Basic concepts of autoimmunity, hypersensitivity and immunodeficiency disorders

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CONTENTS

AUTOIMMUNITY

Introduction
Causes
Classification of Autoimmune Diseases
Symptoms of Autoimmunity
Diagnosis of Autoimmune diseases
Important autoimmune diseases
  Hashimoto’s Thyroiditis
  Autoimmune Anemias
  Goodpasture’s Syndrome
  Insulin-Dependent Diabetes Mellitus (Diabetes mellitus-type 1)
  Graves disease
  Myasthenia gravis
  Systemic Lupus Erythematosus (SLE)
  Rheumatoid Arthritis
  Sjögren's syndrome
  Multiple Sclerosis (MS)
  Mechanisms for induction of Autoimmunity
  Treatment of Autoimmune Diseases

HYPERSENSITIVITY

Introduction
Classification

IMMUNODEFICIENCY DISORDER

Introduction
Classification
Secondary (Acquired) Immunodeficiency
Diagnostic features
Treatment
Experimental Models of Immunodeficiency
**Keywords**

allergy, anaphylaxis, anergy, antigen, atopy, autoantibody, autologous, cytokines, cytotoxin, degranulation, delayed type hypersensitivity, hematopoiesis, immunocompromised, inflammation, lymphokine, tolerance.
AUTOIMMUNITY

Introduction

One of the essential properties of the immune system is its ability to recognize and respond to foreign antigens but not to self-antigens. This ability is highly regulated to ensure that when pathogens are eliminated, the immune response is shut down. At times, the immune system, can go wrong in its ordered duty and instead of reacting against foreign antigens, it starts attacking self-antigens. Paul Ehrlich in the beginning of twentieth century termed this condition “horror autotoxicus”, wherein a 'normal' body does not mount an immune response against its own tissues.

The unresponsiveness of the immune system to antigenic stimulation is termed immunological tolerance and maintaining tolerance to self-antigens is referred to as self-tolerance. Mechanisms of self-tolerance normally protect an individual from potentially self-reactive lymphocytes. Loss of self-tolerance i.e. the failure of an organism to recognize its own constituents as "Self", results in an inappropriate immune reaction against its own cells and tissues or autologous antigens. Such reactions are called autoimmunity. Any disease that results from such an aberrant immune response is termed an autoimmune disease, the prominent examples being Hashimoto’s Thyroiditis, Graves disease, Goodpasture’s syndrome, Systemic Lupus Erythematosus (SLE), Sjögren's syndrome and Rheumatoid Arthritis (RA) etc. to name a few.

Thus, in autoimmune diseases, antibodies or T cells directed against self, the so called auto antibodies or auto reactive T cells, are thought to be causally associated with a range of different pathologies.

Causes of Autoimmunity

The exact causes of autoimmunity and the underlying genetics are not known. The potential for autoimmunity exists in all individuals because all of them inherit genes that code for lymphocyte receptors that may recognize self-antigens, and also many self-antigens are readily accessible to the immune system. Autoimmunity is normally prevented by selection processes that prevent the maturation of specific lymphocytes that recognize self-antigen, and by mechanisms that inactivate mature self-reactive lymphocytes. Loss of self-tolerance is then thought to result from abnormal selection or regulation of self-reactive lymphocytes, and from abnormalities in the way self-antigens are presented to the immune system. Several important findings have emerged from analyses of autoimmunity till date and scientists probably think that our genes (singly or in combination), multiple interacting factors or some environmental factor(s) turns on our system against self and puts us at higher risk of developing the disease. Presence of certain HLA alleles puts the individual at greater risk. The multiple interacting factors include immunologic abnormalities affecting APCs or lymphocytes, genetic backgrounds that predispose to autoimmunity, gender, tissue injury and microbial infections. The environmental factors may include the sun, infections, drugs, or, in some women, pregnancy. Because combinations of these factors may be operative in different disorders, it is not surprising that autoimmune diseases comprise a heterogeneous group of clinical and pathologic abnormalities.
Classification of Autoimmune Diseases

Depending on the body part affected and the clinico-pathological features, autoimmune diseases have been broadly classified into two major groups - systemic and organ-specific (localized). Different types of antigens and different immunologic abnormalities have been implicated in their cause. For instance, the formation of circulating immune complexes typically produces systemic diseases. In contrast, auto-antibody or T cell responses against antigens with restricted tissue distribution lead to organ-specific injury (Table-1). Various effector mechanisms are responsible for tissue injury in different autoimmune diseases. These mechanisms include circulating autoantibodies, immune complexes or auto-reactive T lymphocytes.

Table 1: List (not inclusive) of body systems and autoimmune diseases that can affect them

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Body system</th>
<th>Autoimmune disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Blood and blood vessels</td>
<td>Autoimmune hemolytic anemia; Pernicious anemia; Polyarteritis nodosa; Systemic lupus erythematosus</td>
</tr>
<tr>
<td>2.</td>
<td>Digestive tract (including the mouth)</td>
<td>Autoimmune hepatitis; Behçet's disease; Crohn's disease; Primary biliary cirrhosis; Scleroderma; Ulcerative colitis</td>
</tr>
<tr>
<td>3.</td>
<td>Eyes</td>
<td>Sjögren's syndrome; Uveitis</td>
</tr>
<tr>
<td>4.</td>
<td>Glands</td>
<td>Graves’ disease; Thyroiditis; Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>5.</td>
<td>Heart</td>
<td>Myocarditis; Rheumatic fever; Scleroderma; Systemic lupus erythematosus</td>
</tr>
<tr>
<td>6.</td>
<td>Joints</td>
<td>Ankylosing spondylitis; Rheumatoid arthritis; Systemic lupus erythematosus</td>
</tr>
<tr>
<td>7.</td>
<td>Kidneys</td>
<td>Glomerulonephritis; Systemic lupus erythematosus; Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>8.</td>
<td>Lungs</td>
<td>Rheumatoid arthritis; Sarcoidosis; Scleroderma; Systemic lupus erythematosus</td>
</tr>
<tr>
<td>9.</td>
<td>Muscles</td>
<td>Dermatomyositis; Myasthenia gravis; Polymyositis</td>
</tr>
<tr>
<td>10.</td>
<td>Nerves and brain</td>
<td>Guillain-Barré syndrome; Multiple sclerosis; Systemic lupus erythematosus</td>
</tr>
<tr>
<td>11.</td>
<td>Skin</td>
<td>Alopecia areata; Pemphigus / pemphigoid; Psoriasis; Scleroderma; Systemic lupus erythematosus; Vitiligo</td>
</tr>
</tbody>
</table>
Organ-specific Autoimmune Diseases or Local syndromes

Local syndromes may be endocrinologic (diabetes, Hashimoto’s thyroiditis, Addison’s disease etc.), dermatologic (Pemphigus vulgaris), haematologic (autoimmune hemolytic anemia), neural (multiple sclerosis) or can involve virtually any circumscribed mass of body tissue. Here, the immune response is directed to unique antigen of a single organ or gland and the manifestations are largely limited to that organ. The cells of the target organs may be damaged directly by humoral or cell-mediated effector mechanisms, e.g. Autoimmune hemolytic anemia (AHA), Hashimoto’s thyroiditis etc. In AHA, antigens on red blood cells are recognized by autoantibodies, which result in anemia. In Hashimoto’s thyroiditis the auto-antibodies reactive with tissue-specific antigens such as thyroid peroxidase and thyroglobulin cause severe tissue destruction. Blistering and raw sores on skin and mucous membranes occur in Pemphigus vulgaris. Multiple sclerosis, a disorder of the central nervous system (brain and spinal cord) is characterised by decreased nerve function due to myelin loss and secondary axonal damage. Alternatively, the antibodies may over stimulate or block the normal function of the target organ e.g. Graves disease and Myasthenia gravis respectively.

Systemic Syndromes

These include diseases like Systemic lupus erythematosis (SLE), Sjogran’s syndrome, Scleroderma, Rheumatoid Arthritis and Polymyositis.

General presenting symptoms of Autoimmunity

Depending upon the body part affected and the specific tissue targeted, the patients with autoimmunity (diseases) represent varying symptoms. With skin as the target, skin rashes, blisters, or color changes appear. If it’s the thyroid gland, general tiredness, weight gain, more sensitivity to cold, and muscle aches are the presenting complaints. On the other hand joint pain, stiffness, and loss of function result when joints are affected. Although specific organ affected is known from the start, the exact site of attack may remain unknown, and patient’s first symptoms are fatigue, muscle aches, and low-grade fever.

Diagnosis of Autoimmune diseases

Autoimmune diseases normally don't show a clear pattern of symptoms at first, so the diagnosis is usually made by keeping in view medical history, including family history, physical examination of the body part or lymph nodes and serological tests, for the presence of auto-antibodies. Auto antibodies may not be present in all diseased individuals and may appear in some healthy subjects too. So blood tests alone may not always help. But if a person has disease symptoms and auto-antibodies, a more sure diagnosis can be made.

Detailed account of some important autoimmune diseases

Diseases Mediated by Direct Cellular Damage

When lymphocytes or antibodies bind to cell-membrane antigens, they cause cellular lysis and/or an inflammatory response in the affected organ with gradual replacement of the damaged cellular structure by connective tissue (scar tissue), and the function of the organ declines e.g.
Hashimoto’s thyroiditis, Autoimmune Anemias, Goodpasture’s syndrome and Insulin Dependent Diabetes Mellitus (IDDM) to name a few.

**Hashimoto’s Thyroiditis**

This disease is a common form of hypothyroidism, characterised by initial inflammation of the thyroid, and, later, dysfunction and goiter (Fig. 1). Here an individual produces autoantibodies and sensitized T\(_H\)1 cells specific for thyroid antigens with ensuing DTH response. There is an intense infiltration of the thyroid gland by lymphocytes, macrophages and plasma cells, forming lymphocytic follicles and germinal centers (Fig. 2 & 3). The ensuing inflammatory response causes a goiter (visible enlargement of the thyroid gland). Antibodies are formed to a number of thyroid proteins, including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine. This interferes with iodine uptake and leads to decreased production of thyroid hormones (hypothyroidism). The disease is more commonly seen in middle-aged women.

![Hashimoto's thyroiditis](http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/17068.jpg)

**Fig. 1: Hashimoto’s thyroiditis**


**Autoimmune Anemias**

**Pernicious anemia**

In Pernicious anemia, the number of functional mature red cell count goes below normal. The low count occurs as a result of diminished absorption of vitamin B\(_{12}\) from small intestine, which is necessary for proper hematopoiesis. The normal absorption from small intestine is facilitated by an intrinsic factor (a membrane-bound intestinal protein) present on gastric parietal cells. Auto-antibodies to intrinsic factor block the intrinsic factor-mediated absorption of vitamin B\(_{12}\),
resulting in lower count. Pernicious anemia is treated with injections of vitamin B_{12}, thus circumventing the defect in its absorption.

**Pathological findings**

Fig. 2: Hashimoto’s thyroiditis. Chronic inflammatory infiltrate and active lymphoid germinal centers are seen within the thyroid gland. There is a marked destruction of thyroid gland. In areas of attempted regeneration are seen large, brightly stained follicular cells called Hurthle cells. These are the stimulated follicular cells. 

