and other heavy metals can be linked to the autoimmune process as the heavy metals stimulates autoantibodies, which in turn, may result in autoimmune diseases.

Toxic Chemical Exposure - Toxins such as pesticides, solvents, industrial chemicals, some household cleaners and hair dyes can be linked to autoimmune diseases.

Vaccinations/Immunizations - Scientists have found a connection between some autoimmune diseases and certain vaccinations. In the February 2000 issue of Autoimmunity, ten research articles evaluate the causal link between vaccinations and autoimmune disease. In one of these articles, the contentious anthrax vaccine has been causally linked to the development of certain autoimmune diseases. [16]
Smoking and Autoimmune Diseases:

Tobacco smoking is one of the most powerful environmental factors that could prompt autoimmune diseases. It has been explained to alter many inflammatory and autoimmune diseases through a variety of mechanisms which include immunomodulation and chemical exposure. Smoking has been associated with systemic lupus erythematosus (SLE); the prevalence rate, ratios for current and past smoking for the development of the disease has been found to be 1.6. In a meta-analysis of studies between 1966 to 2002 on the role of smoking as a risk factor for the development of SLE, the odds thereof in current smokers versus individuals who have never smoked was 1.5. Concerning clinical manifestations, SLE patients who were current smokers were found to suffer more from pleuritis and peritonitis and expressed more symptoms one of the strongest smokers can contribute to Idiopathic Thrombocytopenic Purpura, Myasthenia Gravis and Systemic Lupus Erythematosus. Toxin exposure can contribute to Scleroderma. Ultraviolet light and stress can contribute to Systemic Lupus Erythematosus. Smoking can contribute to Goodpasture’s Syndrome, Rheumatoid Arthritis and Systemic Lupus Erythematosus. Nutritional influence can contribute to Rheumatoid Arthritis. [19]

Occupational exposure to silica dust has been examined as a possible risk factor with respect to several systemic autoimmune diseases, namely scleroderma, rheumatoid arthritis and systemic lupus erythematosus. Crystalline silica, or quartz, is a rich mineral present in sand, rock, and soil. High-level exposure to silica dust particles can cause chronic inflammation and fibrosis in the lungs as well as in other organs. [20] Mine workers and mining machine operators are especially susceptible to autoimmune disease due to the above mentioned exposures. Farming occupations can also be associated with death from systemic autoimmune diseases, in which increased risk has been seen with occupational exposure to animals and certain pesticides. [21]

Mechanisms of Autoimmunity.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a chronic auto-inflammatory disease of unfamiliar etiology, predominating in the female gender. Clinical criteria and immunological characteristics are necessary for diagnosis. Clinical sources of systemic lupus erythematosus are interchangeable and can be characterized by episodes of remissions and chronic relapses. New and various symptoms are often challenging with regard to differential diagnosis. Diagnosis and therapy should not be neglected in the case of systemic lupus erythematosus. Lifestyle modifications should be started early and cardiovascular risk factors need to be controlled. [23] Systemic lupus erythematosus begins with a general autoimmune stage which is characterized by autoantibodies common to other systemic autoimmune diseases. Antibodies against nuclear proteins including nucleic DNA and RNA dictate the immune responses in SLE. Factors which are important in the initiation of the autoimmune response in SLE are increased production of auto antigens during handling and presentations of lupus flares [24]. Stress, UV-radiation and viral infections are well known causes of flares of SLE. This happens through the activation of various sensors of the innate immune response and can contribute to the initiation of the disease. [24]

Acute Anterior Uveitis

Acute anterior uveitis is the most common form of uveitis. HLA-B27-associated acute anterior uveitis is a distinct clinical entity that has wide-ranging medical significance due to its ocular, systemic, immunologic, and genetic features. The association between HLA-B27 and the range of HLA-B27-associated inflammatory diseases remains one of the strongest HLA-disease associations known to date. HLA-B27-associated acute anterior uveitis is an important clinical entity that is common, affects relatively young patients in their most productive years, and is associated with significant ocular morbidity due to its typically persistent attacks of inflammation and its potentially vision-threatening ocular
Ankylosing Spondylitis

Ankylosing spondylitis, a form of spondyloarthritis, is a chronic, inflammatory arthritis and autoimmune disease. It mainly affects joints in the spine and the sacroiliac joint in the pelvis, and can cause eventual fusion of the spine. The condition is known to be hereditary. Symptoms of the disease first appear, on average, at age 23 years. Men are affected more than women by a ratio about of 3:1. The average onset-to-diagnosis lag time has been estimated to be approximately 8.5 years to 11.4 years. These first symptoms are typically chronic pain and stiffness in the middle part of the spine or sometimes the entire spine, often with pain referred to one or other buttock or the back of thigh from the sacroiliac joint. Symptoms appear gradually.

In 40% of cases, ankylosing spondylitis is associated with an inflammation of the eye (iritis and uveitis), causing redness, eye pain, vision loss, floaters and photophobia. Other common symptoms are generalized fatigue and sometimes nausea. This is possibly due to the relation these two conditions have with inheritance of HLA-B27.

