17BCU403 IMMUNOLOGY 4H-4C

SCOPE

To facilitate the students with basics of immunology like immune organs and cells and derangement of immune system along with immunotechniques.

OBJECTIVES

To understand the humoral and cell mediated immunity and the mechanism of hypersensitive, transplantation , vaccination with immuno techniques.

Unit 1

Cells and organs of the immune system and immunity

Hematopoiesis, cells of the immune system, primary and secondary lymphoid organs and tissues (MALT). Anatomical barriers, cell types of innate immunity, soluble molecules and membrane associated receptors (PRR), connections between innate and adaptive immunity, cell adhesion molecules, chemokines, leukocyte extravasation, localized and systemic response.

Unit 2

Antigens, Antibodies and receptor diversity

Antigens and haptens, factors that dictate immunogenicity, B and T cell epitopes. Structure and distribution of classes and subclasses of immunoglobulins (Ig), Ig fold, effector functions of antibody, antigenic determinants on Ig and Ig super family**.** Dreyer-Bennett hypothesis, multigene organization of Ig locus, mechanism of V region DNA rearrangement, ways of antibody diversification.

Unit 3

Biology of the B and T lymphocyte and complement system

Antigen independent phase of B cell maturation and selection, humoral response – T-dependent and T-independent response, anatomical distribution of B cell populations. Structure and role of T cell receptor, and co-receptor, T cell development, generation of receptor diversity, selection and differentiation. Complement activation by classical, alternate and MB lectin pathway, biological

consequences of complement activation, regulation and complement deficiencies.

Unit 4

Cell mediated cytotoxic responses and hypersensitivity

General properties of effector T cells, cytotoxic T cells (Tc), natural killer cells; NKT cells and antibody dependent cellular cytotoxicity (ADCC). Organ specific and systemic autoimmune diseases, possible mechanisms of induction of autoimmunity, Gell and Coombs classification, IgE mediated (Type I) hypersensitivity antibody mediated cytotoxic (Type II) hypersensitivity, immune complex mediated (type III) hypersensitivity and cell mediated (Type IV) hypersensitivity.

Unit 5

Antigen presentation, MHC complex and transplantation

General organization and inheritance of MHC, structure, distribution and role of MHC class I and class II proteins, linkage disequilibrium, pathways of antigen processing and presentation. Immunological basis of graft rejection, clinical manifestations, immunosuppressive therapy and privileged sites. Vaccines - active and passive immunization, types of vaccines.

REFERENCES:

Kuby., (2007). Immunology ; 6th ed., Kindt, T.L., Goldsby, R.A. and Osborne, B.A., W.H Freeman and Company (New York), ISBN:13: 978-0-7167-8590-3 / ISBN: 10:0-7617-8590-0.

Coico, R., and Sunshine, G., (2009). Immunology: A Short Course 6th ed., John Wiley& sons, Inc (New Jersey), ISBN: 978-0-470-08158-7.

Murphy, K., Mowat, A., and Weaver, C.T., (2012). Janeway's Immunobiology 8th ed., Garland Science (London & New York), ISBN: 978-0-8153-4243-4.

KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed to be University Established Under Section 3 of UGC Act 1956)

Coimbatore – 641 021.

LECTURE PLAN
DEPARTMENT OF BIOCHEMISTRY

STAFF NAME: Ms.P.LOGANAYAKI
SUBJECT NAME: IMMUNOLOGY

SUB.CODE: 17BCU403

SEMESTER: IV **CLASS: II B.Sc (BC)**

Duration of period	Topics covered	Books referred	Page No
	UNIT- I		
1.	Hematopoiesis	T1	25
2.	cells of the immune system	T1	32-33, 36-43
3.	primary and secondary lymphoid organs and tissues (MALT)	T1, T2	43-47 21
4.	Anatomical barriers, cell types of innate immunity	T2	38-48
5.	soluble molecules and membrane associated receptors (PRR)	T1	4
6.	connections between innate and adaptive immunity	T1	16-17
7.	cell adhesion molecules, chemokines, leukocyte extravasation	T1	8, 277, 358
8.	localized and systemic response	T1	8
	Total No of Hours Planned For Unit II= 8		
	UNIT- II		
1.	Antigens and haptens	T1	92-98
2.	factors that dictate immunogenicity	T1	87-90
3.	B and T cell epitopes	T1	92-98
4.	Structure and distribution of classes and subclasses of immunoglobulins (Ig)	T1 T3	107-122 115
5.	Ig fold, effector functions of antibody, antigenic determinants on Ig and Ig super family**.**	T1	92-98
6.	Dreyer-Bennett hypothesis	T1	130-134

7.	Multigene organization of Ig locus, mechanism of V region DNA rearrangement	T1	134
8.	Ways of antibody diversification.	T1	127
	Total No of Hours Planned For Unit II= 8		
	UNIT- III		
1	Antigen independent phase of B cell maturation and selection	T1	250
2	Humoral response – T-dependent and T-independent response	T1	264- 268
3	Anatomical distribution of B cell populations	J1	-
4	Structure and role of T cell receptor, and co-receptor.	T1	212
5	T cell development, generation of receptor diversity, selection and differentiation.	T1	221- 225
6	Complement activation by classical, alternate Pathway	R1	235-239
7	MB lectin pathway	R1	244-246
8	Biological consequences of complement activation, regulation and complement deficiencies.	R1	246-247
	Total No of Hours Planned For Unit II= 8		
	UNIT- IV		
1	General properties of effector T cells, cytotoxic T cells (Tc)	T1	61-64
2	Natural killer cells; NKT cells	T1	61-64
3	Antibody dependent cellular cytotoxicity (ADCC)	T3	203-208
4	Organ specific and systemic autoimmune diseases	T1	489-490
5	possible mechanisms of induction of autoimmunity	T1	556-562
6	Gell and Coombs classification	T1 T2	362- 363 601
7	IgE mediated (Type I) hypersensitivity antibody mediated cytotoxic (Type II) hypersensitivity,	T1	413-430 430-436
8	Immune complex mediated (type III) hypersensitivity and cell mediated (Type IV) hypersensitivity.	T1	436-437

Total No of Hours Planned For Unit II= 8			
	UNIT- V		
1	General organization and inheritance of MHC, structure and distribution.	T1	161
2	Role of MHC class I and class II proteins, linkage disequilibrium	T1	166- 170
3	pathways of antigen processing and presentation	R1	4.14-4.19
4	Immunological basis of graft rejection, clinical manifestations	T1	556-562
5	Immunosuppressive therapy and privileged sites.	T2	685
6	Vaccines - active and passive immunization	T1	445-446
7	Types of vaccines.	T1	445-446
Total No of Hours Planned For Unit II= 7			
1	Previous year End Semester Exam- QP discussion : 1 Hour		
Total no of hours required to complete the course: 40			

REFERENCE:

T1- Kuby., (2007). Immunology ; 6th ed., Kindt, T.L., Goldsby, R.A. and Osborne, B.A., W.H Freeman and Company (New York), ISBN:13: 978-0-7167-8590-3 / ISBN: 10:0-7617-8590-0.

T2-Murphy, K., Mowat, A., and Weaver, C.T., (2012). Janeway's Immunobiology 8th ed., Garland Science (London & New York), ISBN: 978-0-8153-4243-4.

T3: Chatterjea MN, Shinde R (2012) . Text book of Medical Biochemistry.Eight editio Jayper Brothers publishers(p) Ltd.

R1: Ivan Roitt, Janathar Brotoft(2006) Immunology 7th edition,Mosby Publishers sydney.

JOURNAL REFERENCE

J1: Irving Goldschneider and D. D. McGregor, Anatomical distribution of T and B lymphocytes in the rat development of lymphocyte-specific antisera, 973 Nov 30; 138(6): 1443–1465.

UNIT-I
SYLLABUS

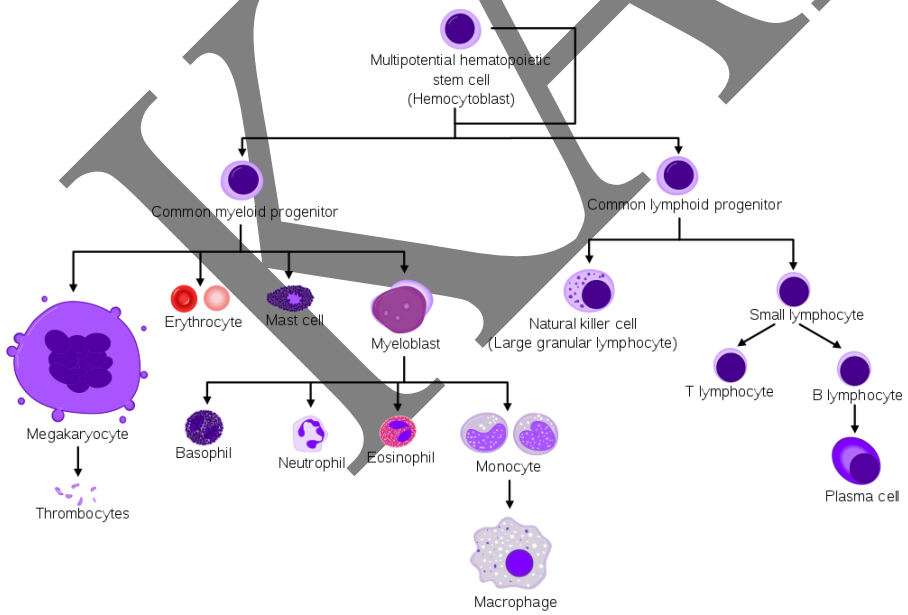
Unit 1

Cells and organs of the immune system and immunity

Hematopoiesis, cells of the immune system, primary and secondary lymphoid organs and tissues (MALT).Anatomical barriers, cell types of innate immunity, soluble molecules and membrane associated receptors(PRR), connections between innate and adaptive immunity, cell adhesion molecules, chemokines, leukocyteextravasation, localized and systemic response.

HEMATOPOIESIS

Haematopoietic stem cells (HSCs) reside in the medulla of the bone (bone marrow) and have the unique ability to give rise to all of the different mature blood cell types and tissues. HSCs are self-renewing cells: when they proliferate, at least some of their daughter cells remain as HSCs, so the pool of stem cells is not depleted.This phenomenon is called asymmetric division. The other daughters of HSCs (myeloid and lymphoid progenitor cells) can follow any of the other differentiation pathways that lead to the production of one or more specific types of blood cell, but cannot renew themselves. The pool of progenitors is heterogeneous and can be divided into two groups; long-term self-renewing HSC and only transiently self-renewing HSC, also called short-terms. This is one of the main vital processes in the body.



All blood cells are divided into three lineages

- Erythroid cells are the oxygen carrying red blood cells. Both reticulocytes and erythrocytes are functional and are released into the blood. In fact, a reticulocyte count estimates the rate of erythropoiesis.
- Lymphocytes are the cornerstone of the adaptive immune system. They are derived from common lymphoid progenitors. The lymphoid lineage is primarily composed of T-cells and B-cells (types of white blood cells). This is lymphopoiesis.
- Myelocytes, which include granulocytes, megakaryocytes and macrophages and are derived from common myeloid progenitors, are involved in such diverse roles as innate immunity, adaptive immunity, and blood clotting. This is myelopoiesis.
- Granulopoiesis (or granulocytopoiesis) is haematopoiesis of granulocytes.
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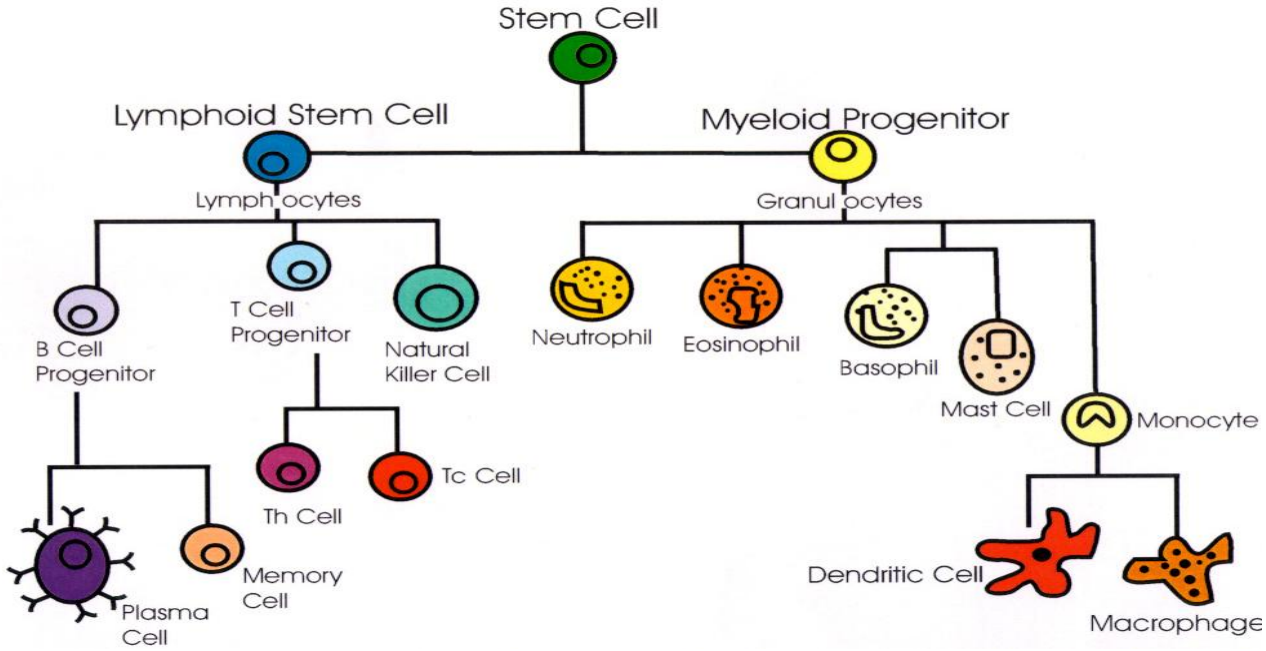
- Megakaryocytopoiesis is haematopoiesis of megakaryocytes.

CELLS OF IMMUNE SYSTEM



Antigen-presenting cells	Cells which do not have antigen-specific receptors. Instead, they capture and process antigens, present them to T cell receptors. These cells include macrophages, dentritic cells and B cells.
B cells	Also known as *B cell lymphocytes*. B cells spend their entire early life in the bone marrow. Upon maturity, their job is to travel throughout the blood and lymph looking for antigens with which they can interlock. Once a B cell has identified an antigen, it starts replicating itself. These cloned cells mature into antibody-manufacturing *plasma cells*.
Basophils	Similar to mast cells, but distributed throughout the body. Like mast cells, basophils release histamine upon encountering certain antigens, thereby triggering an allergic reaction.
Cytotoxic T cells	Also called *cytotoxic T lymphocytes* or CTLs.
Dendritic cells	Mostly found in the skin and mucosal epithelium, where they are referred to as Langerhan's cells. Unlike macrophages, dendritic cells can also recognize viral particles as non-self. In addition, they can present antigens via **both** MHC I and MHC II, and can thus activate both CD8 and CD4 T cells, directly.
Granulocytes	Leukocytes (white blood cells) containing granules in the cytoplasm. Also known as a granular leukocyte. They seem to act as a first line of defense, as they rush toward an infected area and engulf the offending microbes. Granulocytes kill microbes by digesting them with killer enzymes contained in small units called lysosomes.
Helper T cells	These cells travel through the blood and lymph, looking for antigens (such as those captured by *antigen-presenting cells*). Upon locating an antigen, they notify other cells to assist in combating the invader.

	This is sometimes done through the use of cytokines (or specifically, lymphokines) which help destroy target cells and stimulate the production of healthy new tissue. Interferon is an example of such a cytokine.
Leukocytes	White blood cells. These are the cells which provide immunity, and they can be subdivided into three classes: lymphocytes, granulocytes and monocytes
Lymphocytes	Small white blood cells which are responsible for much of the work of the immune system. Lymphocytes can be divided into three classes: B cells, T cells and null cells.
Macrophages	Literally, "large eaters." These are large, long-lived phagocytes which capture foreign cells, digest them, and present protein fragments (peptides) from these cells and manifest them on their exterior. In this manner, they present the antigens to the T cells. Macrophages are strategically located in lymphoid tissues, connective tissues and body cavities, where they are likely to encounter antigens. They also act as effector cells in cell-mediated immunity.
Mast cells	Cells concentrated within the respiratory and gastrointestinal tracts, and within the deep layers of the skin. These cells release histamine upon encountering certain antigens, thereby triggering an allergic reaction.
Memory cells	Specialized B cells which grant the body the ability to manufacture more of a particular antibody as needed, in case a particular antigen is ever encountered again.
Monocytes	Large, agranular leukocytes with relatively small, eccentric, oval or kidney-shaped nuclei.
Plasma cells	Specialized B cells which churn out antibodies—more than two thousand per second. Most of these die after four to five days; however, a few survive to become *memory cells*.

T cells	Also known as *T cell lymphocytes.* Unlike B cells, these cells leave the marrow at an early age and travel to the thymus, where they mature. Here they are imprinted with critical information for recognizing "self" and "non-self" substances. Among the subclasses of T cells are *helper T cells* and *cytotoxic (or killer) T cells*.

PRIMARY LYMPHOID ORGANS:

Immature lymphocytes generated in hematopoiesis mature and become committed to a particular antigenic specificity within the primary lymphoid organs. Only after a lympho cyte has matured within a primary lymphoid organ is the cell immunocompetent (capable of mounting an immune re-sponse). T cells arise in the thymus, and in many mammals—humans and mice for example—B cells origi-nate in bone marrow.

Also called central lymphoid organs, these are responsible for synthesis and maturation of immunocompetant cells. These include the bone marrow and the thymus.

(i) BONE MARROW:

In humans and mice, bone marrow is the site of B-cell origin and development. Arising from lymphoid progenitors, im-mature B cells proliferate and differentiate within the bone marrow, and stromal cells within the bone marrow interact directly with the B cells and secrete various cytokines that are required for development. Like thymic selection during T-cell maturation, a selection process within the bone marrow eliminates B cells with self-reactive antibody receptors.

Bone marrow is not the site of B-cell development in all species. In birds, a lymphoid organ called the bursa of Fabricius, In cattle and sheep, the primary lymphoid tis-sue hosting the maturation, proliferation, and diversification of B cells early in gestation is the fetal spleen. Later in gesta-tion, this

function is assumed by a patch of tissue embedded in the wall of the intestine called the ileal Peyer's patch The rabbit, too, uses gut-associated tissues such as the appendix as primary lym-phoid tissue

(ii) THYMUS:

The thymus is a gland located in the anterior mediastinum just above the heart, which reaches its greatest size just prior to birth, then atrophies with age.

The thymus is the site of T-cell development and maturation. It is a flat, bilobed organ situated above the heart. Each lobe is surrounded by a capsule and is divided into lobules, which are separated from each other by strands of connective tissue called trabeculae. Each lobule is organized into two compart-ments: the outer compartment, or *cortex,* is densely packed with immature T cells, called thymocytes, whereas the inner compartment, or *medulla,* is sparsely populated with thymo-cytes.

Both the cortex and medulla of the thymus are criss-crossed by a three-dimensional stromal-cell network com-posed of epithelial cells, dendritic cells, and macrophages, which make up the framework of the organ and contribute to the growth and maturation of thymocytes. Many of these stromal cells interact physically with the developing thymo-cytes (Figure). Some thymic epithelial cells in the outer cortex, called nurse cells, have long membrane extensions that surround as many as 50 thymocytes, forming large mul-ticellular complexes. Other cortical epithelial cells have long interconnecting cytoplasmic extensions that form a network and have been shown to interact with numerous thymocytes as they traverse the cortex.

The function of the thymus is to generate and select a repertoire of T cells that will protect the body from infection. As thymocytes develop, an enormous diversity of T-cell re-ceptors is generated by a random process that produces some T cells with receptors capable of recognizing antigen-MHC complexes. However, most of the T-cell recep-tors produced by this random process are incapable of recog-nizing antigen-MHC complexes and a small portion react with combinations of self antigen-MHC complexes. Using mechanisms that are discussed in Chapter 10, the thymus in-duces the death of those T cells that cannot recognize anti-gen-MHC complexes and those that react with self-antigen– MHC and pose a danger of causing autoimmune disease. More than 95% of all thymocytes die by apoptosis in the thy-mus without ever reaching maturity.

Children with no development of thymus suffer from DiGeorge syndrome that is characterized by deficiency in T cell development but normal numbers of B cells.

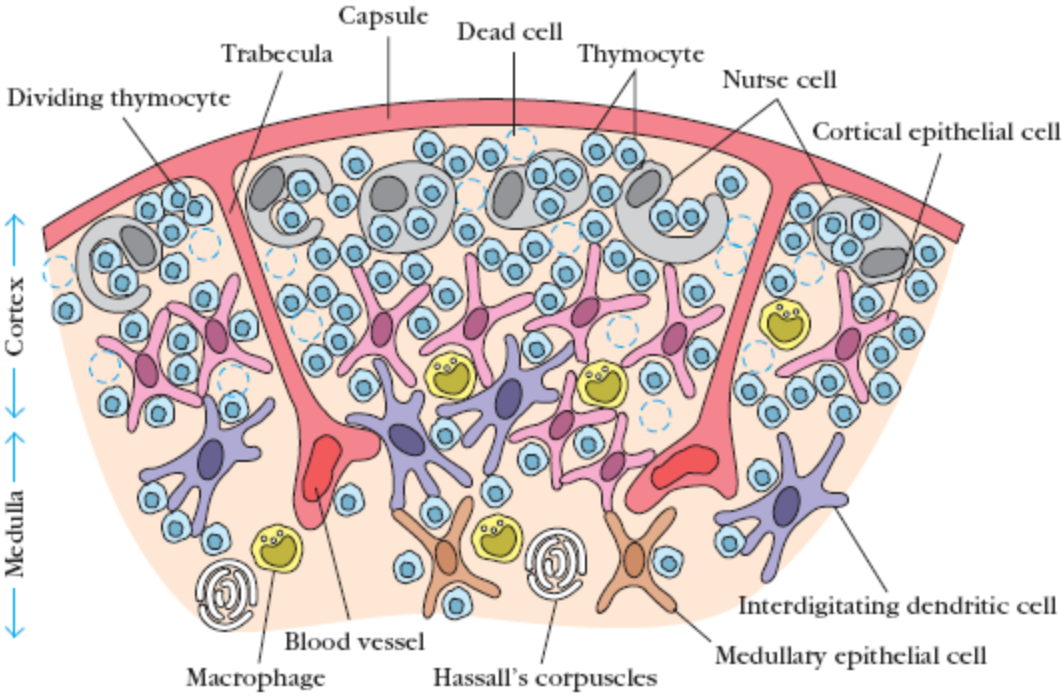


Fig: Diagrammatic cross section of a portion of the thymus, showing several lobules separated by connective tissue strands (trabeculae). The densely populated outer cortex is thought to con-tain many immature thymocytes (blue), which undergo rapid prolif-eration coupled with an enormous rate of cell death. Also present in the outer cortex are thymic nurse cells (gray), which are specialized epithelial cells with long membrane extensions that surround as many as 50 thymocytes. The medulla is sparsely populated and is thought to contain thymocytes that are more mature. During their stay within the thymus, thymocytes interact with various stromal cells, including cortical epithelial cells (light red), medullary epithelial cells (tan), interdigitating dendritic cells (purple), and macrophages (yellow). These cells produce thymic hormones and express high lev-els of class I and class II MHC molecules. Hassalls corpuscles, found in the medulla, contain concentric layers of degenerating ep-ithelial cells.

Lymphatic System

As blood circulates under pressure, its fluid component (plasma) seeps through the thin wall of the capillaries into the surrounding tissue. Much of this fluid, called interstitial fluid, returns to the blood through the capillary membranes. The remainder of the interstitial fluid, now called lymph, flows from the spaces in connective tissue into a network of tiny open lymphatic capillaries and then into a series of pro gressively larger collecting vessels called lymphatic vessels (Figure).

The largest lymphatic vessel, the thoracic duct, empties into the left subclavian vein near the heart. In this way, the lymphatic system captures fluid lost from the blood and returns it to the blood, thus ensuring steady-state levels of fluid within the circulatory system. The heart does not pump the lymph through the lymphatic system; instead the flow of lymph is achieved as the lymph vessels are squeezed by movements of the body's muscles. A series of one-way valves along the lymphatic vessels ensures that lymph flows only in one direction.

When a foreign antigen gains entrance to the tissues, it is picked up by the lymphatic system (which drains all the tissues of the body) and is carried to various organized lymphoid tissues such as lymph nodes, which trap the foreign antigen. As lymph passes from the tissues to lym-phatic vessels, it becomes progressively enriched in lympho-cytes. Thus, the lymphatic system also serves as a means of transporting lymphocytes and antigen from the connec-tive tissues to organized lymphoid tissues where the lympho-cytes may interact with the trapped antigen and undergo activation.

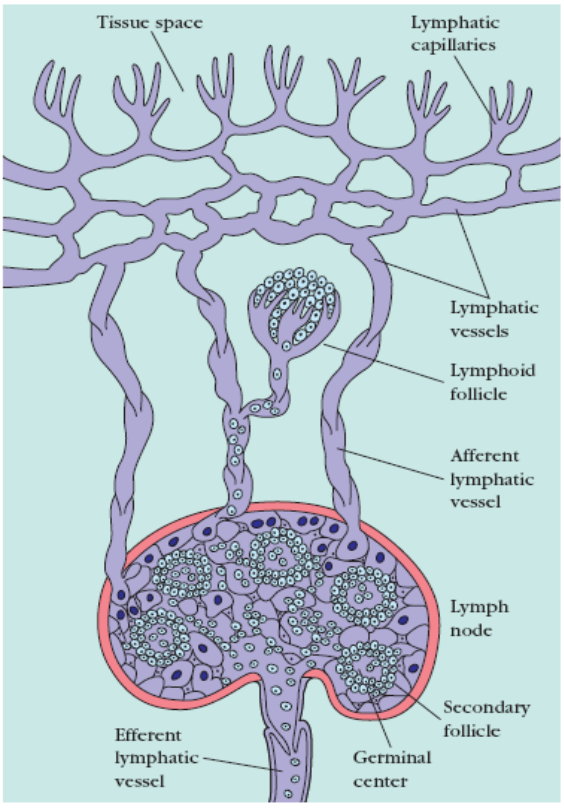


Fig: Lymphatic vessels. Small lymphatic capillaries open-ing into the tissue spaces pick up interstitial tissue fluid and carry it into progressively larger lymphatic vessels, which carry the fluid, now called lymph, into regional lymph nodes. As lymph leaves the nodes, it is carried through larger efferent lymphatic vessels, which eventu-ally drain into the circulatory system at the thoracic duct or right lymph duct

PERIPHERAL LYMPHOID ORGANS (SECONDARY):

While primary lymphoid organs are concerned with production and maturation of lymphoid cells, the secondary or peripheral lymphoid organs are sites where the lymphocytes localise, recognise foreign antigen and mount response against it. These include the lymph nodes, spleen, tonsils, adenoids, appendix, and clumps of lymphoid tissue in the small intestine known as Peyer's patches. They trap and concentrate foreign substances, and they are the main sites of production of antibodies. Some lymphoid organs are capsulated such as lymph node and spleen while others are non-capsulated, which include mostly mucosa-associated lymphoid tissue (MALT).