(Source: www.nlm.nih.gov, medsci.indiana.edu)

Fig. 3. Lymphoid aggregates with germinal center formation within the thyroid tissue itself (right). Clusters of lymphocytes as well as fibrosis giving a lobulated look to the thyroid in general.
Autoimmune hemolytic anemia

Auto-antibody to RBC antigens triggers complement-mediated lysis or antibody-mediated opsonization and phagcytosis of the red blood cells, resulting in autoimmune hemolytic anemia. One form of autoimmune anemia is drug-introduced. Certain drugs, such as penicillin or anti-hypertensive agent methyldopa on interacting with the red blood cells, make them antigenic. The immunodiagnostic test for autoimmune hemolytic anemias generally involves Coombs test, in which the red cells are incubated with an anti-human IgG antiserum. If IgG autoantibodies are present on the red cells, the cells are agglutinated by the antiserum.

Goodpasture’s Syndrome

The disease is characterised by rapid destruction of the kidneys and haemorrhage of the lungs through autoimmune reaction against an antigen found in both organs. Here auto antibodies specific for certain basement-membrane antigens bind to the basement membranes of the kidney glomeruli and the alveoli of the lungs. Subsequent complement activation leads to direct cellular damage and resulting buildup of complement split products results in inflammation. The damage to the glomerular and alveolar basement membranes leads to progressive kidney damage and pulmonary hemorrhage. Death may ensue within several months of the onset of symptoms. The reason for the dual targeting of kidney and lungs is due to the sharing of epitopes on epithelial cells of these two organs.

Insulin-Dependent Diabetes Mellitus (Diabetes mellitus-type 1)

Diabetes mellitus (type 1) is the result of an autoimmune attack on the pancreatic islet cells. It is a chronic disease characterized by hyperglycemia resulting from defects in insulin secretion or signaling. Insulin, a hormone produced by the β cells of the pancreatic islets of Lagerhans, is indispensable for glucose metabolism. Around 0.2% of the world population and an estimated 10% of India’s population are afflicted with it. India has earned the dubious distinction of being the diabetes capital of the world. The destruction of the beta cells, results in decreased production of insulin and consequently increased level of blood glucose. Two forms of diabetes are recognized clinically. Type 1, Insulin-Dependent Diabetes Mellitus (IDDM) or juvenile onset diabetes is caused by the deficiency in the production of insulin due to the immune-mediated destruction of β cells. By contrast, type 2, non-insulin dependent (or adult onset) diabetes is caused by inappropriate or inadequate insulin secretion coupled to insulin resistance.

Several factors are important in the destruction of beta cells. These include migration of activated CTLs into an islet and their subsequent attack on the insulin-producing cells (Insulitis), coupled with local cytokine production, resulting in DTH response. Lytic enzymes released from the activated macrophages also destroy beta cells. Auto-antibody production can also be a contributing factor in IDDM. Auto-antibodies to beta cells may contribute to cell destruction by facilitating either complement mediated lysis or antibody-dependent cell-mediated cytotoxicity (ADCC). The disease is most commonly treated with oral tablets or injection of Insulin in doses according to individual needs.
**Diseases Mediated by Stimulating or Blocking Auto antibody**

**Graves disease**

Graves Disease is caused by anti-thyroid antibodies that have the effect of stimulating the thyroid into overproduction of thyroid hormone (Fig. 4). Pituitary gland produces thyroid-stimulating hormone (TSH), which regulates the production of thyroid hormones. TSH binds to a receptor on thyroid cells and activates adenylate cyclase, which in turn stimulates the synthesis of two thyroid hormones, thyroxine and triiodothyronine. Auto-antibodies are produced which mimic the action of TSH and binds to the receptor for TSH. This binding results in activation of adenylate cyclase, which results in production of thyroid hormones. The auto-antibodies, also named ‘long acting thyroid-stimulating antibodies’ (LATS) are not regulated and thus results in over-stimulation of thyroid gland. The incidence of Graves’ diseases has been shown to increase steadily throughout the first decade of life, reaching a peak during adolescence. Girls are affected 3-6 times more often than boys. The disease runs in families.

![Fig. 4: Graves’s Disease](http://www-immuno.path.cam.ac.uk/~immuno/part1/lec12/LATS.gif; http://members.lycos.co.uk/diseaseDIR/imagesd/d0102.gif)

**STIMULATING AUTO-ANTIBODIES (Graves' disease)**

- **Pituitary gland**
- **TSH (Thyroid-stimulating hormone)**
- **Auto-antibody to receptor**
- **TSH receptor**
- **Thyroid cell**
- **Regulated production of thyroid hormones**
- **Unregulated overproduction of thyroid hormones**

Fig. 4: Grave’s Disease. Here auto antibodies against receptors for thyroid stimulating hormone (TSH) present on thyroid cells are produced. TSH is produced by the pituitary gland. Binding of auto antibodies mimics the normal action of TSH thereby stimulating the production of two thyroid hormones, thyroxine and triiodothyronine. However the auto antibodies are not under a negative feedback control system and therefore lead to overproduction of thyroid hormones. For this reason auto antibodies have been termed long-acting thyroid stimulating (LATS) antibodies.

(Source: [http://www-immuno.path.cam.ac.uk/~immuno/part1/lec12/LATS.gif](http://www-immuno.path.cam.ac.uk/~immuno/part1/lec12/LATS.gif); [http://members.lycos.co.uk/diseaseDIR/imagesd/d0102.gif](http://members.lycos.co.uk/diseaseDIR/imagesd/d0102.gif))
Myasthenia gravis

Myasthenia gravis (MG) is a chronic disorder of neuromuscular transmission deriving its name from Latin and Greek words meaning ‘grave muscle weakness’ leading to fluctuating weakness and fatigue. Individual of any age or race can be affected; however it occurs most frequently in young adult females and older males. It is not hereditary. Here, autoantibodies are produced that bind the acetylcholine receptor on the motor end plate of muscles. This blocks normal binding of acetylcholine and induces complement-mediated lysis of the cells. Ultimately cells bearing receptors are destroyed (Fig. 5). This results in progressive weakening of the skeletal muscles. Early symptoms of the disease include drooping eyelids and inability to retract corners of the mouth, gives the appearance of snarling. The disease can be managed well with appropriate treatment otherwise progressive weakening of the muscles can lead to severe impairment of eating as well as other movements.

Systemic Autoimmune Diseases

Herein the response is directed towards a wide range of target antigens and involves number of organs and tissues reflecting a general defect in immune regulation that results in hyperactive T and B cells. Tissue damage is widespread, from both cell mediated immune responses and direct cellular damage caused by autoantibodies or by accumulation of immune complexes.

Systemic Lupus Erythematosus (SLE)

Lupus erythematosus is a chronic (long-lasting) autoimmune disease with many manifestations, affecting all organ systems of the body. The immune system, for unknown reasons, becomes hyperactive and attacks normal tissue resulting in inflammation and brings about symptoms.
Genetic, environmental and hormonal factors play a role in mediating this disease. It can occur at all ages but at younger age, where it is seen more commonly, it is associated with much severity. SLE is characterised by symptoms like fever, weakness, arthritis, skin rashes, pleurisy and kidney dysfunction. Skin rashes are commonly seen across the face on both cheeks. These so called ‘butterfly rash’ becomes more in intensity due to sun exposure (Fig. 6).

Fig. 6: Systemic lupus erythematosus (SLE). Classical butterfly rash on cheeks.

Auto antibodies to a vast array of tissue antigens, such as DNA, histones, RBC’s, platelets, leukocytes and clotting factors are produced in affected individuals. Auto-antibodies specific for RBC’s and platelets can lead to complement mediated lysis resulting in hemolytic anemia and thrombocytopenia respectively. A type III hypersensitivity reaction develops when immune complexes of auto antibodies with various nuclear antigen gets deposited along the walls of small blood vessels, leading to vasculitis and glomerulonephritis. These develop when complexes activate the complement system, generating membrane attack complex and excessive amounts of complement split products that damage the walls of the blood vessels. Serum levels of complement split products like C3a and C5a are seen in patients with severe SLE. C5a induces increased expression of type 3 complement receptor (CR3) on neutrophils. This results in their aggregation and attachment to vascular endothelium; thereby reducing their apparent count in circulating pool (neutropenia), resulting in vasculitis (various occlusions of small blood vessels). These occlusions can lead to widespread tissue damage. Laboratory diagnosis of SLE relies on detecting antinuclear antibodies against double or single stranded DNA, nucleoprotein, histones, and nucleolar RNA. Indirect immunoflourescent staining produces characteristic nucleus –staining patterns with serum from SLE patients.

Rheumatoid Arthritis

Rheumatoid arthritis (RA), a disease in which the immune system is believed to attack the linings of the joints resulting in joint pain, stiffness, swelling, and destruction (Fig. 7). It is one of the commonest, best-known, and usually heritable autoimmune diseases that show a distinct, higher prevalence amongst females. Its incidence also increases with age. Onset of RA is characterized by presence of IgM antibodies (auto antibody) directed against the antigenic determinants on the Fc portion of IgG. This autoantibody is known as Rheumatoid Factor (RF). The complexes of IgM-IgG get deposited in joints and can activate complement cascade, resulting in type III hypersensitive reactions, which leads to chronic inflammation of the joints.
Also present in diseased joint fluid (synovium) are complexes of collagen-anti collagen, and large numbers of neutrophills, which are otherwise absent from healthy synovium. Neutrophills release degradative enzymes including elastase, cathepsins (break down proteoglycan), glycosidases and collgenases. Activators of complement, kinin, clotting and fibrinolytic cascades are also released. Myeloperoxidase sustains the production of reactive oxygen species (ROS) and these together with prostaglandins, leukotriens, platelet activating factor and complement factors C3a and C4a results in continued inflammation of the synovium.

![Fig. 7: Normal and rheumatic arthritis](http://www.medicinenet.com/images/illustrations/arthritic_joints.jpg)

The laboratory diagnosis of RA relies on full blood count (showing anemia with mild leukocytosis, eosinophilia and thrombocytopenia), raised ESR and presence of Rheumatoid factor in serum. The diseased is treated with anti inflammatory and analgesic drugs, which reduce inflammation and pain.

**Sjögren's syndrome**

It is a chronic systemic autoimmune disease with symptoms overlapping with those of RA and SLE. Here, the body’s exocrine gland particularly the ear and salivary gland become the targets of autoimmune attack. The glands cannot produce fluids that lubricate the eyes, mouth, joints and other mucosal surfaces. Other organs can also be involved. The presenting symptoms for clinical diagnosis are: dry eyes, dry mouth and aching joints.

**Multiple Sclerosis (MS)**

It is a chronic disease of the central nervous system (CNS). In this disease the specific auto-reactive T cells attack on nerve cells producing chronic neurological disability in young adults that often leads to complete loss of the ability to walk within 2 years of onset and total disability after 8 – 10 years. The disease is most commonly seen in people of Northern hemisphere.
particularly United States. The disease has a strong environmental component and gender bias. Scientific data suggests that infection by certain viruses may predispose a person to multiple sclerosis. Pathologically inflammatory lesions are formed along the myelin sheath of nerve fibres. The cerebrospinal fluid of patients with active MS contains activated T lymphocytes, which infiltrate the brain tissue and cause characteristic inflammatory lesions, destroying the myelin. Since myelin functions to insulate the nerve fibres, a breakdown in the myelin sheath leads to numerous neurological dysfunctions (Fig. 8).