When the condition presents before the age of 18, it is relatively likely to cause pain and swelling of large limb joints, particularly the knee. In prepubescent cases, pain and swelling may also manifest in the ankles and feet. Ankylosing spondylitis (AS) is a systemic disease. Approximately 90% of AS patients express the HLA-B27 genotype, meaning there is a strong genetic association. Only 5% of individuals with the HLA-B27 genotype contract the disease. Tumour necrosis factor-alpha (TNF α) and IL-1 are also implicated in ankylosing spondylitis. The association of AS with HLA-B27 suggests the condition involves CD8+ T cells, which interact with HLA-B. This interaction is not proven to involve a self-antigen, and at least in the related Reiter's syndrome, the antigens involved are likely to be derived from intracellular microorganisms. There is, however, a possibility that CD4+ T cells are involved in an aberrant way, since HLA-B27 appears to have a number of unusual properties, including possibly an ability to interact with T cell receptors in association with CD4. [26]

Reactive Arthritis

Reactive arthritis, or Reiter's Syndrome, is classified as an autoimmune condition that develops in response to an infection in another part of the body. Reiter's syndrome has symptoms similar to various other conditions collectively known as "arthritis".

This condition is also known as arthritus urethritica, venerale arthritis and polyarteritis enterica. It is a type of seronegative spondyloarthropathy. The manifestations of Reactive arthritis include the following triad of symptoms: an inflammatory arthritis of large joints including commonly the knee and the back (due to involvement of the sacroiliac joint), inflammation of the eyes in the form of conjunctivitis or uveitis, and urethritis in men or cervicitis in women. Patients can also present with mucocutaneous lesions, as well as psoriasis-like skin lesions such as circinate balanitis, and keratoderma blennorrhagica. Enthesitis (the inflammation of the entheses, which are the sites where tendons or ligaments insert into the bone) can involve the Achilles tendon resulting in heel pain.

Reiter's syndrome is an RF-seronegative, HLA-B27-linked spondyloarthropathy (autoimmune damage to the cartilages of joints) often precipitated by gastrointestinal infections. The most common triggers are sexually transmitted Chlamydial infections and perhaps, less commonly, Neisseria gonorrhoea; and Salmonella, Shigella, or Campylobacter intestinal infections.

Reactive arthritis most commonly strikes individuals aged 20–40 years of age, and is more common in men than in women, and more common in white people than in black people. This is owing to the high frequency the of HLA-B27 gene in the white population. Patients with HIV have an increased risk of developing reactive arthritis as well. [27]

Autoimmune Hepatitis

Autoimmune Hepatitis is a disease of the liver that occurs when the body's immune system attacks cells of the liver. Anomalous presentation of human leukocyte antigen (HLA) class II on the surface of hepatocytes, possibly due to genetic predisposition or acute liver infection, causes a cell-mediated immune response against the body's own liver, resulting in autoimmune hepatitis. This abnormal immune response results in inflammation of the liver, which can lead to further complications including cirrhosis.

Autoimmune hepatitis has an incidence of 1-2 people per 100,000 per year. As with most other autoimmune diseases, it affects women much more often than men (70%).

Sjögren's Syndrome (SS)

Diagnosing Sjögren's syndrome is complicated by the range of symptoms a patient may manifest, and the similarity between symptoms from Sjögren’s syndrome and those caused by other conditions. Nevertheless, the combination of several tests can lead to a diagnosis of Sjögren's syndrome.

Blood tests can be done to determine if a patient has high levels of antibodies that are indicative of the condition, such as anti-nuclear antibody (ANA) and rheumatoid factor (because SS frequently occurs secondary to rheumatoid arthritis), which are associated with autoimmune diseases. Typical Sjögren's syndrome ANA patterns are SSA/Ro and SSB/La, of which SSB/La is far more specific; SSA/Ro is associated with numerous other autoimmune conditions but are often present in Sjögren's syndrome. [28]
Diabetes Mellitus Type 1

Diabetes mellitus type 1 is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The typical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss.

Type 1 diabetes is generally fatal unless treated with insulin. Pancreatic transplants and pancreatic islet cell transplantation have been used to treat type I diabetes; however, pancreatic islet cell transplantation is still viewed as experimental, although utilization of the procedure is growing. [29]

21 - Hydroxylase Deficiency

21-hydroxylase deficiency is an inherited disorder that affects the adrenal glands. The adrenal glands are located on top of the kidneys and produce a variety of hormones that regulate many essential functions in the body. In people with 21-hydroxylase deficiency, the adrenal glands produce excess androgens, which are male sex hormones.

There are three types of 21-hydroxylase deficiency. Two types are classic forms, the first is known as the salt-wasting type, which is the most severe, second is the simple virilising type, which is less severe. The third type is called the non-classic type which is the least severe form.

Approximately 75% of individuals with classic 21-hydroxylase deficiency have the salt-wasting type. Hormone production is extremely low in this form of the disorder. Affected individuals lose large amounts of sodium in their urine, which can be life-threatening in early infancy. Babies with the salt-wasting type can experience poor feeding, weight loss, dehydration and vomiting. [50]

Scleroderma

Scleroderma is a type of autoimmune disease, specifically a connective tissue disease that involves changes in the skin, blood vessels, muscles, and internal organs. The cause of scleroderma is unknown. People with this condition have a build-up of collagen in the skin and other organs which leads to the symptoms of the disease. The disease usually affects people 30 to 50 years of age, and women get scleroderma more often than men do. A few people with scleroderma have a history of being around silica dust and polyvinyl chloride, but most do not. Widespread scleroderma can occur with other autoimmune diseases, including systemic lupus erythematosus (SLE) and polymyositis. In those types of cases, the disorder is referred to as mixed connective disease. [31]

Dermatomyositis

Dermatomyositis is a muscle disease characterized by inflammation and a skin rash and is a type of inflammatory myopathy. The cause of dermatomyositis is unknown. Experts think it may be due to a viral infection of the muscles or a problem with the body's immune system. It can also sometimes occur in patients who have cancer of the abdomen, lung or other body area.

