GENETIC DISORDERS AND IMMUNITY

Autosomal Disorders

An **autosomal** recessive **disorder** means two copies of an abnormal gene must be present in order for the **disease** or trait to develop.

Disorders of the autosomes are much more frequent that disorders of the sex chromosomes (Klinefelter syndrome, Turner syndrome). Typical are **numeric abnormalities** and we then recognize two types of disorders:

1. **monosomy –** the carrier lost one copy of a chromosome (45,XY);
2. **trisomy –** there are one more copy of a chromosome (47,XY).

- Althought the trisomies of *chromosomes 18 and 13* were discovered early, there is another trisomy which occurs most – *trisomy 21* (Down syndrome).

There are also **structural disorders** of the automosomes. The most important are deletions. Very well known are deletion of *short arm of 5 chromosome* (Cri du chat syndrome) and deletion of *long arm of 22 chromosome* (DiGeorge syndrome).

Most of carriers of autosomal mutations die during their development and usually not born. Especially monosomies in fetus are connected with abortion. Children with trisomies and deletions who are born, suffer from physical and mental retardation and have shorter life at all.

The cause of these disorders is usually **meiotic nondisjunction –** parents have normal karyotype.

TRISOMY 21 (DOWN SYNDROME)

Down syndrome is very well-known trisomy. It was described in 1866 for the first time by John Down, but the karyotype of 21 trisomy was discover much more later – in 1959.

Down syndrome is the best-known trisomy. It was described in 1866 for the first time by John Down[1], but the karyotype of 21 trisomy was discover much more later – in 1959 by prof. Jerome Lejeune [2]. The incidence of trisomy 21 is about 1 in 800 newborns. It is important to say that that´s just a small part of all the affected fetuses. Most of the fetuses with Down syndrome die because of the abortion.

Origin of Trisomy 21

1. The most common is *an extra chromosome 21* (95%) (**full trisomy**);
2. Sometimes small parts of chromosome *21 translocate to 14 or 22* chromosome (4%) (**translocation variant**);
3. In some cases we can find *mosaic* – it means that person has some cells with trisomy and some without (2%) (**Mosaic variant**).

The clinical significance of mosaic variant of the Down syndrome depends on the number of trisomic cells. However - it is very difficult to estimate the severity of the symptomps using the plain numbers, since the clinical significance also depends on the number of trisomic cells in specific body tissues, what is very difficult to diagnose. Basically - it is possible to say, that the full trisomy is significantly worse than the mosaic variant of the Down syndrome.

Symptomes

People with Down syndrome have typical **physical appearance**. They have *short body*, *flat faces profile*, *epicanthic folds* (part of skin over the inner corner of the eye – the reason why they

are sometimes called "Mongoloid"), *small low-set ears* and relatively *large tongue*. They have also motor problems because of *low muscle tone*.
Carriers suffer more from leukemias, infections, cardiac malformations, epilepsy, hypothyroidism and Alzheimer disease.
The **mental abilities** are also worse. The IQ of people with Down syndrome is about 50. It means that they reach a level of a small child – about 6 years old. On the second side their character is very friendly, warm and loving.

The Cause of Trisomy 21

The cause of 21 trisomy is **meiotic nondisjunction**. Parents of the children have normal karyotype and no symptomes. Very strong influence has **the age of the mother**. The higher age is connected with higher risks (maternal age of 35 years and more is considered especially risky)[3]. The incidence is 1 in 25 live births in women older than 45 years. [4]
Boy with Down syndrome
The role of the **father´s age** is less important. Just 4% of Down syndrome is caused by the mistake of meiosis in sperms. The reason is very simple. The evolution of sperm takes just 72 hours. It is the time when the meiosis underway. On the other side, ovum (female reproduction cell) is present in woman´s body from her birth. So the meiosis is underwaying for years and it is pretty easier to make a mistake. The higher age of the mother, the more meiosis, the higher risk of nondisjunction.

Trisomy 18 (Edwards syndrome)

Edwards syndrome is connected with a *trisomy of chromosome 18*. The most of the affected individuals die during the prenatal stage. Newborns have multiple defects – micrognathia, short neck, congenital heart defects and renal malformations. The children look weak and fragile.
The incidence is 1 in 8000. Boys are more affected than girls. As the Down syndrome, Edwards syndrome is also **influenced by the age of the mother**. Nowadays there is no therapy and the cure is just palliative. Most children with trisomy 18 is not able to survive their first year and they die.

Trisomy 13 (Patau syndrome)

Bartholin-Patau syndrome, also called autosomal Trisomy 13, is a very severe condition first described by *Dr. Klaus Patau* in 1960. This genetic disorder is associated with severe intellectual disability and physical abnormalities in many parts of the body. The affected individuals often have heart defects, brain or spinal cord abnormalities, microphthalmia (very small or poorly developed eyes), cleft lip, extra fingers and/or toes, among other features.
Causes
Trisomy 13 is a chromosomal condition in which the sex ratio at birth is slightly higher in females than in males. This fact could be related to the decreased survival rate among male fetuses.
Like most other trisomies (aneuploidy), *Patau syndrome* increasing incidence is associated with advanced maternal age, and the additional chromosome usually arises from nondisjunction in

maternal meiosis resulting in three copies of 13 chromosome genetic material. This is a noninheritate case, is the result of random events during meiosis.
The extra genetic material disrupts the normal course of development, causing the characteristic features of *trisomy 13*. However, some cases derived from germinal mosaicism or by balanced chromosomal rearrangements (Robertsonian translocations), where the extra material is attached to another chromosome, are situations in which the trisomy can be inherited.
The person who carries the balanced translocation involving chromosome 13 has an increased chance of passing extra material from chromosome 13 to their children.

Symptoms

The small percentage of babies with full *Patau's syndrome* and who survived birth, may express the following internal and external conditions:
Hands and feet showing polydactyly (postaxial).

Facial defects:

Mouth: cleft lip and/or palate.
Nose: absent, malformed or proboscis (prominent).
Ears: malformed ears.
Eye: structural eye defects (microphthalmia, iris coloboma or even absence of the eyes).
Hands: abnormal palm pattern.
Muscle: Hypotonia (decreased muscle tone).
Hernias: umbilical hernia, inguinal hernia.
Severe central nervous system malformation:
Severe mental retardation.
Cephalic disorder: arhinencephaly and holoprosencephaly.
Spinal cord defects.
Cardiac defects.
Urogenital defects:
Abnormal genitalia (e. g. undescended testicle).
Kidney defects.

Diagnosis

Prenatal diagnosis is possible by amniocentesis, with the study of amniotic cells' chromosome.
Detected patients with fetus affected by *trisomy 13* caused by a translocation, should have genetic testing counseling with a care provider. The specialist may give parents the information about recurrence risk, screening, and diagnostic testing options for future pregnancies. This pregnancy management varies according to the gestational age at diagnosis.