![Multiple Sclerosis](http://www.humanillnesses.com/original/images/hdc_0001_001_0_img0066.jpg)

**Fig. 8:** Multiple Sclerosis. It is a degeneration of the myelin sheath surrounding nerves in the brain and spinal cord. The part of the body affected by this disease is dependant on the nerves that are damaged.

(Source: [http://www.humanillnesses.com/original/images/hdc_0001_0001_0_img0066.jpg](http://www.humanillnesses.com/original/images/hdc_0001_0001_0_img0066.jpg))

**Mechanisms for induction of Autoimmunity**

Several mechanisms have been proposed to account for T cell mediated generation of autoimmune diseases. Genetic predisposition and environmental factors also play a role in its pathogenesis, and it is likely that autoimmunity develops from number of different mechanisms.

- **Release of Sequestered Antigens**—It is a well established fact that self-tolerance to T cells results from exposure of immature thymocytes to self antigens and the subsequent clonal deletion of those that are self reactive. Tolerance will not develop in case of self tissue antigens that are sequestered from the circulation and not seen by the developing T
cells in the thymus. Exposure of mature T cells to such normally sequestered antigens at a later stage probably results in their activation e.g. Myelin basic protein (MBP), an antigen that is sequestered from immune system by the blood brain barrier. Other examples include sperm, lens protein and heart muscle antigens. Sperms appear late in development and hence remain sequestered. On the other hand lens protein appear only when lens is damaged and heart muscle antigen may appear after myocardial infarction and thus occasionally lead to formation of autoantibodies.

- **T-Cell Bypass** – A normal immune system requires the activation of B-cells by T-cells before the former can produce antibodies in large quantities. This requirement of a T-cell can be by-passed in rare instances, such as infection by organisms producing “Super-Antigens” which are capable of initiating polyclonal activation of B-cells, or even of T-cells, by directly binding to β-subunit of T-cell receptor in a non-specific fashion. Super-Antigens are the powerful immunostimulatory and disease-causing toxins produced by certain organisms. These properties of Super-Antigens occur even at their picomolar concentrations as a result of their simultaneous interaction with Vβ domain of the T-cell receptor (TCR) and the major histocompatibility complex (MHC) class II molecules on the surface of an antigen-presenting cell. Example: Virulence factor of *Staphylococcus aureus* and *Streptococcus pyogenes*.

- **Molecular Mimicry** – An exogenous antigen may share structural similarities with certain host antigens; thus, any antibody produced against this antigen (which mimics the self-antigens) can also, in theory, bind to the host antigens and amplify the immune response. The most striking form of molecular mimicry is observed in Group A haemolytic Streptococci, which shares antigens with human myocardium and is responsible for the cardiac manifestations of Rheumatic fever. Another classical example is seen in persons who develop post-rabies encephalitis. It is a disease, which develops in some individuals who had received the rabies vaccine. In the past, the rabies virus was grown in rabbit brain-cell cultures and preparations of the vaccine included antigens derived from the rabbit brain cells. These rabbit brain cell antigens were responsible for formation of antibodies and activated T cells, which could react with recipient’s own brain cells, leading to encephalitis in the vaccinated person.

- **Idiotype Cross-Reaction** – Idiotypes are antigenic epitopes found in the antigen-binding portion (Fab) of the immunoglobulin molecule. Autoimmunity can arise as a result of a cross-reaction between the idiotype on an antiviral antibody and a host cell receptor for the virus in question. In this case, the host-cell receptor is envisioned as an internal image of the virus, and the anti-idiotype antibodies can react with the host cells.

- **Cytokine Dysregulation** – Cytokines have recently been divided into two groups according to the population of cells, whose functions they promote: Helper T-cells type 1 or type 2. The second category of cytokines, which include IL-4, IL-10 and TGF-β, seem to have a role in prevention of exaggeration of certain immune responses. Autoimmune diseases are initiated by activation of antigen-specific T cells. Th2 cells activate B cells to make auto-antibodies, which (by activating complement) damage tissues directly or initiate prolonged inflammation. CTL and macrophages activated by Th1 cells are directly cytotoxic and also promote inflammation. The damage done by some
autoimmune responses is limited to a single organ, while other diseases cause systemic damage. The events that initiate specific autoimmune diseases are not known.

- **Inappropriate Expression of Class II MHC molecules** – The inappropriate expression of class II molecules (which are normally expressed on antigen presenting cells), on certain cells of the body (e.g. beta cells or thyroid cells) help in activation of B cells or TC or sensitization of TH1 cells against self antigens. In patients of IDDM, the pancreatic beta cells express high levels of both class I and class II MHC molecules in comparison to healthy cells where class I is expressed in lower levels and class II molecules are not expressed at all. Similarly class II molecules are expressed in higher amounts on thyroid acinar cells in patients with Graves’ disease. Certain agents are known to induce expression of MHC molecules that otherwise do not express. For example, the T-cell mitogen – phytohemagglutinin (PHA) induces expression of class II molecules on thyroid cells. IFNγ have been shown to induce increase in class II molecules on a wide variety of cells, including intestinal epithelial cells, pancreatic beta cells, melanoma cells and thyroid acinar cells. Certain viral infection and trauma may induce a localized inflammatory response resulting in higher levels of IFNγ in the affected organ. This increased level of IFNγ have been linked to autoimmune disease of the affected organ.

- **Infection** – Development of autoimmunity has been linked to infection; for example, many people who develop IDDM have experienced recent infection with a Coxsackie virus (which generally causes only mild symptoms). It is believed that infection induces inflammation that stimulates APC to express B7 that can activate T cells to self-antigens. Lack of APC B7, in the absence of inflammation, leads to T cell anergy.

**Treatment of Autoimmune Diseases**

The goal of treatment has been to selectively reduce autoimmune responses while leaving the rest of the desirable immune responses intact. Presently, the treatment revolves around curing the symptoms of autoimmune diseases so that patients can lead acceptable quality of life, which is provided by non-specific suppression of the immune system. As it fails to distinguish between pathologic autoimmune response and a protective immune response, the patient is put at a greater risk of other infections or the development of cancer.

**Current therapies**

- Immunosuppressive drugs (e.g. corticosteroids, azathioprine and cyclophosphamide) are given which help in slowing the proliferation of lymphocytes.

- Drug Cyclosporin A or FK 506 have been employed to treat autoimmunity. These help in inhibiting antigen activated T cells by blocking signal transduction mediated by T-cell receptor. The non-activated T cells are thus spared.

- Removal of thymus in some patients of Mysthenia Gravis has shown positive results as patients here often have thymic abnormalities (e.g., thymic hyperplasia or thymomas) and adult thymectomy helps in remission of symptoms.
• Short-term benefits are also seen by “Plasmapharesis” in patients with SLE, RA, MG and Grave’s disease. By this technique, antigen-antibody complexes are removed from plasma. Removal of complexes, although only temporarily, can result in short term reduction in symptoms.

Possible therapies

Experimental evidence from studies with animal models has led to the use of possible therapies in some of the autoimmune diseases. These include:

• **Vaccination with T cells specific for a given auto antigen.** Clones of T – cells specific for Myelin Basic Protein (MBP) from Experimental Autoimmune Encephalitis (EAE) animal model were injected into rats at low doses. The symptoms of Experimental Autoimmune Encephalitis (EAE) did no appear in these rats. Instead they became resistant to the development of EAE when later challenged with a lethal dose of activated MBP-specific T cells.

• **Peptide blockade of MHC molecules.** More recently peptides have been synthesized which differ from actual auto-antigen by 1 amino acid. These synthetic peptides on administration compete with the auto-antigen for binding site on MHC molecule. In EAE animals, the competition between MBP and its synthetic counterpart helps in preventing the binding of MBP peptide with MHC.

• **Monoclonal antibodies.** These have been used successfully in several animal models. Treatments with monoclonal antibody that could react with some component specifically involved in an autoimmune reaction e.g., anti CD4 monoclonal antibody that block or deplete all T\textsubscript{H} cells regardless of their specificity. This can lead to total reduction of immune responsiveness of an individual. To do away with nonspecific depletion of T\textsubscript{H} clones, researchers have used monoclonal antibody directed against the \(\alpha\) subunit of the high affinity IL-2 receptor, which is expressed only by antigen activated T\textsubscript{H} cells. Since IL-2R \(\alpha\) subunit is expressed at higher levels on autoimmune T cells, monoclonal antibody to the \(\alpha\) subunit (anti-TAC antibody) might preferentially block auto reactive T cells.

• **Oral administration of antigens.** Induction of tolerance (the state of immunologic unresponsiveness) to auto antigens have been observed when antigens have been given orally. Mice that were fed earlier with MBP did not develop EAE after subsequent challenge / injection of MBP. These studies have shown promising results in animals and it is very likely that they shall show promising benefits in humans too.

Tolerance

Natural tolerance means the inability of the immune system to mount an immune response to an antigen. Self-tolerance is the state of immunological unresponsiveness to self-antigens. Different mechanisms and regulatory processes occur in both peripheral and lymphoid organs to maintain this state. In brief, it is seen that interaction of antigen with immature clones of lymphocytes
already expressing antigen receptors (mainly during fetal life), would result in an unresponsive state. Clones of self-reactive lymphocytes (both B and T cells) get eliminated during embryo development on contact with self-antigens present in thymus or bone marrow. This is termed **Clonal deletion.** Immature stem cell, precursors of lymphocytes derived from marrow migrate to central lymphoid organs like thymus and bone marrow to become mature and functional T and B cells respectively. In both these organs, self reactive T and B cells (i.e. those T and B cells which have receptors for self-antigens) are clonally eliminated by negative selection processes as part of the normal maturation processes. This is also known as **Central tolerance.** On the other hand mature lymphocytes escaping tolerance in the primary lymphoid organs are eliminated or anergised (made unresponsive) in the peripheral organs through **Peripheral tolerance** mechanisms. This is termed **Clonal anergy** and maintains tolerance to some (but not all) self-antigens that are not available for clonal deletion in the thymus and marrow. It occurs in the peripheral organs like lymph node, spleen, etc where immature B cells when encounter soluble antigen that cross-links BCR and T cells encounter unprocessed antigen or processed antigen in the absence of co-stimulatory signals.

**Immunological ignorance** is a state of non-reactivity to antigen that would otherwise induce humoral or CMI response. Tolerance can be induced by different mechanisms in both T and B cells.

**Summary**

- The ability of the immune system to recognize foreign antigens and effectively eliminates them from body is very well regulated. But, at times, when it fails, it starts recognizing self antigens as non self and results in an immune attack against self antigens. This is termed **Autoimmunity,** which primarily results due to breakdown in self-tolerance or loss of self-regulation.

- Autoimmune diseases show strong gender bias and association with certain MHC alleles. Multiple interacting factors, genetic make up of individual and environmental factors together contribute to the manifestation of autoimmune diseases.