Anyone can develop dermatomyositis, but it most commonly occurs in children age 5 - 15 and adults age 40 - 60. Women develop this condition more often than men do. [32]

Dermatomyositis may result from either a viral infection or an autoimmune reaction. In the latter case it is a systemic autoimmune disease. A large amount of people diagnosed with dermatomyositis were previously diagnosed with infectious mononucleosis and Epstein-Barr virus. Some cases of dermatomyositis are actually combined with other autoimmune diseases such as Sjögren's syndrome, lupus, scleroderma, or vasculitis.

Several cases of polymyositis and dermatomyositis were reported as being triggered by the use of various statin drugs used to control blood cholesterol. Muscle biopsies of these patients showed rhabdomyolysis (a condition in which damaged skeletal muscle tissue breaks down rapidly), and degeneration and regeneration of muscle tissue. [33]

Autoimmune Thyroiditis

Chronic thyroiditis is swelling/inflammation of the thyroid gland which often results in reduced thyroid function called hypothyroidism. Chronic thyroiditis or Hashimoto's disease is a common thyroid gland disorder which can occur at any age, most often seen in middle-aged women. It is caused by a reaction of the immune system against the thyroid gland. The disease begins slowly and may take months or even years to be detected. Chronic thyroiditis is found most commonly in women and people with a family history of thyroid disease. It affects between 0.1% and 5% of all adults in Western countries. Hashimoto's disease may, in rare cases, be associated with other endocrine disorders caused by the immune system such as adrenal insufficiency and type 1 diabetes. In these cases, the condition is called type 2 polyglandular autoimmune syndrome (PGA II). [34]

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic, systemic inflammatory illness that may affect many tissues and organs, but primarily attacks synovial joints. The disease produces a surplus of synovial fluid. The pathology of the disease process often leads to the severe damage of articular cartilage and ankylosis of the joints. Rheumatoid arthritis can also generate diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most frequent in subcutaneous tissue. The cause of rheumatoid arthritis is unknown, although autoimmunity plays a pivotal role in both its chronicity and progression, and rheumatoid arthritis is considered a systemic autoimmune disease. [35]

Multiple Sclerosis

Multiple sclerosis is an autoimmune disease that affects the brain and the central nervous system. Multiple sclerosis is caused by damage to the myelin sheath, which is the protective covering that surrounds nerve cells. When this
nerve covering is damaged, nerve impulses are slowed down or stopped. The nerve damage is caused by inflammation, which arises when the body's own immune cells attack the nervous system. Recurring incidents of inflammation can occur along any region of the brain, optic nerve, and spinal cord. People with a family history of multiple sclerosis, have a slightly higher risk of the disease. [36]

Graves' Disease
Graves’ disease is an autoimmune disease that leads to over activity of the thyroid gland (hyperthyroidism). The thyroid gland is an important organ of the endocrine system, and is located in the front of the neck just below the voice box. The thyroid gland releases the hormones thyroxine (T4) and triiodothyronine (T3), which regulate body metabolism. Controlling metabolism is essential for regulating mood, weight, and mental and physical energy levels.

Graves’ disease is the most common cause of hyperthyroidism. It is caused by an abnormal immune system response that causes the thyroid gland to produce too much thyroid hormone. Graves’ disease is most common in women over the age of 20 years. [37]

Polyarteritis nodosa
Polyarteritis nodosa is defined as a severe blood vessel disease in which small and medium-sized arteries become inflamed and damaged. This is a disease of unidentified cause that affects arteries, the blood vessels that carry oxygenated blood to organs and tissues. It occurs when certain immune cells attack the affected arteries. People with active hepatitis B and C are more susceptible to develop this disease. Symptoms result from damage to affected organs, most commonly, the skin, heart, kidneys, and nervous system.

Nerve involvement may produce sensory changes with numbness, pain, burning, and weakness. Central nervous system participation could cause strokes or seizures. Kidney involvement can produce various degrees of renal (kidney) failure. When heart arteries are implicated, heart attack, heart failure, and inflammation of the sac around the heart (pericarditis) may arise. [38]

Autoimmune Pancreatitis (AIP)
Autoimmune pancreatitis is an idiopathic inflammatory disease that produces pancreatic masses and ductal strictures. This benign disease is similar to pancreatic carcinoma both clinically and radiographically. The diagnosis of autoimmune pancreatitis is not easy to make. Nevertheless, an accurate and timely diagnosis may prevent the misdiagnosis of cancer and lessen the number of unnecessary pancreatic resections. [39]

Autoimmune pancreatitis (AIP) is an increasingly documented type of chronic pancreatitis. It can be difficult to differentiate autoimmune pancreatitis from pancreatic carcinoma. Autoimmune pancreatitis responds to treatment with corticosteroids, particularly prednisone. It is increasingly regarded as a form of hyper-IgG4 disease.

Histopathologic examination of the pancreas exposes a characteristic lymphoplasmacytic infiltrate of CD4- or CD8-positive lymphocytes and IgG4-positive plasma cells. It also exhibits interstitial fibrosis and acinar cell atrophy in later stages however; localization and the level of duct wall infiltration are unpredictable. Although histopathology examination remains the principal method for differentiation of AIP from acute and chronic pancreatitis, lymphoma, and cancer, not much is known concerning the cytopathology diagnosis of AIP. It has been proposed that a cytological smear rich in inflammatory cells (lymphocytes, plasma cells, granulocytes), with rare epithelial cells lacking atypia, supports the diagnosis of AIP. The sensitivity and the certainty of these criteria for differentiating AIP from neoplasia are currently unknown. [40]