Recurrence risk

The recurrence risk is low. Even when one parent of translocation patient is carrier of the translocation in chromosome 13, the risk for the liveborn child to get the syndrome is still minimum (less than 1%).
Patau's syndrome incidence figures is shown approximately 1 out of every 10,000 newborns and convey a very poor prognosis, with only 10% of affected infants living past their first year (mortality rate is very high among neonates culminating mainly in miscarriages).

What Is a Sex Linked Genetic Disease?

A disorder caused by a gene located on a sex chromosome, usually the X chromosome.
Sex-linked genetic disorders are any diseases or abnormal conditions that are caused by a defective gene on the X chromosome, one of the sex chromosomes. These disorders may also

involve a deviation in the number of X or Y chromosomes. Turner Syndrome, a disorder in which all or part of one of the female's X chromosomes is missing, is an example of this.

Turner Syndrome

Turner Syndrome (TS) is a chromosomal condition that affects females. It is caused by a complete or partial absence of the second sex chromosome. It is also known as Ullrich-Turner Syndrome or Gonadal dysgenesis. In some instances, the chromosome is missing in some cells, but not all. This is called mosiacism.

TS is found in 1 out of every 2,500 female births and is present in as many as 10% of all miscarriages. Only 1% of fetuses with the syndrome survive to term. TS is not linked to advanced maternal age.

Characteristics of Turner syndrome include:

- Short stature (generally the average height is less than 4'8")
- Premature ovarian failure
- Narrow, high-arched palate
- Receding lower jaw
- Low-set ears
- Low hairline at the neck
- Webbed neck
- Slight droop to eyes
- Broad chest
- Arms that turn out slightly at the elbows
- Scoliosis
- Flat feet
- Small, narrow fingernails and toenails that turn up
- Normal intelligence with deficiencies in math, sense of direction and social skills.

KLINEFELTER SYNDROME

Klinefelter syndrome is a genetic disorder that affects males. Klinefelter syndrome occurs when a boy is born with one or more extra X chromosomes. Having extra X chromosomes can cause a male to have some physical traits unusual for males.

XXY is one of the most common genetic conditions, affecting about 1 in 660 genetic males.

Klinefelter syndrome is named for Dr. Harry Klinefelter, who first reported its symptoms in 1942.

47, XXY (or XXY) is a genetic condition caused when someone has two X chromosomes and one Y chromosome. Because people with an XXY chromosome arrangement have a Y chromosome, they are considered genetic males. Most XXY individuals develop as males, often not knowing they have an extra chromosome. Physical characteristics may appear around the time of puberty, when gender identity and sexual characteristics begin to take shape.

XXY is usually caused by what is called nondisjunction. Nondisjunction happens when a pair of sex chromosomes fails to separate during egg (or sperm) formation. When an egg (or sperm) with an extra X chromosomes joins with a normal sperm (or egg), the resulting embryo will end up with three sex chromosomes (XXY) instead of the normal two (XX or XY). As the baby develops, the extra chromosome is then copied in every cell.

Nondisjunction leading to XXY is equally likely to happen in the mother's egg and the father's sperm. In about 10% of cases, chromosomes fail to separate when a cell divides very early in embryonic development, and only some of the baby's cells have an extra X chromosome.
The XXY chromosome arrangement affects primarily sexual development. Typically, testes don't fully develop, and the levels of the hormone testosterone (important for male sexual development) are lower than average. As adults, nearly all XXY males are unable to make sperm and so cannot have biological children.
The symptoms of XXY (Klinefelter syndrome) can be very subtle and are highly varied. Children and adults may be taller than average, with proportionally longer arms and legs, and they may have less-muscular bodies, more belly fat, wider hips, narrower shoulders. Changes that appear at puberty can include low growth of facial and body hair, development of breast tissue, and small testes.
XXY individuals are also more likely to develop certain medical conditions, including osteoporosis (weak bones), varicose veins, type 2 diabetes, and heart valve defects.

STORAGE DISORDER

Storage disease **is** a metabolic disorder in which certain cells accumulate excessive amounts of lipids, proteins, or other substances.

A metabolic disorder characterized by excessive storage in certain cells of normal metabolic intermediates, as fats, iron, and carbohydrates.

The abnormal accumulation in the body of one or more specific substances and especially metabolic substances (as cerebrosides in Gaucher's disease)—called also *thesaurosis*;

Glycogen Storage Disease (GSD)

Glucose is a large energy source for the body. It is stored by the body in the form of glycogen and released into the blood as needed with the help of special proteins called enzymes.
There are different types of GSD but all people who have GSD are born with the disease. When a person has GSD:

- The liver cannot control the use of glycogen and glucose because certain enzymes are missing that control the change of sugar (glucose) into its storage form (glycogen) or release of glucose from glycogen.
- An abnormal amount of glycogen is stored in the liver.
- Not enough glucose is in the blood (also called hypoglycemia).

Many sugars (including glucose) are found in foods and are used by the body as a source of energy. After a meal, blood glucose levels rise. The body stores the extra glucose that is not needed right away as glycogen in the liver and muscles. Later, as the blood glucose levels in the body begin to drop, the body uses this stored energy.
These sugars, stored in the form of glycogen, need to be processed by enzymes in the body before they can carry out their functions. If the enzymes needed to process them are missing, the glycogen or one of its related starches can build up in the liver, causing problems.

Types of GSD

There are at least 10 different types of GSDs. The types are put into groups based on the enzyme that is missing. The most common forms of GSD are types I (one), III (three) and IV (four). About one in 20,000 people have a type of GSD.

GSD I, also known as von Gierke disease: Results from a lack of the enzyme Glucose-6-Phosphatase.

GSD III, also known as Cori disease: Results from a lack of the debrancher enzyme. This causes the body to form glycogen molecules that have an abnormal structure which prevents the glycogen from being broken down into free glucose.

GSD IV, also known as amylopectinosis: There is not an increased amount of glycogen in the tissues. Instead, the glycogen that does build up in the tissues has very long outer branches. With this type of GSD, there is lack of the branching enzyme. This abnormal glycogen is thought to stimulate the immune system. The result is a great deal of scarring (cirrhosis) of the liver as well as other organs, such as muscle and heart.

Causes

When glucose is changed into glycogen, a different enzyme is required at each step. If one of these enzymes is defective (not normal) and fails to complete its step, the process stops. These enzyme defects cause glycogen storage diseases.

GSD is passed down through families (genetic) and occurs because of an inherited gene change from both parents. We normally have two copies of each gene. In order for people to have GSD both of their gene copies must not work properly. When people are carriers, it means that only one of their genes is not working properly. If both parents carry the defective gene, there is:

- A 25 percent chance that their child will develop the disorder
- A 50 percent chance that their child will receive a gene change from one of the parents, which means the child will not show symptoms of the disorder but is a "carrier"
- A 25 percent chance their child will have two working copies and will not have a GSD

Signs and Symptoms

Symptoms vary based on the enzyme that is missing. They usually result from the buildup of glycogen or from not being able to produce glucose when needed. Because GSD occurs mainly in muscles and the liver, those areas show the most symptoms.