- Autoimmune diseases have been broadly classified into two groups: organ specific (Hashimoto thyroiditis, autoimmune pernicious anemia, IDDM, MS, etc.) and systemic diseases (SLE, RA, etc.) on the basis of their ability to strike the body part.

- Various mechanisms, either singly or in combination, can elicit autoimmune diseases. The important factors among them include: release of sequestered antigens, molecular-mimicry, cytokine dysregulation and inappropriate expression of class II MHC molecules.

- The diagnosis of autoimmune diseases is never direct. Final diagnosis is reached on the basis of observations of medical history, physical examination and serological tests that account for the presence of auto-antibodies.

- Treatment of autoimmune diseases revolves around selectively reducing the undesirable autoimmune response while sparing the protective desirable one. Since it is yet too far a
HYPERSENSITIVITY

Introduction

In the previous section we saw how loss of tolerance to self-antigens could result in attack on self-tissues and organs. In this section, we shall see that despite normal functioning of the immune response in recognizing the foreign tissue, the response could be damaging to the host. Our immune system normally responds to a variety of pathogens with little or practically no damage to the host. However there are instances where the immune response is over reactive or exaggerated and harmful resulting sometimes even in death. This inappropriate immune response that is harmful to the host is termed “hypersensitivity”, commonly known as allergic reactions. This undesirable response is directed against foreign microbial pathogens, inert particles (allergens) and self-tissues. Hypersensitive reactions, as the name suggests, are reactions of greater sensitivity. For these reactions to occur, two contacts with allergen are needed. First contact induces sensitization to particular antigen and second contact with the same specific antigen results in allergic or the hypersensitivity reaction as a result of antigen specific memory response.

It is very interesting to note that these reactions are part of normal immune defense mechanisms of the host. These reactions could be local or wide spread in the body involving interactions between large amounts of antigen with antibodies or immune cells. Some common allergens include pollen, grass, insect venom, dust particles, seafood, animal dander, serum, penicillin etc. It is still unclear as to why some persons mount responses to certain allergen and why only some give a strong response. The reaction may cause a range of symptoms from minor inconvenience to death. A strong genetic inheritance is seen in some cases of hypersensitivity reactions.

Classification of hypersensitivity

P.H.G. Gell and Robin Coombs in 1968 grouped different hypersensitivity reactions into four major types according to the time taken by the reactions to appear in the body as well as the type of immune cells involved. These are: type I, type II, type III and type IV. The hypersensitive reaction may range from few seconds or minutes after secondary contact with the antigen/allergen (i.e. immediate), minutes to hours (intermediate) to many hours (delayed) (Table 2). It is normally noted that type I-III are mediated by the humoral responses including antibodies and the complement, and delayed type IV (DTH or Delayed Type Hypersensitivity) is mediated by cellular immune responses. In some books a type V hypersensitive reaction termed stimulatory hypersensitivity has also been reported (Table 3).

Type I Hypersensitivity - Ig E mediated

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity or simply allergy. It is mediated by IgE antibody on reexposure to a specific antigen. Allergic persons are
often sensitive to more than one type of antigen or allergen. The reaction may range in symptoms from minor inconvenience to death. The exposure may be by ingestion, inhalation, injection, or direct contact with an allergen which could be a harmless substance or pathogen. The reaction may involve skin, eyes, nasopharynx, bronchopulmonary tissues and gastrointestinal tract. The primary cellular components in this hypersensitivity are the mast cells or basophils. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils.

### Table 2: Summary of Hypersensitivity classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Descriptive Name</th>
<th>Initiation Time</th>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-mediated hypersensitivity</td>
<td>2-30 mins.</td>
<td>Ag induces cross-linking of IgE bound to mast cells with release of vasoactive mediators</td>
<td>Systemic anaphylaxis, Local anaphylaxis, Hay fever, Asthma, Eczema</td>
</tr>
<tr>
<td>II</td>
<td>Antibody-mediated cytotoxic hypersensitivity</td>
<td>5-8hrs.</td>
<td>Ab directed against cell-surface antigens mediates cell destruction via ADCC or complement</td>
<td>Blood transfusion reactions, Haemolytic disease of the newborn, Autoimmune Haemolytic anaemia</td>
</tr>
<tr>
<td>III</td>
<td>Immune-complex mediated hypersensitivity</td>
<td>2-8hrs.</td>
<td>Ag-Ab complexes deposited at various sites induces mast cell degranulation via FcγRIII, PMN degranulation damages tissue</td>
<td>Arthus reaction (Localised); Systemic reactions disseminated rash, arthritis, glomerulonephritis</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-mediated hypersensitivity (Delayed Type Hypersensitivity)</td>
<td>24-72hrs.</td>
<td>Memory TH1 cells release cytokines that recruit and activate macrophages</td>
<td>Contact dermatitis, Tubercular lesions</td>
</tr>
</tbody>
</table>

**Sensitization phase**

The mechanism of reaction involves preferential production of high levels of IgE antibody instead of other antibody isotypes, in response to certain antigens /allergens. During the initial contact (primary response) with the allergen, IgE is made but the patients do not show any symptoms. The IgE antibodies produced during the primary exposure gets attached via their Fc portion to the Fc receptors present on tissue mast cells, and circulating basophils. This occurs as a result of very high affinity between the Fc portions of IgE antibodies with the Fc receptors present on mast cells and circulating basophils. Cytokine IL-4 is, in part, responsible for isotypes switch from IgM to IgE. A second signal, which can come from a variety of sources, is needed to complete the switch. Many other cytokines also actively regulate IgE production.
<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Time taken to develop</th>
<th>Response/ effect</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Allergy or Immediate type</td>
<td>Occurs within 5-30 min. of exposure</td>
<td>1. Mediated by IgE antibody, to specific antigens.</td>
<td>Common allergies to food, dust, medicine, insect venom, spores pollens etc, anaphylaxis (e.g. Penicillin), urticaria, angioedema, atopic allergy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Causes degranulation of Mast cells and Basophils. These ells release inflammatory mediators.</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Cytotoxic or antibody dependent cell mediated</td>
<td>It can occur within few hours to a whole day</td>
<td>1. It is mediated by IgG and IgM antibodies to specific antigens.</td>
<td>Transfusion reactions, Rh incompatibility, Hashimoto’s thyroiditis, delayed transplant rejection etc.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Causes complement mediated lysis.</td>
<td></td>
</tr>
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</tr>
<tr>
<td>III</td>
<td>Immune complex mediated</td>
<td>Takes hours to days to develop (usually 1-3 weeks after exposure).</td>
<td>1. Mediated by antigen antibody complexes.</td>
<td>SLE, Arthus Reaction (Farmer’s lung), Serum sickness, Rheumatoid Arthritis, etc.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. The complexes get deposited in tissues and organs.</td>
<td></td>
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</tr>
<tr>
<td>IV</td>
<td>T cell mediated or Delayed Type (DTH)</td>
<td>Takes 2-7 days after exposure.</td>
<td>1. Mediated by T cells responses to specific antigens.</td>
<td>Mantoux test (Tuberculin skin testing), allergic contact dermatitis (metal allergy), etc.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Causes granuloma formation and involves participation of MHC.</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-a</td>
<td>Stimulatory</td>
<td>Takes days to develop</td>
<td>1. Mediated by IgG antibodies to thyroid gland - Humoral antibody activates receptor sites.</td>
<td>Graves’s disease or thyrotoxicosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Causes stimulation of thyroid gland even in the absence of TSH.</td>
<td></td>
</tr>
<tr>
<td>V-b</td>
<td>Septicaemia or septic shock</td>
<td>Takes few hours to a day to develop after exposure</td>
<td>Cytokines mediated. Causes hypotension and tachycardia.</td>
<td>Toxic shock syndrome (TSS)</td>
</tr>
</tbody>
</table>
**Effector phase**

On second and subsequent exposures to the same allergen the surface bound IgE antibodies binds antigen in such a way that cross linking of adjacent IgE molecules takes place. This triggers the bound mast cell to degranulate (i.e. liberate the contents of their cytoplasmic granules which contain pharmacologically active substances which cause allergic responses) (Fig. 9). Cross-linking of IgE - Fc-receptor is important in mast cell degranulation. The granules release various pharmacologically active and preformed inflammatory mediators. These include histamine, leukotrienes, prostaglandins, kinins, slow reacting substances of anaphylaxis (SRS-A), platelet-activating factor (PFA) etc. Histamine binds to target receptors in the nose, lungs, skin, gastrointestinal tract and near blood vessels via H1 receptors. Series of events follow and results in increased vascular permeability and dilation, stimulation of nerve fibers and initiation of inflammatory cascades that are together responsible for the signs and symptoms of immediate hypersensitivity. Locally, e.g. in nose, symptoms of redness, itching, and sneezing and increased secretions by mucosal epithelial cells leads to a running nose. Systemic release of histamine and other mediators from mast cells can lead to severe vasodilation and vascular collapse often resulting in life threatening systemic anaphylactic reactions needing immediate medical attention.

![Type I hypersensitivity](image)

**Fig. 9: Hypersensitivity Type I.** It is described as a rapid (Immediate) type Allergic reaction. Symptoms result due to liberation of pharmacologically active mediators which are released as a result of degranulation of Mast cells. It results upon contact of Allergen (antigen) with preexisting IgE antibodies. Much of the IgE in the body is bound to high affinity receptors (Fc epsilonRI) found on mast cells and basophils. Each cell has a high density of these receptors (40-250,000 per cell) so that a wide spectrum of antigen specificities is represented. The cells are activated by the cross-linking of the Fc epsilonRI receptors via antigen binding to the bound IgE molecules.
Mast cell degranulation is preceded by increased Ca\(^{++}\) influx, which is a crucial process; ionophores, which increase cytoplasmic Ca\(^{++}\), also promote degranulation, whereas agents, who deplete cytoplasmic Ca\(^{++}\), suppress degranulation. Mast cells themselves produce and respond both to cytokines e.g IL - 4. This IL - 4 is important in stimulation and multiplication of Ig E producing B cells as well as in the differentiation of T helper cells to the Th 2 pathway, both of which are needed in Ig E production. IL 4 is an important growth factor for mast cells. Mast cells may be triggered by other stimuli such as exercise, emotional stress, chemicals (e.g., photographic developing medium, calcium ionophores, codeine, etc.), anaphylatoxins (e.g., C4a, C3a, C5a etc). These reactions, mediated by agents without IgE-allergen interaction, are not hypersensitivity reactions although they produce the same symptoms.

Activated basophils are known to secrete many cytokines that serves to enhance and sustain the allergic inflammatory process. These include IL - 3, GM –CSF (granulocytes macrophage colony stimulating factor), TNF \(\alpha\) and IL-1. Mast cell activation is carried out with the help of IL-3 and TNF- \(\alpha\) helps further eosinophil recruitment that ultimately alter the target tissue and even cause direct tissue damage.

