IMMUNOPATHOLOGY

IMMUNITY- Immune response

Immunty is our protection from foreign macromolecules or invading organisms and our response to them, these include viruses, bacteria, protzoa, or even larger parasites and tumor antigens. The immune response is vital for life since when they are defective as in the immune-deficiency states this can lead to life threatning diseases.

The mechanisms of protection against infection and disease are diverse. Primarily they can be divided into two major categories:
1- Innate immune response.
2- Adaptive immune response (acquired immunity)

1. Non Specific ***Natural or innate immunity:***
a) mechanical (skin) b) physical (↑temperature) c) chemical (lysozyme-tears-saliva) d) cellular (micro & macrophages) e) **natural killer lymphocytes** (non specific cytotoxic cells) & **opsonins** (antibodies which help phagocytic process by causing roughening of the surface).
2. Acquired(***Specific immunity) :***Is the second line of defense.
-Includes humoral and cell mediated responses.
-The response is more rapid on re-exposure to the pathogen due to activation of memory cells and improves upon repeated exposure.
It passes in 2 stages:

A) **Primary** (first exposure to antigen) → No Disease / Disease (clinical /subclinical)
1-In acute infections: Recovery from infection & memory to specific antigen from stimulation of the immune system by the new antigen.
2-Chronic infections: On going process (immune response starts 10-14 days after infection) Antigen destruction occurs & memory to specific antigen e.g. caseation later in 1ry TB. The chronic inflammatory cells are joined10 days later by the immune cells

B) **Secondary** (re- exposure to antigen). The specific memory produced in 1ry reaction will produce a very rapid response on re exposure to the same antigen (humoral) (minutes-hours) or (cell mediated) (24-48 hrs). This results in rapid elimination of the offending agent & no disease occurs

Non specific immunity	**Specific immunity**
Response is antigen independent	Response is antigen dependant
There is immediate maximal response	There is lag time between exposure and maximal response
No antigen specific	antigen specific
Exposure results in no immunologic memory	Exposure results in no immunologic memory

SOURCES OF IMMUNE CELLS:

- Bone marrow stem cells are differentiatted into : T lymphocytes, B lymphocytes and non T & non B lymphocytes (NK cells).
- These cells go and populate lymphoid organs: lymph nodes and spleen Follicles in cortex contain B cells & Paracortex contains T cells.

B cells and T cells recognize different substances as antigens and in a different forms.

- The B cell uses cell surface-bound immunoglobulin as a receptor and the specificity of that receptor is the same as the immunoglobulin that it is able to secrete after activation. B cells recognize the antigens in soluble form.
- In contrast, the overwhelming majority of antigens for T cells are proteins(not in soluble form), and these must be fragmented and recognized in association with MHC products expressed on the surface of nucleated cells by antigen presenting cells

IMMUNOPATHOLOGY

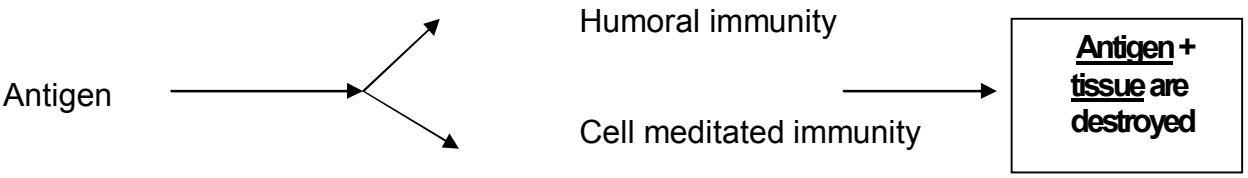
DEFINITION: It is the study of abnormal immune responses

Abnormal Immune Response

EXAGGERATED	DEFICIENT	LOSS OF TOLERANCE
Hypersensitivity	***Immunodeficiency***	***Autoimmunity***
Types I-V	↓ B or ↓T lymphocytes ↓ macrophages ↓ complement ↓ phagocytosis (↓number or function)	Hypersensitivity Types II-V
Harmful:**tissue destruction**	↓ **or no** immune **reaction**	Immune reaction to **self**

I) HYPERSENSITIVITY

It is a **harmful** exaggerated immune response on re-exposure to antigen (i.e. 2nd exposure). This **harmful reaction** of the immune system in response to entry or presence of a foreign or altered protein (antigen) is in the form of a humoral (antibody), cell mediated (lymphoid cells, T cell) response or both combined in an attempt to **destroy the antigen, BUT HOST TISSUE is also destroyed.**