(i) LYMPH NODE:

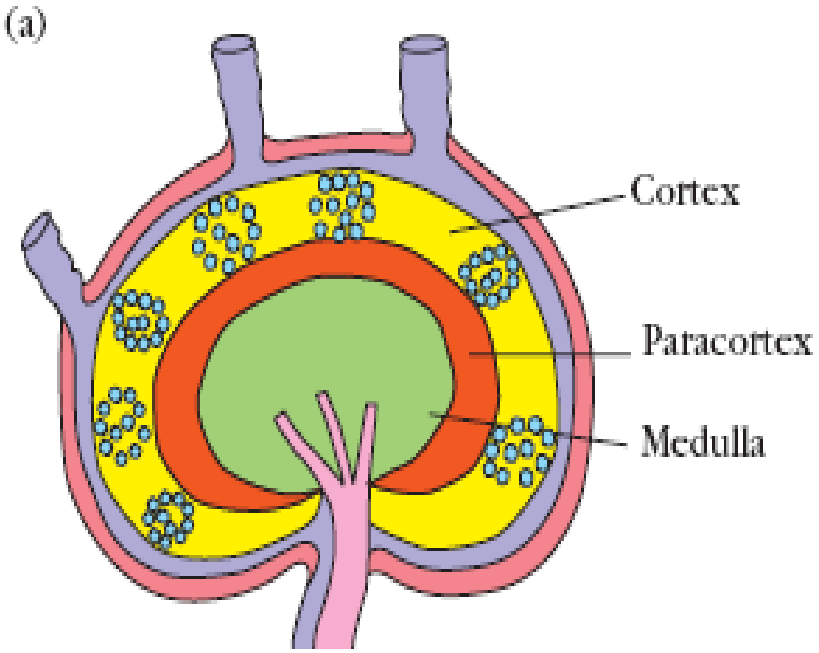
Clusters of lymph nodes are strategically placed in the neck, axillae, groin, mediastinum and abdominal cavity, where they filter antigens from the interstitial tissue fluid and the lymph during its passage from the periphery to the thoracic duct. The key lymph nodes are the axillary lymph nodes, the inguinal lymph nodes, the mesenteric lymph nodes and the cervical lymph nodes. Lymph nodes are encapsulated bean-shaped structures containing a reticular network packed with lymphocytes, macrophages, and dendritic cells. Clus-tered at junctions of the lymphatic vessels, lymph nodes are the first organized lymphoid structure to encounter antigens that enter the tissue spaces. As lymph percolates through a node, any particulate antigen that is brought in with the lymph will be trapped by the cellular network of phagocytic cells and dendritic cells (follicular and interdigitating). The overall architecture of a lymph node supports an ideal mi-croenvironment for lymphocytes to effectively encounter and respond to trapped antigens.

Morphologically, a lymph node can be divided into three roughly concentric regions: the cortex, the paracortex, and the medulla, each of which supports a distinct microenviron-ment (Figure 2-18). The outermost layer, the cortex, contains lymphocytes (mostly B cells), macro-phages, and follicular dendritic cells arranged in primary follicles. After antigenic challenge, the primary follicles enlarge into secondary folli-cles, each containing a germinal center. In children with B-cell deficiencies, the cortex lacks primary follicles and germinal centers. Beneath the cortex is the paracortex, which is popu-lated largely by T lymphocytes and also contains interdigitat-ing dendritic cells thought to have migrated from tissues to the node. These interdigitating dendritic cells express high levels of class II MHC molecules, which are necessary for pre-senting antigen to T_H cells. Lymph nodes taken from neona-tally thymectomized mice have unusually few cells in the paracortical region; the paracortex is therefore sometimes re-ferred to as a thymus-dependent area in contrast to the cor-tex, which is a thymus-independent area. The innermost layer of a lymph node, the medulla, is more sparsely popu-lated with lymphoid-lineage cells; of those present, many are plasma cells actively secreting antibody molecules.

As antigen is carried into a regional node by the lymph, it is trapped, processed, and presented together with class II MHC molecules by interdigitating dendritic cells in the para-cortex, resulting in

the activation of T_H cells. The initial acti-vation of B cells is also thought to take place within the T-cell-rich paracortex. Once activated, T_H and B cells form small foci consisting largely of proliferating B cells at the edges of the paracortex. Some B cells within the foci differen-tiate into plasma cells secreting IgM and IgG. These foci reach maximum size within 4–6 days of antigen challenge. Within 4–7 days of antigen challenge, a few B cells and T_H cells migrate to the primary follicles of the cortex. It is not known what causes this migration. Within a primary follicle, cellular interactions between follicular dendritic cells, B cells, and T_H cells take place, leading to development of a sec-ondary follicle with a central germinal center. Some of the plasma cells generated in the germinal center move to the medullary areas of the lymph node, and many migrate to bone marrow.

Afferent lymphatic vessels pierce the capsule of a lymph node at numerous sites and empty lymph into the subcapsu-lar sinus (Figure b). Lymph coming from the tissues percolates slowly inward through the cortex, paracortex, and medulla, allowing phagocytic cells and dendritic cells to trap any bacteria or particulate material (e.g., antigen-antibody complexes) carried by the lymph. After infection or the introduction of other antigens into the body, the lymph leav-ing a node through its single efferent lymphatic vessel is en-riched with antibodies newly secreted by medullary plasma cells and also has a fiftyfold higher concentration of lympho-cytes than the afferent lymph.



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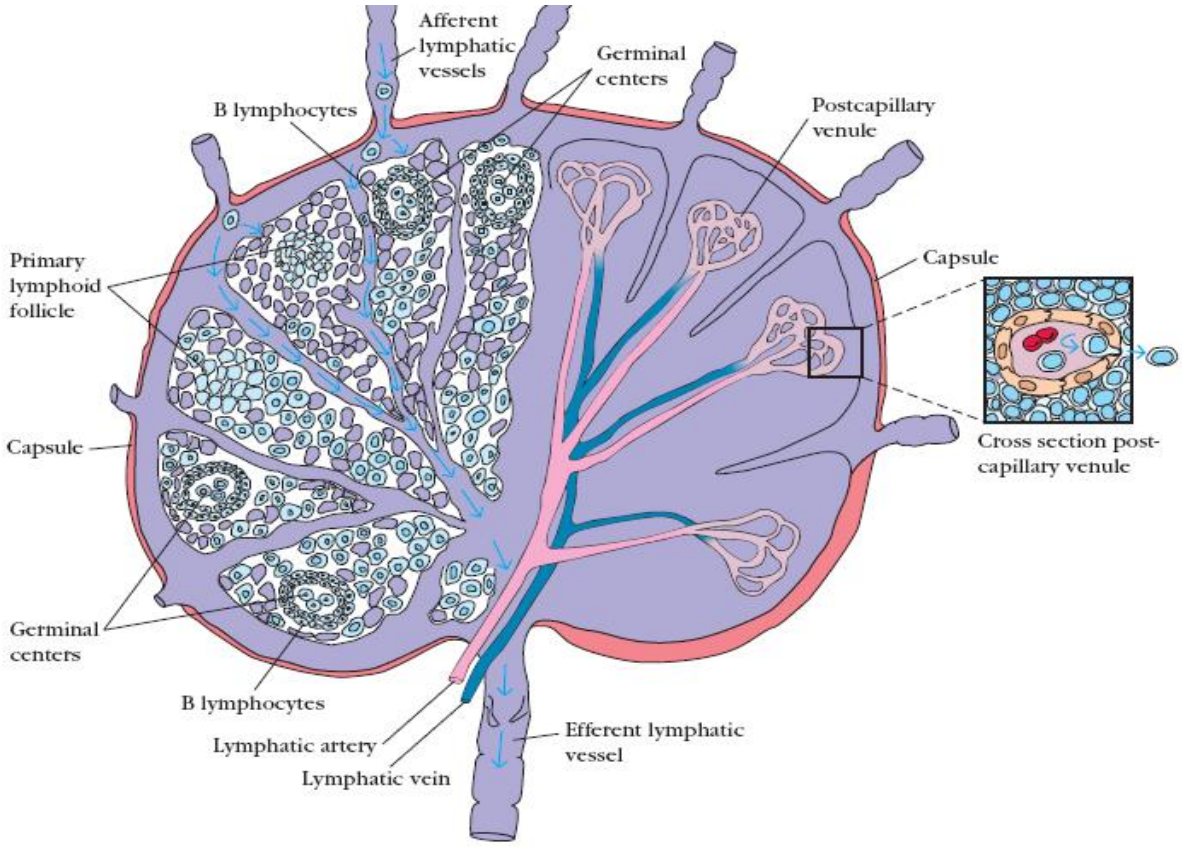

Fig: Structure of a lymph node. (a) The three layers of a lymph node support distinct microenvironments. **(b)** The left side depicts the arrangement of reticulum and lymphocytes within the various regions of a lymph node. Macrophages and dendritic cells, which trap antigen, are present in the cortex and paracortex. T_H cells are concentrated in the paracortex; B cells are located primarily in the cortex, within follicles and germinal centers. The medulla is populated largely by antibody-producing plasma cells. Lymphocytes circu-lating in the lymph are carried into the node by afferent lymphatic vessels; they either enter the reticular matrix of the node or pass through it and leave by the efferent lymphatic vessel. The right side of (b) depicts the lymphatic artery and vein and the postcapillary venules. Lymphocytes in the circulation can pass into the node from the postcapillary venules by a process called extravasation

SPLEEN

The spleen plays a major role in mounting immune re-sponses to antigens in the blood stream. It is a large, ovoid secondary lymphoid organ situated high in the left abdomi-nal cavity and weighing about

150 grams. It is the largest single lymphoid organ in the body.While lymph nodes are specialized for trapping antigen from local tissues, the spleen specializes in filtering blood and trapping blood-borne antigens; thus, it can re-spond to systemic infections. Unlike the lymph nodes, the spleen is not supplied by lymphatic vessels. Instead, blood-borne antigens and lymphocytes are carried into the spleen through the splenic artery. Experiments with radioactively labeled lymphocytes show that more recirculating lympho-cytes pass daily through the spleen than through all the lymph nodes combined.

The spleen is surrounded by a capsule that extends a num-ber of projections (trabeculae) into the interior to form a compartmentalized structure. The compartments are of two types, the red pulp and white pulp, which are separated by a diffuse marginal zone (Figure 2-19). The splenic red pulp consists of a network of sinusoids populated by macrophages and numerous red blood cells (erythrocytes) and few lym-phocytes; it is the site where old and defective red blood cells are destroyed and removed. Many of the macrophages within the red pulp contain engulfed red blood cells or iron pigments from degraded hemoglobin. The splenic white pulp sur-rounds the branches of the splenic artery, forming a periarte-riolar lymphoid sheath (PALS) populated mainly by T lymphocytes. Primary lymphoid follicles are attached to the

PALS. These follicles are rich in B cells and some of them con-tain germinal centers. The marginal zone, located peripheral to the PALS, is populated by lymphocytes and macrophages.

Blood-borne antigens and lymphocytes enter the spleen through the splenic artery, which empties into the marginal zone. In the marginal zone, antigen is trapped by interdigi-tating dendritic cells, which carry it to the PALS. Lympho-cytes in the blood also enter sinuses in the marginal zone and migrate to the PALS.

The initial activation of B and T cells takes place in the T-cell-rich PALS. Here interdigitating dendritic cells capture antigen and present it combined with class II MHC mole-cules to T_H cells. Once activated, these T_H cells can then acti-vate B cells. The activated B cells, together with some T_H cells, then migrate to primary follicles in the marginal zone. Upon antigenic challenge, these primary follicles develop into char-acteristic secondary follicles containing germinal centers (like those in the lymph nodes), where rapidly dividing B cells (centroblasts) and plasma cells are surrounded by dense clusters of concentrically arranged lymphocytes.

In children, splenectomy often leads to an increased incidence of bacterial sepsis caused primarily by *Streptococcus pneumoniae, Neisse-ria meningitidis,* and *Haemophilus influenzae.* Splenectomy in adults has less adverse effects, although it leads to some in-crease in blood-borne bacterial infections (bacteremia).

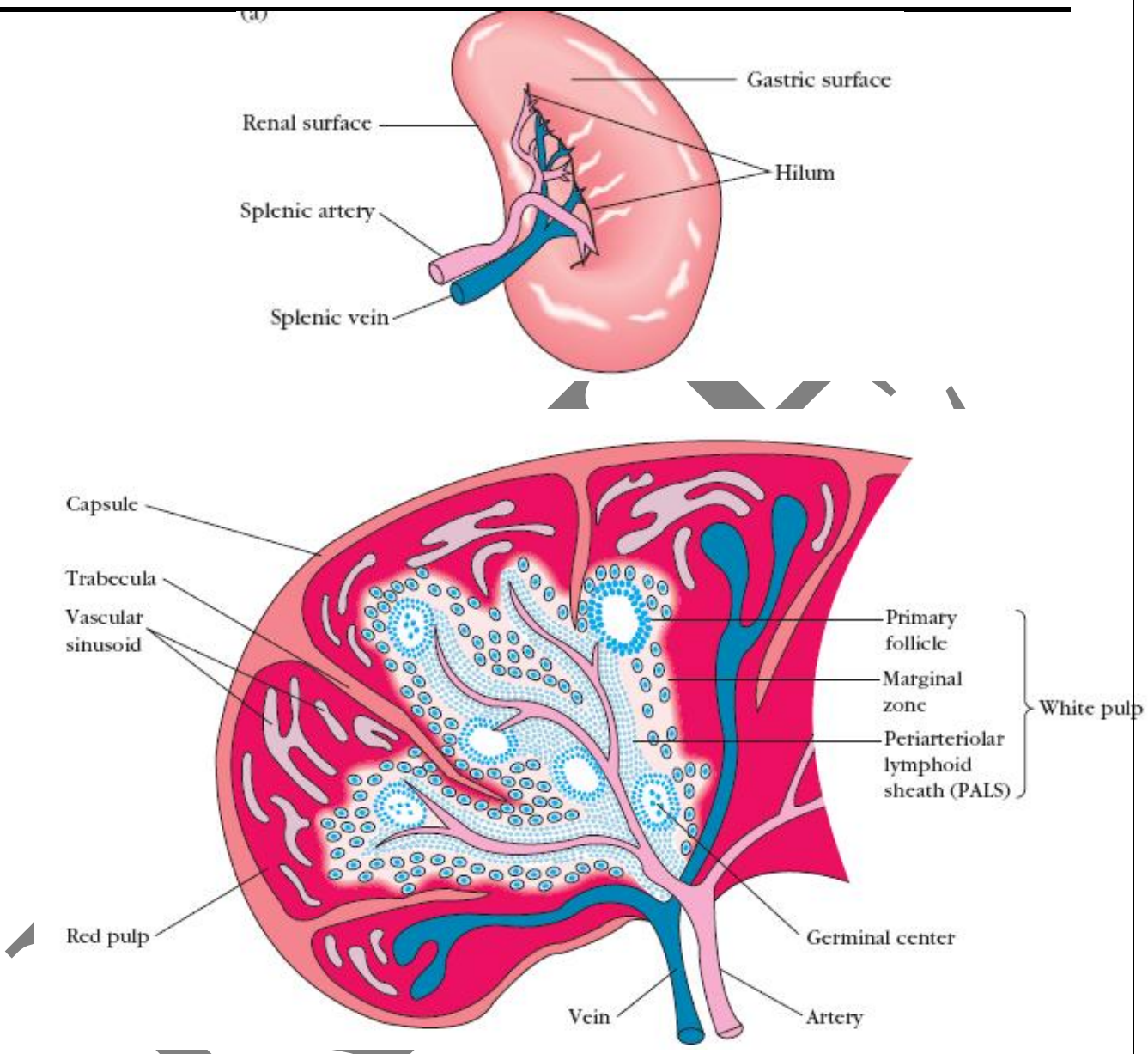

Fig: (a) The spleen, which is about 5 inches long in adults, is the largest secondary lymphoid organ. It is specialized for trapping blood-borne antigens**. (b) Diagram-matic cross section of the spleen**. The splenic artery pierces the capsule and divides into progressively smaller arterioles, ending in vascular sinusoids that drain back into the splenic vein. The erythrocyte-filled red pulp surrounds the sinusoids. The white pulp forms a sleeve, the periarteriolar lymphoid sheath (PALS), around the arterioles; this sheath contains numerous T cells. Closely associated with the PALS is the marginal zone, an area rich in B cells that contains lymphoid follicles that can develop into secondary follicles contain-ing germinal centers

MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT):

Approximately >50% of lymphoid tissue in the body is found associated with the mucosal system. MALT is composed of gut-associated lymphoid tissues (GALT) lining the intestinal tract, bronchus-associated lymphoid tissue (BALT) lining the respiratory tract, and lymphoid tissue lining the genitourinary tract. The respiratory, alimentary and genitourinary tracts are guarded by subepithelial accumulations of lymphoid tissue that are not covered by connective tissue capsule. They may occur as diffuse collections of lymphocytes, plasma cells and phagocytes throughout the lung and lamina propria of intestine or as clearly organised tissue with well-formed lymphoid follicles. The well-formed follicles include the tonsils (lingual, palatine and pharyngeal), Peyer's patches in the intestine and appendix. The major function of these organs is to provide local immunity by way of sIgA (also IgE) production. Diffuse accumulations of lymphoid tissue are seen in the lamina propria of the intestinal wall. The intestinal epithelium overlying the Peyer's patches is specialized to allow the transport of antigens into the lymphoid tissue. This function is carried out by cuboidal absorptive epithelial cells termed "M" cells, so called because they have numerous microfolds on their luminal surface. M cells endocytosise, transport and present antigens to subepithelial lymphoid cells. Majority of intra-epithelial lymphocytes are T cells, and most often CD8+ lymphocytes. The intestinal lamina propria contains CD4+ lymphocytes, large number of B cells, plasma cells, macrophages, dendritic cells, eosinophils and mast cells. Peyer's patches contain both B cells and CD4+ T cells.

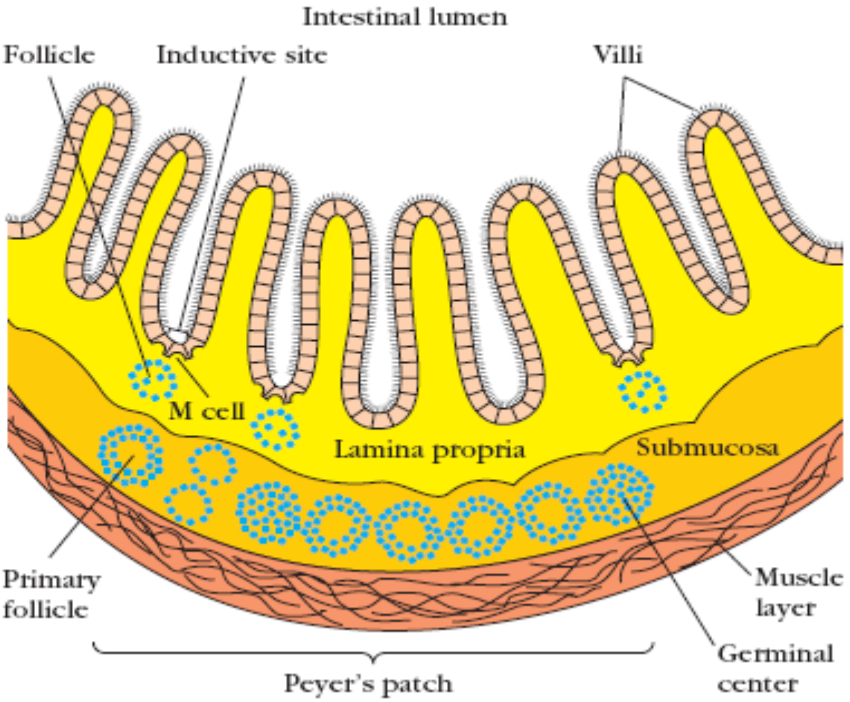

Fig: Cross-sectional diagram of the mucous membrane lining the intestine showing a nodule of lymphoid follicles that con-stitutes a Peyer's patch in the submucosa. The intestinal lamina pro-pria contains loose clusters of lymphoid cells and diffuse follicles.

CUTANEOUS-ASSOCIATED LYMPHOID TISSUE(CALT)

The skin is an important anatomic barrier to the external environment, and its large surface area makes this tissue important in nonspecific (innate) defenses. The epidermal (outer) layer of the skin is composed largely of specialized epithelial cells called keratinocytes. These cells secrete a number of cytokines that may function to induce a local inflammatory reaction. In addition, keratinocytes can be induced to express class II MHC molecules and may function as antigen-presenting cells. Scattered among the epithelial-cell matrix of the epidermis are Langerhans cells, a type of dendritic cell, which internalize antigen by phagocytosis or endocytosis. The Langerhans cells then migrate from the epidermis to regional lymph nodes, where they differentiate into interdigitating dendritic cells. These cells express high levels of class II MHC molecules and function as potent activators of naive TH cells.

(I) **Innate immunity**, or nonspecific, immunity is the natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches.

(i) Anatomic barrier:

Skin: Microbes first encounter the epithelial layers, physical barriers that line our skin and mucous membranes preventbthe entry of microbes

Sebum: Secretion of skin sebum, secretion of sebaseous glnad contains lactic and fratty acid , maintain a pH of 3-5 and inhibit the growth of microbes.

The conjunctivae , alimentary, respiratory and uorgenetal tracts are lined by mucous membrane and afford protection by entrapping foreign micro organism.

(ii)Physiological barrier:

The physiologic barrier that contribute to immunity include

Temperature- Some species body temperature prevent the growth of microbesEg: Chicken display innate immunity to anthrax because of its high temperature

pH : If ingested micro organism enter Into stomach , they can not survive with its low pH

Oxygen tension

Variable soluble factor : -Lysozyme a comnponnet of tears from eye is able to clear peptidoglyucan layer of bacterial cell wall

Interferon produced from the virus infected cell protects the near by cells from viral infection

Complement a circulating protein in serum activated thro immunologis response damage the membrane of micro organism

(iii) Endocytic and phagocytic barriers:

It is an important innate defence mechanism where extreacellular macromolecules are ingested via endocytosis and particulate material via phagocytosis and phagocytic activity is associated with the inflammatory response. The phagocytes express cell surface receptors that can bind and respond to common molecular patterns expressed on the surface of invading microbes. Through these approaches, innate immunity can prevent the colonization, entry, and spread of microbes.

Pattern recognition receptors (PRRs)

PRR play a crucial role in the proper function of the innate immune system. PRRs are germline-encoded host sensors, which detect molecules typical for the pathogens. They are proteins expressed, mainly, by cells of the innate immune system, such as dendritic cells, macrophages, monocytes, neutrophils and epithelial cells, to identify two classes of molecules: pathogen-associated molecular patterns (PAMPs), which are associated with microbial pathogens, and damage-associated molecular patterns (DAMPs), which are associated with components of host's cells that are released during cell damage or death. They are also called primitive pattern recognition receptors because they evolved before other parts of the immune system, particularly before adaptive immunity. PRRs also mediate the initiation of antigen-specific adaptive immune response and release of inflammatory cytokines

Connection between innate and adaptive immune system

The immune system as a whole represents a very complex interacting network that includes within it proinflammatory and anti-inflammatory mediators. The communication between the innate and adaptive immune systems involves cell-cell interactions in relation to antigen presentation or soluble molecules such as cytokines or chemokines. These are not necessarily mutually exclusive interactions. The response to presented antigens is often a major basis for the stimulation of adaptive immune cells to produce cytokines. These interactions can result in either target cell activation or suppression. Such networks of communication are likely at play between innate and adaptive immune systems or between components within each of these systems themselves. For example, NK cells can lyse immature dendritic cells as well as positively regulate dendritic cell maturation

Furthermore, cross-talk between the innate and adaptive systems may be bidirectional. The major cytokines implicated in atherosclerosis are produced by cells of both the adaptive and innate immune systems, acting upon one another in both a paracrine and an autocrine manner. For instance, IFNγ produced by the effector T-helper 1 (Th1) cell activates phagocytes such as macrophages, and interleukin-4 (IL-4) and IL-5 produced by Th2 cells may stimulate some macrophage and dendritic cell subset.

Leukocyte extravasation, less commonly called diapedesis, is the movement of leukocytes out of the circulatory system and towards the site of tissue damage or infection. This process forms part of the innate immune response, involving the recruitment of non-specific leukocytes. Monocytes also use this process in the absence of infection or tissue damage during their development into macrophages.

Leukocyte extravasation occurs mainly in post-capillary venules, where haemodynamic shear forces are minimised. This process can be understood in several steps, outlined below as **"chemoattraction", "rolling adhesion", "tight adhesion"** and **"(endothelial) transmigration".**

Chemoattraction

Upon recognition of and activation by pathogens, resident macrophages in the affected tissue release cytokines such as IL-1, TNFα and chemokines. IL-1, TNFα and C5a cause the endothelial cells of blood vessels near the site of infection to express cellular adhesion molecules, including selectins. Circulating leukocytes are localised towards the site of injury or infection due to the presence of chemokines.

Rolling adhesion

Like velcro, carbohydrate ligands on the circulating leukocytes bind to selectin molecules on the inner wall of the vessel, with marginal affinity. This causes the leukocytes to slow down and begin rolling along the inner surface of the vessel wall. During this rolling motion, transitory bonds are formed and broken between selectins and their ligands.

For example, the carbohydrate ligand for P-selectin, P-selectin glycoprotein ligand-1 (PSGL-1), is expressed by different types of leukocytes (white blood cells). The binding of PSGL-1 on the leukocyte to P-selectin on the endothelial cell allows for the leukocyte to roll along the endothelial surface. This interaction can be tuned by the glycosylation pattern of PSGL-1, such that certain glycovariants of PSGL-1 will have unique affinities for different selectins, allowing in some cases for cells to migrate to specific sites within the body (e.g. the skin).