The immediate type allergic reactions tend to be more rapid, occurring in few minutes and more severe. The severity of symptoms depend on the site in the body where mast cell degranulation takes place e.g. a sting bite on arm results in a painful or itchy swelling but same insect if swallowed and its bite on respiratory tract can then obstruct person’s normal breathing due to bronchospasm (narrowing of the of the bronchial passages/airways in the lungs) initiated due to swelling of the respiratory tract induced by inflammatory mediators like of histamine. Anaphylactic shock is a dramatic allergic reaction that can result in collapse of the affected individual or death as the onset is rapid and symptoms develop within 5-30 minutes of exposure to the allergen and further 15 minutes for death to occur unless given immediate medical attention. Two events participate in the production of shock symptoms. These include vasodilation and increased vascular permeability. Increased vascular permeability brings about a rapid and massive loss in intra vascular volume because of a shift of fluid from intra vascular to extra vascular space. This change can severely constrict the airways causing death. A classical example is seen in patients receiving injections of the drug Penicillin wherein patient receiving the injection is monitored every time for anaphylactic responses. The symptoms of anaphylactic shock can be reversed too. The treatment aims to reverse the action of mediators, by maintaining the airways, providing artificial ventilation if necessary, and supporting cardiac function. Injections of epinephrine, antihistamines and corticosteroids are sought in emergency situations. Some common examples of immediate type hypersensitivity reaction include: allergic asthma, allergic conjunctivitis, allergic rhinitis (“hay fever”), urticaria (hives), food allergies (peanuts, fish, eggs, milk, wheat, soy) etc.

Late phase reactions

The reappearance of symptoms after an apparent but temporary disappearance of the same is referred to as late phase in the type 1 hypersensitivity response. The recurrent episodes are due to recruitment of other cells activated by chemotactic mediators released from mast cells and basophils, whose degranulations thus becomes an ongoing process, sometimes with fatal consequences.
Diagnosis and Treatment

Skin testing is normally carried out to confirm the type of allergen responsible. It is most sensitive and least costly diagnostic aid available. Here, a diluted extract of each kind of allergen presumed to be present near a local area or in immediate vicinity of the affected individual is injected under the patient skin or is applied to a scratch or puncture made on the patient’s arm or back. A positive reaction called “wheal” is an important diagnostic test but doesn’t prove that a particular allergen is the only cause of patient’s symptoms. The demonstration of positive skin test to specific allergen is termed **atopy**. Atopic individuals show higher genetic predisposition to allergies and thus have high Ig E levels. There are other tests available, which detect high Ig E levels in blood, and one such test is RAST (radioallergosorbent test). It is expensive to perform, time consuming and somewhat less sensitive.

There are three general approaches that are followed for the treatment of allergies. These include: avoidance of the causative allergen, medication to relieve symptoms and allergic immunization. Total avoidance to allergens is not always possible as a person normally develops allergies to new but related allergens after repeated exposure. The effective medications, which are normally given to such individuals, include antihistamines (these counters the affect of histamines), topical nasal steroids (anti inflammatory drug) and sodium cromoglycate (interferes with release of pharmacologically active mediators). These can be used either alone or in combination.

**Hyposensitization** (or desensitization) is another treatment modality, which is successful in a number of allergies, particularly to insect venoms and, to some extent, pollens. The exact mechanism is not clear, but a reduction in the amount of IgE antibodies and appearance of IgG (blocking) antibodies with relief from symptoms is seen. With this therapy, long-term positive results have been reported. Suppressor T cells that specifically inhibit production of IgE antibodies may play a role here.

Recently it has been well documented that allergy results due to imbalance between Th I and Th2 activity. This has led to development of cytokine-based therapies that modulate specific cytokine profile.

**Type II Cytotoxic or antibody dependent cell mediated cytotoxicity**

Type II hypersensitivity is also known as cytotoxic hypersensitivity and is mediated by antibody (IgG or IgM) alone or together with complement. These reactions can be against foreign (erythrocytes) or against self- cells (auto antigens) and cause direct lysis or removal of the cell. Cell death is mediated through normal mechanisms by which antibodies and complement carry out their function including phagocytosis, lysis and ADCC (antibody dependent cell mediated cytotoxicity). These may affect a variety of organs resulting in anemias and autoimmune diseases respectively. IgG or IgM antibody form complexes with cells presenting foreign antigens. Activate the complement, whose inflammatory mediators are generated at the site and cause lysis of cells through MAC (membrane attack complex). The reaction may take few hours to a day to develop (Fig. 10).
Fig. 10: Hypersensitivity Type II. The second class of damaging reactions is caused by specific antibody binding to cells or tissue antigens. The antibodies are of the IgM or IgG classes and cause cell destruction by Fc dependent mechanisms either directly or by recruiting complement via the classical pathway. Except where the reaction is autoimmune, the target cells are foreign to the host.

Another form of type II hypersensitivity is termed ADCC. Here, cells exhibiting foreign antigens are coated with IgG or IgM antibodies and recognized by Natural Killer (NK) cells and macrophages, which in turn kill them. Few common examples include: Rhesus incompatibility, blood transfusion reactions and auto immune anemias (hemolytic, pernicious), pemphigus etc. Good pastures syndrome, Hashimoto’s thyroiditis, Graves’s disease, and Myasthenia gravis etc. Treatment here involves use of anti-inflammatory and immunosuppressive agents.
Type III Hypersensitivity - immune complex mediated

Fig. 11: Hypersensitivity Type III. It is mediated by immune complexes essentially of IgG antibodies with soluble antigens. This hypersensitivity has a lot in common with type I except that the antibody involved is IgG and therefore not prebound to mast cells, so that only preformed complexes can bind to the low affinity FcγRIII.

The antigen–antibody complexes are normally cleared by the phagocytic cells and there is no tissue damage. In situations where these immune complexes are not cleared from the body, these get deposited in various tissues of the body (typically the skin, kidney and joints) causing localised or systemic damage. The damage occurs as a result of complement activation resulting
in neutrophil chemoattraction and release of lytic enzymes by the degranulating neutrophils. The reaction takes hours to days to develop. Soluble immune complexes mediate the reaction. They are mostly of the IgG class, although IgM may also be involved (Fig. 11). The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity). The antigen is soluble and not attached to the organ involved. The reaction may be general or may involve individual organs including, kidneys, lungs, blood vessels, joints or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms. Some diseases included here are Immune complex glomerulonephritis, Rheumatoid arthritis, Serum sickness, Subacute bacterial endocarditis, SLE and Arthus reaction.

**Type IV Cell mediated or Delayed –type hypersensitivity (DTH)**

Type IV hypersensitivity is alternatively termed delayed because it takes 48 to 72 hours i.e. 2-3 days to develop. It is the only reaction that is not mediated by antibody; instead it occurs through cell-mediated responses. The T cells participating in this reaction are termed T\(_{\text{DTH}}\) cells (delayed type hypersensitive). This hypersensitivity can be transferred from infected to a healthy person through transfer of T\(_{\text{DTH}}\) cells.

The classical example of this hypersensitivity is tuberculin (Montoux) skin reaction, which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation. Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, leishmaniasis etc) and granulomas due to infections and foreign antigens. Another form of delayed type hypersensitivity is contact dermatitis (poison ivy, chemicals, heavy metals, etc) in which lesions are more popular.

Mechanisms of damage in delayed hypersensitivity include involvement of T lymphocytes and monocytes and / or macrophages. Cytotoxic T cells (Tc) cause direct damage whereas helper T (Th1) cells secrete cytokines, which activate cytotoxic T cells and recruit and activate monocytes and macrophages, which cause the bulk of the damage (Fig. 12). The delayed hypersensitivity lesions mainly contain monocytes and a few T cells. Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, interleukin-2, interferon-gamma, TNF alpha/beta, etc.

**Granuloma formation**

CD4+ population of T cell generally controls mycobacterial infections. Mycobacteria along with few other intracellular pathogens have adopted escape mechanisms to prevent their killing inside macrophages. Thus macrophage activation factors even though produced in abundance fails to eliminate mycobacteria and antigen always persist in the body leading to chronic stimulation of CD4+ cells and continuous production of cytokines. These mediate fusion of the macrophage containing the microbes and fibroblast proliferation, which creates a kind of wall around the microbes. This is known as granuloma formation.
Fig. 12: Hypersensitivity Type IV. Only class of hypersensitive reactions to be triggered by antigen-specific T cells previously termed T \textit{DTH} but presently classified as T_{H1} cells. Thus this reaction is often termed - delayed type hypersensitivity. It results when an antigen presenting cell, typically a tissue dendritic cell which has picked up antigen, processed it and displayed appropriate peptide fragments bound to class II MHC is contacted by an antigen specific T_{H1} cell patrolling the tissue. The resulting activation of the T cell produces cytokines such as chemokines for macrophages, other T cells and, to a lesser extent, neutrophils as well as TNFbeta and IFNgamma. The consequences are a cellular infiltrate in which mononuclear cells (T cells and macrophages) tend to predominate. It is usually maximal in 48-72 hours.

Contact dermatitis/sensitivity

A small number of chemicals penetrate the skin, cause contact sensitivity, which is clinically seen as dermatitis. Common examples include the reactions against metal fastners on watchstraps and rashes that appear in response to poison ivy. Removal of the contact usually ends the sensitivity. Sensitization against dermatitis causing molecules occurs via binding of skin proteins and the langerhan’s cells (dendritic cells) present in the skin, which presents antigen through MHC class II molecules to CD4+ Th1 cells. The subsequent contact sensitivity reaction involves the presentation of the antigen to memory CD4+ T cells, which release cytokines, causing symptoms of dermatitis.

Diagnosis and Treatment

Diagnostic tests \textit{in vivo} include delayed cutaneous reaction and patch test. In vitro tests for delayed hypersensitivity include mitogenic response, lympho-cytotoxicity and IL-2 production. Corticosteroids and other immunosuppressive agents are used in the treatment of delayed type hypersensitivity reactions that are seen in patients of tuberculosis, leprosy, contact dermatitis and transplant rejection.
Other Hypersensitivity reactions

There has been a mention of a fifth category of hypersensitivity reactions, which were not included in the original Gel and Coombs classification. Some books have mentioned it as stimulatory hypersensitivity and in one of the books a reference to Septic shock has been noted. Both of these are described below.

Type V Stimulatory hypersensitivity (antibody mediated)

It is an example of hypersensitivity mediated by Ig G antibody but with a difference, example - Graves disease (Hyperthyroidism). It is seen that antibodies (antithyroid antibodies), directed against the cell surface receptor molecule on thyroid gland mimic the function of thyroid stimulating hormone by binding to the hormone (TSH) receptors on thyroid cells. The anti-thyroid antibodies results in stimulation of thyroid gland (even in the absence of thyroid stimulating hormones) into over production of thyroid hormones (Fig. 13). These antibodies are not regulated. Hence it results in over stimulation of thyroid gland.

Fig. 13: Hypersensitivity Type V. Both TSH and autoantibodies can stimulate the TSHR on thymocytes to induce release of hormones such as thyroxine.