Symptoms may include:

- Poor growth
- Muscle cramps
- Low blood sugar
- A greatly enlarged liver
- A swollen belly
- Abnormal blood test

The age when symptoms begin and how severe they are depends on the type of GSD. Children with GSD I rarely develop cirrhosis (liver disease), but they are at an increased risk for developing liver tumors.

In some ways, GSD III is a milder version of GSD I. It also is a very rare cause of liver failure, but it may cause fibrosis (early scarring of the liver, which may be caused by a healing response to injury, infection or inflammation). GSD II is a muscle disease and does not affect the liver.

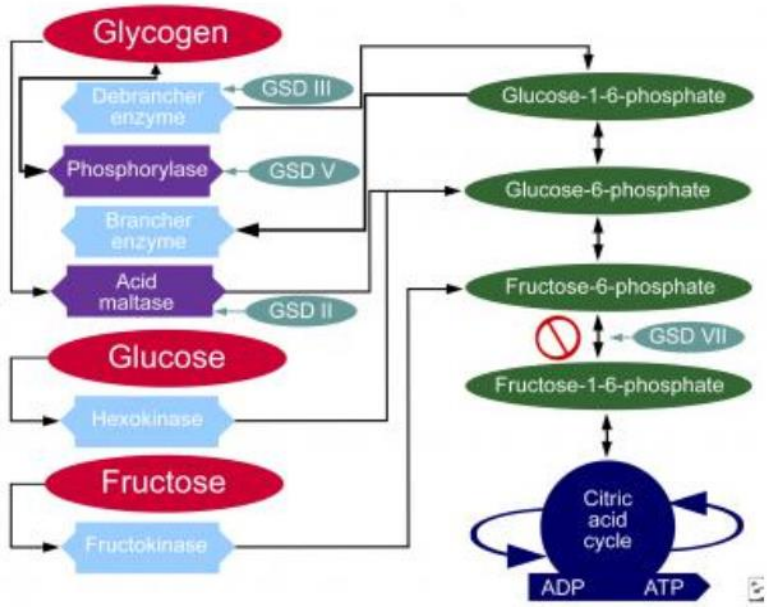
Glycogen storage disease IV causes cirrhosis; it may also cause heart or muscle dysfunction. Often, infants born with GSD IV are diagnosed with enlarged livers and failure to thrive within their first year of life. They develop cirrhosis of the liver by age 3-5.

A glycogen storage disease (GSD) is the result of an enzyme defect. These enzymes normally catalyze reactions that ultimately convert glycogen compounds to glucose. Enzyme deficiency results in glycogen accumulation in tissues. In many cases, the defect has systemic consequences, but in some cases, the defect is limited to specific tissues. Most patients experience muscle symptoms, such as weakness and cramps, although certain GSDs manifest as specific syndromes, such as hypoglycemic seizures or cardiomegaly.[1, 2]

The following list contains a quick reference for 8 of the GSD types:

- 0 - Glycogen synthase deficiency
- Ia - Glucose-6-phosphatase deficiency (von Gierke disease)
- II - Acid maltase deficiency (Pompe disease)
- III - Debranching enzyme deficiency (Forbes-Cori disease)
- IV - Transglucosidase deficiency (Andersen disease, amylopectinosis)
- V - Myophosphorylase deficiency (McArdle disease)
- VI - Phosphorylase deficiency (Hers disease)
- VII - Phosphofructokinase deficiency (Tauri disease)

The chart below demonstrates where various forms of GSD affect metabolic carbohydrate pathways.



Metabolic pathways of carbohydrates

Although at least 14 unique GSDs are discussed in the literature, the 4 that cause clinically significant muscle weakness are Pompe disease (GSD type II, acid maltase deficiency), Cori disease (GSD type III, debranching enzyme deficiency), McArdle disease (GSD type V, myophosphorylase deficiency), and Tarui disease (GSD type VII, phosphofructokinase deficiency). One form, von Gierke disease (GSD type Ia, glucose-6-phosphatase deficiency), causes clinically significant end-organ disease with significant morbidity. The remaining GSDs are not necessarily benign but are less clinically significant; therefore, the physician should

consider the aforementioned GSDs when initially entertaining the diagnosis of a GSD. Interestingly, GSD type 0 also is described, which is due to defective glycogen synthase.
These inherited enzyme defects usually present in childhood, although some, such as McArdle disease and Pompe disease (also known as acid maltase deficiency), have separate adult-onset forms. In general, GSDs are inherited as autosomal recessive conditions. Several different mutations have been reported for each disorder.
Unfortunately, no specific treatment or cure exists, although diet therapy may be highly effective at reducing clinical manifestations. In some cases, liver transplantation may abolish biochemical abnormalities. Active research continues.
Diagnosis depends on findings from patient history and physical examination, muscle biopsy, electromyography, ischemic forearm testing, and creatine kinase testing. Biochemical assay for enzyme activity is the method of definitive diagnosis.
In patients with Hers disease, defective liver phosphorylase results in hepatomegaly and hypoglycemia. The liver phosphorylase enzyme is found in the liver and in red blood cells.

Pathophysiology

With an enzyme defect, carbohydrate metabolic pathways are blocked and excess glycogen accumulates in affected tissues. Each GSD represents a specific enzyme defect, and each enzyme is in specific, or most, body tissues. Liver phosphorylase, which is found in the liver and red blood cells, is deficient, which results in glycogen accumulation in the liver and subsequent hypoglycemia.

LYSOSOMAL STORAGE DISEASES

Lysosomal storage diseases describe a heterogeneous group of dozens of rare inherited disorders characterized by the accumulation of undigested or partially digested macromolecules, which ultimately results in cellular dysfunction and clinical abnormalities. Organomegaly, connective-tissue and ocular pathology, and central nervous system dysfunction may result. Classically, lysosomal storage diseases encompassed only enzyme deficiencies of the lysosomal hydrolases. More recently, the concept of lysosomal storage disease has been expanded to include deficiencies or defects in proteins necessary for the normal post-translational modification of lysosomal enzymes (which themselves are often glycoproteins), activator proteins, or proteins important for proper intracellular trafficking between the lysosome and other intracellular compartments.

Standard classification

The lysosomal storage diseases are generally classified by the nature of the primary stored material involved, and can be broadly broken into the following: (ICD-10 codes are provided where available)

- (E75) lipid storage disorders, mainly sphingolipidoses (including Gaucher's and Niemann-Pick diseases (E75.0-E75.1) gangliosidosis (including Tay-Sachs disease (E75.2) leukodystrophies
- (E76.0) mucopolysaccharidoses (including Hunter syndrome and Hurler disease)
- (E77) glycoprotein storage disorders
- (E77.0-E77.1) mucolipidoses

Also, glycogen storage disease type II (Pompe disease) is also a defect in lysosomal metabolism, although it is otherwise classified into E74.0 in ICD-10. Cystinosis is a lysosomal storage disease characterized by the abnormal accumulation of the amino acid cystine.