Autoimmune pancreatitis (AIP) is a rare disorder of recognized autoimmune etiology that is related to characteristic clinical, histologic, and morphologic discoveries. Most of the early literature pertaining to AIP came from Japan, where there may be an increasing frequency, perhaps due to increased acknowledgment. It has however, been illustrated in several countries in Europe as well as the United States and Korea, suggesting that it is a worldwide entity. AIP can occur as a primary pancreatic disease or in correlation with other diseases of believed autoimmune etiology including primary sclerosing cholangitis (PSC), primary biliary cirrhosis, retroperitoneal fibrosis, rheumatoid arthritis, sarcoidosis, and Sjögren's syndrome. [41]

Acquired Autoimmune Disorders
Human Immunodeficiency Virus
Infection with HIV leads to the destruction of the immune system clinically distinguished by a progressive rise in the HIV viral load and by the decrease of the number of CD4+ T-cells. [42] Recent research done on the elite controllers has shown a wide heterogeneity in the immunological and clinical path of HIV infection regardless of certain similarities in genetic determinants. This suggests that HIV control should be seen in a context which integrates the host genetics, immune function and the virological diversity. The enormous depletion of CD4+ T-cells, general inflammation and immune activation all occur at the point when the adaptive immune system has not mounted an effective immune response as yet. [42] The interleukin-10 (IL-10) protein is a pleiotropic cytokine which is involved in various anti-inflammatory and immunosuppressive actions. These actions include the inhibition of cytokine production by macrophages, as well as the inhibition of accessory functions during T-cell activations. The immune system uses IL-10 to suppress inflammatory responses. Due to this fact, IL-10 plays a significant role in the pathogenesis of an immune disease; an example being HIV and systemic lupus erythematosus. [42]

Surgeries for Autoimmune Diseases.
Emergent interventions for autoimmune disease include biomarker development, bioinformatics, and presentation of new technologies. The advancement of biomarkers can enable an earlier diagnosis as well as aid physicians in deciding on and monitoring appropriate treatment. New technologies, such as genomics and proteomics, provide scientists with the tools
Systemic Lupus Erythematosus.

Surgery is not necessary to treat mild symptoms of Systemic Lupus Erythematosus (SLE). Surgery may be considered for people with SLE who have permanent, life-threatening kidney impairment. A kidney transplant or kidney dialysis may be done instead of ongoing long-term treatment with high doses of medicines, many of which have acute side effects. If kidney disease from lupus does not respond to high-dose corticosteroids and other immunosuppressive medicines, kidney dialysis or transplant are sensible alternatives.[44]

Cardiac involvement in patients with Systemic Lupus Erythematosus has been documented since the early 20th century. SLE includes all the sections of the heart, including the pericardium, conduction system, myocardium, heart valves, and coronary arteries. Cardiac valvular irregularities and coronary artery disease are common complications of Systemic Lupus Erythematosus. Findings of clinical results for coronary artery disease have shown a prevalence of 8.3% in patients with Systemic Lupus Erythematosus. More sensitive examinations including myocardial perfusion imaging and electron-beam computed tomography have proven a frequency of ischemic heart disease in about 30–40% of Systemic Lupus Erythematosus patients.[45]

Acute Anterior Uveitis

There is no specific surgical treatment for Acute Anterior Uveitis. Surgery is reserved for dealing with the complications thereof. Acute Anterior Uveitis may have complications. One example includes the iris sticking against the lens of the eye. These bonds are called synechiae. They are a troublesome complication if they spread around the whole pupil. Acute Anterior Uveitis can be related to an increase in intraocular pressure, which may advance to glaucoma. Acute Anterior Uveitis can also cause fluid to collect in the macula which is the part of the retina responsible for central vision. This difficulty is known as cystoid macular edema (CME). These complications may affect the options for treatment.[46]

Ankylosing Spondylitis Surgery

The majority of individuals who are diagnosed with Ankylosing Spondylitis do not need surgery; however, surgery may be an option for patients suffering from severe deformities related to it, especially in the spine or hip joints. There are two types of surgery that may be an option for these severe cases, depending on the patient’s clinical condition and symptoms namely a joint replacement or an osteotomy. Joint replacement surgery (for the hip, shoulder or knee) can allow people to regain the use of joints that have been affected by Ankylosing Spondylitis. These replacements are becoming progressively successful for people with acute pain and partial mobility in those joints.

Surgical rectification of the spine itself is also possible to address distinct deformities such as a humpback or swayback, or the chin-on-chest posture distinctive of individuals with advanced Ankylosing Spondylitis. Patients may benefit from this type of surgery if they present with severe, unrelenting pain that is not adequately eased by non-surgical care; neurological deficits; spinal instability; decreased ability to hold the head up and see horizontally and difficulty in completing basic daily actions due to spinal deformity.

For patients who have not profited from various forms of treatment, surgery can also provide relief from some of the physical and related emotional struggles of spinal deformity brought about by advanced Ankylosing Spondylitis. The choice whether to have surgery or not may be difficult, and it requires patients to weigh the advantages and disadvantages cautiously.[47]

Autoimmune Hepatitis

Individuals who do not respond to regular immune treatment or who may have acute side effects may gain more from supplementary immunosuppressive agents such as mycophenylate mofetil, cyclosporine, or tacrolimus. People who advance to end-stage liver disease (liver failure) or cirrhosis may need a liver transplant. Transplantation has a one year survival rate of 90% and a five year survival rate of 70% to 80%.[48]