Tight adhesion

At the same time, chemokines released by macrophages activate the rolling leukocytes and cause surface integrin molecules to switch from the default low-affinity state to a high-affinity state. This is assisted through juxtacrine activation of integrins by chemokines and soluble factors released by endothelial cells. In the activated state, integrins bind tightly to complementary receptors expressed on endothelial cells, with high affinity. This causes the immobilisation of the leukocytes, despite the sheer forces of the ongoing blood flow.

Transmigration

The cytoskeletons of the leukocytes are reorganised in such a way that the leukocytes are spread out over the endothelial cells. In this form, leukocytes extend pseudopodia and pass through gaps between endothelial cells. Transmigration of the leukocyte occurs as PECAM proteins, found on the leukocyte and endothelial cell surfaces, interact and effectively pull the cell through the endothelium. Once through the endothelium, the leukocyte must penetrate the basement membrane. The mechanism for penetration is disputed, but may involve proteolytic digestion of the membrane, mechanical force, or both. The entire process of blood vessel escape is known as diapedesis. Once in the interstitial fluid, leukocytes migrate along a chemotactic gradient towards the site of injury or infection.

Leukocyte adhesion deficiency

Leukocyte adhesion deficiency (LAD) is a genetic disease associated with a defect in the leukocyte extravasation process, caused by a defective integrin β2 chain (found in LFA-1 and Mac-1). This impairs the ability of the leukocytes to stop and undergo diapedesis. People with LAD suffer from recurrent bacterial infections and impaired wound healing. Neutrophilia is a hallmark of LAD.

Localized and Systemic Anaphylaxis

A sudden, severe allergic reaction between an allergenic antigen and immunoglobulin E (IgE) bound to mast cells, which stimulates the sudden release of immunological mediators locally or throughout the body. The first symptoms occur within minutes, and a recurrence may follow hours later (late-stage response). Anaphylaxis can only occur in someone previously sensitized to an allergen because the initial exposure causes immunoglobulin E (IgE) to bind to mast cells. Anaphylaxis may be local or systemic. Local anaphylactic reactions include hay fever, hives, and allergic gastroenteritis. Systemic anaphylaxis produces peripheral vasodilation, bronchospasm, and laryngeal edema and can be life-threatening. anaphylactic (-lak'tik), adjective

Etiology

IgE antibodies react when the allergen is introduced a second time. The mast cells release packets containing chemical mediators (degranulators) that attract neutrophils and eosinophils and stimulate urticaria, vasodilation, increased vascular permeability, and smooth muscle spasm, esp. in the bronchi

and gastrointestinal tract. Chemical anaphylactic mediators include histamine, proteases, chemotactic factors, leukotrienes, prostaglandin D, and cytokines, e.g., TNF-a and interleukins 1, 3, 4, 5, and 6. The most common agents triggering anaphylaxis are food, drugs, and insect stings. Local anaphylactic reactions are also commonly triggered by pollens, e.g., hay fever, allergic rhinitis, allergic asthma. See: anaphylactic shock

Symptoms

Local anaphylaxis causes such signs as urticaria (hives), edema, warmth, and erythema to appear at the site of allergen-antibody interaction. In systemic anaphylaxis the respiratory tract, cardiovascular system, skin, and gastrointestinal system are involved. The primary signs are urticaria, angioedema, flushing, wheezing, dyspnea, increased mucus production, nausea and vomiting, and feelings of generalized anxiety. Systemic anaphylaxis may be mild or severe enough to cause shock when massive vasodilation is present.

Treatment

Local anaphylaxis is treated with antihistamines or, occasionally, epinephrine if the reaction is severe. Treatment for systemic anaphylaxis includes protection of the airway and administration of oxygen; antihistamines, e.g., diphenhydramine or cimetidine to block histamine H1 and H2 receptors; IV fluids to support blood pressure; and vasopressors, e.g., epinephrine or dopamine, to prevent or treat shock. Epinephrine is also used to treat bronchospasm. Generally, drugs are given intravenously; drugs may also be given intramuscularly, e.g., diphenhydramine, or endotracheally, e.g., epinephrine. In mild cases they may be given subcutaneously. Corticosteroids may be used to prevent recurrence of bronchospasm and increased vascular permeability.

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15BCU503- Immunology
UNIT- I

S.NO	QUESTION	A	B	C	D	Answer
1	A hematopoietic stem is a	Progeniter	Pluripotent	Stem cell	Mast cell	Pluripotent
2	Lymphoid and myeloid stem cells differentiate into	Progeniter cells	White blood cells	Red blood cells	Lymphoid cells	Progeniter cells
3	In adult bone marrow, the hematopoietic cells grow and mature on a meshwork of	Stem cells	Lymphoid	Stromal cells	Myeloid cells	Stromal cells
4	The colony stimulating factor is a	Acidic glycoproteins	Basic glycoproteins	Neutral glycoproteins	glycoprotein	Acidic glycoproteins
5	Multilineage CSF is also known as	IL-2	IL-3	Il-4	IL-7	IL-3
6	Erytropoietin is a	Protein	Glycans	Glycoproteins	Cytokines	Glycoproteins
7	Cells undergoing programmed cell death is reffered to as	**Apoptosis**	Degeneration	Denaturation	Cell cycle	Apoptosis
8	Apoptosis differs markly from	Necrosis	Cell cycle	Degeneration	Denaturation	Degeneration
9	A normal adult has about 5litres of blood with about……lymphocytes/mm^3	3000	2000	4000	2500	2000

10	Activated lymphocytes have been found to express lower levels of	Bcl-X^2	Bcl-.3	Bcl-2	Bcl-4	Bcl-2
11	Lymphocytes constitute …….. of WBC	20-40%	40-60%	30-50%	40-50%	20-40%
12	T,B& Null cells are	phagocytic cells	Non-phagocytic cells	Mast cells	WBC	Non-phagocytic cells
13	CD^{34+} are	Potent	Stem cells	Pluripotent stem cells	Mast cells	Pluripotent stem cells
14	Lymphocytes enlarge into 15mm diameter blast cells known as	lymph cells	lymphoid cells	lymphocytes	lymphoblasts	lymphoblasts
15	CD is a	Cluster of differentiation	Cluster of designation	Colony of differentiation	Colony of designation	Cluster of differentiation
16	B^{220} is also a	CD45	CD20	CD30	CD50	CD45
17	Absence of NK cells results in disorder	Cushion syndrome	Chediak-Higashi syndrome	Necrosis	X-linked syndrome	Chediak-Higashi syndrome
18	Alveolar macrophages is found in	Kidney	Brain	Lung	Tissue	Lung
19	Kupffer cells is found in	Brain	Liver	Lung	Kidney	Liver
20	Macrophages present in kidney is known as	Mesangial cells	Microglial cells	Kupffer cells	Histocytes	Mesangial cells
21	Microglial cells found in	Kidney	Lung	Tissue	Brain	Brain
22	The neutrophil has a…….. nucleus	Bilobed	Lobed	Multilobed	Polylobed	Multilobed
23	The eosinophil has a…….. nucleus	Bilobed	Lobed	Multilobed	Polylobed	Lobed

24	Neutrophils are produced in	Bone marrow	Tissue	Liver	Blood	Bone marrow
25	Movement of circulating neutrophils into tissues called	Vasation	Vascular endothelium	Extravasation	Endothelial cells	Extravasation
26	Chemotactic factors promote accumulation of	Basophils	Eosinophils	Neutrophils	Mast cells	Neutrophils
27	…… cells found in epidermis and mucous membranes.	Interstitial dendritic	Inter digitating	Circulating	Langerhans	Langerhans
28	The pre-TCR consists of protein	CD2	CD4	CD3	CD5	CD3
29	The pre-TCR consists of	Alpha chain	Beta chain	Gamma chain	Alpha-Beta cells	Beta chain
30	Thy-1 is a	Protein	Membrane	Membrane protein	Membrane molecules	Membrane protein
31	TH-Cell activation is initiated by	TCR-CD2	TCR-CD4	TCR-CD5	TCR-CD3	TCR-CD3
32	Exogenous super antigens are soluble proteins secreted by	Bacteria	Fungus	Algae	Chlorophyll	Bacteria
33	Exogenous super antigens are soluble	Cells	Tissues	Membranes	Proteins	Proteins
34	Gram positive bacteria secretes	Endotoxins	Toxins	Exotoxins	Mesotoxins	Exotoxins
35	Endogenous super antigens are	Cell protein	Cell-membrane protein	Membrane protein	Protein	Cell-membrane protein
36	The generation of mature B cells first occurs in	Cell	Tissue	Embryo	Bone marrow	Embryo
37	B-cells response to antigens	TA	TB	TC	TD	TD
38	Antigens that activate B-cells in the absence of TH cells are known as	TI	TG	TH	TK	TI

39	Polyclonal B-cell activatirs are known as	Mesogens	Mitogens	Mycogens	Minogens	Mitogens
40	Signals that drives B cell from G_0 into G_1 is	Progression	Pre-Progression	Competence	Pre-competence	Competence
41	Signal that drives the B-Cell from G_1 into S is	Competence	Pre-competence	Progression	Pre-progression	Progression
42	T1 antigens are in nature of	monovalent	Divalent	Trivalent	Multivalent	Multivalent
43	Initial activation of bothB&T cells are thought to take place in	Cortex	Paracortex	Precortex	Procortex	Paracortex
44	The proliferating activated B cells known as	Centromeres	Centrocytes	Centroblasts	Centeromeres	Centroblasts
45	TH cells failsto express CD40 results in	X-Linked hyper Ig-M syndrome	X-Linked hyper Ig-K syndrome	X-Linked hyper Ig-L syndrome	X-Linked hyper Ig-I syndrome	X-Linked hyper Ig-M syndrome
46	NK cells play an important role in	Mesocells	Mast cell	Tumour cells	TH cells	Tumour cells
47	A signal transduction molecule is	CD 43	CD 45	CD 46	CD 47	CD 45
48	The adhesion molecule is a	CD 52	CD 53	CD 55	CD 56	CD 56
49	B & T lymphocytes recognize discrete sites on the antigen called	Epitopes	Endotopes	Exotopes	Isotopes	Epitopes
50	The main component of the blood clot	Platelets	Fibrin	Fibrous	Fibroblast	Fibrin
51	The B cell receptor is a membrane bound …… molecule	Antigen	Antibody	Epitope	Endotope	Antibody
52	Memory B cells & effector B cells are called as	Mast cells	Mesocells	Plasma cells	Membrane cells	Plasma cells
53	Receptor mediated endocytosis is also known as	Phagocytosis	Endocytosis	Exocytosis	Pinocytosis	Pinocytosis

54	The engorged capillaries are responsible for tissue rednessis known as	edema	erythema	extravasation	Chemotaxis	extravasation
55	An accumulation of fluid results in tissue swelling leads to	edema	erythema	extravasation	Chemotaxis	edema
56	Which hydrolytic enzyme found in mucous secretions	Lytizyme	Pre- Lytizyme	Lysozyme	Pre-Lysozyme	Lysozyme
57	……..comprises a group of proteins produced by virus- in fected cells.	Interferon	Interleukins	Cytokinins	Cytooxic.	Interferon
58	The adhesion molecule that binds to class I MHC molecule is	CD5	CD 6	CD7	CD 8.	CD 8.
59	Monocytes is found in	Blood	bone marrow	tissue	Cells.	Blood
60	Macrophages is found in	Blood	Bone marrow	tissues	Cells.	tissues

UNIT-II
SYLLABUS

Unit 2

Antigens and haptens, factors that dictate immunogenicity, B and T cell epitopes. Structure and distributionof classes and subclasses of immunoglobulins (Ig), Ig fold, effector functions of antibody, antigenicdeterminants on Ig and Ig super family. Dreyer-Bennett hypothesis, multigene organization of Ig locus,mechanism of V region DNA rearrangement, ways of antibody diversification.

ANTIGEN

An antigen is any substance that causes immune system to produce antibodies against it. An antigen may be a foreign substance from the environment such as chemicals, bacteria, viruses, or pollen. An antigen may also be formed within the body, as with bacterial toxins or tissue cells.

Properties of Antigen:

- Antigen, foreign substance that, when introduced into the body, is capable of stimulating an immune response, specifically activating lymphocytes
- Virtually any large foreign molecule can act as an antigen, including those contained in bacteria, viruses, protozoa, helminths, foods, snake venoms, egg white, serum components, red blood cells, and other cells and tissues of various species including humans.
- An antigen that induces an immune response stimulates the lymphocytes to produce antibody
- On the surface of the antigens are regions, called antigenic determinants(epitope), that fit and bind to receptor molecules of complementary structure on the surface of the lymphocytes
- The binding of the lymphocytes' receptors to the antigens' surface molecules stimulates the lymphocytes to multiply and to initiate an immune response by the production of antibody, activation of cytotoxic cells, or both .
- The amount of antibody formed in response to stimulation depends on the kind and amount of antigen involved, the route of entry to the body, and individual characteristics of the host

Factors influencing antigenecity:

Molecular size: Large molecules are better antigan thansmall moleculesEg: hemocyanin- a large protein is a potent antigen

Structural stability: To recognise a molecule or part of a molecule as foreign, the cells of immune system must recognise its specific shape. Consequently, highly flexible molecules that have fixed shape are poor antigens.Eg: Gelatin-poor antigen

Degradability: The cells of immune system recognise small molecular fragments and soluble antigens. If a moleculecannot be broken up or solubilised, then it cannot acts as an antigen.Eg-Stainless steel pin

Foreignness: The cells whose function is ti respond to antigen are selected in such a way that they do not usually respond to normal body componenets. They will respond, how ever, to foreign molecules differ even in minor respects from those usually found with in the body. This property is immunogenecity and this depends on the degree of foreingnness.

Specificity and Cross-Reactivity

Specificity measures the degree to which the immune system differentiates between different antigens. Cross-reactivity measures the extent to which different antigens appear similar to the immune system. The molecular determinants of specificity and cross-reactivity define the nature of antigenic variation and the selective processes that shape the distribution of variants in populations.

The surfaces of parasite molecules contain many overlapping antibody-binding sites (epitopes). An antibody bound to an epitope covers about 15 amino acids on the surface of a parasite molecule. However, only about 5 of the parasite's amino acids contribute to the binding energy. A change in any of those 5 key amino acids can greatly reduce the strength of antibody binding.

Antibodies have a variable region of about 50 amino acids that contains many overlapping paratopes. Each paratope has about 15 amino acids, of which about 5 contribute most of the binding energy for epitopes. Paratopes and epitopes define complementary regions of shape and charge rather than particular amino acid compositions. A single paratope can bind to unrelated epitopes, and a single epitope can bind to unrelated paratopes.

Naive B cells make IgM antibodies that typically bind with low affinity to epitopes. A particular epitope stimulates division of B cells with relatively higher-affinity IgM antibodies for the epitope. As the stimulated B cell clones divide rapidly, they also mutate their antibody-binding regions at a high rate. Mutant lineages that bind with higher affinity to the target antigen divide more rapidly and out compete weaker-binding lineages. This mutation and selection produces high-affinity antibodies, typically of type IgA or IgG.

Each natural antibody can bind with low affinity to many different epitopes. Natural antibodies from different B cell lineages form a diverse set that binds with low affinity to almost any antigen. One in vitro study of HIV suggested that these background antibodies bind to the viruses with such low affinity that they do not interfere with infection. By contrast, in vivo inoculations with several different pathogens showed that the initial binding by natural antibodies lowered the concentrations of pathogens early in infection by one or two orders of magnitude.

Poor binding conditions cause low-affinity binding to be highly specific because detectable bonds form only between the strongest complementary partners. By contrast, favorable binding conditions cause low-affinity binding to develop a relatively broad set of complementary partners, causing relatively low specificity. The appropriate measure of affinity varies with the particular immune process. Early stimulation of B cells appears to depend on the equilibrium binding affinity for antigens. By contrast, competition between B cell clones for producing affinity-matured antibodies appears to depend on the dynamic rates of association between B cell receptors and antigens.

Polyclonal immune responses raise antibodies against many epitopes on the surface of an antigen. Cross-reactivity declines linearly with the number of amino acid substitutions between variant antigens because each exposed amino acid contributes only a small amount to the total binding between all antibodies and all epitopes. By contrast, a monoclonal antibody usually binds to a single epitope on the antigen surface. Cross-reactivity declines rapidly and nonlinearly with the number of amino acid substitutions in the target epitope because a small number of amino acids control most of the binding energy.

Immunogenicity

Immunogenicity is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human or animal. In other words, immunogenicity is the ability to induce a humoral and/or cell mediated immune response.

The ability of an antigen to elicit immune responses is called immunogenicity, which can be humoral and/or cell-mediatedimmuneresponses.
Differentiation has to be made between wanted and unwanted immunogenicity.

- Wanted immunogenicity is typically related with vaccines, where the injection of an antigen (the vaccine) has to lead to an immune response against the pathogen (the virus, bacterium or substance).
- Unwanted immunogenicity is when the organism mounts an immune response against an antigen which is undesired. Unwanted immunogenicity is strongly linked with therapeutic proteins. A fraction of the patient treated with those drugs mount anti-drug-antibodies, which leads to inactivation of the drug and in rare cases to adverse effects .

ANTIBODY

Antibodies are glycoprotein belonging to the immunoglobulin superfamily; the terms antibody and immunoglobulin are often used interchangeably. They present on the B-cell membrane and secreted by plasma cells. Membrane-bound antibody confers antigenic specificity on B cells; antigen-specific prolifer-ation of B-cell clones is elicted by the interaction of membrane antibody with antigen. Secreted antibodies cir-culate in the blood, where they serve as the effectors of hu-moral immunity by searching out and neutralizing antigens or marking them for elimination. All antibodies share struc-tural features, bind to antigen, and participate in a limited number of effector functions.

The antibodies produced in response to a particular anti-gen are heterogeneous. Most antigens are complex and contain many different antigenic determinants, and the immune system usually responds by producing antibodies to several epitopes on the antigen. This response requires the recruit-ment of several clones of B cells. Their outputs are mono-clonal antibodies, each of which specifically binds a

single antigenic determinant. Together, these monoclonal antibod-ies make up the polyclonal and heterogeneous serum anti-body response to an immunizing antigen.

Immunoglobulins generally assume one of two roles: immunoglobulins may act as i) plasma membrane bound antigen receptors on the surface of a B-cell or ii) as antibodies free in cellular fluids functioning to intercept and eliminate antigenic determinants.

ANTIBODY-Structure

- Antibodies are typically made of basic structural units—each with two large heavy chains and two small light chains.

Structure

- Antibodies are heavy (~150 kDa) globular plasma proteins
- They have sugar chains added to some of their amino acid residues, so antibodies are glycoproteins.
- Immunoglobulins are composed of four polypeptide chains: two "light" chains (lambda or kappa), and two "heavy" chains (alpha, delta, gamma, epsilon or mu).
- The type of heavy chain determines the immunoglobulin isotype (IgA, IgD, IgG, IgE, IgM, respectively).
- Light chains are composed of 220 amino acid residues while heavy chains are composed of 440-550 amino acids. Each chain has "constant" and "variable" regions as shown in the figure.
- Variable regions(V region) are contained within the amino (NH2) terminal end of the polypeptide chain (amino acids 1-110). When comparing one antibody to another, these amino acid sequences are quite distinct.
- Constant regions (C region), comprising amino acids 111-220 (or 440-550), are rather uniform, in comparison, from one antibody to another, within the same isotype.
- "Hypervariable" regions, or "Complementarity Determining Regions" (CDRs) are found within the variable regions of both the heavy and light chains. These regions serve to recognize and bind specifically to antigen.
- The four polypeptide chains are held together by covalent disulfide (-S-S-) bonds
-

Fig:Heavy and light chains are folded into domains, each containing about 110 amino acid residues and an intrachain disulfide bond that forms a loop of 60 amino acids. The amino-terminal domains, corresponding to the V regions, bind to antigen effector functions are mediated by the other domains. (b) The and heavy chains contain an additional domain that replaces the hinge region.

Immunoglobulin domains

The Ig monomer is a "Y"-shaped molecule that consists of four polypeptide chains; two identical heavy chains and two identical light chains connected by disulfide bonds. Each chain is composed of structural

domains called immunoglobulin domains. These domains contain about 70-110 amino acids and are classified into different categories (for example, variable or IgV, and constant or IgC) according to their size and function. They have a characteristic immunoglobulin fold in which two beta sheets create a "sandwich" shape, held together by interactions between conserved cysteines and other charged amino acids.

Heavy chain

There are five types of mammalian Ig heavy chain denoted by the Greek letters: α, δ, ε, γ, and μ. The type of heavy chain present defines the class of antibody; these chains are found in IgA, IgD, IgE, IgG, and IgM antibodies, respectively. Distinct heavy chains differ in size and composition; α and γ contain approximately 450 amino acids, while μ and ε have approximately 550 amino acids.

1. Fab region
2. Fc region
3. Heavy chain (blue) with one variable (VH) domain followed by a constant domain (CH1), a hinge region, and two more constant (CH2 and CH3) domains.
4. Light chain (green) with one variable (VL) and one constant (CL) domain
5. Antigen binding site (paratope)
6. Hinge regions.

Each heavy chain has two regions, the constant region and the variable region. The constant region is identical in all antibodies of the same isotype, but differs in antibodies of different isotypes. Heavy chains γ, α and δ have a constant region composed of three tandem (in a line) Ig domains, and a hinge region for added flexibility; heavy chains μ and ε have a constant region composed of four immunoglobulin domains. The variable region of the heavy chain differs in antibodies produced by different B cells, but is the same for all antibodies produced by a single B cell or B cell clone. The variable region of each heavy chain is approximately 110 amino acids long and is composed of a single Ig domain.

Light chain

In mammals there are two types of immunoglobulin light chain, which are called lambda (λ) and kappa (κ). A light chain has two successive domains: one constant domain and one variable domain. The approximate length of a light chain is 211 to 217 amino acids. Each antibody contains two light chains that are always identical; only one type of light chain, κ or λ, is present per antibody in mammals. Other types of light chains, such as the iota (ι) chain, are found in lower vertebrates like sharks (Chondrichthyes) and bony fishes (Teleostei).

Immunoglobulin Classes and Subclasses

- Immunglobulin molecules are divided into distinct classes and subclasses in terms of the differences in amino acid sequence of constant region of heavy chain, i.e.γ,α,μ,δ,and εchains
- Immunoglobulin Classes of Mammals
- IgG - Gamma (γ) heavy chains
- IgM - Mu (μ) heavy chains
- IgA - Alpha (α) heavy chains

- IgD - Delta (δ) heavy chains
- IgE - Epsilon (ε) heavy chains

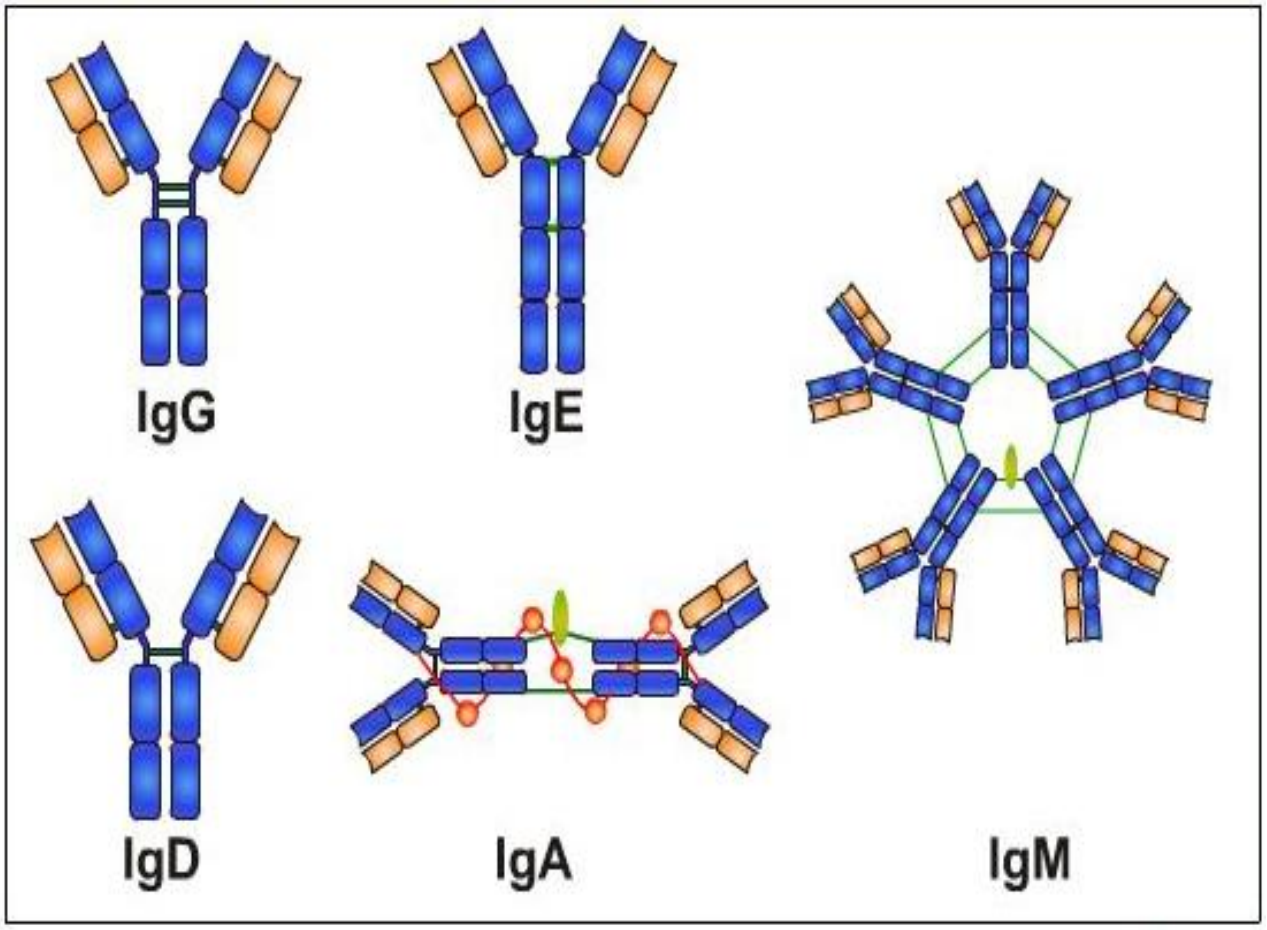


Fig:Five Classes of Immunoglobulin

- IgG has a family of subclass, IgG1, IgG2, IgG3, IgG4(cattle has no)
- IgA is divided into two subclasses, IgA1 and IgA2(sheep)
- Mammalian antibodies can be divided into five classes: IgG, IgM, IgA, IgD and IgE, based on the number of Y units and the type of heavy chain
- The light chains of any antibody can be classified as either a kappa or Antibody Structure lambda type based on small polypeptide structural differences
- The heavy chain determines the subclass of each antibody
- The subclasses of antibodies differ in the number of disulfide bonds and the length of the hinge region
- The most commonly used antibody in immunochemical procedures is of the IgG class because they are the major immunoglobulin (Ig) released in serum

IgG Immunoglobulins

IgG, a monomer, is the predominant Ig class present in human serum. Produced as part of the secondary immune response to an antigen, this class of immunoglobulin constitutes approximately 80% of total

serum Ig. IgG is the only class of Ig that can cross the placenta in humans, and it is largely responsible for protection of the newborn during the first months of life. Because of its relative abundance and excellent specificity toward antigens, IgG is the principle antibody used in immunological research and clinical diagnostics.