TYPES OF ANTIGENS
Foreign antigen → **Hypersensitivity** & Graft rejection

Self antigen → **Autoimmune** disease e.g. connective tissue disease

TYPES OF HYPERSENSITIVITY
1) HUMORAL MECHANISMS
Type I: Allergy – Anaphylaxis(systemic) & Atopy(local) (Immediate hypersensitivity)
Type II : Antibody mediated cytotoxicity.
Type III: Immune complex

2)DELAYED HYPERSENSTIVITY (Cell mediated reaction)
Type IV: e.g. T cell granulomas

TYPE I HYPERSENSITIVITY

Type I reactions involve immunoglobulin E (IgE)–mediated release of histamine and other mediators from mast cells and basophils.

Mechanism
1st exposure Antigen :causes tissue B lymphocytes & plasma cells to produce IgE which attaches on surface of Mast cells/basophils (sensitized cell)
2nd exposure Antigen causes antigen to attach to Fab fragment of antibody and produce degranulation of mast cell or basophil with release of vasoactive amines or chemical mediators (chemotactic to eosinophils & neutrophils). It is an acute inflammation rich in eosinophils.

Gross: Picture of acute inflammation

Microscopic:
Many eosinophils + macrophages + some PNL+ lymphocytes & plasma cells + vasodilatation + marked edema

Examples

ANAPHYLAXIS	**ATOPY**	
Systemic reaction	Local reaction	
In blood stream(injection) Antitoxic sera Drugs-penicillin Bee stings	**Hay fever** grass –pollen	**Bronchial asthma** mite dust animal fur
Wide spread reaction Basophils are in circulation	**localized** at site of IgE production It has a genetic predisposition. Mast cells are involved	
Edema larynx→death Bronchospasm secretions Skin rash(urticaria) Hypotension **Shock**	local sensitization -conjunctiva -nasal passages -upper resp tract	bronchospasm ↑ mucus ↓ difficult breathing +wheezing
Vomiting & diarrhea	**Acute catarrhal Inflammation**	

TYPE II HYPERSENSITIVITY antibody dependant cellmediated cytotoxicty(ADCC)

Type II reactions (ie, cytotoxic hypersensitivity reactions) involve immunoglobulin G or immunoglobulin M antibodies bound to cell surface antigens, with subsequent complement fixation.

- The antigens are normally endogenous, although exogenous chemicals can attach to cell membranes .
- Cytolysis (cell lysis) is primarily mediated by antibodies of the IgM or IgG classes and complement . Phagocytes and K cells may also play a role (ADCC).

Examples:

- Hemolytic anemia
- Incompatible blood transfusion reactions
- Rh incompatibility(erythroblastosis fetalis)

Microscopic picture: plasma cells & B lymphocytes + macrophages + vasodilatation + edema

TYPE III HYPERSENSITIVITY-IMMUNE COMPLEX DISORDERS (Arthus type)

Type III reactions involve circulating antigen-antibody immune complexes that deposit in postcapillary venules, with subsequent complement fixation.

Mechanism

Antigen + Antibody (IgG/IgM) (**Immune complex**), circulate in blood then get trapped in blood vessel basement membrane & activate the complement (anaphylatoxin & PNL chemotaxis) resulting in **VASCULITIS**. This produces damage to endothelium with platelet aggregation & **THROMBOSIS.** Ischemia occurs ending in **NECROSIS** of surrounding tissue

Examples:

- Post streptococcal **glomerulonephritis**-**Rheumatic** fever

- Acute serum sickness

1 dose of serum injected produces slow release of antigenic proteins (long exposure) produces urticaria-fever-glomerulonephritis-joint pains-lymph node enlargement

- Arthus reaction

Repeated injections e.g. insulin causes vasculitis-necrosis-edema & hemorrhage

- Parasitic infestation

Microscopic picture: Vasculitis(Fibrinoid Necrosis of blood vessel wall + Acute inflammation of wall with PNLs & macrophages) & Necrosis with acute inflammation of tissue (PNLs- macrophages- vasodilatation -edema)

TYPE IV HYPERSENSITIVITY-CELL MEDIATED hypersensitivity

Type IV reactions (ie, delayed hypersensitivity reactions, cell-mediated immunity) are mediated by T cells rather than by antibodies. Delayed hypersensitivity reactions are inflammatory reactions initiated by mononuclear leukocytes. The term delayed is used to differentiate a secondary cellular response, which appears 48-72 hours after antigen exposure, from an immediate hypersensitivity response, which generally appears within 12 minutes of an antigen challenge. These reactions are mediated by T cells and monocytes/macrophages rather than by antibodies.