Sjögren's Syndrome

Surgery does not play a key role in the treatment of Sjögren's syndrome. Blockage of lacrimal puncta (punctal occlusion) to help maintain tears in eyes is one option that may help some people (http://www.emedicinehealth.com/sjogren_syndrome/page8_em.htm). To relieve dry eyes, an individual may contemplate undergoing a minor surgical procedure to close the tear ducts that drain tears from one’s eyes (punctal occlusion). Collagen or silicone plugs may be implanted into the ducts for provisional closure. Collagen plugs dissolve in due course, but silicone plugs stay in place until they fall out or are removed. Alternatively, a patient’s physician may use a laser to seal their tear ducts permanently.[49]

The endogenous insulin production achieved by islet transplantation, combined with optimal insulin therapy, is necessary for maintaining near-average glucose levels. In terms of glucose management, islet transplantation provides results which are similar to those attained with pancreas transplantation as in one particular study. Simultaneous pancreas-kidney transplantation results in a higher rate of insulin independence, even though at the cost of more surgical complications. These results have led to a new prototype in islet transplantation, where the main goal is not insulin independence, but suitable glucose control and prevention of acute hypoglycaemia.[50]

21-hydroxylase Deficiency

Surgery does not need to be considered for genetically male (XY) infants as they have an excess of androgens, and do not develop anatomic abnormalities. However, surgery for affected XX infants is often performed and has become a subject of discussion in the last decade. Surgical reconstruction of malformed genitalia has been offered to parents of severely virilized girls with CAH since the first half of the 20th century. The functions of surgery have most
commonly been an amalgamation of the following reconstructions: to make the external genitalia look more female than male; to make it possible for these girls to participate in normal sexual intercourse when they grow up; to improve their chances of fertility and to decrease the occurrence of urinary infections. [51]

Scleroderma
Surgery may be used to treat joint stiffness in individuals with scleroderma. The surgery may decrease joint deformities and improve joint function. Surgery for scleroderma may include arthrodesis, which is a fusion of two adjacent bones, in order to stabilize a joint and is commonly performed in the spine; arthroplasty which is the replacement of a damaged joint with an artificial joint; an osteotomy which is the removal of a portion of bone to better realign the joint; resection which is the removal of a portion of diseased bone in the joint and a synovectomy which is the removal of a segment of the diseased soft tissue in the affected joint. [52]

Hand surgery in scleroderma has been infrequently documented. In one specific study, out of a sequence of 813 successive patients with scleroderma, 31 have had one or more surgical procedures on their affected hands, altogether a sum of 52 operations. Raynaud’s phenomenon, which is a complication of scleroderma, has been controlled medically by vasodilators and thorough wound care. Most digital ulcers which have progressed to gangrene have been allowed to auto-amputate to maximize the length of the salvaged appendage, but 23 digital amputations have been performed in this specific study when conventional measures have been unsuccessful. Digital sympathectomy and microsurgical revascularization have resulted in the relief of symptoms in a few of the patients. Severe flexion contractures of the proximal interphalangeal joints, with secondary hyperextension of the metacarpophalangeal joints, have been successfully treated by arthrodesis of the proximal interphalangeal joints in 44 to 55 degrees of flexion. This has allowed both better hand function and primary recovery of dorsal ulcers in 53 proximal interphalangeal joints in twelve patients. [53]

Surgery is sometimes an option if medications are unable to manage the symptoms of scleroderma. Surgery is a Nissen fundoplication (surgical procedure), which encompasses wrapping the upper portion of the stomach around the bottom of the oesophagus, to strengthen the valve between the oesophagus and the stomach. This will help prevent reflux of acid into the oesophagus. Due to the decreased muscular activity within the oesophagus in patients with scleroderma, surgery may lead to additional problems in the ability to swallow and therefore is not frequently an option.

Dermatomyositis
The most common treatment for dermatomyositis is oral corticosteroids. However, the dose and length of treatment is still a debate. Adding to the confusion, there have been no randomized studies comparing the use of various corticosteroid doses and reduction rates, and no long term controlled studies assessing the hypothesis that, unlike systemic lupus erythematosus, patients with dermatomyositis can retain long term effective remission stages off therapy or medication. As we learn more about the pathophysiology of dermatomyositis, newer medications that target certain mechanisms in the immune response may help a physician better treat the disease. Surgery may sometimes be needed to remove any calcium deposits that may cause nerve pain and frequent infections as a result of dermatomyositis.

Thyroid surgery
Thyroid surgery is performed for many various reasons. A nodule or lobe of the thyroid is sometimes removed for biopsy or for the presence of an autonomously functioning adenoma causing hyperthyroidism. A large majority of the thyroid may be removed, a subtotal thyroidectomy, to treat the hyperthyroidism of Graves' disease, or to remove a goiter that is unsightly or impinges on vital structures.

If the thyroid gland is to be removed surgically, care must be taken to avoid damage to bordering structures such as the parathyroid glands and the recurrent laryngeal nerve. Both are susceptible to accidental removal and/or damage during thyroid surgery. The parathyroid glands produce parathyroid hormone (PTH), a hormone needed to maintain adequate amounts of calcium in the blood. Removal results in hypoparathyroidism and results in a need for supplemental calcium and vitamin D daily after surgery. In the event that the blood supply to any one of the parathyroid glands is endangered due to surgery, the parathyroid gland(s) concerned may be re-implanted in encompassing muscle tissue. The recurrent laryngeal nerves provide motor control for all external muscles of the larynx except for the cricothyroid muscle, which also runs along the posterior thyroid. Accidental grazing of either of the two or both recurrent laryngeal nerves may result in paralysis of the vocal cords and their associated muscles, changing the quality of an individual’s voice. [54]