- IgG, the most abundant class in serum, constitutes about 80% of the total serum immunoglobulin. The IgG molecule consists of two heavy chains and two or two light chain.s There are four human IgG subclasses, dis-tinguished by differences in -chain sequence and numbered according to their decreasing average serum concentrations: IgG1, IgG2, IgG3, and IgG4 .

- IgG1, IgG3, and IgG4 readily cross the placenta and play an important role in protecting the developing fetus.

- IgG3 is the most effective complement activator, followed by IgG1; IgG2 is less efficient, and IgG4 is not able to activate complement at all.

- IgG1 and IgG3 bind with high affinity to Fc receptors on phagocytic cells and thus mediate opsonization. IgG4 has an intermediate affinity for Fc receptors, and IgG2 has an extremely low affinity.

Properties of IgG:

- Molecular weight: 150,000
- H-chain type (MW): gamma (53,000)
- Serum concentration: 10 to 16mg/mL
- Percent of total immunoglobulin: 80%
- Glycosylation (by weight): 3%
- Distribution: intra- and extravascular
- Function: secondary response

IgM Immunoglobulins

Serum IgM exists as a pentamer in mammals, predominates in primary immune responses to most antigens, is the most efficient complement fixing immunoglobulin and comprises approximately 10% of normal human serum Ig content. IgM is also expressed on the plasma mem- brane of the B lymphocytes as a monomer. It is the B cell antigen receptor and the H chains each contain an additional hydrophobic domain for anchoring in the membrane. Monomers of serum IgM are bound together by disulfide bonds and a joining (J) chain.

Each of the five monomers is composed of two light chains (either kappa or lambda) and two heavy chains. Unlike in IgG (and the generalized structure shown above), the heavy chain in IgM monomers is composed of one variable and four constant regions, the additional constant domain replacing the hinge region. IgM can cause cell agglutination as a result of recognition of epitopes on invading microorganisms. This antibody-antigen immune complex is then destroyed by complement fixation or receptor mediated endocytosis by macrophages. IgM is the first immunoglobulin class to be synthesized by the neonate and plays a role in the pathogenesis of some autoimmune diseases.

IgM accounts for 5%–10% of the total serum immunoglob-ulin, with an average serum concentration of 1.5 mg/ml. Monomeric IgM, with a molecular weight of 180,000, is ex-pressed as membrane-bound antibody on B cells.

IgM is se-creted by plasma cells as a pentamer in which five monomer units are held together. The five monomer subunits are arranged with their Fc regions in the center of the pentamer and the ten antigen-binding sites on the periphery of the molecule. Each pentamer contains an additional Fc-linked polypeptide called the J (joining) chain, which is disulfide-bonded to the carboxyl-terminal cysteine residue of two of the ten chains. The J chain ap-pears to be required for polymerization of the monomers to form pentameric IgM; it is added just before secretion of the pentamer.

IgM is the first immunoglobulin class produced in a pri-mary response to an antigen, and it is also the first im-munoglobulin to be synthesized by the neonate. Because of its pentameric structure with 10 antigen-binding sites, serum IgM has a higher valency than the other isotypes. An IgM molecule can bind 10 small hapten molecules.

Because of its large size, IgM does not diffuse well and therefore is found in very low concentrations in the intercel-lular tissue fluids. The presence of the J chain allows IgM to bind to receptors on secretory cells, which transport it across epithelial linings to enter the external secretions that bathe mucosal surfaces.

Properties of IgM:

- Molecular weight: 900,000
- H-chain type (MW): mu (65,000)
- Serum concentration: 0.5 to 2mg/mL
- Percent of total immunoglobulin: 10%
- Glycosylation (by weight): 12%
- Distribution: mostly intravascular
- Function: primary response

IgA Immunoglobulins

Although IgA constitutes only 10%–15% of the total im-munoglobulin in serum, it is the predominant im-munoglobulin class in external secretions such as breast milk, saliva, tears, and mucus of the bronchial, genitouri-nary, and digestive tracts. In serum, IgA exists primarily as a monomer, but polymeric forms (dimers, trimers, and some tetramers) are sometimes seen, all containing a J-chain polypeptide. The IgA of external secre-tions, called secretory IgA, consists of a dimer or tetramer, a J-chain polypeptide, and a polypeptide chain called secre-tory component

IgA exists in serum in both monomeric and dimeric forms, comprising approximately 15% of the total serum Ig. Secretory IgA, a dimer, provides the primary defense mechanism against some local infections because of its abundance in mucosal secretions (e.g., saliva, tears). The principal function of secretory IgA may not be to destroy antigen but to prevent passage of foreign substances into the circulatory system.

Properties of IgA:

- Molecular weight: 320,000 (secretory)
- H-chain type (MW): alpha (55,000)

- Serum concentration: 1 to 4mg/mL
- Percent of total immunoglobulin: 15%
- Glycosylation (by weight): 10%
- Distribution: intravascular and secretions
- Function: protect mucus membranes.IgA-secreting plasma cells are concentrated along mucous membrane surfaces. Breast milk contains secretory IgA and many other mole-cules that help protect the newborn against infection during the first month of life

IgD and IgE Immunoglobulins

IgD and IgE are found in serum in much smaller quantities than other Igs. Membrane IgD is a receptor for antigen found mostly on mature B-lymphocytes. IgE primarily defends against parasitic invasion and is responsible for allergic reactions.

Properties of IgD:

- Molecular weight: 180,000
- H-chain type (MW): delta (70,000)
- Serum concentration: 0 to 0.4mg/mL
- Percent of total immunoglobulin: 0.2%
- Glycosylation (by weight): 13%
- Distribution: lymphocyte surface
- Function: unknown
- IgD was first discovered when a patient developed a multiple myeloma whose myeloma protein failed to react with anti-isotype antisera against the then-known isotypes: IgA, IgM, and IgG. When rabbits were immunized with this myeloma protein, the resulting antisera were used to identify the same class of antibody at low levels in normal human serum. The new class, called IgD, has a serum concentration of 30 g/ml and constitutes about 0.2% of the total immunoglobulin in serum. IgD, together with IgM, is the major membrane-bound immunoglobulin expressed by mature B cells, and its role in the physiology of B cells is under investigation. No biological effector function has been identified for IgD.

Properties of IgE:

- Molecular weight: 200,000
- H-chain type (MW): epsilon (73,000)
- Serum concentration: 10 to 400ng/mL
- Percent of total immunoglobulin: 0.002%
- Glycosylation (by weight): 12%
- Distribution: basophils and mast cells in salive and nasal secretions
- Function: protect against parasites
- IgE binds to Fc receptors on the membranes of blood ba-sophils and tissue mast cells. Cross-linkage of receptor-bound IgE molecules by antigen (allergen) induces basophils and mast cells to translocate their granules to the plasma membrane and release their contents to the extracellular en-

vironment, a process known as degranulation. As a result, a variety of pharmacologically active mediators are released and give rise to allergic manifestations

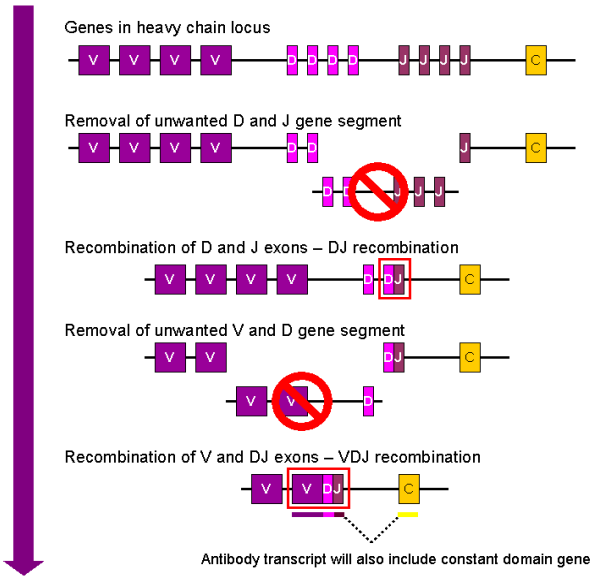
Dreyer and Bennett Hypothesis

In 1965, William Dreyer and Claude Bennett proposed that multiple V (variable) genes are separate from a single C (constant) gene in embryonic (germ-line) DNA. According to their model, one of these V genes becomes joined to the C gene in the course of differentiation of the antibody-producing cell. A critical test of this novel hypothesis had to await the isolation of pure immunoglobulin mRNA and the development of techniques for analyzing mammalian genomes. Twenty years later, Susumu Tonegawa found that V and C genes are indeed far apart in embryonic DNA but are closely associated in the DNA of antibody-producing cells. Thus, immunoglobulin genes are rearranged in the differentiation of lymphocytes.

V(D)J recombination

V(D)J recombination is the unique mechanism of genetic recombination that occurs only in developing lymphocytes during the early stages of T and B cell maturation. It involves somatic recombination, and results in the highly diverse repertoire of antibodies/immunoglobulins (Igs) and T cell receptors (TCRs) found on B cells and T cells, respectively. The process is a defining feature of the adaptive immune system and its development was a key event in the evolution of jawed vertebrates.

V(D)J recombination occurs in the primary lymphoid organs (bone marrow for B cells and thymus for T cells) and in a nearly random fashion rearranges variable (V), joining (J), and in some cases, diversity (D) gene segments. The process ultimately results in novel amino acid sequences in the antigen-binding regions of Igs and TCRs that allow for the recognition of antigens from nearly all pathogens including bacteria, viruses, parasites, and worms as well as "altered self cells" as seen in cancer. The recognition can also be allergic in nature (e.g., to pollen or other allergens) or may be "autoreactive" and lead to autoimmunity.



Human antibody molecules (and B cell receptors) are composed of heavy and light chains (each of which contains both constant (C) and variable (V) regions), which are encoded by genes on three loci:

* The immunoglobulin heavy locus (IGH@) on chromosome 14, containing the gene segments for the immunoglobulin heavy chain.
* The immunoglobulin kappa (κ) locus (IGK@) on chromosome 2, containing the gene segments for part of the immunoglobulin light chain.
* The immunoglobulin lambda (λ) locus (IGL@) on chromosome 22, containing the gene segments for the remainder of the immunoglobulin light chain.

Each heavy chain and light chain gene contains multiple copies of three different types of gene segments for the variable regions of the antibody proteins. For example, the human immunoglobulin heavy chain region contains 2 Constant (Cμ and Cδ) gene segments and 44 Variable (V) gene segments, plus 27 Diversity (D) gene segments and 6 Joining (J) gene segments. The light chains also possess 2 Constant (Cμ and Cδ) gene segments and numerous V and J gene segments, but do not have D gene segments. DNA rearrangement causes one copy of each type of gene segment to go in any given lymphocyte, generating an enormous antibody repertoire; roughly 3×1011 combinations are possible, although some are removed due to self reactivity.

V(D)J recombination begins when V(D)J recombinase (through the activity of RAG1) binds an RSS flanking a coding gene segment (V, D, or J) and creates a single-strand nick in the DNA between the first base of the RSS (just before the heptamer) and the coding segment. This is essentially energetically neutral (no need for ATP hydrolysis) and results in the formation of a free 3' hydroxyl group and a 5' phosphate group on the same strand. The reactive hydroxyl group is positioned by the recombinase to attack the phosphodiester bond of opposite strand, forming two DNA ends: a hairpin (stem-loop) on the coding segment and a blunt end on the signal segment. The current model is that DNA nicking and

hairpin formation occurs on both strands simultaneously (or nearly so) in a complex known as a recombination center.

The blunt signal ends are flushly ligated together to form a circular piece of DNA containing all of the intervening sequences between the coding segments known as a signal joint (although circular in nature, this is not to be confused with a plasmid). While originally thought to be lost during successive cell divisions, there is evidence that signal joints may re-enter the genome and lead to pathologies by activating oncogenes or interrupting tumor suppressor gene function(s)

The coding ends are processed further prior to their ligation by several events that ultimately lead to junctional diversity. Processing begins when DNA-PK binds to each broken DNA end and recruits several other proteins including Artemis, XRCC4, DNA ligase IV, Cernunnos, and several DNA polymerases. DNA-PK forms a complex that leads to its autophosphorylation, resulting in activation of Artemis. The coding end hairpins are opened by the activity of Artemis. If they are opened at the center, a blunt DNA end will result; however in many cases, the opening is "off-center" and results in extra bases remaining on one strand (an overhang). These are known as palindromic (P) nucleotides due to the palindromic nature of the sequence produced when DNA repair enzymes resolve the overhang. The process of hairpin opening by Artemis is a crucial step of V(D)J recombination and is defective in the severe combined immunodeficiency (scid) mouse model.

Next, XRCC4, Cernunnos, and DNA-PK align the DNA ends and recruit terminal deoxynucleotidyl transferase (TdT), a template-independent DNA polymerase that adds non-templated (N) nucleotides to the coding end. The addition is mostly random, but TdT does exhibit a preference for G/C nucleotides. As with all known DNA polymerases, the TdT adds nucleotides to one strand in a 5' to 3' direction.

Lastly, exonucleases can remove bases from the coding ends (including any P or N nucleotides that may have formed). DNA polymerases λ and μ then insert additional nucleotides as needed to make the two ends compatible for joining. This is a stochastic process, therefore any combination of the addition of P and N nucleotides and exonucleolytic removal can occur (or none at all). Finally, the processed coding ends are ligated together by DNA ligase IV.

Somatic hypermutation (or SHM) is a cellular mechanism by which the immune system adapts to the new foreign elements that confront it (e.g. microbes), as seen during class switching. A major component of the process of affinity maturation, SHM diversifies B cell receptors used to recognize foreign elements (antigens) and allows the immune system to adapt its response to new threats during the lifetime of an organism. Somatic hypermutation involves a programmed process of mutation affecting the variable regions of immunoglobulin genes

Affinity maturation is the process by which Tfh cell-activated B cells produce antibodies with increased affinity for antigen during the course of an immune response. With repeated exposures to the same antigen, a host will produce antibodies of successively greater affinities. A secondary response can elicit antibodies with several fold greater affinity than in a primary response. Affinity maturation

primarily occurs on surface immunoglobulin of germinal center B cells and as a direct result of somatic hypermutation (SHM) and selection by Tfh cells.

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Department of Biochemistry
III B,.Sc., Biochemistry
15BCU503- Immunology
UNIT- II

S.NO	QUESTION	A	B	C	D	Answer
1	Which one has the ability to induce a humoral immune response	Antigenicity	immunogencity	T cells	B cells.	immunogencity
2	Substances that induce a specific immune response is known as	Antigen	Antibody	haptens	Cytokines.	haptens
3	Which one has the ability to combine specifically to the cell surface receptors.	haptens	Cytokines	Antigenicity	immunogenicity.	haptens
4	Haptens are	large molecules	small molecule	very large molecules	very small molecules.	small molecule
5	In cell mediated immunity which one serves as immunogens.	antigen	Antibody	protein	haptens.	protein
6	Analogue of dihydrofolic acid is _____	xanthine	uric acid	aminopterin	arginine	aminopterin
7	Which one of the following acts as fusogen	hypoxanthine	PRPP	polyethylene glycc	glycerol	polyethylene glycol
8	Which are the substances serves to enhance the immunogenicity.	proteins	cytokines	haptens	Adjuvants	Adjuvants
9	The formation of macrophage- trich mass of cells called as	Granuloma	granules	endo granules	exogranules.	Granuloma

10	---------- are the immunologically active regions of an immunogen	exotopes	epitopes	endotopes	exotopes.	epitopes
11	Sperm whale myoglobin contains abundance of ---------- regions.	µ - helical	b - helical	g- helical	helical	µ - helical
12	Complex proteins contains multiple overlapping ---------- epitopes.	T cell	B cell	NK cells	T_H cells.	B cell
13	Haptens are	Immunogenic	immune	antigens	antigenic	antigenic
14	Chemical coupling of a hapten to a large protein called as	Carrier	hapten – carrier	antigen – carrier	antibody carrier.	Carrier
15	Which one is capable of inducing cell division in a high percentage of T and B cells	mesogens	mitogens	endogens	exogens.	mitogens
16	polyclonal activators are also known as	exogens	endogens	mesogens	mitogens.	mitogens.
17	Mitogens are sugar-binding protein called as	lectins	endolectin	exolectin	mesolectin.	lectins
18	Cancerous plasma cell is also called as	Myeloma cell	plasma cell	cancer cell	grauloma cell	grauloma cell
19	The light chains in urine of myleoma patients	Jonce protiens	Bence Jones proteins	proteins	myleoma proteins.	Bence Jones proteins
20	The clones of maliginant plasma cells that develop are called	Plasma	cytoma	plasmacytomas	Myeloma	plasmacytomas
21	Which is a transmembrane protein complex	B-cell receptor	T cell	T cell receptor	B cell.	B-cell receptor
22	The g- chain allotypes are referred to as	GI markers	Gl markers	Gn markers	Gm markers.	Gm markers.
23	Which Immunogloubulin is found abundance in serum	Ig K	IgG	IgM	IgG1.	IgG
24	5% - 10% of the total serum immunoglobulin was	IgG	IgG1	Ig K	IgM	IgM
25	Monomeric IgM has a molecular weight of	180,000	188,000	181,000	190,000	180,000

26	Antigenic cells are readily aggluitaned by	IgG	IgA	Ig K	IgM	IgM
27	The biological role of -------- is found in the development of allergic symptoms	IgG	IgA	IgE	IgM	IgE
28	Second largest class of immunogluoblins present in human serum	IgG	IgA	IgE	IgM	IgA
29	The two monomeric IgA molecules are cross linked by short polypeptide chain called	J chain	B chain	A chain	K chain.	J chain
30	Immunogluoblins, which are isotypically as well as allotypically similar are refferd to as	IgE	IgM	Idiotypes	endotypes.	Idiotypes
31	Who proposed the basic structure of	Rodney proter	Koular &	Perlman	Dreyer	Rodney proter
32	When an immunogloublin does not reactswith an antigen, it is known as	Antigen	Antibody	Antigen – antibody	Immunoglobulins.	Immunoglobulins.
33	When the immunogloublin contains kappa chain, it is known as	L type	K type	KL type	K_1 type.	K type
34	When the immunogloublin contains lambda chain, it is known as	L type	K type	KL type	K_1 type	L type
35	g- chain in the immunogloublin is	Ig A	Ig M	I gG	Ig D	I gG
36	a- chain in the immunogloublin is	Ig A	Ig M	I gG	Ig D	Ig A
37	m- chain in the immunogloublin is	Ig A	Ig M	I gG	Ig D	Ig M
38	d - chain in the immunogloublin is	Ig A	Ig M	I gG	Ig D	Ig D
39	Epsilon chain in the immunogloublin is	Ig A	Ig M	I gE	Ig D	I gE
40	Antigen binding fragments is also known as	Fab	Fc	VL	VHL	Fab

41	Crystalline fragment is also known as	Fab	Fc	VL	VHL	Fc
42	Amino acid sequence and the shape of the combining site together constitute the	epitope	endotope	paratope	exotope	paratope
43	Paratope is complementary to the specific shape of the ---------- in the antigen	epitope	endotope	paratope	exotope.	epitope
44	---------- is the only immunogloublin that crosses the human placenta.	Ig A	Ig M	I gG	Ig D	I gG
45	IgG neutralizes	Bacteira	Viruses	fungi	algae.	Viruses
46	Which one is the largest immunoglobulin	Ig A	Ig M	I gG	Ig D	Ig M
47	Which immunogloublin is limited to the blood serum	Ig A	Ig M	I gG	Ig D	Ig D
48	Which one is heat stable immunogloublins.	Ig E	Ig M	I gG	Ig G	Ig E
49	Which immunogloublin has a special attraction to mast cells	Ig A	Ig E	I gG	Ig D	Ig E
50	In IgE carbohydrate content found to be	12 %	13%	14 %	15%	12 %
51	---------- is a process of clumping of particulate antigens.	Precipitation	agglutination	covalent binding	Cross – linking	agglutination
52	The first injection of the antigen producing primary immune response is called as	Primary dose	secondary dose	tertiary dose	Quantery dose.	Primary dose
53	The injection of the same antigen for the second time is called as	Primary dose	Booster dose	tertiary dose	Quantery dose.	Booster dose
54	The amount of antibodies produced by the immune response.	Antigen titre	antibody titre	antigen- antibody titre	immuno titre	Antigen titre
55	Aminopterin blocks which DNA synthetic pathway	Salwage pathway	Denovo pathway	Both	cAMP Pathway	Denovo pathway

56	Catalytic antibodies are called as	enzymes	abzymes	ribozymes	ribulozyme	
57	Among the following which one is not involved in antibody diversity	junctional flexibility	somatic hyper mutation	P addition	negative selection	negative selection
58	In heavy chain gene rearrangement which genes are involved	V genes	D genes	J genes	all	all
59	Among the following which plays important role in antibody diversity	class switching	flipflop movement	Transition	transversion	class switching
60	In human heavy chain genes are located at chromosome	2	7	14	21	14

UNIT-III

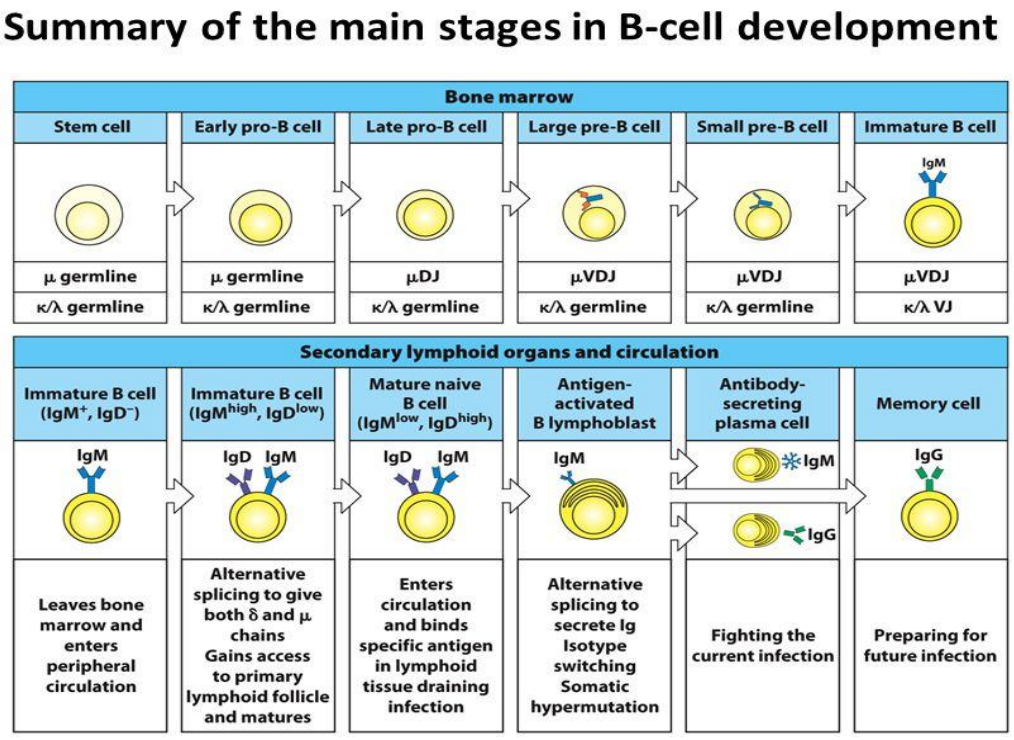
SYLLABUS

Biology of the B and T lymphocyte and complement system

Antigen independent phase of B cell maturation and selection, humoral response – T-dependent and T-independent response, anatomical distribution of B cell populations. Structure and role of T cell receptor, and co-receptor, T cell development, generation of receptor diversity, selection and differentiation. Complement activation by classical, alternate and MB lectin pathway, biological consequences of complement activation, regulation and complement deficiencies.

The development of B cells can be divided into six functionally distinct phases

The first two phases correspond to development in the **bone marrow**; the last four phases correspond to development in the **secondary lymphoid tissues**.



B cells develop in bone marrow and then migrate to secondary lymphoid tissues

B cells leaving the bone marrow (yellow) are carried in the blood to lymph nodes, the spleen, Peyer's patches, and other secondary lymphoid tissues such as those lining the respiratory tract.

Pro-B cells develop from the pluripotent hematopoietic stem cell

Cells at different stages of development are identified by different combinations of CD proteins on their surface. CD127 is the α chain of the receptor for interleukin-7. IL7-Rα

The early stages of B-cell development are dependent on bone marrow stromal cells

60 billion B cells/day

The early stages of B-cell development are dependent on bone marrow stromal cells.

The panels show the interactions of developing B cells with bone marrow stromal cells. Stem cells and early pro-B cells use the integrin VLA-4 to bind to the adhesion molecule VCAM-1 on stromal cells. This and interactions between other cell-adhesion molecules (CAMs) promote the binding of the receptor Kit on the B cell to stem-cell factor (SCF) on the stromal cell. Activation of Kit causes the B cell to proliferate. B cells at a later stage of maturation require interleukin-7 (IL-7) to stimulate their growth and proliferation.

The development of B cells in the bone marrow proceeds through stages defined by the rearrangement and expression of the immunoglobulin genes In the stem cell, the immunoglobulin (Ig) genes are in the germline configuration. The first rearrangements are of the heavy-chain (H-chain) genes. Joining DH to JH defines the early pro-B cell, which becomes a late pro-B cell on joining VH to DJH. Expression of a functional μ chain defines the large pre-B cell. Large pre-B cells proliferate, producing small pre-B cells in which rearrangement of the light-chain (L-chain) gene occurs. Successful light-chain gene rearrangement and expression of IgM on the cell surface define the immature B cell.