(Source: www-immuno.path.cam.ac.uk//lec13_97.html)

Type V Hypersensitivity: Septic shock

Septic shock is most commonly caused by endotoxins found as components of Gram-negative bacterial cell wall. Gram-Positive bacteria can also cause it. The most powerful stimulant of this
syndrome is lipopolysaccharide (LPS), a component of bacterial cell wall. The LPS molecule is complex but the precise immunostimulant is thought to be the lipid core, the lipid A. Following its interaction with cell surface molecules, including CD 14, a wide range of immunological responses are triggered. The LPS is a potent stimulant of the pro – inflammatory cytokines TNF-, IL-1 and IL-6, which are released by macrophages. IL-1, TNF-α, and IFN-γ causes tachycardia and hypotension. Tumor necrosis factor increases the procoagualant activity of endothelial cells and the expression of adhesion molecules. All these events facilitate the accumulation of inflammatory cells. The symptoms include hypotension, insufficient tissue perfusion, uncontrolled bleeding and multisystem organ failure caused mainly by hypoxia, tissue acidosis and severe local alterations of metabolism. The development of septicemia is frequently recognized only at a relatively late stage then there is a drop in blood pressure. The massive deterioration of haemostasis is also known as disseminated intra vascular coagulation (DIC) which involves blood vessels, platelets, blood coagulation and fibrinolytic processes.

One example of septic shock is the so called toxic shock syndrome (TSS), which is observed mainly in young menstruating women who use tampons. The tampon can get contaminated with Staphylococcus aureus. This bacterium produces an exotoxin that induces the synthesis of IL-1 and TNF - α, which sets in symptoms of TSS. Specific neutralizing antibodies directed against bacterial endo-toxins and exo- toxins have been developed that inactivate the bacterial toxin. These antibodies have remained useful for prophylactic purposes only and cannot be used to treat acute cases. Recently, cytokine inhibitors have been used for treatment of septic shock patients. But using them deprives the individual of the beneficial effects of cytokines. It is hoped that soon genetically engineered cytokine inhibitors shall be able to specifically regulate cytokine levels and functions so that only their pathogenic effects get eliminated while sparing their benefits.

Summary

• Hypersensitivity results due to exaggerated immune responses to both inert particles and pathogens.

• It is primarily classified into four major types. A fifth type has been described recently.

• A genetic predisposition to allergy is seen in certain individuals.

• The immediate or allergy type develops within minutes of exposure and at times can cause anaphylactic shock.

• The other four types can be mediated by antibody (IgG, or IgM) bound to modified cell surfaces, T cells or by antigen -antibody complexes that gets deposited in various tissues and organs. The antibody responses appear within minutes to hrs. or even days after exposure.

• The treatment involves avoidance of allergens in case of type 1 and use of steroids and immunosuppressive drugs in other cases.
IMMUNODEFICIENCY DISORDERS

Introduction

Our immune system is highly evolved and very complex with each of its components effectively playing their role in protecting the host from various diseases. This system, like any other systems of the body is well regulated but any situation that results in impaired immune function may contribute to a wide spectrum of disorders referred to as Immunodeficiency Diseases. In autoimmunity, the immune system has lost its ability to differentiate between specific self-tissues and foreign non-self antigens and attack self-tissues. In hypersensitivity, there is an over reactive immune response against inert particles, and harmless and harmful microbes. Immunodeficiency as the name suggest, is a state of weakened or totally deficient immune responses to foreign non-self-antigens. It leads to an increased susceptibility to infections. The components of immune system (e.g.: - T cells, B cells, Macrophages, Complement etc.) are all intimately integrated into a program of immune defense that could be severely compromised even if one were absent or deficient. Although a deficiency may result from any component of the immune system, yet in most cases the deficiency is more restricted and results in susceptibility to infection by some but not all microbes. E.g.: - defects in T cells usually results in infections due to intra-cellular pathogens whereas increased susceptibility to extra-cellular infection may involve defects in other components of the immune system. The absence, deficiency or abnormality of any single component of the immune system may compromise the individual, but it’s usually not life threatening as long as other components of the immune system compensate for this deficiency.

Classification

The immunodeficiency diseases have been broadly classified as either Primary or Secondary. Primary, also termed congenital are present right from birth. These result in a compromised immune response and are rare in their occurrence. They occur as a result of failure of proper development of any one or more components of humoral or cellular limb of the immune system. The abnormality could be either due to absence of the specific component or its number could be reduced or abnormality in its function. Hence, both quantitative and / or qualitative abnormalities of various cells of the immune system or various molecules participating in an immune reaction (antibodies, cytokines, complement proteins etc.) could result in the disorder. Some common examples of primary immunodeficiency disorders are listed in (Table 4).

Secondary immunodeficiency diseases also known as acquired immunodeficiencies occur more commonly and appear later in life as a result of an underlying disease or following treatment of a disease. Recurrent infections could occur in patients as a result of a large number of both congenital and acquired abnormalities in the immune system.

Primary Immunodeficiencies

The consequence of primary immunodeficiency disorders or diseases depends on the number and type of the immune components involved. Defects, in components appearing early in the hematopoietic development pathway affects the entire system e.g. Reticular Dysgenesis. It is a stem cell defect that affects the maturation of all lymphocytes, resulting in general failure of immunity. It makes the host susceptible to variety of infections. Some serious infections can
prove fatal at young age if not treated properly. Defects in more highly differentiated components of immune system are specific and less severe. The primary / congenital immunodeficiency disorders are mainly divided into 4 categories, involving defects of complement system, phagocytes, humoral lineage and cell mediated limb.

Table 4: Primary immunodeficiency diseases

<table>
<thead>
<tr>
<th>Immunodeficiency Disease</th>
<th>Impaired Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal inheritance</strong></td>
<td></td>
</tr>
<tr>
<td>Severe Combined Immunodeficiency (SCID)</td>
<td>No TCR or Ig gene rearrangement</td>
</tr>
<tr>
<td>Bare lymphocyte syndrome</td>
<td>No class II MHC molecules</td>
</tr>
<tr>
<td>Di George syndrome</td>
<td>T and B cell development</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Low IgA, IgE</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>Inability to lyse bacteria</td>
</tr>
<tr>
<td>Leukocyte – adhesion defect</td>
<td>Leukocyte extravasation</td>
</tr>
<tr>
<td><strong>X Linked inheritance</strong></td>
<td></td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome (WAS)</td>
<td>Defective T cells and platelets</td>
</tr>
<tr>
<td>Gammaglobulinemias</td>
<td>Bruton’s tyrosine kinase; No mature B cells</td>
</tr>
<tr>
<td>Chronic granulomatous disease (CGD)</td>
<td>No oxidative burst for bacterial killing</td>
</tr>
</tbody>
</table>

*One form of SCID is X-linked and one form of CGD is Autosomal inherited.*

Complement defects
Defects have been described for many of the complement components and their inhibitors. Specific gene defects have been mapped in some cases. In general, it has been seen that people with deficiency of complement component C3 are prone to recurrent infections with encapsulated bacteria such as *Pneumococcus* and *Streptococcus* as well as with *Neisseria* (Table 5).

Phagocyte defects
Defects related to phagocytes are broadly divided into two groups - intrinsic and extrinsic. Intrinsic defects in phagocytes can occur as a result of problems during their differentiation from stem cell, or in their function involving either chemoattraction to the microbial site or it’s intracellular killing e.g. LAD (Leukocyte Adhesion Disease), Chediak-Higashi syndrome etc. (detailed description in later sections). Extrinsic defects on the other hand can occur either
because of deficiency of antibody or complement or due to suppression of phagocytic activity by drugs or auto-antibodies (Table 6).

**Table 5: Complement deficiencies**

<table>
<thead>
<tr>
<th>Component deficient</th>
<th>Disease caused /common infection seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q inhibitor</td>
<td>Hereditary angiodema</td>
</tr>
<tr>
<td>Decay Accelerating Factor</td>
<td>Paroxysmal nocturnal haemoglobulinuria</td>
</tr>
<tr>
<td>C1, C2 or C4</td>
<td>Immune complex disease; SLE</td>
</tr>
<tr>
<td>C3</td>
<td>Recurrent pyogenic infections</td>
</tr>
<tr>
<td>MAC Complement component deficiencies (C5-8)</td>
<td>Meningococcal infections, e.g. <em>Niesseria</em></td>
</tr>
</tbody>
</table>

**Table 6: Phagocytic defects**

<table>
<thead>
<tr>
<th>Defect</th>
<th>Disease / Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem cell differentiation / early development</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Lack of adhesion to endothelium for margination</td>
<td>Leucocyte adhesion deficiency (LAD)</td>
</tr>
<tr>
<td>Defective phagocytosis</td>
<td>Chediak-Higashi syndrome</td>
</tr>
<tr>
<td>Defective intracellular killing</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Defects in IFNγ or IL-12 receptors</td>
<td>Mycobacterial infections</td>
</tr>
</tbody>
</table>

**Defects of Humoral Immunity**

B cell deficiency disorders make up a diverse spectrum of diseases ranging from complete absence of mature recirculating B cells, plasma cells and immunoglobulins to selective absence of only certain classes of immunoglobulins. Abnormal development of B cell lineage or blocking of any of the steps of in its development results in primary antibody deficiency. As a result an individual suffers from recurrent bacterial infection mainly by *Pnumococcus, Strptococcus* and *Haemophilus* commonly manifesting as Several Combined Immunodeficiency Disease (SCID), Bruton’s disease etc (Table 7). Many of the disorders grouped here are due to basic biochemical abnormalities and others result from defective regulation by T cells. Two different forms of CVD (Common variable Immunodeficiency) are seen depending upon the lack of T helper activity or B cells not responding to signals from other cells. Even monocyte presentation or some cytokine production abnormality may be the causative factor in some of these disorders. It is well known that T helper cell subpopulations regulate different classes of immunoglobulins (e.g. Th1 cells help IgG1 and IgG3 responses; Th2 cells help IgA and IgE responses). An abnormality in
number or activities of these helper T cell subpopulations leads to selective antibody class (IgA or IgG) deficiencies.

Table 7: B cell Deficiencies

<table>
<thead>
<tr>
<th>Stage of differentiation / Maturation</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of stem cells</td>
<td>Severe combined Immunodeficiency (SCID), also affects T cell development.</td>
</tr>
<tr>
<td>B cells failed to develop from B cell precursors</td>
<td>Bruton’s disease</td>
</tr>
<tr>
<td>B cell do not switch antibody classes from IgM</td>
<td>Hyper-IgM syndrome</td>
</tr>
</tbody>
</table>
| Common variable immunodeficiency (CVID) | IgG / IgA deficiency  
1) B cells do not undergo terminal differentiation; IgA deficiency most common  
2) B cells normal; T cell signaling defective |
| Transient Hypogammaglobulinemia       | B cells normal; absence of T helper activity early in life |

Defects of Cellular immunity

Deficiencies due only to loss of cellular immunity are rare as these results in severely compromised humoral immunity as well. In general, children are seen to have recurrent infections with intracellular pathogens. *Candida albicans, Pneumocystis carinii* and *Mycobacteria* are often implicated in such cases. An increased susceptibility to viral, protozoan and fungal infections is also seen. Even mildest infection with Cytomegalovirus could prove to be fatal in such immunocompromised individuals. T cells defects during development results in Di George’s syndrome and SCID. In some cases, selective T cell population may be absent while other population of cells are present in normal values (Table 8).