Rheumatoid Arthritis
Surgery in rheumatoid arthritis is performed in order to relieve acute pain and improve the function of severely deformed joints which do not respond to medication and physical therapy. Complete joint replacement (arthroplasty) can be done for various joints in the body. Its success varies depending on which joint is replaced. Surgeries considered for people who have severe rheumatoid arthritis include finger and hand surgeries, to correct joint problems in the hand; arthroscopy, which removes debris or inflamed tissue in a joint through a small lighted instrument; synovectomy, to remove inflamed joint tissue; arthroplasty, to replace part or all of a joint in the hip or knee; cervical spinal fusion, to treat severe neck pain and nerve problems and resection of metatarsal heads, to remove deformed bone in the feet. [55]

Multiple Sclerosis
People with multiple sclerosis who have severe tremors affecting general movement may be helped by surgery. Individuals with acute spasticity may be helped by inserting a spinal pump to deliver medicines when oral medicines fail.
Deep brain stimulation for tremors may be one solution. Acute and disabling tremors that occur with the slightest movement of the individual’s limbs may be helped by an implanted device that stimulates a specific area of the brain. Implantation of a drug catheter or pump, for spasticity is another option to individuals affected by multiple sclerosis. Individuals with acute pain or spasticity may benefit from having a catheter or pump placed in the lower spinal area to deliver a constant flow of medicine, such as baclofen (Lioresal). [56]

Graves’ Disease

With no permanent cure, Graves’ disease should be treated by reducing the thyroid’s ability to produce hormones. With a surgery to remove some or all of the thyroid gland (known as a thyroidectomy), better control of hormone production can be gained.

Polyarteritis Nodosa

Surgery may be necessary for gastrointestinal tract manifestations of Polyarteritis Nodosa, including bowel ischemia, cholecystitis, and appendicitis. Microcoil embolization of cerebral aneurysms may also be indicated. Postsurgical care may be needed for patients with polyarteritis nodosa who develop a bowel infarction. [57]

Autoimmune Pancreatitis

Established surgery for Chronic Pancreatitis tends to be divided into two areas, namely, resectional and drainage techniques. New and proven transplantation options prevent the patient from becoming diabetic following the surgical removal (resection) of their pancreas. This is accomplished by transplanting back in the patients’ own insulin-producing beta cells.[58] Most people with chronic pancreatitis do not need surgery but on occasion, one is needed. The most common reason for surgery is because of persistent acute pain that is not alleviated by painkillers or other methods. Total recuperation from pain occurs in about 7 in 10 patients who undergo surgery. The operation usually involves removing a section of the pancreas. There are different procedures that can remove different amounts of the pancreas. The procedure which is appropriate depends on the severity of an individual’s condition, whether the pancreatic duct is blocked, and also on various other factors. Other operations may be advised in some cases, one example being the removal of calcium stones that may be blocking the main pancreatic duct. Another procedure that may help in some individuals is to expand a narrowed pancreatic duct to allow better drainage of pancreatic enzymes. Surgery may also be needed if complications develop, for instance, if a blocked bile duct or pseudocyst develops. [59]

Risk Factors and Risk Assessment for Autoimmune Diseases.

People of all genders, races, and ages can be affected by autoimmune diseases, but some people are at larger risk of developing an autoimmune disease. An individual’s chance of developing an autoimmune disease is elevated if the following factors are present:

- **Gender:** It is a known fact that women are at higher risk of developing autoimmune diseases, since they tend to affect women about 75% more than men. It is not entirely clear why women are more vulnerable to autoimmunity, although some researchers speculate that women’s enhanced immune systems and specific hormones may make them more subject to autoimmune diseases.

- **Age:** Most autoimmune diseases affect young and middle-aged individuals. Each autoimmune disease is different, and disorders such as rheumatoid arthritis are found more commonly in elderly people.

- **Ethnicity:** People who are in African American, American Indian, or Latino ethnic groups are more likely than Caucasians to develop autoimmune diseases.

- **Family history of autoimmune disorders.** Numerous studies have shown that the tendency to develop autoimmune disorders can be genetic. If a family has members who have an autoimmune disorder, others within that family have increased chances of getting the same disorder or one that is closely related.

- **Exposure to environmental agents.** There is some evidence that exposure to certain things in an individual’s immediate environment may increase their risk of developing an autoimmune disease. For example, research shows that exposure to some medications (for example, procainamide or hydroxyzine) and certain metals (mercury, gold, or silver) may be associated with the development of specific autoimmune disorders. Even though the scientific evidence relating environmental exposure to the onset of autoimmune disorders is not entirely conclusive, researchers are still working to find out how environmental exposures may play a role.

- **Previous infection.** There is an increasing amount of evidence which suggests that genetically susceptible people who have had certain bacterial and viral infections may be at higher risk for some types of autoimmune disorders. It is still unclear just how these infections may increase the risk of autoimmune diseases and as a result, researchers are currently looking into various proposed mechanisms.

Given that the precise cause of autoimmune disorders is still largely unknown and probably mainly due to factors that cannot be controlled (i.e. gender and genetics), it is difficult to say whether an individual can take steps towards reducing their risk of the development of an autoimmune disease.

As researchers learn more about the link between previous infection and the risk of developing an autoimmune disease, taking steps toward reducing the individual’s risk of bacterial and viral infections would be sensible. Precautions that can be taken include personal cleanliness and hygiene, avoiding being exposed to others who are sick/ill and remaining up to date with one’s vaccinations. [60]

Defining particular pathogenic environmental mediators that may cause the initiation and progression of autoimmune disease remains a focus of mounting investigative effort.
Factors promoting disease may not be the same as factors that influence the severity or progression thereof. Human monozygotic twin studies, animal studies, and genetic models validate that genetic influences effectively determine whether one will develop an autoimmune disease, yet genes affecting the metabolism of exogenous causes that may trigger disease manifestation have only recently come into awareness.