Various cell adhesion molecules cytokines and transcription factors regulate B cell development

* PU.1
* Ikaros
* EBF, E2A
* Pax5
* CLP
* early
* pro-B
* c-Kit
* Receptor
* Stem cell factor (SCF)
* Cell membrane bound
* VLA-4
* (Integrin)

* adhesion
* molecules
* VCAM-1
* (Ig superfamily)
* Stroma cell

Cell-fate specification of multipotent haematopoietic stem cells (HSCs) is determined by unique expression patterns of combinations of transcription factors, and for B cells, the five most important factors are PU.1, Ikaros, E2A, EBF (early B-cell factor) and PAX5 (paired box protein 5).
Cytokines and cell adhesion molecules change with successive steps of development

* Interleukin-7
* receptor
* Interleukin-7
* Growth factor
* Early
* pro-B
* VLA-4
* (Integrin)
* VCAM-1
* (Ig superfamily)

Interleukin-7 (IL-7) is a key cytokine during B cell development and is produced by stromal cells in the bone marrow. IL-7 receptor (IL-7R) signaling leads to the proliferation and survival of B cell progenitors as well as aids in the commitment of cells to the B lineage. Mice with targeted deletions of IL-7 or the IL-7R display a severe block at the early pro-B cell stage of development.

Immunoglobulin heavy-chain gene rearrangement in pro-B cells gives rise to productive and nonproductive rearrangements

A productive rearrangement enables the B cell to proceed to the next stage of development. Rearrangements occur at the H-chain genes on both chromosomes, and if neither is successful the cell dies.

The pre B-cell receptor monitors the quality of heavy chain rearrangement

Distinguishing the pre-B-cell receptor from the B-cell receptor is the absence of a κ or λ immunoglobulin light chain, and the presence instead of the surrogate light chain composed of the VpreB and λ5 polypeptides. In low abundance at the cell surface, the pre-B-cell receptor is largely retained inside the cell in membrane-enclosed vesicles, from where it generates signals that lead to the cessation of heavy-chain gene rearrangements. In addition to forming the two Ig-like domains of the surrogate light chain, VpreB and λ5 have extensions that cause oligomerization of pre-B-cell receptors and the transduction of signals necessary for pre-B-cell survival.

Successful somatic rearrangement in one chromosome

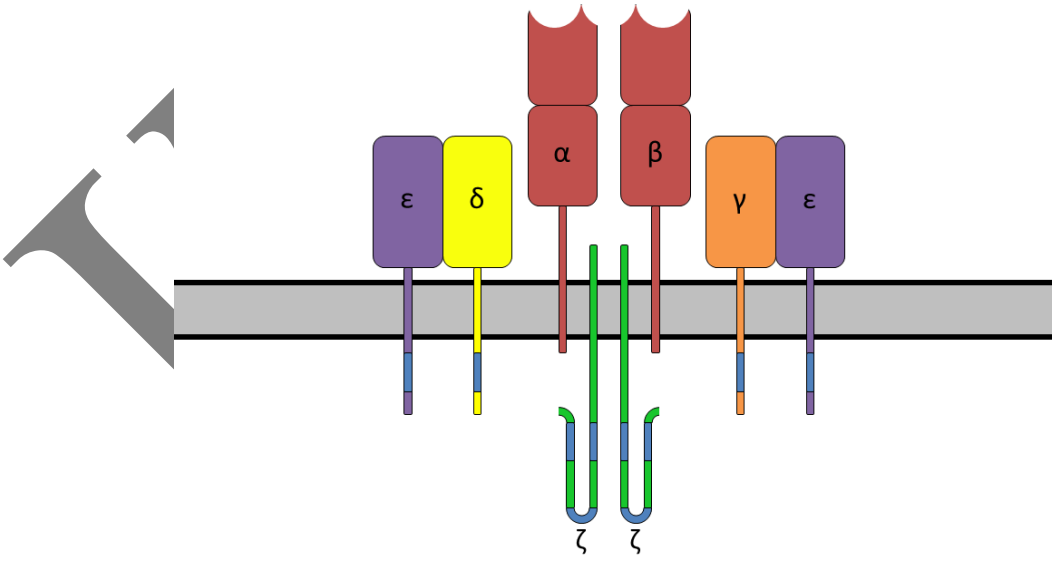
ALLELIC EXCLUSION

Successful somatic rearrangement in one chromosome inhibits gene rearrangement in the other chromosome.

Allelic exclusion at the immunoglobulin loci gives rise to B cells having antigen receptors of a single specificity The top panel shows the binding to antigen of B-cell receptors produced in a B cell expressing immunoglobulin from one immunoglobulin heavy-chain locus and one immunoglobulin light-chain locus only. All the receptors have identical antigen-binding sites and bind their antigen with high avidity. The bottom panel shows the B-cell receptors formed in a hypothetical B cell expressing immunoglobulin from both the immunoglobulin heavy-chain loci and one light-chain locus. Hybrid immunoglobulins are formed with disparate antigen-binding sites and bind the antigen poorly and with low avidity. The disparities would be even greater in a B cell expressing two heavy-chain and two light-chain genes.

T Cell Receptor

The T-cell receptor, or TCR, is a molecule found on the surface of T cells, or T lymphocytes, that is responsible for recognizing fragments of antigen as peptides bound to major histocompatibility complex (MHC) molecules.



The binding between TCR and antigen peptides is of relatively low affinity and is degenerate: that is, many TCRs recognize the same antigen peptide and many antigen peptides are recognized by the same TCR.

The TCR is composed of two different protein chains (that is, it is a heterodimer). In humans, in 95% of T cells the TCR consists of an alpha (α) chain and a beta (β) chain (encoded by TRA and TRB, respectively), whereas in 5% of T cells the TCR consists of gamma and delta (γ/δ) chains (encoded by TRG and TRD, respectively). This ratio changes during ontogeny and in diseased states (such as leukemia). It also differs between species. Orthologues of the 4 loci have been mapped in various species. Each locus can produce a variety of polypeptides with constant and variable regions.

When the TCR engages with antigenic peptide and MHC (peptide/MHC), the T lymphocyte is activated through signal transduction, that is, a series of biochemical events mediated by associated enzymes, co-receptors, specialized adaptor molecules, and activated or released transcription factors.

THE COMPLEMENT SYSTEM

Complement (C) was used to refer to a heat-labile serum component that was able to lyse bacteria (activity is destroyed (inactivated) by heating serum at 56 degrees C for 30 minutes). However, complement is now known to contribute to host defenses in other ways as well. Complement can opsonize bacteria for enhanced phagocytosis; it can recruit and activate various cells including polymorphonuclear cells (PMNs) and macrophages; it can participate in regulation of antibody responses and it can aid in the clearance of immune complexes and apoptotic cells. Complement can also have detrimental effects for the host; it contributes to inflammation and tissue damage and it can trigger anaphylaxis.

Complement comprises over 20 different serum proteins (see Table 1) that are produced by a variety of cells including, hepatocytes, macrophages and gut epithelial cells. Some complement proteins bind to immunoglobulins or to membrane components of cells. Others are proenzymes that, when activated, cleave one or more other complement proteins. Upon cleavage some of the complement proteins yield fragments that activate cells, increase vascular permeability or opsonize bacteria.

The following are the basic functions of the complement

1. Opsonisation - enhancing phagocytosis of antigens
2. Chemotaxis - attracting macrophages and neutrophils
3. Cell Lysis - rupturing membranes of foreign cells
4. Clumping of antigen-bearing agents

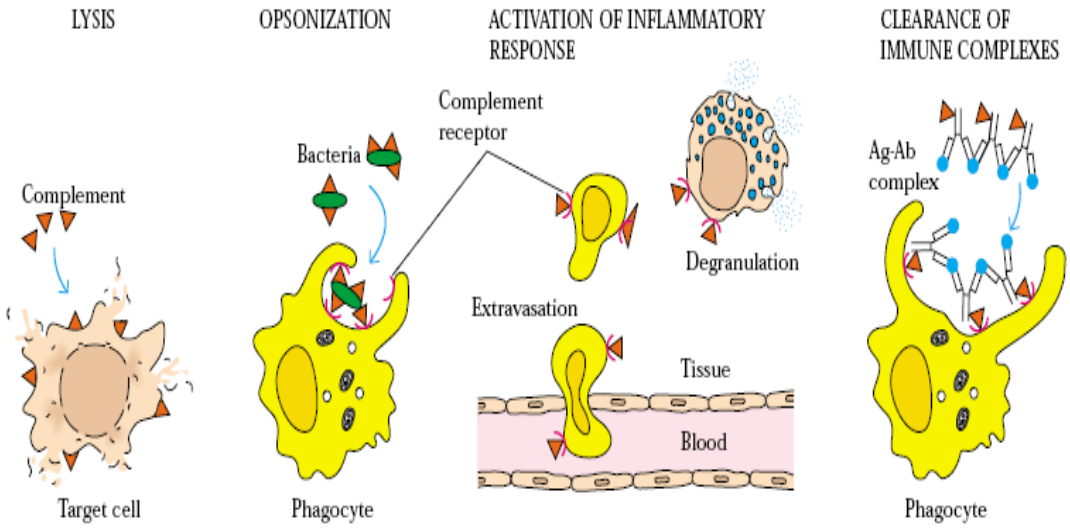


Fig: Multiple activities of the complement system.

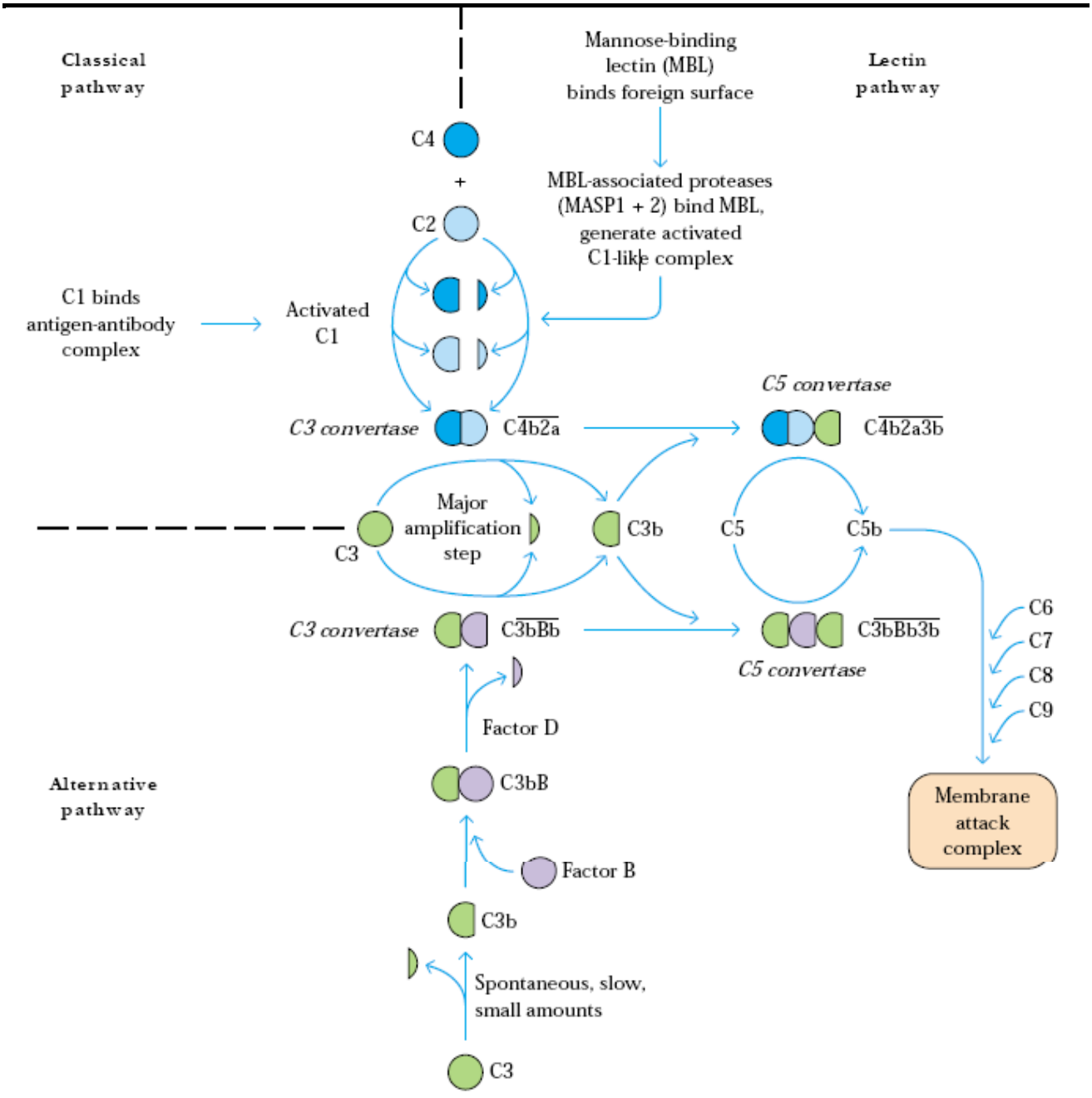


FIG: Overview of the complement activation pathways. The classical pathway is initiated when C1 binds to antigen-antibody complexes. The alternative pathway is initiated by binding of spon-taneously generated C3b to activating surfaces such as microbial cell walls. The lectin pathway is initiated by binding of the serum protein MBL to the surface of a pathogen. All three pathways generate C3 and C5 convertases and bound C5b, which is converted into a mem brane-attack complex (MAC) by a common sequence of terminal reactions. Hydrolysis of C3 is the major amplification step in all path-ways, generating large amounts of C3b, which forms part of C5 con-vertase. C3b also can diffuse away from the activating surface and bind to immune complexes or foreign cell surfaces, where it func-tions as an opsonin.

Complement Deficiency Disease

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening disease of the blood characterized by destruction of red blood cells by the complement system, a part of the body's innate immune system. This destructive process occurs due to the presence of defective surface proteins on the red blood cell, **decay acceleration factor**, which normally function to inhibit such immune reactions. Since the complement cascade attacks the red blood cells within the blood vessels of the circulatory system, the red blood cell destruction (hemolysis) is considered an intravascular hemolytic anemia.

Hereditary angioedema (HAE) is disorder that results in recurrent attacks of severe swelling due to deficieny of C1 esterase which inactivates the C1q. The swelling most commonly affects the arms, legs, face, intestinal tract, and airway.Itchiness does not typically occur. If the intestinal tract is affected abdominal pain and vomiting may occur.

Properdin deficiency is an X-linked disorder that also causes susceptibility to Neisseria infections

In terms of **deficiency of C3**, it has been found that 17 mutations in the C3 gene cause problems with C3. This rare condition mutates or prevents C3 protein from forming, lowering the immune system's ability to protect.

C4 deficiency is highly associated with systemic lupus erythematosus. Aβ42, a protein involved in Alzheimer's disease, can cause activation of C4 (even in plasma deficient of C1q)

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UNIT- III

S.NO						
	---------- Reactions are responsible for tackling invasion of foreign antigens.	Antigen	Immune	Antibody	Antigen- antibody	Immune
1	The visible feature of hypersensitive states is the inflammation developed at the site of	Antigen	Antibody	Antigen-antibody	Foreign antigens.	Antigen- antibody
2	Type I is acute in nature and mediated by	IgM	IgA	Ig D	IgE	IgE
3	Which type of hypersensitivity resulting mainly from blood transfusion methods.	Type I	Type II	Type III	TypeIV	Type II
4	Which hypersentivity involves formationof complexes btwn Ab &Ag lodged capillaries	Type I	Type II	Type III	TypeIV	Type III
5	Which type hypersentivity involves in delayed type of reaction mediated by lymphocytes.	Type I	Type II	Type III	TypeIV	TypeIV
6	-------- release causes peripheral vasodilation	Histamine	anaphylaxis	Edema	erytherma.	Histamine
7	Histamine is a	amine	bio amine	di amine	tri amine.	bio amine
8	In anaphlyaxis ,antibodies are only the indirect cause of the	Influx	lnfection	lnflammation	Vasodilation	lnflammation
9	The antibodies are collectively called	reagins	pre-reagins	exo-reagins	endo-reagins	reagins

10	Influx of Ca_2+ ions activate phospholipase	A_1	A_2	A_3	A_4	A_2
11	The prostagladin pathway is initiated by the enzyme	oxygenase	non-cyclooxygenase	cyclo oxygenase	endooxygenase	cyclo oxygenase
12	Prostagladin biosynthesis may be blocked by	aspirin	salicylate	salicylic acid	streptomycin	aspirin
13	The PGE_1 also enhances immunogenecity of	liver cells	spleen cells	mast cells	lymph cells	mast cells
14	Antigens which give rise to allergic reactions are called	allergic	allergic response	allergens	allergen response	allergens
15	ABO blood group antigens are	Lipids	Glycolipids	Oligosaccharides	galactose	Glycolipids
16	The T cell subsets operate by releasing chemical substances called	lymphocytes	lymphokines	lymphoma	pre-lymphocytes	lymphokines
17	C_3 has molecular weight of	190KD	192KD	194KD	195KD	195KD
18	Activation of first complement component is triggered by	Ag complex	Antibody complex	Ag-Ab complex	Cross-linking	Ag-Ab complex
19	The…… region has key role in activating the complement	Fc	fab	C_1	C_3 `	Fc
20	The complement system can activate phagocytes, a phenomenon called as	phagocytosis	opsonisation	Immune response	endotoxins	opsonisation
21	Classical pathway is a ……dependant	Ag	Ag-Ab	Ab	C_3	Ab
22	……is the most potent antibody to activate classical pathway	IgG	IgM	IgG_1	IgG_3	IgM
23	The alternative pathway starts at	C_3	C3a	C3b	C5a	C_3
24	SLE disease is caused by the deficiency of	C1	C1p	C1 q	C1 r	C1 q
25	Meningococcal infections is caused by the deficiency of	C5	C6	C7	C9	C6

26	Gococcal infections is caused by the deficiency of	C_5	C_6	C_7	C_9	C_5
27	---------- has proved to be chemo tactic	C_5	C_{5a}	C_6	C_9	C_{5a}
28	Bacteria are coated with ---------- molecules.	Antigen	divalent	Antibody	Antigen- antibody	Antibody
29	Which is the agent that enhances phagocytosis by immune adherence are	C3	C3a	C3a1	C3b	C3b
30	Histocompability antigen found on the surface of	mast cell	nucleated cell	spleen cell	stem cell	nucleated cell
31	Histocompability antigen are highly	Monomer	Dimer	Polymorphic	multimorphic	Polymorphic
32	All MHC genes are	silent	Activate	intermediate	suppress.	silent
33	Which region in HLA complex contains several different genes	D	R	DR	HLA-D	DR
34	HLA-D antigens are	hetero dimer	dimer	homodimer	hexodimer.	hetero dimer
35	The MHC genes coding for …….. antigens in the mouse	H	H-1	H-2	H-3	H-2
36	HLA genes are	dominant	recessive	co-recessive	co-dominant	co-dominant
37	In MHC class II Ag, which one is found on surface of B cells macrophages &active cells	Ag	Ab	Ag-Ab	B cell Ag	Ag
38	The human MHC region has …….coding sequence	1	2	3	4	3
39	In mouse MHC region has	H-2K	H-2D	H-K&H-D	H2K-H-2D	H2K-H-2D
40	HLA locus has about …….different alleles.	23	24	25	26	25

41	In mouse H-2 region has more than ……different alleles.	210	220	230	200	200
42	Class I antigens are	glycans	glycoproteins	proteins	peptides	glycoproteins
43	In MHC classII antigen α chain has its molecular weight	30,000	29,000	31,000	32,000	32,000
44	In MHC classII antigen ß chain has its molecular weight	30,000	29,000	31,000	32,000	29,000
45	MHC classI antigens cause cell mediated lysis of……infected cell.	bacteria	fungi	virus	algae	virus
46	MHC classII antigens play an important role in	graft	autograft	isograft	allograft	graft
47	Blood transfusion,is a good example of transplantation of	liver	tissue	heart	kidney	tissue
48	grafting of one part to another in same individual is	xeno graft	autograft	isograft	allograft	isograft
49	Trasplantation of two individuals from identical twins are called as	xeno graft	autograft	isograft	allograft	isograft
50	Transplantation of tissue between two animals of same species	autograft	isograft	allograft	xenograft	allograft
51	Grafts between two individuals of different species is	xeno graft	autograft	isograft	allograft	xeno graft
52	Humoral Ab play an important role in……rejection	hyper acute	acute	graft	delayed	graft
53	Syngeneic are also known as	Isograft	allograft	autograft	xenogaft	Isograft
54	Acute rejection occurs usually in about	7 days	8 days	9 days	10 days	10 days
55	Antigen from donor kidney is processed by a	macrophage	monocyte	mast cell	lymphocytes	macrophage

56	Exposure to radiation causes depletion of	macrophage	monocyte	mast cell	lymphocytes	lymphocytes
57	Bone-marrow grafting leads to	leukemia	hypertension	Wilson’s disease	Renal failure	leukemia
58	Graft rejection is controlled by	cytotoxic	cytokines	lymphoma	lymphocytes	cytotoxic
59	According to Sir Peter Medawar,graft rejection is mainly due to……..reactions	Ag-Ab	immune	cytotoxic	Ab reaction	cytotoxic
60	Macrophages is found in	Blood	Bone marrow	tissues	Cells.	tissues

UNIT-IV

General properties of effector T cells, cytotoxic T cells (Tc), natural killer cells; NKT cells and antibody dependent cellular cytotoxicity (ADCC). Organ specific and systemic autoimmune diseases, possible mechanisms of induction of autoimmunity, Gell and Coombs classification, IgE mediated (Type I) hypersensitivity antibody mediated cytotoxic (Type II) hypersensitivity, immune complex mediated (type III) hypersensitivity and cell mediated (Type IV) hypersensitivity.

A T cell, or T lymphocyte, is a type of lymphocyte (a subtype of white blood cell) that plays a central role in cell-mediated immunity. T cells can be distinguished from other lymphocytes, such as B cells and natural killer cells, by the presence of a T-cell receptor on the cell surface. They are called T cells because they mature in the thymus from thymocytes

T helper cells (TH cells) assist other white blood cells in immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and macrophages. These cells are also known as CD4+ T cells because they express the CD4 glycoprotein on their surfaces. Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen-presenting cells (APCs). Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or assist in the active immune response. These cells can differentiate into one of several subtypes, including TH1, TH2, TH3, TH17, TH9, or TFH, which secrete different cytokines to facilitate different types of immune responses. Signalling from the APC directs T cells into particular subtypes

Cytotoxic (Killer) CD8 +ve

Cytotoxic T cells (TC cells, CTLs, T-killer cells, killer T cells) destroy virus-infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as CD8+ T cells since they express the CD8 glycoprotein at their surfaces. These cells recognize their targets by binding to antigen associated with MHC class I molecules, which are present on the surface of all nucleated cells. Through IL-10, adenosine, and other molecules secreted by regulatory T cells, the CD8+ cells can be inactivated to an anergic state, which prevents autoimmune diseases.

Natural killer T cell

Natural killer T cells (NKT cells – not to be confused with natural killer cells of the innate immune system) bridge the adaptive immune system with the innate immune system. Unlike conventional T cells that recognize peptide antigens presented by major histocompatibility complex (MHC) molecules, NKT

cells recognize glycolipid antigen presented by a molecule called CD1d. Once activated, these cells can perform functions ascribed to both Th and Tc cells (i.e., cytokine production and release of cytolytic/cell killing molecules). They are also able to recognize and eliminate some tumor cells and cells infected with herpes viruses.

The **antibody-dependent cell-mediated cytotoxicity** (ADCC), also referred to as antibody-dependent cellular cytotoxicity, is a mechanism of cell-mediated immune defense whereby an effector cell of the immune system actively lyses a target cell, whose membrane-surface antigens have been bound by specific antibodies. It is one of the mechanisms through which antibodies, as part of the humoral immune response, can act to limit and contain infection.

ADCC is independent of the immune complement system that also lyses targets but does not require any other cell. ADCC requires an effector cell which classically is known to be natural killer (NK) cells that typically interact with IgG antibodies. However, macrophages, neutrophils and eosinophils can also mediate ADCC, such as eosinophils killing certain parasitic worms known as helminths via IgE antibodies. ADCC is part of the adaptive immune response due to its dependence on a prior antibody response. The coating of target cells with antibodies is sometimes referred to as opsonization.

Autoimmune diseases

Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. In other words, the body actually attacks its own cells. The immune system mistakes some part of the body as a pathogen and attacks it. This may be restricted to certain organs (e.g. in chagas disease) or involve a particular tissue in different places (e.g. Goodpasture's disease which may affect the basement membrane in both the lung and the kidney).

The treatment of autoimmune diseases is typically with immunosuppression—medication which decreases the immune response.

The cause of autoimmune diseases is unknown, but it appears that there is an inherited predisposition to develop autoimmune disease in many cases. In a few types of autoimmune disease (such as rheumatic fever), a bacteria or virus triggers an immune response, and the antibodies or T-cells attack normal cells because they have some part of their structure that resembles a part of the structure of the infecting microorganism.

EFFECTOR MECHANISMS IN AUTOIMMUNE DISEASES

Both antibodies and effector T cells can be involved in the damage in autoimmune diseases.

GENERAL CLASSIFICATION

Autoimmune diseases are generally classified on the basis of the organ or tissue involved. These diseases may fall in an organ-specific category in which the immune response is directed against antigen(s) associated with the target organ being damaged or a non-organ-specific category in which the antibody is directed against an antigen not associated with the target organ. The antigen involved in most autoimmune diseases is evident from the name of the disease .

Autoimmune disorders fall into two general types: those that damage many organs (systemic autoimmune diseases) and those where only a single organ or tissue is directly damaged by the autoimmune process (localized). However, the distinctions become blurred as the effect of localized autoimmune disorders frequently extends beyond the targeted tissues, indirectly affecting other body organs and systems. Some of the most common types of autoimmune disorders include:

Systemic Autoimmune Diseases

- Rheumatoid arthritis (RA) and Juvenile RA (JRA) (joints; less commonly lung, skin)
- Lupus [Systemic Lupus Erythematosus] (skin, joints, kidneys, heart, brain, red blood cells, other)

- Scleroderma (skin, intestine, less commonly lung)
- Sjögren's syndrome (salivary glands, tear glands, joints)
- Goodpasture's syndrome (lungs, kidneys)
- Wegener's granulomatosis (blood vessels, sinuses, lungs, kidneys)
- Polymyalgia Rheumatica (large muscle groups)
- Guillain-Barre syndrome (nervous system)

Localized Autoimmune Diseases

- Type 1 Diabetes Mellitus (pancreas islets)
- Hashimoto's thyroiditis, Graves' disease (thyroid)
- Celiac disease, Crohn's disease, Ulcerative colitis (GI tract)
- Multiple sclerosis (There is still some debate as to whetherMS is an autoimmune disease.)
- Addison's disease (adrenal)
- Primary biliary cirrhosis, Sclerosing cholangitis, Autoimmune hepatitis (liver)
- Temporal Arteritis / Giant Cell Arteritis (arteries of the head and neck)

ETIOLOGY OF AUTOIMMUNITY DISEASE

The exact etiology of autoimmune diseases is not known. However, various theories have been offered. These include sequestered antigen, escape of auto-reactive clones, loss of suppressor cells, cross reactive antigens including exogenous antigens (pathogens) and altered self antigens (chemical and viral infections).