Signs and symptoms

The symptoms of lysosomal storage disease vary, depending on the particular disorder and other variables like the age of onset, and can be mild to severe. They can include developmental delay, movement disorders, seizures, dementia, deafness and/or blindness. Some people with lysosomal storage disease have enlarged livers (hepatomegaly) and enlarged spleens (splenomegaly), pulmonary and cardiac problems, and bones that grow abnormally.

Diagnosis

The majority of patients are initially screened by enzyme assay, which is the most efficient method to arrive at a definitive diagnosis. In some families where the disease-causing mutation(s) is known and in certain genetic isolates, mutation analysis may be performed. In addition, after a diagnosis is made by biochemical means, mutation analysis may be performed for certain disorders.

Pathophysiology

Although in general the accumulation of undegraded substrate is thought to relate to the cellular dysfunction and death that accompanies lysosomal storage diseases, the precise mechanisms underlying this degeneration are incompletely defined. The pattern of neuronal degeneration in subtypes of lysosomal storage diseases may be surprisingly cell-type specific. In some cases, substrate accumulation is also associated with sequestration of important component molecules, leading to a relative deficiency state.

The lysosome serves as a central component of the endosomal-lysosomal system. This system is crucial for the maintenance of normal cellular metabolism, working in conjunction with the chaperone-mediated autophagy and ubiquitin-proteasomal systems. Abnormal function of this system may lead to ectopic dendritic sprouting (a feature relatively unique to lysosomal storage diseases) and impaired recycling of glutamatergic AMPA receptors. Neuroaxonal spheroid formation is a feature of the ganglioside storage diseases, Niemann-Pick types A and C, and a-mannosidosis, implicating a shared pathology that leads to the production of these compact accumulations of mitochondria and tubulovesicular bodies.

HYPERSENSITIVITY REACTIONS

Hypersensitivity (also called **hypersensitivity reaction** or **intolerance**) is a set of undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal.

The immune system is an integral part of human protection against disease, but the normally protective immune mechanisms can sometimes cause detrimental reactions in the host. Such

reactions are known as hypersensitivity reactions, and the study of these is termed immunopathology. The traditional classification for hypersensitivity reactions is that of Gell and Coombs and is currently the most commonly known classification system.[1] It divides the hypersensitivity reactions into the following 4 types:

- Type I reactions (ie, immediate hypersensitivity reactions) involve immunoglobulin E (IgE)–mediated release of histamine and other mediators from mast cells and basophils.[2] Examples include anaphylaxis and allergic rhinoconjunctivitis.
- Type II reactions (ie, cytotoxic hypersensitivity reactions) involve immunoglobulin G or immunoglobulin M antibodies bound to cell surface antigens, with subsequent complement fixation. An example is drug-induced hemolytic anemia.
- Type III reactions (ie, immune-complex reactions) involve circulating antigen-antibody immune complexes that deposit in postcapillary venules, with subsequent complement fixation. An example is serum sickness.
- Type IV reactions (ie, delayed hypersensitivity reactions, cell-mediated immunity) are mediated by T cells rather than by antibodies. An example is contact dermatitis from poison ivy or nickel allergy.

Hypersensitivity refers to undesirable (damaging, discomfort producing and sometimes fatal) reactions produced by the normal immune system . Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Hypersensitivity reactions can be divided into four types : type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

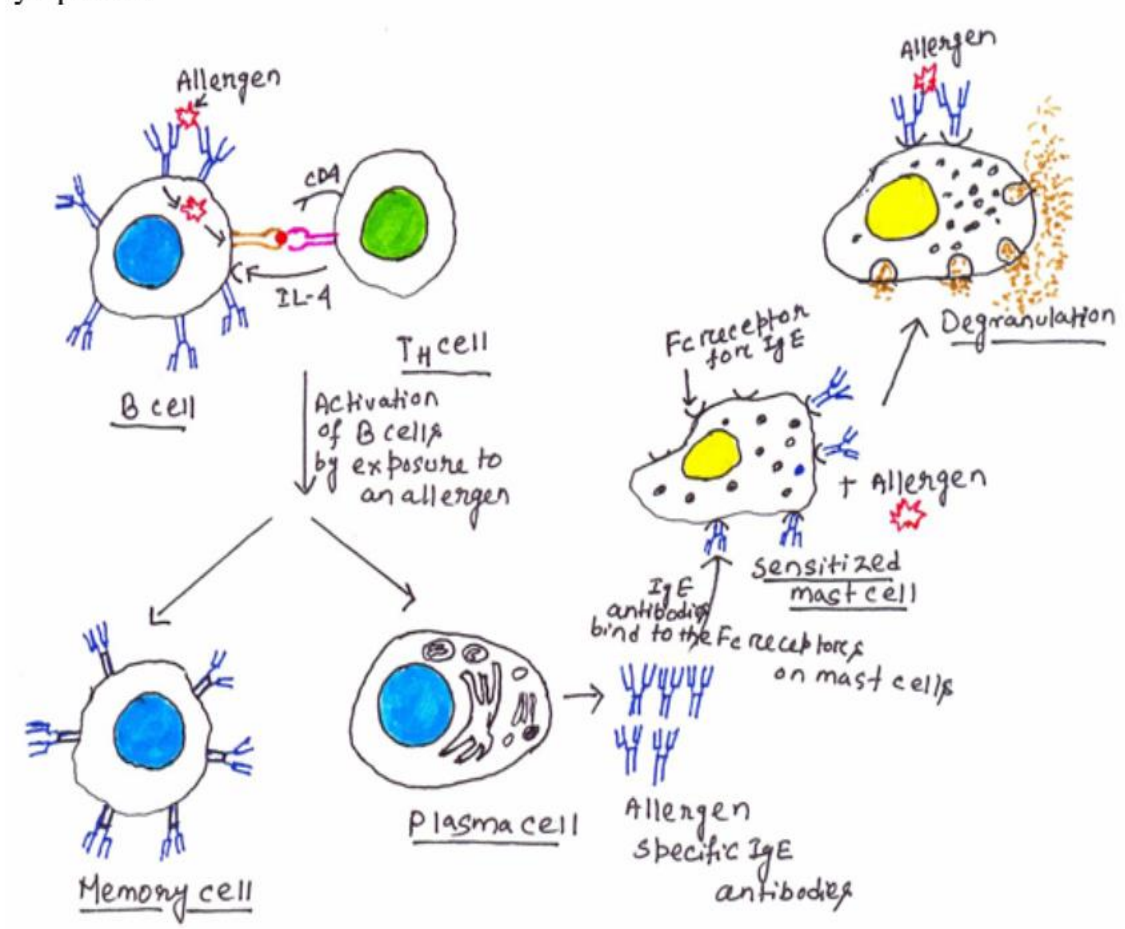
Type I Hypersensitivity

It is also known as immediate or anaphylactichypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gas troenteritis). The reaction may cause from minor inconvenience to death. The reaction takes 15-30 minutes from the time of exposure to the antigen. Sometimes the reaction may have a delayed onset (10-12 hours). Immediate hypersensitivity is mediated by IgE .