The assessment of genetic influences in human autoimmunity has recurrently relied on family studies, in particular, twin studies. Twin studies have been criticized for comprising mainly of a larger proportion of monozygotic, female, and disease concordant volunteers. Previous twin studies have reported significantly higher concordance rates of 24 to 50% in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus among monozygotic twins. [61]

Incidence, Prevalence, Morbidity, and Mortality of Autoimmune Diseases

Incidence represents how quickly new cases of autoimmune diseases occur relative to population size and passage of time. It is determined as a ratio of the number of new cases of a disease occurring within a population during a given time according to the total number of people within the specific population. For instance, there are an estimated 30,000 new cases of type 1 diabetes in the United States per annum, meaning there is an incidence rate of 10 new cases per year per 100,000 populations.

A very small amount of data exists to estimate the occurrence of autoimmune diseases on a national scale. Although many published studies estimate the frequency of individual autoimmune diseases, the majority of these estimates are resultant from fairly small or geographically restricted populations. One example includes studies conducted in Olmstead County, Minnesota which produces estimates of the occurrence of multiple sclerosis, systemic lupus erythematosus and autoimmune thyroid diseases. It is, however, not possible to generalize from this data collected, to the diverse population of the United States.

In a comprehensive review of the published literature, Jacobsen et al. [62] recognized 140 studies, published between 1965 and 1995, which incorporate frequency estimations for one or more autoimmune diseases. These studies were performed in numerous locations throughout the United States, and represent only 24 of the more than 80 known autoimmune diseases. Using information from these reports, Jacobsen et al. predicted that the total number of incident cases of these 24 autoimmune diseases in 1996 would be 237,200 new cases – about 172,700 in women and 64,500 in men. These statistics can be interpreted as an incidence of 1.3 new cases for every 1,000 women and 0.5 new cases for every 1,000 men in the United States in 1996. The autoimmune diseases with the highest incidence recognized in these studies were rheumatoid arthritis, autoimmune thyroid disease, and uveitis. Nevertheless, it is probable that these statistics considerably underestimate the occurrence of all autoimmune diseases on a national scale. Additionally, a number of fairly common autoimmune diseases were not included in this evaluation, for example, psoriasis, ulcerative colitis, and Crohn’s disease.

Both the incidence and duration of disease are a function of prevalence. Sequentially, duration is influenced by the accessibility and effectiveness of treatments and by survival times of affected individuals. For most autoimmune diseases, a total cure is rare, and survival is generally measured in months or years. Therefore, the chronicity of autoimmune disease leads to an elevated prevalence despite a relatively low annual occurrence thereof.

Morbidity signifies the state of being by, and the severity and impact of disease. As in prevalence, degrees of morbidity represent the burden that a disease places on a population. Compared to prevalence, morbidity estimations use more involved approaches that are possibly more instructive than a simple count of cases for example. Frequently used morbidity measures include the number of hospitalization days caused by a specific disease, number of days the affected individual is absent from work or school, the number of physician appointments resultant due to the disease, and days of restricted activity. These events measure the influence of a disease and often weigh the nonmonetary costs associated with specific disorders.

Mortality quantifies deaths caused by a specific autoimmune disease, deaths resulting from treatment for a specific disease, or deaths in which a specific disease is a causal factor, meaning it is a secondary cause. Mortality is the number of deaths due to a disease during a specific time divided by the number of individuals in a specific population at the beginning of a set time period. Thus, mortality is a rate in the sense that it represents how quickly deaths occur, comparative to the size of the population and a specific passing of time. [63]

Emergent Interventions for Autoimmune Disease

There have been new medicinal intervention trials regarding systemic lupus erythematosus, although some are still pending regarding the success in the reduction of the disease. [64]

Regarding acute anterior uveitis, there are currently experiments being done on certain strains of inbred and outbred rat strains for the immunization of bovine ocular melanin. Multiple occurrences of this disease are still common. Research groups have used experimental melanin protein induced uveitis to investigate different aspects of the pathogenesis of inflammation of the tissues. This has also been used to evaluate certain biological interventions regarding the potential implications for the treatment of the human strain of the disease. Research is currently on going. [65]

Exercise programs for people suffering from ankylosing spondylitis are currently being tested and evaluated for their effectiveness. These exercise programs specifically target cardiorespiratory fitness, muscular strength and flexibility. These programs are monitored for their effectiveness during the trials. [66]

Physiotherapy is another alternative intervention for ankylosing spondylitis. Studies have proven that physiotherapy, specifically exercise, spa therapy, manual therapy and electrotherapeutic modalities are examples of effective interventions. Studies are in progress regarding this type of intervention for ankylosing spondylitis. Autoimmune
hepatitis can be treated with corticosteroids, which is effective to a large degree. In some studies there are certain pharmacological, molecular and cellular interventions trials under construction as to alternative treatments for autoimmune hepatitis. [67]

An ideal treatment for Sjogren’s Syndrome is still in progress, although animal models have shed some light on the connections between specific pathways and symptoms of the disease. Disease models still need to be improved in order to understand Sjogren’s Syndrome better. An optimal model should include the reasons immune tolerance is lost and potential therapeutic interventions. Is should also be able to detect disease biomarkers, as It is a possibility that injury to the salivary glands may precede lymphocytic infiltration. [68]

There have been numerous studies on the transplantation of pancreatic islets into the liver as a cure for diabetes mellitus type I. Complications occur due to massive early β-cell deaths which require a larger number of islets to be transplanted to restore glucose homeostasis; as well an instant blood-mediated inflammatory reaction when exposing human islets to the blood microenvironment in the portal vein and the low oxygenated milieu of islets transplanted into the liver. Clinical trials are continuously being conducted in order to improve results in islet transplantation.