Mechanism

Dendritic cells at site of entry in draining LN, process antigen & present it to T lymphocytes. These become **activated T lymphoblasts** and **divide** producing **memory** cells & **sensitized** T cells. Sensitized T lymphocytes **migrate** to the affected area where they **recruit** other cells (lymphocytes, macrophages, fibroblasts), **sensitize local lymphocytes** & produce **more lymphokines** as well as cause **antigen destruction**.

Sensitized T lymphocyte subtypes & their functions:

cytotoxic cells **CD8+** cause direct cytotoxicity with lysis of cell surface antigens
T helper cells **CD4+:** these cells produce lymphokine. Lymphotoxin is one of the lymphokines which destroys antigen, but mostly lymphokines are geared to recruit other **lymphocytes, macrophages & fibroblasts to the area**
Examples:

- Granulomas e.g. TB & sarcoidosis
- Viral infection with intracellular organism
- Contact dermatitis
- Insect bite
- Parasitic infestation

Viral infection : Virus enters cell as an obligate nuclear parasite, replicates & change the DNA sequence of the cell producing a foreign protein. This induces a T cell reaction with killing of virus & the cell containing the virus
3 steps are involved:

1-Antigen processing by dendritic macrophages in draining LN with production of Memory cells & sensitized T helper & Cytotoxic T cells
2- Sensitized T helper cells cause accumulation & stimulation of T lymphocytes as well as macrophages at site of viral infection
3- Sensitized T cytotoxic cells & macrophages at the site, destroys the virus & the cell harboring it

Bacterial – Granuloma
A) TB: Bacteria living inside macrophage (e.g. TB bacilli) produce antigens, which is processed in the dendritic macrophages of regional LN. These present the processed antigen to the T lymphocytes to transform them into T lymphoblasts. These cells divide & produce **memory** T & **sensitized T cells**. On arrival of the sensitized T cells at site of antigen, they produce lymphokines (MAF, MF& others) which lead to further accumulation & activation of macrophages, lymphocytes, and fibroblasts as well as synthesis of collagen. The TB or any type of granuloma is thus formed with central destruction due to cytotoxic lymphokines released from Cd4+ cells or the direct cytotoxicity of CD8 + T lymphocyte subsets

B)SARCOIDOSIS
Sarcoidosis is an immune system disorder of unknown cause. It is characterized by multisystemic affection that involves lung in 90% of cases. Usually occurs in 20-40 year old males and females , but it is more common in females.

Patholgical lesions:
Sarcodosis is characterised by **non-caseating granulomas** . Virtually any organ can be affected; however, granulomas most often appear in the lungs or the lymph nodes**.**

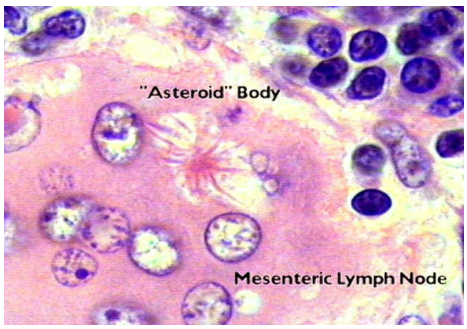
Sarcoidosis of the lung: It is primarily an interstitial lung disease in which the inflammatory process involves the alveoli, small bronchi, and small blood vessels. These individuals typically have dyspnea, particularly with exercise and dry cough. Hemoptysis is rare, as is production of sputum.

Lymphadenopathy: It is very common in sarcoidosis. Intrathoracic nodes are enlarged in 75 to 90% of all patients; usually this involves the hilar nodes bilaterally, and the paratracheal nodes are commonly involved. Peripheral lymphadenopathy is very common, particularly the cervical, axillary, epitrochlear, and inguinal nodes.

Other organs may also involved by sarcoidosis like skin, liver, eye and bone.