The primary cellular component in this hypersensitivity is mast cell or basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils. A biopsy of the reaction site demonstrates mainly mast cells and eosinophils.

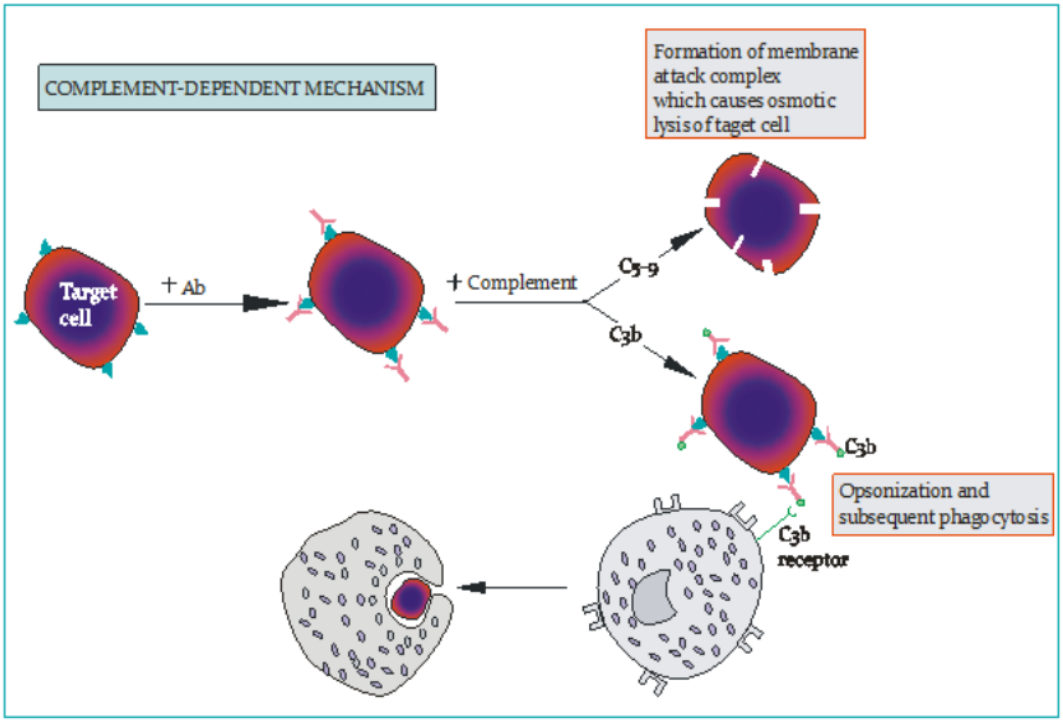
The mechanism of reaction involves preferential production of IgE, in response to certain antigens, allergens (Figure 1). IgE has very high affinity for its receptor on mast cells and basophils. A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances (Figure 1). Cross-linking of IgE Fc-receptor is importa nt in mast cell triggering.Mast cell degranulation is preceded by increased Ca++influx , which is a crucial process; ionophores which increase cytoplasmic Ca ++ also promote degranulation, whereas, agents which deplete cytoplasmic Ca ++ suppress degranulation. The agents released from mast cells and their effects are listed in Table 1. Mast cells may be triggered by other stimuli such as exercise, em otional stress, chemicals. These reactions mediated by agents without IgE-allergen hese reactions mediated by agents without

IgE-allergen interaction are not hypersensitivity reactions , although they produce the same symptoms.



Type II Hypersensitivity

It is also known as cyto toxic hypersensitivity and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity. Drug-induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples. The reaction time is minutes to hours. It is primarily mediated by antibodies of IgM or IgG class and complement. Phagocytes and K cells may also play a role (ADCC). The lesion contains antibody, complement and neutrophils . Diagnostic tests include detection of circulating antibody against tissues involved and the presence of antibody and complement in the lesion (biopsy) by immunofluorescence. The staining pattern is normally smooth and linear, such as that seen in Goodpasture's nephritis (renal and lung basement membrane) and pemphigus (skin intercellular protein, desmosome). Treatment involves anti-inflammatory and immunosuppressive agents.



Type III Hypersensitivity

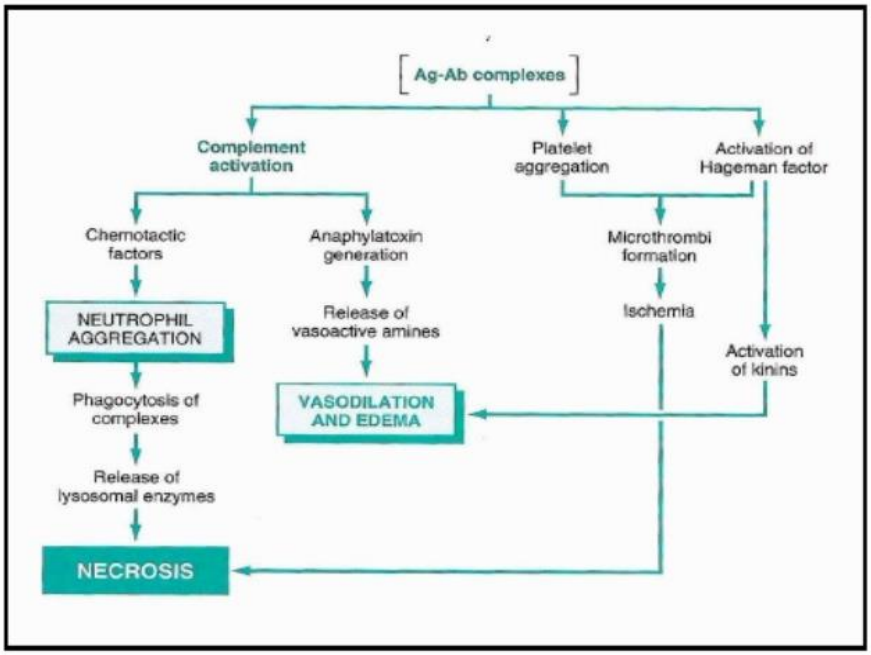
It is also known as immune complex hypersensitivity . The reaction may be general (e.g. , serum sickness) or may involve individual organs including skin (e.g. , systemic lupus erythematosus, Arthus reaction), kidneys (e.g., lupus nephritis), lungs (e.g., aspergillosis), blood vessels (e.g., polyarteritis), joints (e.g., rheumatoid arthritis) or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms.

The reaction may take 3-10 hours after exposure to the antigen (as in Arthus reaction). It is mediated by soluble immune complexes. They are mostly of IgG class, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infec
tions), or endogenous (non-organ specific autoimmunity:e.g., systemic lupus eythematosus, SLE). The antigen is soluble and not attached to the organ involved. Primary components are soluble immune complexes and complement (C3a, 4a and 5a). The damage is caused by platelets and neutrophils.