Sequestered antigen

Lymphoid cells may not be exposed to some self antigens during their differentiation, because they may be late-developing antigens or may be confined to specialized organs (*e.g*., testes, brain, eye, *etc*.). A release of antigens from these organs resulting from accidental traumatic injury or surgery can result in the stimulation of an immune response and initiation of an autoimmune disease.

Escape of auto-reactive clones

The negative selection in the thymus may not be fully functional to eliminate self reactive cells. Not all self antigens may be represented in the thymus or certain antigens may not be properly processed and presented.

Lack of regulatory T cells

There are fewer regulatory T-cells in many autoimmune diseases

Cross reactive antigens

Antigens on certain pathogens may have determinants which cross react with self antigens and an immune response against these determinants may lead to effector cell or antibodies against tissue

antigens. Post streptococcal nephritis and carditis, anticardiolipin antibodies during syphilis and association between *Klebsiella*and ankylosing spondylitis are examples of such cross reactivity.

DIAGNOSIS

Diagnosis of autoimmune diseases is based on symptoms and detection of antibodies (and/or very early T cells) reactive against antigens of tissues and cells involved. Antibodies against cell/tissue associated antigens are detected by immunofluorescence. Antibodies against soluble antigens are normally detected ELISA or radioimmunoassay (see table above). In some cases, a biological /biochemical assay may be used (*e.g.*, Graves diseases, pernicious anemia). Autoimmune disorders are diagnosed, evaluated, and monitored through a combination of autoantibody blood tests, blood tests to measure inflammation and organ function, clinical presentation, and through non-laboratory examinations such as X-rays.

TREATMENT

There is currently no cure for autoimmune disorders, although in rare cases they may disappear on their own. The goals of treatment of autoimmune disorders are to reduce symptoms and control the autoimmune response while maintaining the body's ability to fight infections. Treatments vary widely and depend on the specific disease and symptoms: Anti-inflammatory (corticosteroid) and immunosuppressive drug therapy (such as cyclophosphamide, azathioprine, cyclosporine) is the present method of treating autoimmune diseases. Extensive research is being carried out to develop innovative treatments which include: anti-TNF alpha therapy against arthritis, feeding antigen orally to trigger tolerance, anti-idiotype antibodies, antigen peptides, anti-IL2 receptor antibodies, anti-CD4 antibodies, anti-TCR antibodies, etc.

MYASTHENIA GRAVIS

Myasthenia gravis is a chronic autoimmune disorder that affects the voluntary muscles of the body. It is characterized by weakness or rapid muscle fatigue. The condition is supposed to occur when there is a dysfunction between the muscles and the nerves that control the same. A defect in the transmission of nerve impulses to the muscles gives rise to the symptoms of the condition.

Myasthenia gravis is usually not inherited but it develops with age. It often affects women after the age of 40 and men after 60. Muscle weakness is a common symptom of many other conditions and hence a diagnosis for myasthenia gravis is often delayed and learnt about quite late.

Pathophysiology:

In MG, the autoantibodies **most commonly act against the nicotinic acetylcholine receptor (nAChR),** the receptor in the motor end plate for the neurotransmitteracetylcholine that stimulates muscular contractions. Some forms of the antibody impair the ability of acetylcholine to bind to receptors. Others lead to the destruction of receptors, either by complement fixation or by inducing the muscle cell to eliminate the receptors through endocytosis.

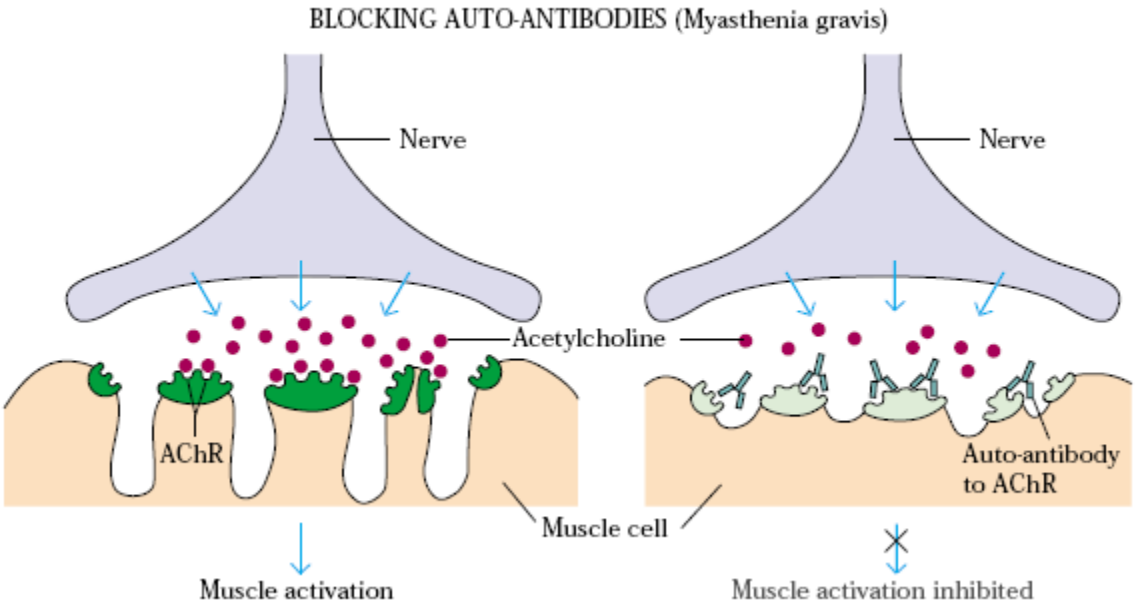
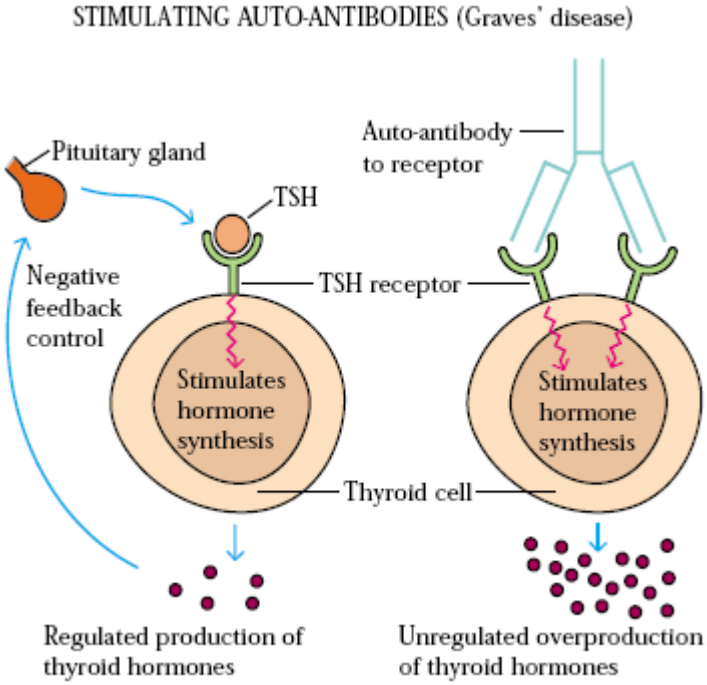


Fig:In MG , binding of auto antibodies to acetyl choline receptor blockksthe normal binding of acetyl choline and subsequent muscle activation. In addition the antiAchR auto antibodies activates complement which damage the muscle end plate

GRAVES' DISEASE

The production of thyroid hormones is carefully regulated by thyroid-stimulating hormone (TSH), which is produced by the pituitary gland. Binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones, thyroxine and triiodothyronine. A patient with **Graves' disease** produces auto-antibodies that bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in produc-tion of the thyroid hormones. Unlike TSH, however, the auto-antibodies are not regulated, and consequently they over-stimulate the thyroid. For this reason these auto-antibodies are called long-acting thyroid-stimulating (LATS) antibod-ies (Figure).



In Graves' disease, binding of auto-antibodies to the receptor for thyroid-stimulating hormone (TSH) induces unregu-lated activation of the thyroid, leading to overproduction of the thy-roid hormones (purple dots).

Common signs and symptoms of Graves' disease include:

Graves' disease is an immune system disorder that results in the overproduction of thyroid hormones (hyperthyroidism). Although a number of disorders may result in hyperthyroidism, Graves' disease is a common cause.Because thyroid hormones affect a number of different body systems, signs and symptoms associated with Graves' disease can be wide ranging and significantly influence your overall well-being. Although Graves' disease may affect anyone, it's more common among women and before the age of 40.

- Anxiety and irritability
- A fine tremor of your hands or fingers
- Heat sensitivity and an increase in perspiration or warm, moist skin
- Weight loss, despite normal eating habits
- Enlargement of your thyroid gland (goiter)
- Change in menstrual cycles

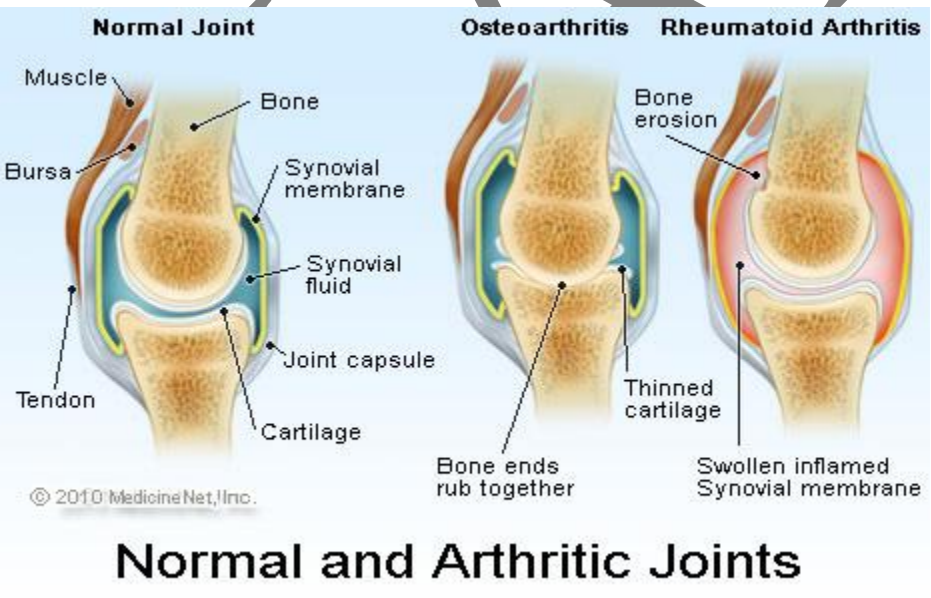
- Erectile dysfunction or reduced libido
- Frequent bowel movements
- Bulging eyes (Graves' ophthalmopathy)
- Thick, red skin usually on the shins or tops of the feet (Graves' dermopathy)
- Rapid or irregular heartbeat (palpitations)

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic inflammatory disorder that typically affects the small joints in hands and feet. Unlike the wear-and-tear damage of osteoarthritis, rheumatoid arthritis affects the lining of joints, causing a painful swelling that can eventually result in bone erosion and joint deformity.

An autoimmune disorder, rheumatoid arthritis occurs when immune system mistakenly attacks own body's tissues. In addition to causing joint problems, rheumatoid arthritis sometimes can affect other organs of the body — such as the skin, eyes, lungs and blood vessels.

Although rheumatoid arthritis can occur at any age, it usually begins after age 40. The disorder is much more common in women than in men. Treatment focuses on controlling symptoms and preventing joint damage.



Normal and Arthritic Joints

Rheumatoid arthritis signs and symptoms may vary in severity and may even come and go. Periods of increased disease activity, called flares, alternate with periods of relative remission — when the swelling and pain fade or disappear. Over time, rheumatoid arthritis can cause joints to deform and shift out of place.

Etiology

Rheumatoid arthritis is a common autoimmune disorder, most often affecting women from 40 to 60 years old. The major symptom is chronic inflammation of the joints, although the hematologic, cardiovascular, and respiratory systems are also frequently affected. Many individuals with rheumatoid arthritis produce a group of auto-antibodies called **rheumatoid factors** that are reactive with determi-nants in the Fc region of IgG. The classic rheumatoid factor is an IgM antibody with that reactivity. Such auto-antibodies bind to normal circulating IgG, forming IgM-IgG complexes that are deposited in the joints. These immune complexes can activate the complement cascade, resulting in a type III hypersensitive reaction, which leads to chronic inflammation of the joints.

Systemic Autoimmune Diseases(SLE)

In systemic autoimmune diseases, the response is directed toward a broad range of target antigens and involves a num-ber of organs and tissues. These diseases reflect a general de-fect in immune regulation that results in hyperactive T cells and B cells. Tissue damage is widespread, both from cell-mediated immune responses and from direct cellular dam-age caused by auto-antibodies or by accumulation of im-mune complexes

Systemic Lupus Erythematosus AttacksMany Tissues

One of the best examples of a systemic autoimmune disease is **systemic lupus erythematosus (SLE),** which typically appears in women between 20 and 40 years of age; the ratio of female to male patients is 10:1. SLE is characterized by fever, weak-ness, arthritis, skin rashes, pleurisy, and kidney dysfunction (Figure 20-6). Lupus is more frequent in African-American and Hispanic women than in Caucasians, although it is not known why this is so. Affected individuals may produce auto-antibodies to a vast array of tissue antigens, such as DNA, his-tones, RBCs, platelets, leukocytes, and clotting factors; inter-action of these auto-antibodies with their specific antigens produces various symptoms. Auto-antibody specific for RBCs and platelets, for example, can lead to complement-mediated lysis, resulting in hemolytic anemia and thrombocytopenia, respectively. When immune complexes of auto-antibodies with various nuclear antigens are deposited along the walls of small blood vessels, a type III hypersensitive reaction

devel-ops. The complexes activate the complement system and generate membrane-attack complexes and complement split products that damage the wall of the blood vessel, resulting in vasculitis and glomerulonephritis.

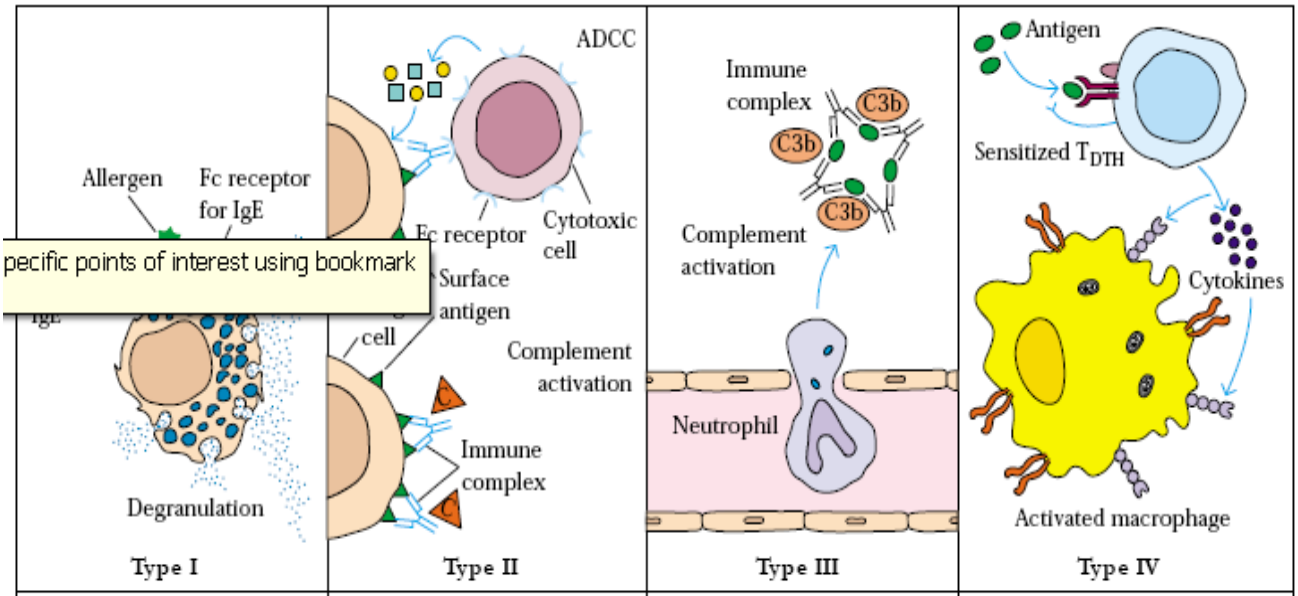
Excessive complement activation in patients with severe SLE produces elevated serum levels of the complement split products C3a and C5a, which may be three to four times higher than normal. C5a induces increased expression of the type 3 complement receptor (CR3) on neutrophils, facilitat-ing neutrophil aggregation and attachment to the vascular endothelium. As neutrophils attach to small blood vessels, the number of circulating neutrophils declines (neutropenia) and various occlusions of the small blood vessels develop (vasculi-tis). These occlusions can lead to widespread tissue damage.

Laboratory diagnosis of SLE focuses on the characteristic antinuclear antibodies, which are directed against double-stranded or single-stranded DNA, nucleoprotein, histones, and nucleolar RNA. Indirect immunofluorescent staining with serum from SLE patients produces various characteris-tic nucleus-staining patterns.

Gell and Coombs classified hypersensitivity reactions into four 'types'. I suggest that the premise that these reactions represent 'hypersensitivity' manifestations is limiting and that they represent four major strategies that the body uses to combat infectious agents.

Table 5 - Comparison of Different Types of hypersensitivity

characteristics	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex)	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	exogenous	cell surface	soluble	tissues & organs
response time	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
appearance	weal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma



Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

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UNIT- IV

S.NO	QUESTION	A	B	C	D	Answer
1	---------- Reactions are responsible for tackling invasion of foreign antigens.	Antigen	Immune	Antibody	Antigen- antibody	Immune
2	The visible feature of hypersensitive states is the inflammation developed at the site of	Antigen	Antibody	Antigen-antibody	Foreign antigens.	Antigen- antibody
3	Type I is acute in nature and mediated by	IgM	IgA	Ig D	IgE	IgE
4	Which type of hypersensitivity resulting mainly from blood transfusion methods.	Type I	Type II	Type III	TypeIV	Type II
5	Which hypersentivity involves formationof complexes btwn Ab &Ag lodged capillaries	Type I	Type II	Type III	TypeIV	Type III
6	Which type hypersentivity involves in delayed type of reaction mediated by lymphocytes.	Type I	Type II	Type III	TypeIV	TypeIV
7	Maternal antibodies present in colostrums provide……..immunity to infant	passive	active	cellular	humoral	passive
8	……..immunization used to provide immediate protection toindividuals exposed to	humoral	active	cellular	Passive	Passive
9	Attenuated strain of Mycobacterium bovis	BCG	Polio	DPT	Hepatitis	BCG

10	The major disadvantage of attenuated vaccine	diversion	inversion	reversion	deletion	inversion
11	One limitation of polysaccharide vaccines is their inability to activate	B cells	Tc cells	NK cells	T_H cells	T_H cells
12	The first recombinant antigen vaccine approved for human use was	Polio	DPT	Hepatitis B	BCG	Hepatitis B
13	A DNA vaccine only induces a response to a single	cytokines	epitopes	haptens	paratopes	epitopes
14	Activated T_H 1 cells produces large number of	Cytokines	epitopes	haptens	paratopes	Cytokines
15	Main components of cell-mediated antiviral defence CD8+ in	T cells	Tc cells	B cell	NK cell	Tc cells
16	Interferon µ and b induce an antiviral protein called	DAI	antibody	cytokine	lnterleukines	DAI
17	The causative agent of common cold	Hepatitis virus	rhinovirus	Epstein-barr virus	herpus virus	rhinovirus
18	The immune system goes against self components of the body suffered	Humoral immunity	Innate immunity	Autoimmunity	cell mediated immunity	Autoimmunity
19	Adrenal hyperplasia and progressive malfunctioning of the adrenal cortex	Addison's disease	Multiple sclerosis	Agranulocytosis	sjogren's syndrome	Addison's disease
20	…….is an autoimmune disease that affects the CNS and causes neurological disability	Addison's disease	Multiple sclerosis	Agranulocytosis	sjogren's syndrome	Multiple sclerosis
21	The genetic basis of most autoimmune disease is	bigenic	isogenic	Agenic	polygenic	polygenic
22	……. play a major role in natural & innate immunity	Neutrophils	phagocytes	macrophages	lymphocytes	phagocytes
23	Reduction in neutrophil counts	neutropenia	aneutropenia	Agranulocytosis	jogren's syndrome	neutropenia
24	Complete absence of neutrophils	Neutropenia	agranulocytosis	agranulopenia	aneutropenia	agranulocytosis

25	Agranulopenia causes decrease in the production of	CSF	M- CSF	G- CSF	C-CSF	G- CSF
26	A autoimmune disease called --------- leads to complete absence of neutrophils	sjogren's syndrome	Graves disease	Addison' s disease	Digeorge syndrome	sjogren's syndrome
27	Which is an indirect test used for the deletion of serum antibody to HIV	RIA	ELISA	DIBA	ELI SPOT	ELISA
28	-------- is an example of a cell mediated immune defect.	Digeorge syndrome	sjogren's syndrome	Graves disease	Addison' s disease	Digeorge syndrome
29	Failure to express MHC molecule is	Digeorge syndrome	sjogren's syndrome	bare lymphocyte syndrome	Graves disease	bare lymphocyte syndrome
30	Most commonly observed clinical feature with HIV infection is the reduction number of	CD^{4+} T cells	CD^{4+} B cells	CD^{4+}	CD^{8+} T cells	CD^{4+} T cells
31	The disease conditions in which immune	Immune response	Antigencity	Immunodeficienc	Immunogenicity	Immunodeficiency
32	Another name for the gel- diffusion technique	single diffusion	Double diffusion	Diffusion	Immuno diffusion	Immuno diffusion
33	The disease characterized by the absence of g-globulins in the blood	X- linked Agamma gloubulinemia	Y- linked Agamma	X- linked Beta gloubulinemia	Y- linked Beta gloubulinemia	X- linked Agamma gloubulinemia
34	Reduction in blood platelets leads to	Wiskott –Aldrich syndrome	Digeorge syndrome	sjogren's syndrome	Graves disease	Wiskott –Aldrich syndrome
35	---------- are antigens expressed on tumor cells but not normal cells.	Tumor specific antibody	Tumor specific antigen	Tumor cells	NK cells.	Tumor specific antigen
36	Solid malignant tumors of lymphoid tissues are called	Lymphocytes	Lymphokines	lymphomas	leukocytes	lymphomas
37	The cytokines produced by activated macrophages that kill tumors but not normal	Malignant tumors	necrosis	Tumor cells	Tumor necrosis factor	Tumor necrosis factor
38	Solid malignant tumors of bone marrow & bloodborn of lymphoctes or other are called	leukemia	Lymphokines	lymphomas	leukocytes	leukemia
39	Cancers derived from epithelial cells are	Sarcoma	Lymphoma	Carcinoma	Myleoma	Carcinoma

40	Malignant tumors of mesenchymal tissues arising from cells like fibroblasts, and fat cells	Sarcoma	Lymphoma	Carcinoma	Myleoma	Sarcoma
41	The antigens do not stimulate immunologic response in the host are	Tumor associated antibody	Tumor associated antigen	Antigen	Antibody	Tumor associated antigen
42	--------- Provide effective anti- tumor immunity invivo	Cytotoxic T-lymphocytes	T- lymphocytes	lymphocytes	cytokines.	Cytotoxic T-lymphocytes
43	Mononuclear cells are found in human solid tumors are	lymphocytes..	Tumor infiltrating	Cytotoxic T-lymphocytes	T- lymphocytes	Tumor infiltrating lymphocytes
44	---------- plays an important role in anti- tumor response.	CD 4 helper T cells	CD $^{4+}$ B cells	CD $^{4+}$	CD $^{8+}$ T cells	CD 4 helper T cells
45	---------- are known to secrete TMF & IFN g on activation by tumor antigens	CD cells	CD 8 cells	CD 4 cells	T cells	CD 4 cells
46	The tumoricidal activity of NK cells is enhanced by	T- lymphocytes	lymphocytes	Cytotoxic T-lymphocytes	Cytokines	Cytokines
47	Tumorcells transfected genes encodingsygernic ---produce effectivecell	MHC	MHC class I	MHC class II	both of MHC class	MHC class II
48	---------- on carcinogen or radiation induced rodent tumors	Tumor specifc transplantation Ag	Tumor specifc transplantation	Transplantation Antigen	Thymus dependent Ag.	Tumor specifc transplantation Ag
49	Grave’s disease, autoantibodies are produced against	Thyroid stimulating hormone receptor	T cell receptor	B cell receptor	T & B cell receptor	Thyroid stimulating hormone receptor
50	---------- is characterized by the abnormal weakness of voluntary muscles.	Wiskott –Aldrich syndrome	Digeorge syndrome	sjogren’s syndrome	Myasthenia Graves disease	Myasthenia Graves disease
51	--------characterized by adrenal hyperplasia & progressive malfunctioning adrenal water	Addison’s disease	Digeorge syndrome	sjogren’s syndrome	Myasthenia Graves disease	Addison’s disease
52	--------- is autoimmune disease that affects the CNS and causes neurological disability	Sclerosis	single sclerosis	Multiple sclerosis	poly sclerosis	Multiple sclerosis
53	A class rheumatoid factor	Ig M	Ig G	Ig D	Ig A	Ig M
54	In innate immune system ---- play important role in inhibiting tumor growth & metastasis	T cells	B cells	NK cells	T_H cells	NK cells

55	------produced resultinfection rolein rhythmicity of sleep & immunity regulator	T- lymphocytes	lymphocytes	Cytotoxic T-lymphocytes	cytokines	cytokines
56	------- capableof internalizing antigensby phagocytosis(or)endocytosis process	Antigen presenting cell	Antibody presenting cell	Antigen	antibody.	Antigen presenting cell
57	The non-cellular part of blood	Tissues	serum	blood	platelets.	serum
58	The state of protection from infections disease	Immunity	Immune response	T cell	B cell	Immunity
59	A group of proteins produced by virus infected cells	Interluekins	Interluekins-2	Interferon	leukocytes	Interferon
60	A group of serum proteins that circulate in an inactive proenzyme state	non- complement	complement	alternate	classical	complement

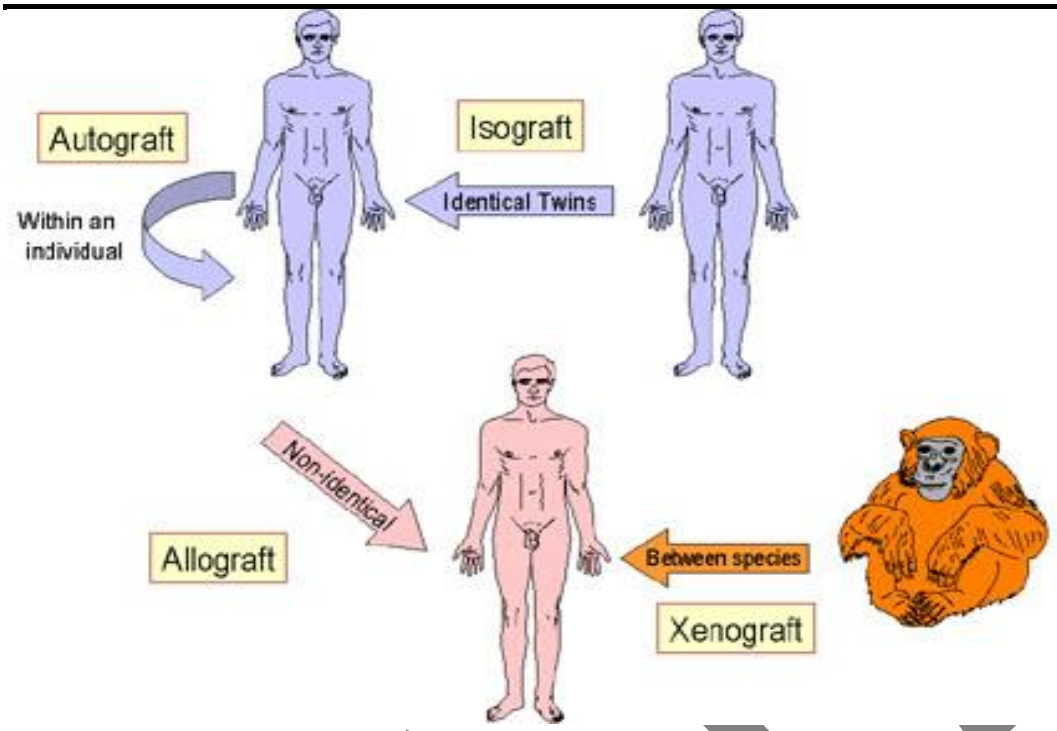
UNIT-V

General organization and inheritance of MHC, structure, distribution and role of MHC class I and class II proteins, linkage disequilibrium, pathways of antigen processing and presentation. Immunological basis of graft rejection, clinical manifestations, immunosuppressive therapy and privileged sites. Vaccines - active and passive immunization, types of vaccines

Transplantation

Types of graft (figure 1)

- **Xenograft**
  Grafts between members of different species (also known as heterologous, xenogeneic or heterografts)
- **Allograft**
  Grafts between two members of the same species (also known as allogeneic or homograft)
- **Isograft**
  Grafts between members of the same species with identical genetic makeup (identical twins or inbred animals)



PRINCIPLES OF TRANSPLANTATION

An immunocompetent host recognizes the foreign antigens on grafted tissues (or cells) and mounts an immune response which results in rejection. On the other hand, if an immunocompromised host is grafted with foreign immunocompetent lymphoid cells, the immunoreactive T-cells in the graft recognize the foreign antigens on the host tissue, leading to damage of the host tissue.