Table 8: T cell deficiencies during development

<table>
<thead>
<tr>
<th>T cell deficiency</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of thymus</td>
<td>Di George’s Syndrome</td>
</tr>
<tr>
<td>Stem cell defect</td>
<td>SCID</td>
</tr>
<tr>
<td>Death of developing thymocytes</td>
<td>SCID</td>
</tr>
</tbody>
</table>

Severe Combined Immunodeficiency (SCID)

These are large group of disorders that involve various types of defects in lymphoid cell development affecting T or both T and B cells. These result in severe recurrent infections that are usually fatal in early years of life. Clinically all individuals with SCID have very low numbers of circulating lymphocytes (although myeloid and erythroid cells appear normal in number and function) and hence fails to mount immune response mediated by T cells. Here, thymus doesn’t
develop and very few circulating T cells do not respond to foreign antigens. SCID infants suffer from chronic diarrhea, pneumonia, and skin, mouth and throat lesions along with large number of opportunistic infections. Even live attenuated vaccines such as Sabin polio vaccine can cause infection and disease.

Various causes have been implicated for this general failure of immunity. Most common among them is the deficiency of common gamma chain of IL-2 receptor, which impedes signaling through receptors for IL – 2, -4, -7, -9 and – 15. More commonly, a deficiency of adenosine deaminase (ADA) is seen that results in accumulation of adenosine, which interferes with purine metabolism and DNA synthesis. Another cause has been traced to a defect in gene that encodes mediators of rearrangement process (recombination activating proteins RAG 1 and RAG 2). This precludes development of B and T cells with functional receptors leading to SCID. *Bare Lymphocyte syndrome* is found to occur when there is a failure to transcript genes that encode class II MHC molecules. Here the patient’s lymphocytes cannot participate in cellular interaction with T helper cells.

**Waldenstrom’s Macrogammaglobulinemia**

Macroglobulinemia of Waldenstrom is a cancer of the B lymphocytes that causes overproduction of monoclonal macroglobulin (IgM antibody). The cause of this disease is unknown. It is characterized by overproduction of IgM, which causes the blood to become too thick (hyperviscosity). This hyperviscosity interferes with blood flow through small blood vessels, which leads to many of the symptoms of the disease. Apheresis (in this case, called plasmapheresis or plasma exchange) is a procedure for removing unwanted substances from the blood. In macroglobulinemia, it is used to control the symptoms caused by hyperviscosity by removing or reducing the high concentration of IgM.

**X-Linked Agammaglobulinemia**

It’s a B cell defect also called X – linked agammaglobulinemia (XLA) or Bruton’s Hypogammaglobulinemia. Here, IgG levels are extremely low along with complete absence of other immunoglobulin classes. Individuals with XLA have no peripheral B cells and suffer from recurrent bacterial infections right from 1st year of life onwards. There is a defect in B cell signal transduction due to a defect in a transduction molecule called Bruton’s Tyrosine Kinase (BTK), named after the investigator who described the syndrome. Although patients are treated with periodic administration of immunoglobin yet they seldom survive past their teens.

**Di George’s Syndrome**

Di George’s Syndrome, alternatively termed congenital thymic aplasia occurs from a developmental defect that results in complete absence of a thymus. It is associated with deletion of a region on chromosome 22 in the embryo. Accompanying features include characteristic facial abnormalities, hypoparathyroidism, and congenital heart disease. This syndrome is sometimes called the *third and fourth pharyngeal pouch syndrome* to reflect the defect at precise stage of development. T cells are present in very low numbers and T cells responses are completely absent. Although B cells are present in normal numbers yet antibody response to immunization with specific antigens does not occur. Thymic transplantation offers some hope for
these patients whose chances for long-term survival are usually poor because of accompanying severe heart disease.

**Common Variable Immunodeficiencies (CVI)**

CVI is an inherited disorder whose exact pattern of inheritance is not known. A marked decrease in number of antibody-producing plasma cells and low levels of most immunoglobulin isotypes (hypogammaglobulinemia) occur here. The B cells fail to mature into plasma cells. It is sometimes called as late onset hypogammaglobulinemia, as the condition appears later in life. The patients have recurrent bacterial infections that are normally controlled by administration of immunoglobulin.

**Chronic Granulomatous Disease (CGD)**

CGD is also an inherited disorder wherein neutrophils fail to kill certain microorganisms. It occurs most commonly in males. Majority of the patients develop disease through an X-linked form of inheritance while a minor percentage of the population inherits through an autosomal recessive pattern. Patients show increased susceptibility to recurrent serious infections by bacteria and fungi and involve skin, soft tissues, respiratory tract, lymph nodes, liver, spleen or bones. These infections lead to formation of granulomas of any part of the body but usually occur in organs just mentioned. These granulomas can cause obstructions of the intestine or the urinary tract. In CGD patients, neutrophils are normally attracted to the sight of microbial invasion and they even ingest the microorganism. However, the phagocytosed organism is not killed because of a defect in oxidative pathway by which phagocytes generate hydrogen peroxide along with resulting reactive products such as hypochlorous acid aid in killing the phagocytosed bacteria. In addition to the general defect of the killing capability of phagocytes, there is also a decrease in the ability of mononuclear cells to serve as APCs. Both processing and presentation of antigen are impaired. The CGD patients are treated with Gammainterferon.

**Congenital Neutropenia**

This disease is also known as severe congenital neutropenia and is an autosomal recessive inherited disorder. Children born with this condition lack neutrophils and suffer from recurrent bacterial infections. They usually die before 3 years of age. Children with this disease have no special problems with viral or fungal infections. They do, however, have an increased risk of developing acute myelogenous leukemia or myelodysplasia, a bone marrow disorder. Apart from agranulocytosis (lack of neutrophils), a lot of other abnormalities including maturational arrest of neutrophil precursors at the promyelocyte stage, absolute monocytosis, eosinophilia and thrombocytosis are seen in both the blood and the bone marrow. The gamma globulin level in blood is also low.

SCN is caused by a defect in a gene on chromosome 1 that code for granulocyte colony-stimulating factor receptor (GCSFR). Treatment with recombinant human granulocyte colony-stimulating factor (GCSF) results in significant improvements in survival and quality of life. Congenital neutropenia is due to diverse causes. Not all patients with congenital neutropenia have mutations in the GCSFR gene.
Alternative names for severe congenital neutropenia (SCN) include: Kostmann's disease or syndrome, infantile genetic agranulocytosis and genetic infantile agranulocytosis.

**Chediak – Higashi Syndrome (CHS)**

CHS is a rare childhood autosomal recessive disorder that affects multiple systems of the body. Patients with CHS exhibit alterations in neutrophils. These alterations include neutropenia, impaired chemotaxis; and delayed phagolysosomal fusion, leading to impaired bactericidal activity, although they contain the giant granules. The CHS locus on human chromosome 1 encodes a lysosomal trafficking regulator, formerly termed *LYST* (currently termed *CHS1*), which is defective in patients with CHS. The mutation impairs the targeting of proteins to secretory lysosomes, which makes them unable to lyse bacteria.

Patients with CHS exhibit hypopigmentation of the skin, eyes, and hair; prolonged bleeding times; easy bruisability; recurrent bacterial infections; abnormal natural killer cell function; and peripheral neuropathy. Infections most commonly involve the skin, the lungs, and the respiratory tract and are usually due to *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pneumococcus* species. The disease is often fatal in childhood as a result of infection or an accelerated lymphoma like phase; therefore, few patients live to adulthood. Viruses, particularly the Epstein-Barr virus precipitates this lymphoma like stage.

**Leukocyte Adhesion Deficiency (LAD)**

LAD although rare worlwide, occurs because of dysfunction of adhesion molecules which are required to facilitate cellular interaction. The infections act similarly to those observed in neutropenic patients because phagocytes are unable to adhere to the endothelium and transmigrate into tissues. Most patients with LAD I express no CD18 on lymphocytes, macrophages, and neutrophils. These patients succumb to infection, commonly when they are younger than 2 years. Less commonly, some patients have a milder form of LAD I, expressing approximately 5-10% of the usual CD18 levels on leukocyte cell surfaces and these survive up to late forties. Leukocyte adhesion deficiency type II (LAD II) is even rarer. It is a defect in the expression of ligands for selections.

Three adhesion molecules belonging to integrin family of proteins have a common $\beta$ chain (CD18) and are variably present on different monocytic cellsDefect is found localized to the common $\beta$ chain and effects expression of all three of the molecules that use this chain. Patients with Leukocyte adhesion deficiency type I (LAD I) fails to express the CD18, which serves as the receptor for C3b on myeloid and lymphoid cells. It causes susceptibility to infection with both gram positive and gram negative bacteria along with various fungi. Viral immunity is also impaired. The clinical picture is of marked leukocytosis and localized bacterial infections that are difficult to detect until they have progressed to an extensive life-threatening level. A detailed description of immunodeficiency is given in Fig.14.
Secondary (Acquired) Immunodeficiency

This is the most common immunodeficiency that affects phagocytic and lymphocyte function. It may result from any of the following factors like HIV infection, malnutrition, ageing, cytotoxic drugs / irradiation, diabetes, tumors, and immunosuppression by microbes. AIDS or Aquired Immunodeficiency Syndrome is caused by human immunodeficiency virus (HIV)–1 or HIV–2. The virus enters the body via infected body fluids such as blood, saliva, semen, and exhibits tropism for monocytes/macrophages and helper T cells. It gains entry through the CD4 molecules on these cells. Cytokine receptors are also involved in HIVgp120 binding to these cells. Loss of CD4+ T cells ultimately compromises the ability of the immune system to combat opportunistic infections.

As we age, although our memory T cells increase yet they are able to expand less. Due to thymic involution with age, very few naive T cells enter the circulation. There is a diminished immune repertoire along with poor quality of T and B cell responses. B cell development in the bone marrow may also decrease. This limits B cell diversity that expresses itself as a change in the

Fig.14: A Comprehensive diagram depicting sites of various immunodeficiency disorders
(Source: http://www.postgradmed.com/issues/2002/07_02/Dube3.jpg)
quality of the antibody response in terms of the specificity of antibody, it’s isotypes and it’s affinity. Specificity of antibody changes from foreign to auto-antigens, isotypes from IgG to IgM and affinity from high to low. These alterations in humoral immunity are thought to be, because of impaired capacity of T cells to induce the maturation of B cells to produce high affinity, isotype-switched antibody. Nutritional deficiency associated with age also contributes to reduced immunocompetence.

Immune responses are dampened with significant injury or trauma including that associated with burn or major surgery. Its basis is not understood. Probably traumatic events induce release of other immunomodulatory factors like glucocorticoids that causes general immunosuppression. A state of general immunosuppression occurs when drugs like corticosteroids, cytotoxic drugs (for tumor therapy) and immunosuppressive drugs given during organ transplants are used for many ailments. These drugs normally kill cells important in immune response, including stem cells, neutrophil progenitors and rapidly dividing lymphocytes in primary lymphoid organs ultimately making the host prone to recurrent opportunistic infections. Severely immunosuppressed individual die as a result of sever infections with organisms like *Pneumocystis carinii* or Kaposis sarcoma.