Therapeutic interventions are being conducted to suppress pathogenic auto-reactivity and to preserve beta-cell mass and function to physiological sufficient levels to maintain good metabolic control. There has not yet been a single successful long term treatment identified for diabetes mellitus. Some studies suggest that a combination of immunotherapeutic methods and islet regeneration or replacement would be the most effective approach. [69]

Investigations are currently underway regarding disease mechanisms on 21 hydroxylase deficient mouse models. Gene therapy is being investigated as an intervention for this disease. New approaches regarding how to include combination therapy to block androgen action, inhibit oestrogen production and bilateral adrenalectomy in severe cases are also currently being conducted. Other approaches, which are in a preclinical stage of investigation, include treatment with a corticotropin-releasing hormone antagonist and gene therapy. [70]

Therapeutics for scleroderma are divided into three main subgroups for systemic sclerosis: antifibrotics, anti-inflammatories, and vasodilators. For localized disease, anti-inflammatories, vitamin D analogs, and UV irradiation have been investigated. There is no single therapy for systemic sclerosis or localized scleroderma that has proven to be significantly disease modifying. Current therapeutic strategies must be initiated early in the disease course for maximum advantageous clinical effects. New interventions such as autologous stem cell transplant and cytokine-directed therapies are currently under investigation as probable treatments for this complex disease. [71]

Dermatomyositis have an effective short term therapy, namely, intravenous immunoglobulin; yet not long term cures are known. Even in randomized trials, the lack of validated and generally acknowledged outcome measures makes it challenging to associate the effect of interventions in different studies. Even though the bulk of evidence suggests that immunosuppressants are equally effective in dermatomyositis and polymyositis, there are no randomized controlled trials to show if any of these drugs, individually or in combination, is best. For uncommon diseases, such as inflammatory myositis, only multicentre randomized controlled trials involving rheumatologists and neurologists will be able to define the optimal therapy necessary. [72]

There are a number of approaches currently being developed to utilise T cells’ potent immunosuppressive properties for rheumatoid arthritis. Genetic manipulation can be used to target specific antigens present in an inflamed joint. Clinical trials for pharmacologic interventions are currently being run, but do not reflect on any innovations in the diagnosis of rheumatoid arthritis.

There is an imperative need to adjust clinical trial inclusion criteria and other study design features to better reflect the current characteristics of people living with rheumatoid arthritis in those countries where new drugs will be used. [73]

Traditional Chinese medicine and western biomedical combination therapy effectiveness in rheumatoid arthritis patients is currently under investigation. Results in one study which explored the associations between tongue colour and appearance and treatment of traditional Chinese medicine combined with western biomedical therapy suggest that tongue coating and body colour might be used to help identify a subset of rheumatoid arthritis patients both for Chinese medicine and western medicine interventions. [74]

Studies are currently being conducted in the changes of social cognitive and physical changes in patients with multiple sclerosis over time. One longitudinal study investigates possible effective behavioural interventions for people with multiple sclerosis. It suggests that there are changes that can be made regarding physical activity by intervening behavioural modifications such as goal setting. [75]

Nutritional interventions can also be introduced during the course of the disease as it is accepted that diet plays a role in the pathogenesis of multiple sclerosis. Furthermore, studies investigate the effectiveness of nutritional intervention by investigating the role of bioactive dietary molecules and their targets, and establish how a dietary control will be able to influence cell metabolism and improve overall wellness in these patients. [76]

Exercise therapy for patients with multiple sclerosis has proven to be successful in a number of recent studies. Intermittent transcranial magnetic theta burst stimulation may induce long term changes of the cerebral cortex and may alleviate spasticity in multiple sclerosis sufferers. One study looks into the combination of exercise therapy and intermittent transcranial magnetic theta burst stimulation to improve motor disability. [77]

For some patients with Graves’ Disease, removal of circulating thyroid hormones and thyroid antibodies by plasmapheresis is an effective therapeutic option. Some patients may, however, present with excess bleeding complications There are other options for the management of a hyperthyroid, such as emergent surgical interventions or pharmacological treatments. [78]
Studies pertaining to autoimmune pancreatitis show that searching for biomarkers for early detection is important. In advanced cases, surgery is an option for treatment. New techniques are currently being applied in search of better ways to diagnose early chronic autoimmune pancreatitis. Emergent studies compare endoscopic and surgical interventions, as well as the complexity of the disease. [39]

References

44. http://icvts.ctsnetjournals.org/cgi/content/full/4/4/618
45. http://eyewiki.aao.org/Acute_Anterior_Uveitis#Surgery
58. http://www.patient.co.uk/health/Pancreatitis-Chronic.htm
60. Clinical Immunologic Immunopathology. 1997. 84:223-243


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Standard Bank
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Reference: SZRC (donation)

UK: Stellenbosch University SA Foundation UK
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Account name: Stellenbosch University SA Foundation
Account number: 39448843
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Bank: Standard Bank
Takkode: 05 06 10
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Rekeningnommer: 073006955
Verwysing: SZRC (skenking)

VK: Stellenbosch University SA Foundation UK
Bank: Natwest City of London Office
Rekeningnaam: Stellenbosch University SA Foundation UK
Rekeningnommer: 39448843
Sorteerkode: 60-00-01
Verwysing: SZRC (skenking)