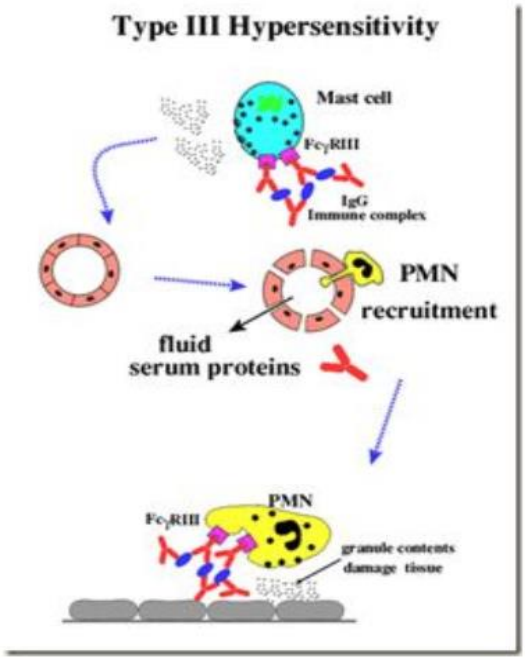
The lesion contains primarily neutrophils and deposits of immune complexes and complement. Macrophages infiltrating in later stages may beinvolved in the healing process.

The affinity of antibody and size of immune complexes are important in production of disease and determining the tissue involved. Diagnosis involves examination of tissue biopsies for deposits of Ig and complement by immunofluorescence. The immunofluorescent staining in type III hypersensitivity is granular (as opposed to linear in type II: Goodpasture). Presence of immune complexes in serum and depletion in complement level are also diagnostic. Polyethylene glycol mediated turbidity (nephelometry), binding of C1q and Raji cell test are utilized to detect immune complexes. Treatment includes anti-inflammatory agents.

Type III Hypersensitivity



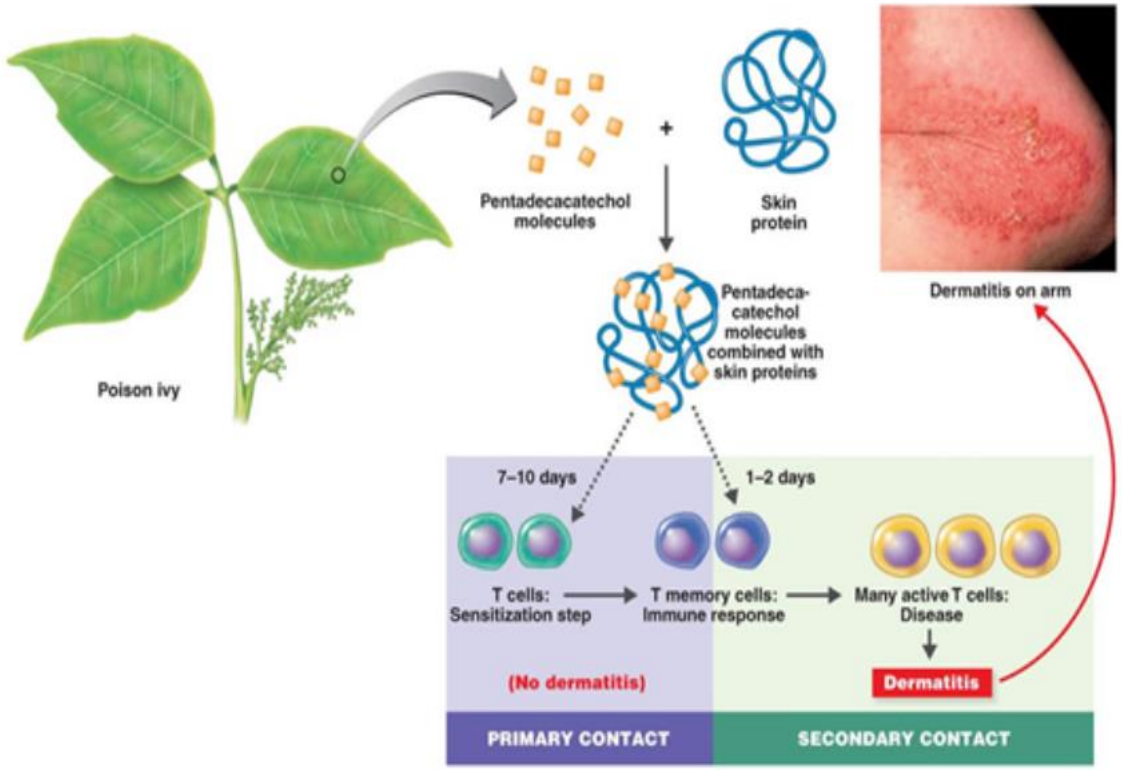
Source: Robbins PATHOLOGIC BASIS OF DISEASE 6th ed.

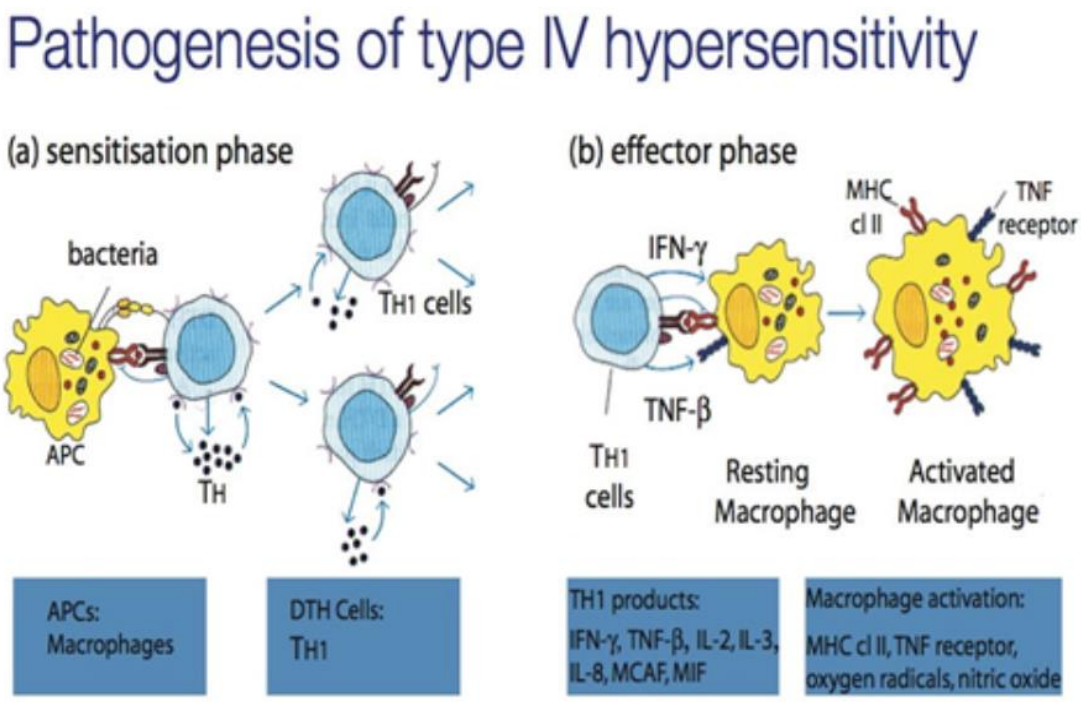


Type IV Hypersensitivity

It is also known as cell mediated or delayed type hypersensitivity. The classical example of this hypersensitivity is tuberculin (Montoux) 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 is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison ivy, chemicals, heavy metals, etc.) in which the lesions are more papular. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation.