**Diagnostic features**

The commonest diagnostic feature of immunodeficiency disesaes include, persistent and recurrent infections, or severe infection by microorganisms that do not usually cause severe infection. Other symptoms include: poor response to treatment ,delayed or incomplete recovery from illness .Also seen are the presence of certain types of cancers such as Kaposi’s sarcoma or non-Hodgkins lymphoma,certain opportunistic infections such as *Pneumocystis carinii* pneumonia [PCP] or recurrent fungal yeast infections.

Various tests that are helpful in identifying an immunodeficiency disorder include: white blood cell count, antibody / immunoglobulin levels, T lymphocyte count, complement levels or other measurements of immune-response components (decreased levels). Other tests may also be used to confirm specific immunodeficiency disorders.

**Treatment**

The goal of treatment for immunodeficiency disorders includes protection against (and treatment of) diseases and infections. Immunocompromised patients are advised to avoid contact with persons who have infections or contagious disorders, including contact with people who have been immunized with live virus vaccines within the past two weeks. Any illness or infection is treated aggressively in patients with immunosuppression. This may involve prolonged use of antimicrobials (antibiotics, antifungal medications), use of powerful antimicrobials to treat any infection, and preventive (prophylactic) treatments. Interferon (used to treat viral infections and some types of cancer) and Zidovudine (AZT, used to treat AIDS) are 2 immunostimulant drugs (medications that increase the efficiency of the immune system). Persons with HIV and AIDS may take combinations of drugs to reduce the amount of virus in their immune systems, thus improving their immunity.
Bone marrow transplant has been used with varying success rates to treat certain immunodeficiency conditions. Passive immunity (administration of antibodies produced by another person or animal) is offered to prevent illness after exposure to a microorganism.

**Experimental Models of Immunodeficiency**

Two well-studied animal models of primary immunodeficiency have been used for a variety of experimental purposes. These are athymic, or nude mouse and Severe Combined Immune Deficiency (SCID) mouse.

**Nude Mouse**

A mouse homozygous for a genetic trait designated *nu*, which is controlled by a recessive gene on chromosome 11, was discovered. These (*nu / nu*) mice are hairless and have a vestigial thymus. Their heterozygotic littermates have hair and a normal thymus. Two very closely linked genes control these defects, which, although unrelated appear together in this mutant mouse. The *nu / nu mice* cannot easily survive under normal conditions. They are maintained under conditions that protect them from infections. These include use of sterilized food, water, cages, and bedding. The cages are placed in a laminar flow to protect them from dust.

These mice lack CMI responses and are unable to make antibodies to most antigens. A thymic transplant can reverse the immunodeficiency in them. These mice can tolerate both allografts and xenografts. They also have a number of experimental uses e.g.: hybridomas or solid Tumors from any origin may be grown as ascites or as implanted tumors in a nude mouse. These mice have a limited population of T cell (from vestigial thymus) that increases with age. The majority of the cells in circulation of a nude mouse carry T cell receptors of the $\gamma\delta$ type instead of the $\alpha\beta$ type that is seen in the circulation of a normal mouse.
**SCID Mouse**

An autosomal recessive mutation in mice termed SCID (mutation in DNA protein kinase) was described that had similarity with human severe combined immunodeficiency. Mice homozygous for the SCID mutation (SCID mice) are severely deficient in functional B and T lymphocytes. They have early B-T-Lineage cells, but there is virtual absence of lymphoid cells in the thymus, spleen, lymph nodes and gut tissue. These mice can neither make antibody nor carry out delayed-type hypersensitivity (DTH) or graft rejection.

The arrest in lymphocyte development is not absolute; some young adult SCID mice are "leaky" (functional mutation) and generate a few clones of functional B and T cells and produce immunoglobulins, suggesting that defective enzyme can function partly in T- and B-cell development, allowing normal differentiation of a small percentage of precursor cells. By 10-14 months of age, virtually all SCID mice are leaky. These animals are kept in an extremely clean environment in order to protect them from infections that can prove fatal for them.

SCID mice readily support normal lymphocyte differentiation and can be reconstituted with normal lymphocytes from other mice and even partially reconstituted with human lymphocytes. They also support the growth of allogeneic and xenogeneic tumors. Thus, SCID mice are of interest for studies of both normal and abnormal lymphocyte development and function. In addition, they can be used to study the function of non-lymphoid cell types in the absence of lymphocytes.

**RAG-Knockout Mouse**

Recently, immunodeficient mouse have been developed by deletion of the recombination-activating enzymes (RAG-1 and RAG-2). The mutation appears to impair the recombination of antigen receptor genes responsible for the rearrangement of immunoglobulin or T-cell-receptor genes in both B- and T-cell precursors. Here both T and B cells are totally absent from the lymphoid organs. Normal graft rejection mechanisms do not operate in these mice. These knockout mice are now very useful animal models. Scientists are using them to study various causes of combined T- and B cell immunodeficiency, transplantation rejection mechanisms in humans, (by grafting cells or organs from various other sources into these mice). These are also used for testing therapeutic or prophylactic strategies against HIV infection of the transplanted human lymphoid tissue in them.

**Summary**

- Immunodeficiency diseases occur due to absence or deficiency of one or more components of the immune system.
- Primary immunodeficiencies are those that are present from birth while secondary or acquired immunodeficiencies are those that appear later in life from a variety of causes.
- The cell types involved also classify the immunodeficiencies and may affect lymphoid or the myeloid cell lineage or both.
- Primary immunodeficiencies are also classified according to the specific gene defect.
- Phagocytic deficiencies affect their function and affected individuals suffer from increased susceptibility to bacterial infections.
• B cell deficiencies result in wide spectrum of diseases and may be detected as decreased levels of all, or some, immunoglobulin isotypes. These lead to recurrent bacterial infections.
• T cell deficiencies are rare because of the pivotal role of T cells in immune responses. Such patients succumb to infections early in their childhood. Viral and fungal infections are common in these deficiencies.
• Combined B and T cell deficiencies pose serious threat to the patients. Babies born with SCID die early from massive infections.
• Immunodeficiency diseases are commonly treated by the use human immunoglobulin or replacement of the defective or missing proteins, cells or genes.
• Two animal models are used to study immunodeficiency. These include Nude and SCID mice.
• The most common example of secondary immunodeficiency is AIDS. It is caused by HIV-1, which results in severe loss of immune function marked by depletion of CD4+ T cells.

Glossary of Terms

Antibodies - Special proteins produced by the body's immune system that help fight and destroy viruses, bacteria, and other foreign substances that invade the body.

Anergy - The phenomenon whereby lymphocytes that have been primed by an antigen fail to respond on second contact with the antigen.

Antigen - A substance (usually foreign) that stimulates the immune response. In people with autoimmune disease, the body's own cells may be seen as antigens.

Auto-antibody - Antibodies specific for self-antigens.

Autoimmune disease--A disease that occurs when the immune system turns against parts of the body it is designed to protect.

Central tolerance - A process whereby immature lymphocytes acquire tolerance to self-antigens during maturation in the primary lymphoid organs by elimination of cells or clones with receptors for self-antigens.

Fever - A rise in body temperature caused by the immune system's response to infection or disease.

Immune response - The response made by the host to defend itself against a foreign invader.

Immune system – Tissues, cells and molecules involved in adaptive immunity; sometimes used to describe the totality of host defense mechanisms.

Immunosuppressive drugs - Drugs that suppress the immune response and can be used to treat autoimmune disease. Unfortunately, because normal immunity is also suppressed with these drugs, they leave the body at risk for infection.

Infection - Invasion of the body tissues by bacteria or other organisms that cause illness.

Inflammation - A reaction of tissues to injury or disease, typically marked by four signs: swelling, redness, heat, and pain.

Peripheral tolerance - It is the process whereby mature lymphocytes acquire tolerance to self-antigens in the peripheral tissues/organs through elimination, lack of co-stimulatory signal, activation induced death or regulation through idiosyncratic network.
**Trigger** - Something that either sets off a disease in people who are genetically predisposed to developing the disease, or that causes a certain symptom to occur in a person who has a disease. For example, sunlight can trigger rashes in people with lupus.

**Glossary of few Autoimmune Diseases**

**Alopecia areata** - A disorder in which the immune system attacks the hair follicles, causing loss of hair on the scalp, face, and other parts of the body.

**Behçet’s Disease** - Behçet's disease (BD or Behçet's syndrome) is a rare, multisystem disease with chronic inflammation of blood vessels (i.e. vasculitis). It is also known as Silk Road Disease. It is a condition characterized by sores in the mouth and on the genitals and by inflammation in parts of the eye. In some people, the disease also results in inflammation of the joints, digestive tract, brain, and spinal cord.

**Crohn’s Disease** - A chronic inflammatory disease of the digestive tract, especially involving the small intestine and large intestine.

**Dermatomyositis** - A rare autoimmune disease that causes patchy red rashes around the knuckles, eyes, and other parts of the body along with chronic inflammation of the muscles. It may occur along with other autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus.

**Guillain Barré Syndrome** - A disease of the nervous system due to damage to the myelin sheath around nerves.

**Polyarteritis nodosa** - An autoimmune disease that causes inflammation of the small and medium-sized arteries. Small and medium-sized arteries become swollen and damaged when they are attacked by rogue immune cells. Polyarteritis nodosa is also called Kussmaul disease or Kussmaul-Maier disease. This leads to problems in the muscles, joints, intestines, nerves, kidney, and skin.

**Polymyositis** - An autoimmune disease causing inflammation of the muscles, usually affecting shoulders, hips, thigh areas and (less commonly) neck muscles. When the skin is also affected, the condition is called dermatomyositis.

**Psoriasis** - A skin condition that is characterized by the presence of rounded, silvery scaly patches of skin. These can appear on the scalp, elbows, knees and genital region. Nail changes are common and include pitting and a yellowish discoloration that resembles a fungal infection. Psoriasis may also cause hair loss.

**Sarcoidosis** - An inflammatory disease marked by the formation of granulomas (small nodules of immune cells) in the lungs, lymph nodes, and other organs.

**Vitiligo** - An autoimmune skin disorder caused by attack of the immune system on the pigment-producing cells within the skin. The loss of the cells responsible for skin color results in milky white patches on the skin surface.

**Suggested Readings**

Useful Web sites

www.en.wikipedia.org/wiki/Autoimmune_diseases
www.TheMedicalStop.com
www.biomed.uchicago.edu/research/autoimmun.html
www-immuno.path.cam.ac.uk/~immuno/part1/lec12/lec12_97.html
www.healthnewsflash.com/conditions/autoimmunity.php
Aaseng, Nathan; Franklin Watts Library Edition: Autoimmune Diseases ISBN 0-531-12553-x
http://www-immuno.path.cam.ac.uk/~immuno/part1/lec12/LATS.gif
http://members.lycos.co.uk/diseaseDIR/images/d/d0102.gif
http://www.humanillnesses.com/original/images/hdc_0001_0001_0_img0066.jpg
http://www.patient.co.uk/showdoc/Pilsinl/060.gif
http://www.mtsinai.on.ca/EBFFRC/images/nerve.jpg
www-immuno.path.cam.ac.uk/.../lec13_97.html