Microsopic:

The granuloma consists of a central collection of modified mononuclear phagocytes (epithelioid cells). There are often multinucleated giant cells in the central part of the granuloma with cytoplasmic inclusion bodies as: laminated calcific Schaumann bodies and stellate asteroid bodies. The central epithelioid and giant cells are surrounded by a rim of lymphocytes, mostly T-helper cells. Early in the formation of a granuloma there may be no surrounding lymphocytes. This is called a naked granuloma..



http://granuloma.homestead.com/A/000p035v.jpg

http://www.lmp.ualberta.ca/resources/pathoimages/Images-

Fate of the granuloma:

Granulomas can resolve spontaneously or following steroid therapy. Resolution can be complete. This can leave an insignificant fibrous scar, or when there is chronic active disease, can cause more extensive tissue damage and fibrosis which results in permanent organ dysfunction. In these cases fibroblasts proliferate and produce collagen. Granulomas become enclosed by fibrous rims and are later replaced by collagenous fibrous tissue.

The disease prognosis:

- In many people with sarcoidosis, the disease appears briefly and then disappears without the person even knowing they have the disease.
- Twenty percent to 30 percent of people have some permanent lung damage due to fibrosis.

- Sarcoidosis can be fatal in up to 5 percent of patients.

GENERAL REACTION IN T CELL responses
A) **Granulomatous**: **Lymphocytes + epithelioid macrophages + giant cells + FT & endarteritis obliterans** OR
B**) Diffuse reaction** e.g. in graft rejection & contact dermatitis
Perivascular lymphocytes & edema
C) **Patchy** e.g. in insect bites

GRAFT REJECTION (pathology of transplantation)

Tissue cells carry specific surface antigens, called Major Histocompatibility Antigens (***MHC***). These can evoke **Type IV** reactions also the RBC content with its ABO system can evoke in addition a **Humoral type II** reaction & **type III** reactions to any complexes in blood
Microscopic:**T Cytotoxic(CD8+), T helper (CD4+ which attack graft cells) + B cells (antibodies) + macrophages**
This rejection can be suppressed by –cyclosporins (drugs), Irradiation orsurgical removal of thymus (source of T cells)

NB: **GRAFT VERSUS HOST reaction (GVH):** It is a reaction which occurs in immunosuppressed patients where graft lymphocytes evoke an immune response to patient (host) tissue i.e. lymphocytes attacks the host & produces disease

AUTOIMMUNE DISORDERS

DEFINITION: Immune system of the host reacts against its own cells i.e. against self-antigens

TOLERANCE
Natural tolerance (self tolerance)
It is a process by which the body's immune system prevents itself from reacting to the body's own antigens
Acquired tolerance: Occurs after neonatal period & throughout adult life when very small doses of foreign antigen are introduced over a long period. This may induce tolerance in an adult & is the basis of desensitization treatments in allergy

Mechanism of tolerance (not yet well understood) possible hypotheses:
1-Burnet's Forbidden clone theory (clonal selection):
a) clonal deletion:In fetal life all lymphoid cells, which could respond immunologically to self-antigens, are eliminated. Self-reactive T lymphocytes are eliminated in the thymus by apoptosis
b) clonal anergy:Is the process of inactivation of some of the self-reactive T lymphocytes which have escaped death by apoptosis in the thymus

2- Peripheral T suppressor cell activity: In adults, acquired tolerance is associated with specific antibodies, which inhibit both helper T cells & B cells TOLERANCE thus protects our bodies from developing autoimmune disorders

PATHOGENESIS OF AUTOIMUNE DISORDERS:

1)Genetic or familial defect
2) Instability of tolerance mechanism
3) Cross reactivity:
   a) Foreign antigen may be similar to a body antigen
   b) Antibody produced against a foreign antigen may also react with certain body antigens
4) Uncovering of sequestrated (hidden) antigens Chronic tissue destruction results in:
   a)release of hidden proteins(thyroglobulin or semen or even intracytoplasmic proteins) thereby presenting the immune system with a new antigen
   b)Alteration of surface antigen **Altered antigen**

5) Absence of T suppressor cell activity examples:

- Autoimmune hemolytic anemia **Type II**
- Connective tissue diseases: Autoimmune diseases characterized by injury to collagen especially in blood vessels and tissues around them Systemic lupus erythematosus (**SLE**) –**Rheumatic fever**-Rheumatoid arthritis- **Polyarteritis nodosa**-scleroderma-polymyositis/dermatomyositis mostly **Type III**

  Microscopic: Fragmentation of collagen producing a fibrin-like, pink mass of Fibrinoid necrosis with Inflammation followed by fibrosis
- **Graves disease Type V** IgG, long acting thyroid stimulator (LATS) attaches to TSH surface receptor on thyroid follicle cell & it takes the place of TSH, stimulating the receptor & escaping the control feed back mechanism. This results in the clinical condition thyrotoxicosis
- Others(**ulcerative colitis-1ry biliary cirrhosis**-some types of male infertility-**Hashimoto thyroiditis Type IV**