Mechanisms of damage in delayed hypersensitivity include 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 (Figure 4). 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, and interferon. Corticosteroids and other immunosuppressive agents are used in treatment.





IMMUNE DEFICIENCY SYNDROME

Immunodeficiency Disorder

Immunodeficiency disorders prevent our body from adequately fighting infections and diseases. An immunodeficiency disorder also makes it easier for you to catch viruses and bacterial infections in the first place. Immunodeficiency disorders as either congenital or acquired. A congenital, or primary, disorder is one you were born with. Acquired, or secondary, disorders are disorders you get later in life. Acquired disorders are more common than congenital disorders.
Immune system includes the following organs:

- spleen
- tonsils
- bone marrow
- lymph nodes

These organs make and release lymphocytes. Lymphocytes are white blood cells classified as B cells and T cells. B and T cells fight invaders called antigens. B cells release antibodies specific to the disease your body detects. T cells kill off cells that are under attack by disease.
Examples of antigens

- bacteria, viruses, cancer cells, parasites

An immunodeficiency disorder disrupts our body's ability to defend itself against these antigens.

Types of Immunodeficiency Disorders

Primary immunodeficiency disorders are immune disorders you are born with. Primary disorders include:

- X-linked agammaglobulinemia (XLA)
- common variable immunodeficiency (CVID)

- severe combined immunodeficiency (SCID)
- alymphocytosis

Secondary disorders happen when an outside source, such as a toxic chemical or infection, attacks your body. Severe burns and radiation also can cause secondary disorders. Secondary disorders include:

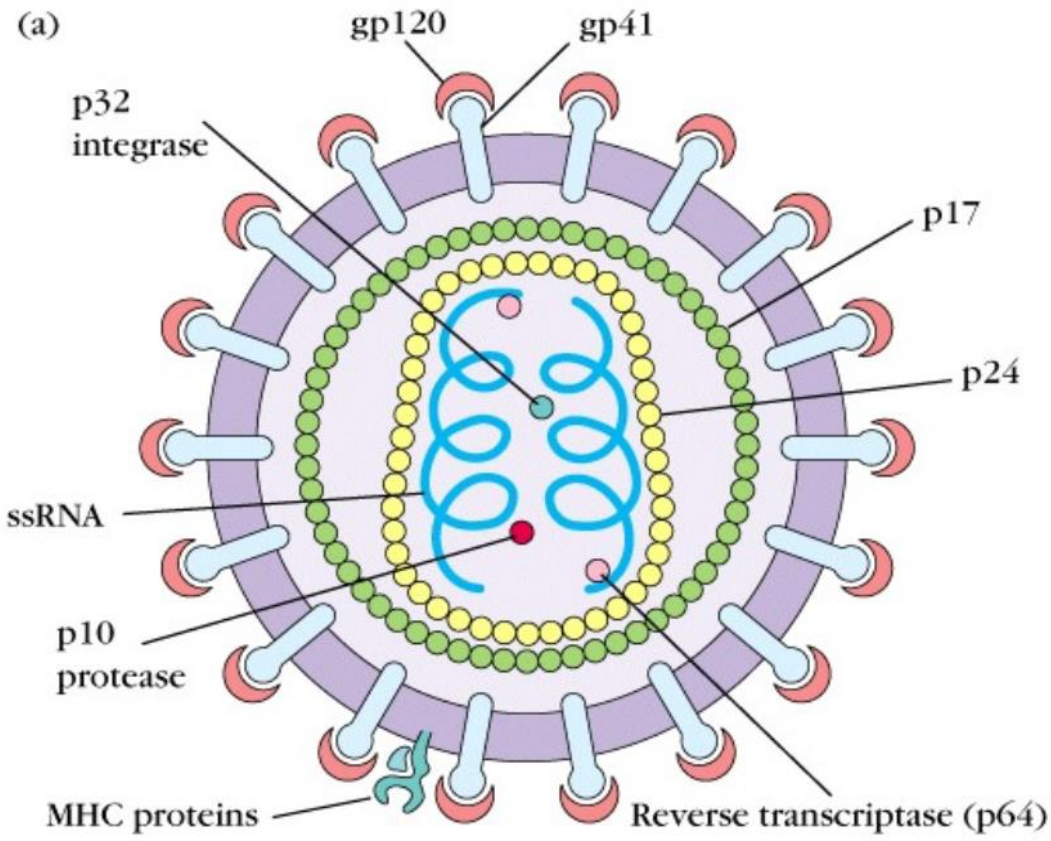
- AIDS
- cancers of the immune system, such as leukemia
- immune-complex diseases, such as viral hepatitis
- multiple myeloma

Secondary immunodeficiencies, also known as acquired immunodeficiencies, can result from various immunosuppressive agents, for example, malnutrition, aging and particular medications (e.g. chemotherapy, disease-modifying antirheumatic drugs, immunosuppressive drugs after organ transplants, glucocorticoids). For medications, the term immunosuppression generally refers to both beneficial and potential adverse effects of decreasing the function of the immune system, while the term *immunodeficiency* generally refers solely to the adverse effect of increased risk for infection.

Many specific diseases directly or indirectly cause immunosuppression. This includes many types of cancer, particularly those of the bone marrow and blood cells (leukemia, lymphoma, multiple myeloma), and certain chronic infections. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS),[6] caused by the human immunodeficiency virus (HIV). HIV directly infects a small number of T helper cells, and also impairs other immune system responses indirectly.

Structure of HIV

HIV is different in structure from other retroviruses. It is around 120 nm in diameter and roughly spherical. HIV-1 is composed of two copies of noncovalently linked, unspliced, single-stranded RNA enclosed by a conical capsid composed of the viral protein p24. The RNA component is 9749 nucleotides long and bears a 5' cap (Gppp), a 3' poly(A) tail, and many open reading frames (ORFs). Viral structural proteins are encoded by long ORFs, whereas smaller ORFs encode regulators of the viral life cycle: attachment, membrane fusion, replication, and assembly.



Structure of HIV

The single-strand RNA is tightly bound to p7 nucleocapsid proteins, late assembly protein p6, and enzymes essential to the development of the virion, such as reverse transcriptase and integrase. Lysine tRNA is the primer of the magnesium-dependent reverse transcriptase. The nucleocapsid associates with the genomic RNA (one molecule per hexamer) and protects the RNA from digestion by nucleases. Also enclosed within the virion particle are Vif, Vpr, Nef, and viral protease. A matrix composed of an association of the viral protein p17 surrounds the capsid, ensuring the integrity of the virion particle. This is in turn surrounded by an envelope of host-cell origin. The envelope is formed when the capsid buds from the host cell, taking some of the host-cell membrane with it. The envelope includes the glycoproteins gp120 and gp41.