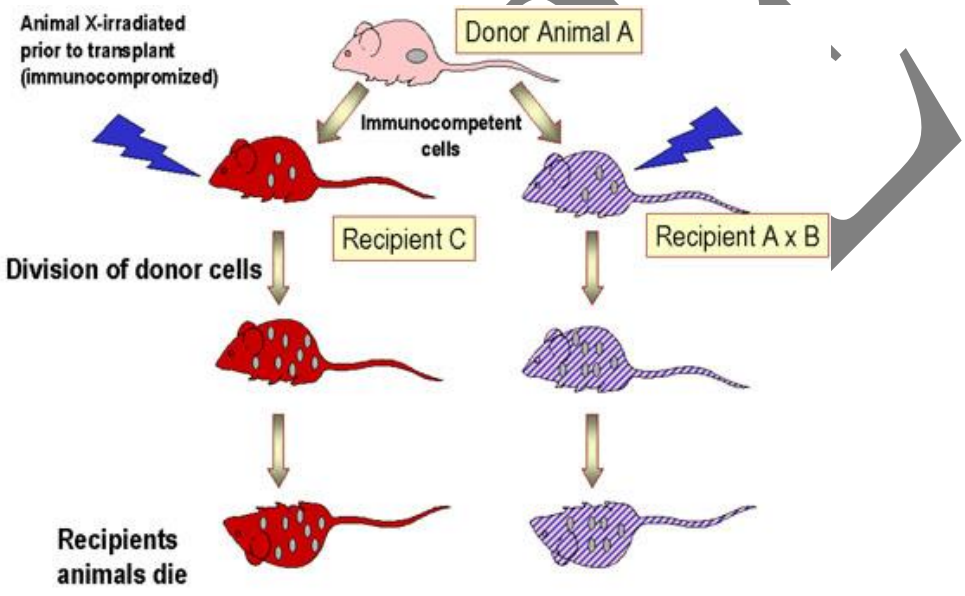
Host-versus-graft-reaction

he duration of graft survival follows the order, xeno- < allo- < iso- = auto- graft. The time of rejection also depends on the antigenic disparity between the donors and recipient. MHC antigens are the major contributors in rejection, but the minor histocompatibility antigens also play a role. Rejection due to disparity in several minor histocompatibility antigens may be as quick or quicker than rejection mediated by an MHC antigen. As in other immune responses, there is immunological memory and secondary response in graft rejection. Thus, once a graft is rejected by a recipient, a second graft from the same donor, or a donor with the same histocompatibility antigens, will be rejected in a much shorter time.

Graft-versus-host (GVH) Reaction

Histocompatible lymphoid cells, when injected into an immunocompromised host, are readily accepted. However, the immunocompetent T lymphocytes among the grafted cells recognize the alloantigens and, in response, they proliferate and progressively cause damage to the host tissues and cells. This condition is known as graft-versus-host (GVH) disease (figure 3) and is often fatal.

Common manifestations (figure 4) of GVH reaction are diarrhea, erythema, weight loss, malaise, fever, joint pains, etc. and ultimately death.



Transplant rejection occurs when a transplanted organ or tissue is not accepted by the body of the transplant recipient. This is explained by the concept that the immune system of the recipient attacks the transplanted organ or tissue. This is expected to happen, because the immune system's purpose is to distinguish foreign material within the body and attempt to destroy it, just as it attempts to destroy infecting organisms such as bacteria and viruses. When possible, transplant rejection can be reduced through serotyping to determine the most appropriate donor-recipient match and through the use of immunosuppressant drugs.

ALLOGRAFT REJECTION

The clinical significance of the MHC is realized in organ transplantation. Cells and tissues are routinely transplanted as a treatment for a number of diseases. However, reaction of the host against allo-antigens of the graft (HVG) results in its rejection and is the major obstacle in organ transplantation. The rejection time of a graft may vary with the antigenic nature of the graft and the immune status of the host and is determined by the immune mechanisms involved (Figure 8 and Table 1).

Hyper-acute rejection

This occurs in instances when the recipient has preformed high titer antibodies. A graft may show signs of rejection within minutes to hours due to immediate reaction of antibodies and complement.

Accelerated (2nd set; secondary) rejection

Transplantation of a second graft, which shares a significant number of antigenic determinants with the first one, results in a rapid (2 - 5 days) rejection. It is due to presence of T-lymphocytes sensitized during the first graft rejection. Accelerated rejection is mediated by immediate production of lymphokines, activation of monocytes and macrophages, and induction of cytotoxic lymphocytes.

Acute (1st set; primary) rejection

The normal reaction that follows the first grafting of a foreign transplant takes 1 - 3 weeks. This is known as acute rejection and is mediated by T lymphocytes sensitized to class I and class II antigens of the allograft, elicitation of lymphokines and activation of monocytes and macrophages.

Chronic rejection

Some grafts may survive for months or even years, but suddenly exhibit symptoms of rejection. This is referred to as chronic rejection, the mechanism of which is not entirely clear. The hypotheses are that this may be due infection, causes which led to failure of the first organ, loss of tolerance induced by the graft, etc.

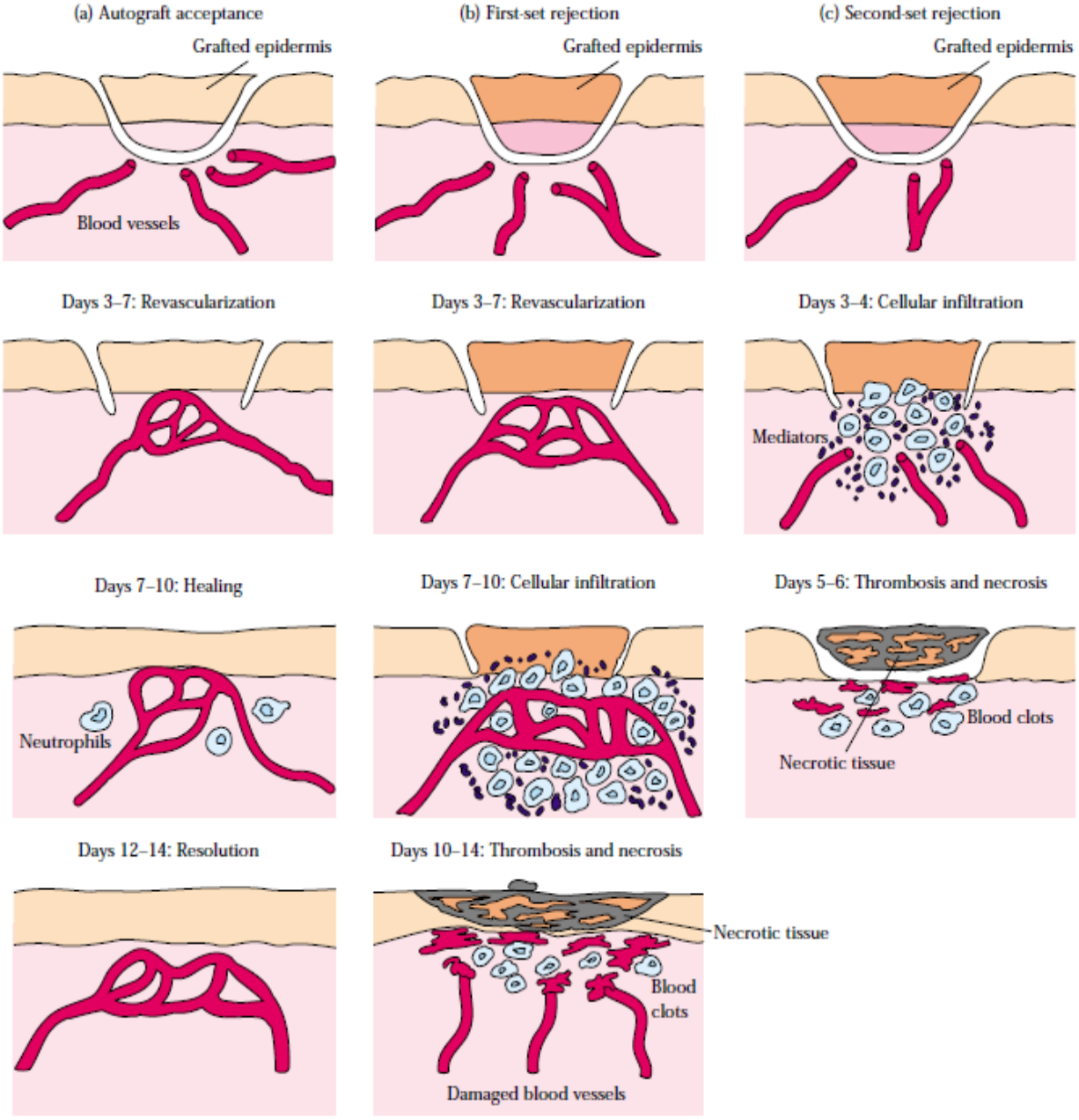


Fig: Schematic diagram of graft rejection and acceptance

REJECTION MECHANISMS

Graft rejection is caused principally by a cell-mediated im-mune response to alloantigens (primarily, MHC molecules) expressed on cells of the graft. Both delayed-type hypersensi-tive and cell-mediated

cytotoxicity reactions have been im-plicated. The process of graft rejection can be divided into two stages: (1) a sensitization phase, in which antigen-reactive lymphocytes of the recipient proliferate in response to allo-antigens on the graft, and (2) an effector stage, in which im-mune destruction of the graft takes place.

i) Sensitization Stage

During the sensitization phase, $CD4^+$ and $CD8^+$ T cells rec-ognize alloantigens expressed on cells of the foreign graft and proliferate in response. Both major and minor histo-compatibility alloantigens can be recognized. In general, the response to minor histocompatibility antigens is weak, al-though the combined response to several minor differences can sometimes be quite vigorous. The response to major histo-compatibility antigens involves recognition of both the donor MHC molecule and an associated peptide ligand in the cleft of the MHC molecule. The peptides present in the groove of allogeneic class I MHC molecules are derived from proteins synthesized within the allogeneic cell. The peptides present in the groove of allogeneic class II MHC molecules are gener-ally proteins taken up and processed through the endocytic pathway of the allogeneic antigen-presenting cell.

A host T_H cell becomes activated when it interacts with an antigen-presenting cell (APC) that both expresses an appro-priate antigenic ligand–MHC molecule complex and pro-vides the requisite co-stimulatory signal. Depending on the tissue, different populations of cells within a graft may func-tion as APCs. Because dendritic cells are found in most tis-sues and because they constitutively express high levels of class II MHC molecules, dendritic cells generally serve as the major APC in grafts. APCs of host origin can also migrate into a graft and endocytose the foreign alloantigens (both major and minor histocompatibility molecules) and present them as processed peptides together with self-MHC mole-cules.

In some organ and tissue grafts (e.g., grafts of kidney, thy-mus, and pancreatic islets), a population of donor APCs called *passenger leukocytes* has been shown to migrate from the graft to the regional lymph nodes. These passenger leuko-cytes are dendritic cells, which express high levels of class II MHC molecules (together with normal levels of class I MHC molecules) and are widespread in mammalian tissues, with the chief exception of the brain. Because passenger leuko-cytes express the allogeneic MHC antigens of the donor graft, they are recognized as foreign and therefore can stimulate immune activation of T lymphocytes in the lymph node. In some experimental situations, the passenger cells have been shown to induce tolerance to their surface antigens by dele-tion of thymic T-cell populations with receptors specific for them. Consistent with the notion that exposure to donor cells can induce

tolerance are data showing that blood tran-fusions from the donor prior to transplantation can aid ac-ceptance of the graft.

Passenger leukocytes are not the only cells involved in im-mune stimulation. For example, they do not seem to play any role in skin grafts. Other cell types that have been implicated in alloantigen presentation to the immune system include

Langerhans cells and endothelial cells lining the blood ves-sels. Both of these cell types express class I and class II MHC antigens.

Recognition of the alloantigens expressed on the cells of a graft induces vigorous T-cell proliferation in the host. This proliferation can be demonstrated in vitro in a mixed-lymphocyte reaction (see Figure 21-4c). Both dendritic cells and vascular endothelial cells from an allogeneic graft induce host T-cell proliferation. The major proliferating cell is the $CD4^+$ T cell, which recognizes class II alloantigens directly or alloantigen peptides presented by host antigen-presenting cells. This amplified population of activated T_H cells is thought to play a central role in inducing the various effector mechanisms of allograft rejection.

ii)Effector Stage

A variety of effector mechanisms participate in allograft re-jection (Figure 21-6). The most common are cell-mediated reactions involving delayed-type hypersensitivity and CTL-mediated cytotoxicity; less common mechanisms are antibody-plus-complement lysis and destruction by antibody-dependent cell-mediated cytotoxicity (ADCC). The hallmark of graft rejection involving cell-mediated reactions is an influx of T cells and macrophages into the graft. Histologically, the in-filtration in many cases resembles that seen during a delayed-type hypersensitive response, in which cytokines produced by T_{DTH} cells promote macrophage infiltration (see Figure 14-15). Recognition of foreign class I alloantigens on the graft by host $CD8^+$ cells can lead to CTL-mediated killing (see Figure 14-4). In some cases, $CD4^+$ T cells that function as class II MHC–restricted cytotoxic cells mediate graft rejection.

In each of these effector mechanisms, cytokines secreted by T_H cells play a central role (see Figure 21-6). For example, IL-2, IFN- , and TNF- have each been shown to be impor-tant mediators of graft rejection. IL-2 promotes T-cell pro-liferation and generally is necessary for the generation of effector CTLs (see Figure 14-1). IFN- is central to the devel-opment of a DTH response, promoting the influx of macro-phages into the graft and their subsequent activation into more destructive cells. TNF- has been shown to have a di-rect cytotoxic effect on the cells of a graft. A number of cyto-kines promote graft rejection by inducing expression of class I or class II MHC molecules on graft cells. The interferons (, ,

and), TNF- , and TNF- all increase class I MHC ex-pression, and IFN- increases class II MHC expression as well. During a rejection episode, the levels of these cytokines increase, inducing a variety of cell types within the graft to express class I or class II MHC molecules. In rat cardiac allo-grafts, for example, dendritic cells are initially the only cells that express class II MHC molecules. However, as an allograft reaction begins, localized production of IFN- in the graft induces vascular endothelial cells and myocytes to express class II MHC molecules as well, making these cells targets for CTL attack.

Rejection is an adaptive immune response via cellular immunity (mediated by killer T cells inducing apoptosis of target cells) as well as humoral immunity (mediated by activated B cells secreting antibody molecules), though the action is joined by components of innate immune response (phagocytes and soluble immune proteins). Different types of transplanted tissues tend to favor different balances of rejection mechanisms.

Humoral immunity in rejection

Developed through an earlier primary exposure that primed adaptive immunity—which matured before the transplant occurring as secondary exposure—a transplant recipient can bear specific antibody crossreacting with donor tissue. This is typical after earlier mismatching among A/B/O blood types. Then components of innate immunity—soluble immune proteins called complement and innate immune cells called phagocytes—inflame and destroy the transplanted tissue.

An antibody molecule, secreted by an activated B cell, then called plasma cell, is a soluble immunoglobulin (Ig) whose constituent unit is configured like the letter *Y*: the two arms are the Fab regions and the single stalk is the Fc region. Each Fab tip is the paratope, which ligates (binds) a cognate (matching) molecular sequence as well as its 3D shape (its conformation), altogether called epitope, within a specific antigen.

When the paratope of Ig class *gamma* (IgG) ligates its epitope, IgG's Fc region conformationally shifts and can host a complement protein, initiating the complement cascade that terminates by punching a hole in a cell membrane. With so many holes punched fluid rushes into the cell and ruptures it. Molecular motifs of necrotic cell debris are recognized as damage associated molecular patterns (DAMPs) when they ligate Toll-like receptors (TLRs) on membranes of innate immune cells, which phagocytes are thereby activated to secrete proinflammatory cytokines recruiting more phagocytes to traffic to the area by sensing the concentration gradient of the secreted cytokines (chemotaxis). IgG's Fc region also enables opsonization by a phagocyte—such as neutrophils in blood and macrophages in tissues—which attains improved uptake of cell debris and tissue by seizing the IgG molecule's Fc stalk.

Cellular immunity in rejection

Transplanted organs are often acquired from a cadaver—usually a host who had succumbed to trauma—and the tissues had already sustained ischemia or inflammation. Dendritic cells (DCs) of the donor tissue

migrate to the recipient's peripheral lymphoid tissue—lymphoid follicles and lymph nodes—and present the donor's *self peptides* to the recipient's naive helper T cells. Primed toward these allogeneic HLA peptides, the helper T cells effect immunomemory at either 1) the donor's self peptides, 2) the allogeneic HLA molecules, or 3) both.

The primed helper T cells establish alloreactive killer T cells whose CD8 receptors dock to the transplanted tissue's MHC class I molecules presenting self peptides, whereupon the T cell receptors (TCRs) of the killer T cells recognize their epitope—self peptide now coupled within MHC class I molecules—and transduce signals into the target cell prompting its programmed cell death by apoptosis.

When the CD4 receptors of helper T cells dock to their hosts, MHC class II molecules, expressed by select cells, their own TCRs—the paratope—might recognize their matching epitope being presented, and thereupon approximate the secretion of cytokines that had prevailed during their priming event, an aggressively proinflammatory balance of cytokines.

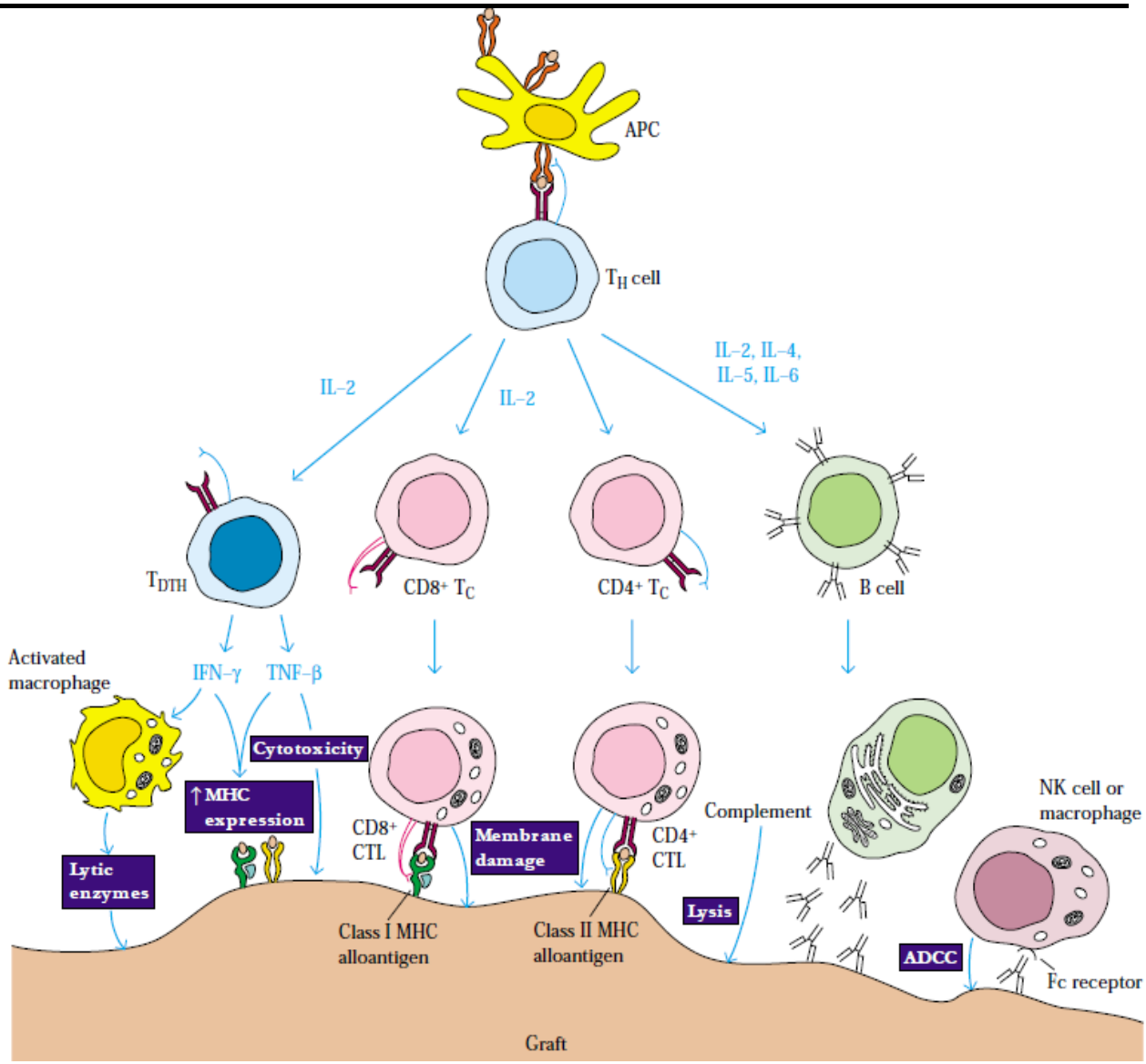


Fig:Effector mechanism involved in rejection

Rejection detection

The laboratory pathologist generally seeks three main histological signs: (1) infiltrating T cells, perhaps accompanied by infiltrating eosinophils, plasma cells, and neutrophils, particularly in telltale ratios, (2) structural compromise of tissue anatomy, varying by tissue type transplanted, and (3) injury to blood vessels.

Rejection treatment

Hyperacute rejection manifests severely and within minutes, and so treatment is immediate: removal of the tissue. **Chronic rejection** is generally considered irreversible and poorly amenable to treatment—only retransplant generally indicated if feasible—though inhaled cyclosporine is being investigated to delay or prevent chronic rejection of lung transplants. **Acute rejection** is treated with one or multiple of a few strategies like immuno supressive therapy, antibobody based treatments and blood transfer

Rejection mechanisms

Rejection is an adaptive immune response and is mediated through both T cell mediated and humoral immune (antibodies) mechanisms. The number of mismatched alleles determines the speed and magnitude of the rejection response. Different mechanisms tend to act against different grafts.

Organ/tissue Mechanism

Blood	Antibodies (isohaemagglutinins)
Kidney	Antibodies, CMI
Heart	Antibodies, CMI
Skin	CMI
Bonemarrow	CMI
Cornea	Usually accepted unless vascularised, CMI

CMI=Cell mediated immunity

Treatment of rejection

Chronic transplant rejection is irreversible and cannot be treated effectively. Treatments with inhaled ciclosporin are being investigated as a means to delay or prevent chronic rejection of the lungs. At present the only definitive treatment is re-transplantation, if patients can be re-allocated and if donors are available.

Acute transplant rejection can be treated using chemotherapeutic drugs designed to suppress the immune system (see list below). Acute rejection is normally treated initially with a short course of high-dose corticosteroids, which is usually sufficient. If this is not enough, the course can be repeated or a *triple therapy* regimen can be used, consisting of a corticosteroid plus a calcineurin inhibitor and an anti-proliferative agent. Antibodies against specific components of the immune system can be added to this

regimen, especially for high-risk patients. mTOR inhibitors can be used in selected patients, where calcineurin inhibitors or steroids are contraindicated. Acute rejection refractory to these treatments may require blood transfusions to remove antibodies against the transplant.