NB see special for disease details

IMMUNODEFICIENCY STATES

Failure in either the specific immune response(Humoral/cell mediated) or the non-specific system (phagocytes-complement) may result in alteration of the immune response, which may be quantitative or qualitative

- Primary genetic
- Secondary to disease

1.Humoral system (Lack of B cells – inability to secrete Ig – activation of suppressors)
2.Cell mediated (Di George's syndrome-AIDS)
3.Phagocytic cell deficiencies(Chronic granulomatous disease-Lazy leukocyte syndrome)

4. Complement deficiencies
a) Primary or inherited deficiencies of B or T cells resulting in recurrent respiratory or alimentary tract infections
b) Secondary deficiencies e.g.

- Infections: Acute viral-chronic bacterial-chronic protozoal(malaria)
- AIDS or acquired immune deficiency syndrome(HIV virus)
- Malnutrition particularly protein deficiency
- Drug induced e.g. corticosteroids & Cytotoxic drugs which cause immunosuppression
- Malignant disease e.g. advanced cancer of lymph nodes (lymphoma/Hodgkin disease)

All the above cause impaired immunity which results in intercurrent infection particularly :

OPORTUNISTIC INFECTIONS:
DEF: These are diseases caused by non pathogenic or low virulence organisms with an impaired immune system and which usually cause death
Causes:

- Congenital immunodeficiencies
- Acquired

a) Result of disease e.g. **HIV** (human Immunodeficiency virus) (see viral infection) causes the acquired Immunodeficiency disorder AIDS or malignancy (lymphoma)
b) 2ry to treatment in patients on immunosuppressives as cyclosporins or antibiotics which may change intestinal flora

Types & manifestations:
1-Bacteria: Low virulence Strept epidermidis or viridans is responsible for bacterial endocarditis & low-grade septicemia
2-Protozoa: Pneumocystis carinii→pneumonia with a foamy (frothy pink) alveolar exudate
Toxoplasmosis produces pneumonia or CNS damage
3-Viruses: cause a generalized infection, severe organ damage e.g.: Herpes encephalitis & cytomegaloviral infection
4-Fungi: Monilia (candidiasis) of GIT-systemic fungemia-endocarditis
Aspergillosis: granulomas in lung – systemic fungemia

IMMUNOLOGY & CANCER
Cancers stimulate immunological reactions since tumor cells have altered genes, which produce altered proteins. On the cell surface, these proteins are considered foreign by the body (tumor associated antigens TAA).

The involvement of the immune mechanism has been recognized since some cancers
1-Tend to regress in some patients
2-Secondaries are relatively rare in spleen, probably due to the spleen's ability to destroy abnormal cells in the circulation
3-In some tumors the presence of lymphocytic response around the tumor is associated with a favorable prognosis

4-BCG is given in some treatment protocols to increase cell mediated immunity in general i.e. non-specific boost of immune system

APPLIED IMMUNOLOGY

A-**DIAGNOSIS:**
1-SEROLOGIC ANTIBODY DETECTION METHODS: by detection of circulating specific antibodies using specific antigens as in: agglutination & complement fixation methods used for detection of infections & autoimmune diseases
2-IMMUNOHISTOCHEMISTRY & TUMOR MARKERS (tissue & serum)
Rabbit/mouse is injected with specific antigen e.g. TAA. The animal is left to live long enough to form antibodies against the antigen, then it is bled & the blood containing the specific antibodies is tagged (i.e. labeled) with several dyes as: fluorescine (a fluorescent dye) or with peroxidase (dye with a brown color in tissue) or alkaline phosphatase (red color). Only cells containing the specific tumor antigen will react with the labeled antibody and staining only of the specific tumor cells will occur

B-**PROPHYLAXIS & TREATMENT** of infectious disease(VACCINES)
A) Passive : Injection sera containing Immunoglobulins specific or non-specific to bacteria or their products e.g. toxins. An important complication is serum sickness or anaphylaxis & shock
B) Active(modified antigen vaccine)
Killed vaccine-----typhoid
Toxoid-----tetanus
Attenuated or weakened vaccine e.g. viral vaccines of polio & measles
Organ transplantation-blood transfusion: Proper matching is mandatory to avoid incompatibility reactions
Desensitization: Introduction of small gradually increasing doses of a specific antigen, which is responsible for a certain allergy, may result in tolerance to this antigen. This is a good method of treatment of atopic disorders (Type I hypersensitivity)