As a result of its role in virus-cell attachment, the structure of the virus envelope spike, consisting of gp120 and gp41, is of particular importance. Determining the envelope spike's structure will contribute to understanding the HIV replication cycle, and may help in the creation of a cure. The first model of its structure was compiled in 2006 using cryo-electron tomography and suggested that each spike consists of a trimer of three gp120–gp41 heterodimers. However, published shortly after was evidence for a single-stalk "mushroom" model, with a head consisting of a trimer gp120s and a gp41 stem, which appears as a compact structure with no obvious separation between the three monomers, anchoring it to the envelope. There are various possibilities as to the source of this difference, as it is unlikely that the viruses imaged by the two

groups were structurally different. More recently, further evidence backing up the heterodimer trimer-based model has been found.

Pathology of AIDS

Acquired immune deficiency syndrome (AIDS) is caused by the HIV or human immunodeficiency virus. The infection causes progressive destruction of the cell-mediated immune (CMI) system, primarily by eliminating CD4+ T-helper lymphocytes.

Decreased immunity leads to opportunistic infections and certain cancers. Opportunistic infections are caused by organisms that do not cause infections in healthy individuals. HIV also directly damages certain organs like the brain.

AIDS indicates advanced HIV disease and has no cure and is considered fatal. The time from HIV infection to death however depends on the management with anti-HIV medications instituted on time and continued over long term.

The time period usually ranges from 6 months (rarely) to 15+ years. In the United Kingdom the average time is around 12 years.

HIV infection passes through a series of steps or stages before it turns into AIDS. These stages of infection as outlined in 1993 by the Centers for Disease Control and prevention are:

1. **Seroconversion illness –** this occurs in 1 to 6 weeks after acquiring the infection. The feeling is similar to a bout of flu.
2. **Asymptomatic infection –** After seroconversion, virus levels are low and replication continues slowly. CD4 and CD8 lymphocyte levels are normal. This stage has no symptoms and may persist for years together.
3. **Persistent generalised lymphadenopathy (PGL) –** The lymph nodes in these patients are swollen for three months or longer and not due to any other cause.
4. **Symptomatic infection –** This stage manifests with symptoms. In addition, there may be opportunistic infections. This collection of symptoms and signs is referred to as the AIDS-related complex (ARC) and is regarded as a prodrome or precursor to AIDS.
5. **AIDS –** this stage is characterized by severe immunodeficiency. There are signs of life-threatening infections and unusual tumors. This stage is characterized by CD4 T-cell count below 200 cells/mm3.
6. There is a small group of patients who develop AIDS very slowly, or never at all. These patients are called non-progressors.

The pathological spectrum of HIV infection is changing as the infection spreads into new communities with different potential opportunistic diseases, and as medical science devises drugs against HIV replication.

Geographical pathology of HIV/AIDS

Genetics and geographical location has a role in the pattern of opportunistic infections. A second determinant is the speed of decline in the immune system. Many of the opportunistic infections are of low virulence and are only encountered if patients survive with low CMI.

Genetics and earlier site of stay also plays a role. For example, African HIV-infected patients reside in the UK have high rates of tuberculosis and this is usually a reactivation of latent infection acquired in the country of origin.

Some opportunistic infections include;

Viral infections

- Cytomegalovirus (CMV)
- Herpes simplex

- Herpes zoster
- Measles
- Human papilloma virus (HPV)
- Human herpes virus 8 (HV8)
- Epstein-Barr virus (EBV)

Bacterial infections

- Recurrent bacterial pneumonia (commonly Streptococcus pneumoniae)
- Mycobacterium tuberculosis
- Non-tuberculosis mycobacteriosis
- Systemic non-typhoid Salmonella infections
- *Pseudomonas spp*. septicaemia and `vasculitis'

Fungal infections

- Candida severe infection
- *Pneumocystis jiroveci pneumonia*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Coccidioides immitis*
- *Aspergillus spp.*
- *Penicillium marneffei*

Protozoal infections

- *Toxoplasma gondii*
- *Cryptosporidium parvum*
- *Isospora belli*
- *Leishmania spp.*
- *Microsporidia spp.*
- *Acanthamoeba spp.*
- *Trypanosoma cruzi*

Tumours

- Kaposi's sarcoma
- Primary cerebral lymphoma
- High-grade non-Hodgkin lymphoma
- Carcinoma (invasive) of the cervix
- Carcinoma of the conjunctiva
- Carcinoma of the anus
- T-cell lymphoma
- Hodgkin's disease
- Lympho proliferative disease, pre-lymphomatous

Risk for Immunodeficiency Disorders

People who have a family history of primary disorders have a higher-than-normal risk for developing primary disorders.

Impaired immune system can lead to a secondary immunodeficiency disorder. For example, exposure to bodily fluids infected with HIV can cause AIDS.

Proteins are important for your immunity. An insufficient amount of protein in the diet can reduce the strength of your immune system. Our body also produces proteins when you sleep that help your immune system fight infection. For this reason, lack of sleep reduces your immune defenses.

Cancers and chemotherapy drugs can also reduce your immunity.

Signs of an Immunodeficiency Disorder

Each disorder has unique symptoms. One symptom of a weakened immune system is frequent or chronic illnesses, including pinkeye, sinus infections, colds, or diarrhea. If these problems don't respond to treatment or you don't completely get better over time, your doctor might test you for an immunodeficiency disorder. Recurrent pneumonia and yeast infections could also suggest you have a disorder.

Diagnosis

- ask about patients medical history
- perform a physical exam
- determine patients T cell count
- determine patients white blood cell count

Vaccines can test our immune system response in what is called an antibody test. Doctor will give you a vaccine and then test your blood for its response to the vaccine a few days or weeks later. If you don't have an immunodeficiency disorder, your immune system will produce antibodies to fight the organisms in the vaccine. You might have a disorder if your blood test doesn't show antibodies.

Treatment

The treatment for each immunodeficiency disorder will be tailored to its specific conditions. For example, AIDS causes several different infections. Your doctor will prescribe medications that are appropriate for each infection.

Treatment for immunodeficiency disorders commonly includes antibiotics and antibody replacement. A drug called interferon is a common treatment for the viral infections caused by a disorder.

If your bone marrow isn't producing enough lymphocytes, your doctor might order a bone marrow transplant.

Prevention

Primary disorders can be controlled and treated, but they cannot be prevented.

Secondary disorders can be prevented in a number of ways. For example, it's possible to prevent yourself from getting AIDS by not having unprotected sex with someone who carries HIV.

Sleep is very important for a healthy immune system. According to the Mayo Clinic, adults need about eight hours of sleep per night. It's important that you stay away from people who are sick if your immune system isn't working properly.

If you have a contagious immunodeficiency disorder like AIDS, you can keep others healthy by practicing safe sex and not sharing bodily fluids with people who don't have the condition.