If a bone marrow transplant can be performed, the transplant recipient's immune system can be replaced with the donor's immune system, thus enabling the recipient's body to accept the new organ without risk of rejection. This requires that the bone marrow, which produces the immune cells, be from the same person as the organ donation (or an identical twin or a clone). There is a risk of graft versus host disease (GVHD) in which the lymphoid cells co-injected with the bone marrow transplant recognize the host tissues as foreign and attack and destroy them accordingly.

Immunosuppressive drugs used to treat transplant rejection

- **Calcineurin inhibitors**
  - Ciclosporin
  - Tacrolimus
- **mTOR inhibitors**
  - Sirolimus
  - Everolimus
- **Anti-proliferatives**
  - Azathioprine
  - Mycophenolic acid
- **Corticosteroids**
  - Prednisolone
  - Hydrocortisone
- **Antibodies**
  - Monoclonal anti-IL-2Rα receptor antibodies
    - Basiliximab
    - Daclizumab
  - Polyclonal anti-T-cell antibodies
    - Anti-thymocyte globulin (ATG)
    - Anti-lymphocyte globulin (ALG)
  - Monoclonal anti-CD20 antibodies
    - Rituximab

The monoclonal anti-T cell antibody OKT3 was formerly used in the prevention of rejection, and is occasionally used in treatment of severe acute rejection, but has fallen out of common use due to the severe cytokine release syndrome and late post-transplant lymphoproliferative disorder, which are both commonly associated with use of OKT3; in the United Kingdom it is available on a named-patient use basis only.

Current diagnosis of organ rejection following transplantation relies on tissue biopsy, which is not ideal due to sampling limitations and risks associated with the invasive procedure. Cellular MRI of in vivo labeled immune cells offers a noninvasive approach to detect and monitor graft rejection after solid organ transplantation. Clinical application of a reliable and noninvasive technique to detect the early signs of graft rejection will improve not only the therapeutic treatment of transplant patients but also improve their quality of life. (Magnetic Resonance in Medicine (2011)

Auto immune diseases- Rheumatoid arthritis, myasthenia gravis.

Autoimmune diseases

Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. In other words, the body actually attacks its own cells. The immune system mistakes some part of the body as a pathogen and attacks it. This may be restricted to certain organs (e.g. in chagas disease) or involve a particular tissue in different places (e.g. Goodpasture's disease which may affect the basement membrane in both the lung and the kidney).

The treatment of autoimmune diseases is typically with immunosuppression—medication which decreases the immune response.

The cause of autoimmune diseases is unknown, but it appears that there is an inherited predisposition to develop autoimmune disease in many cases. In a few types of autoimmune disease (such as rheumatic fever), a bacteria or virus triggers an immune response, and the antibodies or T-cells attack normal cells because they have some part of their structure that resembles a part of the structure of the infecting microorganism.

EFFECTOR MECHANISMS IN AUTOIMMUNE DISEASES

Both antibodies and effector T cells can be involved in the damage in autoimmune diseases.

GENERAL CLASSIFICATION

Autoimmune diseases are generally classified on the basis of the organ or tissue involved. These diseases may fall in an organ-specific category in which the immune response is directed against antigen(s) associated with the target organ being damaged or a non-organ-specific category in which the antibody is directed against an antigen not associated with the target organ. The antigen involved in most autoimmune diseases is evident from the name of the disease .

Autoimmune disorders fall into two general types: those that damage many organs (systemic autoimmune diseases) and those where only a single organ or tissue is directly damaged by the autoimmune process (localized). However, the distinctions become blurred as the effect of localized autoimmune disorders frequently extends beyond the targeted tissues, indirectly affecting other body organs and systems. Some of the most common types of autoimmune disorders include:

Systemic Autoimmune Diseases

- Rheumatoid arthritis (RA) and Juvenile RA (JRA) (joints; less commonly lung, skin)
- Lupus [Systemic Lupus Erythematosus] (skin, joints, kidneys, heart, brain, red blood cells, other)
- Scleroderma (skin, intestine, less commonly lung)
- Sjögren's syndrome (salivary glands, tear glands, joints)
- Goodpasture's syndrome (lungs, kidneys)
- Wegener's granulomatosis (blood vessels, sinuses, lungs, kidneys)
- Polymyalgia Rheumatica (large muscle groups)
- Guillain-Barre syndrome (nervous system)

Localized Autoimmune Diseases

- Type 1 Diabetes Mellitus (pancreas islets)
- Hashimoto's thyroiditis, Graves' disease (thyroid)
- Celiac disease, Crohn's disease, Ulcerative colitis (GI tract)
- Multiple sclerosis (There is still some debate as to whetherMS is an autoimmune disease.)
- Addison's disease (adrenal)
- Primary biliary cirrhosis, Sclerosing cholangitis, Autoimmune hepatitis (liver)
- Temporal Arteritis / Giant Cell Arteritis (arteries of the head and neck)

ETIOLOGY OF AUTOIMMUNITY DISEASE

The exact etiology of autoimmune diseases is not known. However, various theories have been offered. These include sequestered antigen, escape of auto-reactive clones, loss of suppressor cells, cross reactive antigens including exogenous antigens (pathogens) and altered self antigens (chemical and viral infections).

Sequestered antigen

Lymphoid cells may not be exposed to some self antigens during their differentiation, because they may be late-developing antigens or may be confined to specialized organs (*e.g*., testes, brain, eye, *etc*.). A

release of antigens from these organs resulting from accidental traumatic injury or surgery can result in the stimulation of an immune response and initiation of an autoimmune disease.

Escape of auto-reactive clones

The negative selection in the thymus may not be fully functional to eliminate self reactive cells. Not all self antigens may be represented in the thymus or certain antigens may not be properly processed and presented.

Lack of regulatory T cells

There are fewer regulatory T-cells in many autoimmune diseases

Cross reactive antigens

Antigens on certain pathogens may have determinants which cross react with self antigens and an immune response against these determinants may lead to effector cell or antibodies against tissue antigens. Post streptococcal nephritis and carditis, anticardiolipin antibodies during syphilis and association between *Klebsiella*and ankylosing spondylitis are examples of such cross reactivity.

DIAGNOSIS

Diagnosis of autoimmune diseases is based on symptoms and detection of antibodies (and/or very early T cells) reactive against antigens of tissues and cells involved. Antibodies against cell/tissue associated antigens are detected by immunofluorescence. Antibodies against soluble antigens are normally detected ELISA or radioimmunoassay (see table above). In some cases, a biological /biochemical assay may be used (*e.g.*, Graves diseases, pernicious anemia). Autoimmune disorders are diagnosed, evaluated, and monitored through a combination of autoantibody blood tests, blood tests to measure inflammation and organ function, clinical presentation, and through non-laboratory examinations such as X-rays.

TREATMENT

There is currently no cure for autoimmune disorders, although in rare cases they may disappear on their own. The goals of treatment of autoimmune disorders are to reduce symptoms and control the autoimmune response while maintaining the body's ability to fight infections. Treatments vary widely and depend on the specific disease and symptoms: Anti-inflammatory (corticosteroid) and immunosuppressive drug therapy (such as cyclophosphamide, azathioprine, cyclosporine) is the present method of treating autoimmune diseases. Extensive research is being carried out to develop innovative treatments which include: anti-TNF alpha therapy against arthritis, feeding antigen orally to trigger tolerance, anti-idiotype antibodies, antigen peptides, anti-IL2 receptor antibodies, anti-CD4 antibodies, anti-TCR antibodies, etc.

MYASTHENIA GRAVIS

Myasthenia gravis is a chronic autoimmune disorder that affects the voluntary muscles of the body. It is characterized by weakness or rapid muscle fatigue. The condition is supposed to occur when there is a dysfunction between the muscles and the nerves that control the same. A defect in the transmission of nerve impulses to the muscles gives rise to the symptoms of the condition.

Myasthenia gravis is usually not inherited but it develops with age. It often affects women after the age of 40 and men after 60. Muscle weakness is a common symptom of many other conditions and hence a diagnosis for myasthenia gravis is often delayed and learnt about quite late.

Pathophysiology:

In MG, the autoantibodies **most commonly act against the nicotinic acetylcholine receptor (nAChR),** the receptor in the motor end plate for the neurotransmitteracetylcholine that stimulates muscular contractions. Some forms of the antibody impair the ability of acetylcholine to bind to receptors. Others lead to the destruction of receptors, either by complement fixation or by inducing the muscle cell to eliminate the receptors through endocytosis.

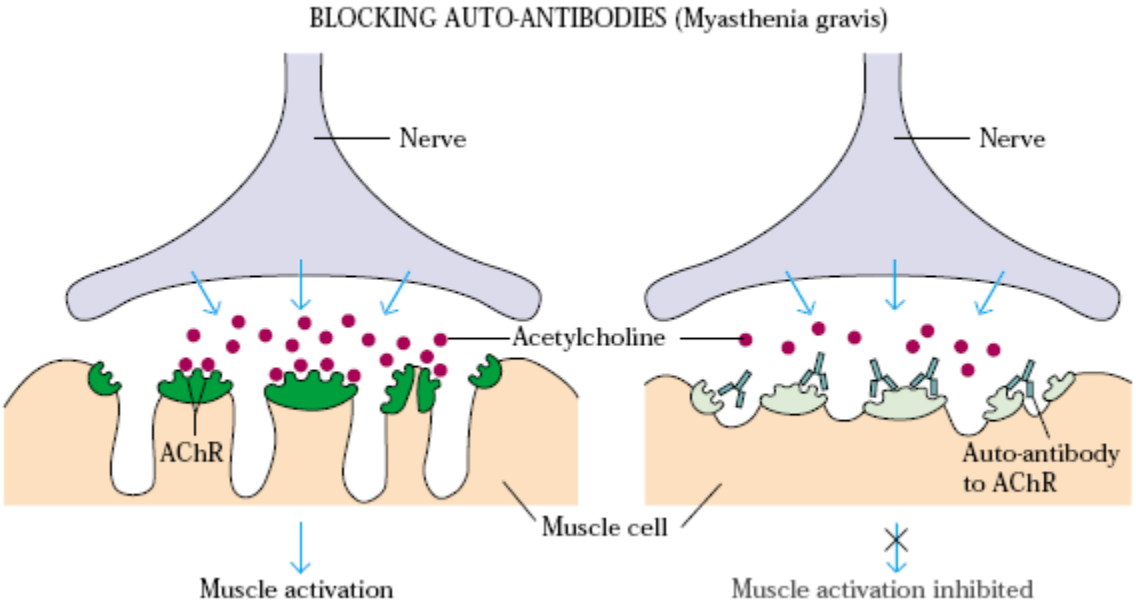
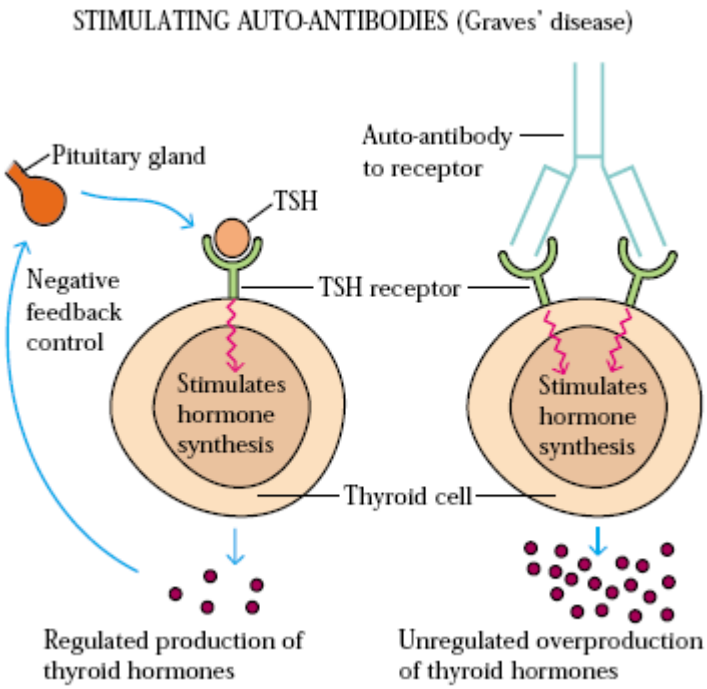


Fig:In MG , binding of auto antibodies to acetyl choline receptor blockksthe normal binding of acetyl choline and subsequent muscle activation. In addition the antiAchR auto antibodies activates complement which damage the muscle end plate

GRAVES' DISEASE

The production of thyroid hormones is carefully regulated by thyroid-stimulating hormone (TSH), which is produced by the pituitary gland. Binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones, thyroxine and triiodothyronine. A patient with **Graves' disease** produces auto-antibodies that bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in produc-tion of the thyroid hormones. Unlike TSH, however, the auto-antibodies are not regulated, and consequently they over-stimulate the thyroid. For this reason these auto-antibodies are called long-acting thyroid-stimulating (LATS) antibod-ies (Figure).



In Graves' disease, binding of auto-antibodies to the receptor for thyroid-stimulating hormone (TSH) induces unregu-lated activation of the thyroid, leading to overproduction of the thy-roid hormones (purple dots).

Common signs and symptoms of Graves' disease include:

Graves' disease is an immune system disorder that results in the overproduction of thyroid hormones (hyperthyroidism). Although a number of disorders may result in hyperthyroidism, Graves' disease is a common cause.Because thyroid hormones affect a number of different body systems, signs and symptoms associated with Graves' disease can be wide ranging and significantly influence your overall well-being. Although Graves' disease may affect anyone, it's more common among women and before the age of 40.

- Anxiety and irritability
- A fine tremor of your hands or fingers

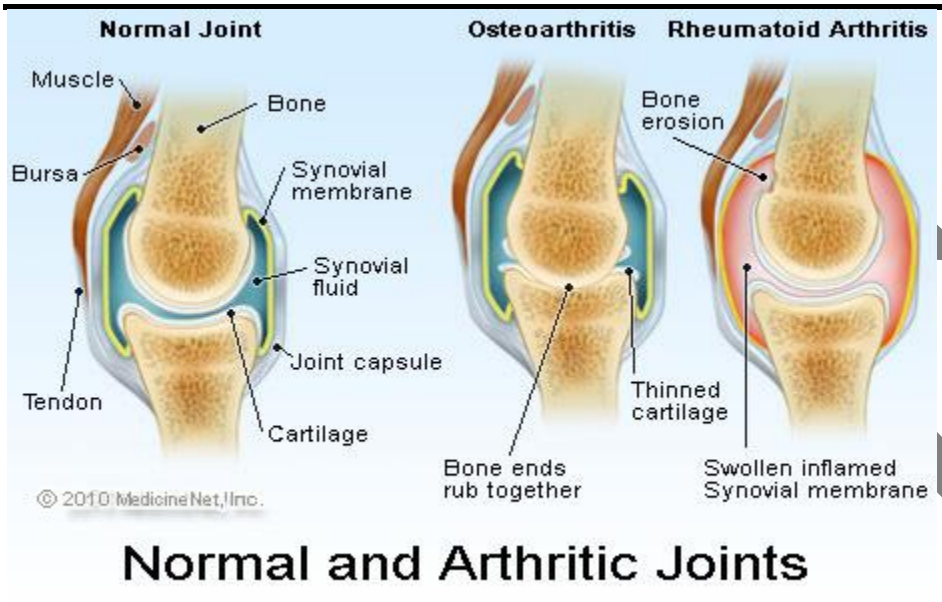
- Heat sensitivity and an increase in perspiration or warm, moist skin
- Weight loss, despite normal eating habits
- Enlargement of your thyroid gland (goiter)
- Change in menstrual cycles
- Erectile dysfunction or reduced libido
- Frequent bowel movements
- Bulging eyes (Graves' ophthalmopathy)
- Thick, red skin usually on the shins or tops of the feet (Graves' dermopathy)
- Rapid or irregular heartbeat (palpitations)

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic inflammatory disorder that typically affects the small joints in hands and feet. Unlike the wear-and-tear damage of osteoarthritis, rheumatoid arthritis affects the lining of joints, causing a painful swelling that can eventually result in bone erosion and joint deformity.

An autoimmune disorder, rheumatoid arthritis occurs when immune system mistakenly attacks own body's tissues. In addition to causing joint problems, rheumatoid arthritis sometimes can affect other organs of the body — such as the skin, eyes, lungs and blood vessels.

Although rheumatoid arthritis can occur at any age, it usually begins after age 40. The disorder is much more common in women than in men. Treatment focuses on controlling symptoms and preventing joint damage.



Normal and Arthritic Joints

Rheumatoid arthritis signs and symptoms may vary in severity and may even come and go. Periods of increased disease activity, called flares, alternate with periods of relative remission — when the swelling and pain fade or disappear. Over time, rheumatoid arthritis can cause joints to deform and shift out of place.

Etiology

Rheumatoid arthritis is a common autoimmune disorder, most often affecting women from 40 to 60 years old. The major symptom is chronic inflammation of the joints, although the hematologic, cardiovascular, and respiratory systems are also frequently affected. Many individuals with rheumatoid arthritis produce a group of auto-antibodies called **rheumatoid factors** that are reactive with determinants in the Fc region of IgG. The classic rheumatoid factor is an IgM antibody with that reactivity. Such auto-antibodies bind to normal circulating IgG, forming IgM-IgG complexes that are deposited in the joints. These immune complexes can activate the complement cascade, resulting in a type III hypersensitive reaction, which leads to chronic inflammation of the joints.

VACCINES

A **vaccine** is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe or its toxins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Vaccines can be prophylactic (e.g. to prevent or ameliorate the effects of a future infection by any natural or "wild" pathogen), or therapeutic (e.g. vaccines against cancer are also being investigated; see cancer vaccine

Types of Vaccines

Scientists take many approaches to designing vaccines against a microbe. These choices are typically based on fundamental information about the microbe, such as how it infects cells and how the immune system responds to it, as well as practical considerations, such as regions of the world where the vaccine would be used. The following are some of the options that researchers might pursue:

- Live, attenuated vaccines
- Inactivated vaccines
- Subunit vaccines
- Toxoid vaccines
- Conjugate vaccines
- DNA vaccines
- Recombinant vector vaccines

Live, Attenuated Vaccines

Live, attenuated vaccines contain a version of the living microbe that has been weakened in the lab so it can't cause disease. Because a live, attenuated vaccine is the closest thing to a natural infection, these vaccines are good "teachers" of the immune system: They elicit strong cellular and antibody responses and often confer lifelong immunity with only one or two doses.

Despite the advantages of live, attenuated vaccines, there are some downsides. It is the nature of living things to change, or mutate, and the organisms used in live, attenuated vaccines are no different. The remote possibility exists that an attenuated microbe in the vaccine could revert to a virulent form and cause disease. Also, not everyone can safely receive live, attenuated vaccines. For their own protection, people who have damaged or weakened immune systems— because they've undergone chemotherapy or have HIV, for example—cannot be given live vaccines.

Another limitation is that live, attenuated vaccines usually need to be refrigerated to stay potent. If the vaccine needs to be shipped overseas and stored by health care workers in developing countries that lack widespread refrigeration, a live vaccine may not be the best choice.

Live, attenuated vaccines are relatively easy to create for certain viruses. Vaccines against measles, mumps, and chickenpox, for example, are made by this method. Viruses are simple microbes containing a small number of genes, and scientists can therefore more readily control their characteristics. Viruses often are attenuated through a method of growing generations of them in cells in which they do not reproduce very well. This hostile environment takes the fight out of viruses: As they evolve to adapt to the new environment, they become weaker with respect to their natural host, human beings.

Live, attenuated vaccines are more difficult to create for bacteria. Bacteria have thousands of genes and thus are much harder to control. Scientists working on a live vaccine for a bacterium, however, might be able to use recombinant DNA technology to remove several key genes. This approach has been used to create a vaccine against the bacterium that causes cholera, *Vibrio cholerae*, although the live cholera vaccine has not been licensed in the United States.

Inactivated Vaccines

Scientists produce inactivated vaccines by killing the disease-causing microbe with chemicals, heat, or radiation. Such vaccines are more stable and safer than live vaccines. The dead microbes can't mutate back to their disease-causing state. Inactivated vaccines usually don't require refrigeration, and they can be easily stored and transported in a freeze-dried form, which makes them accessible to people in developing countries.

Most inactivated vaccines, however, stimulate a weaker immune system response than do live vaccines. So it would likely take several additional doses, or booster shots, to maintain a person's immunity. This could be a drawback in areas where people don't have regular access to health care and can't get booster shots on time.

Subunit Vaccines

Instead of the entire microbe, subunit vaccines include only the antigens that best stimulate the immune system. In some cases, these vaccines use epitopes—the very specific parts of the antigen that antibodies or T cells recognize and bind to. Because subunit vaccines contain only the essential antigens and not all the other molecules that make up the microbe, the chances of adverse reactions to the vaccine are lower.

Subunit vaccines can contain anywhere from 1 to 20 or more antigens. Of course, identifying which antigens best stimulate the immune system is a tricky, time-consuming process. Once scientists do that, however, they can make subunit vaccines in one of two ways:

- They can grow the microbe in the laboratory and then use chemicals to break it apart and gather the important antigens.
- They can manufacture the antigen molecules from the microbe using recombinant DNA technology. Vaccines produced this way are called "recombinant subunit vaccines."

A recombinant subunit vaccine has been made for the hepatitis B virus. Scientists inserted hepatitis B genes that code for important antigens into common baker's yeast. The yeast then produced the antigens, which the scientists collected and purified for use in the vaccine. Research is continuing on a recombinant subunit vaccine against hepatitis C virus.

Toxoid Vaccines

For bacteria that secrete toxins, or harmful chemicals, a toxoid vaccine might be the answer. These vaccines are used when a bacterial toxin is the main cause of illness. Scientists have found that they can inactivate toxins by treating them with formalin, a solution of formaldehyde and sterilized water. Such "detoxified" toxins, called toxoids, are safe for use in vaccines.

When the immune system receives a vaccine containing a harmless toxoid, it learns how to fight off the natural toxin. The immune system produces antibodies that lock onto and block the toxin. Vaccines against diphtheria and tetanus are examples of toxoid vaccines.

Conjugate Vaccines

If a bacterium possesses an outer coating of sugar molecules called polysaccharides, as many harmful bacteria do, researchers may try making a conjugate vaccine for it. Polysaccharide coatings disguise a bacterium's antigens so that the immature immune systems of infants and younger children can't recognize or respond to them. Conjugate vaccines, a special type of subunit vaccine, get around this problem.

When making a conjugate vaccine, scientists link antigens or toxoids from a microbe that an infant's immune system can recognize to the polysaccharides. The linkage helps the immature immune system react to polysaccharide coatings and defend against the disease-causing bacterium.

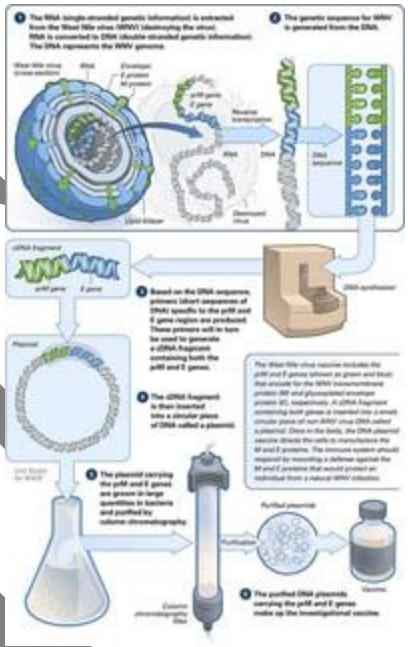
The vaccine that protects against *Haemophilus influenzae* type B (Hib) is a conjugate vaccine.

DNA Vaccines

Once the genes from a microbe have been analyzed, scientists could attempt to create a DNA vaccine against it.

Still in the experimental stages, these vaccines show great promise, and several types are being tested in humans. DNA vaccines take immunization to a new technological level. These vaccines dispense with both the whole organism and its parts and get right down to the essentials: the microbe's genetic material. In particular, DNA vaccines use the genes that code for those all-important antigens.

Researchers have found that when the genes for a microbe's antigens are introduced into the body, some cells will take up that DNA. The DNA then instructs those cells to make the antigen molecules. The cells secrete the antigens and display them on their surfaces. In other words, the body's own cells become vaccine-making factories, creating the antigens necessary to stimulate the immune system.



The Making of a DNA Vaccine Against West Nile Virus. View the illustration. Credit: NIAID

A DNA vaccine against a microbe would evoke a strong antibody response to the free-floating antigen secreted by cells, and the vaccine also would stimulate a strong cellular response against the microbial antigens displayed on cell surfaces. The DNA vaccine couldn't cause the disease because it wouldn't contain the microbe, just copies of a few of its genes. In addition, DNA vaccines are relatively easy and inexpensive to design and produce.

So-called naked DNA vaccines consist of DNA that is administered directly into the body. These vaccines can be administered with a needle and syringe or with a needle-less device that uses high-pressure gas to shoot microscopic gold particles coated with DNA directly into cells. Sometimes, the DNA is mixed with molecules that facilitate its uptake by the body's cells. Naked DNA vaccines being tested in humans include those against the viruses that cause influenza and herpes.

Recombinant Vector Vaccines

Recombinant vector vaccines are experimental vaccines similar to DNA vaccines, but they use an attenuated virus or bacterium to introduce microbial DNA to cells of the body. "Vector" refers to the virus or bacterium used as the carrier.

In nature, viruses latch on to cells and inject their genetic material into them. In the lab, scientists have taken advantage of this process. They have figured out how to take the roomy genomes of certain harmless or attenuated viruses and insert portions of the genetic material from other microbes into them.

The carrier viruses then ferry that microbial DNA to cells. Recombinant vector vaccines closely mimic a natural infection and therefore do a good job of stimulating the immune system.

Attenuated bacteria also can be used as vectors. In this case, the inserted genetic material causes the bacteria to display the antigens of other microbes on its surface. In effect, the harmless bacterium mimics a harmful microbe, provoking an immune response.

Researchers are working on both bacterial and viral-based recombinant vector vaccines for HIV, rabies, and measle

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UNIT- V

S.NO	QUESTION	A	B	C	D	Answer
1	Precipitins are antibodies that insolublise	Ag	Ab	Ag-Ab	antigenic determinants	Ag
2	Antibodies are ……..molecules	Mono	Di	unique	poly	unique
3	An ……..that produces a precipitate when mixed with antigen solution	Ag	Ab	Ag-Ab	Antiserum	Antiserum
4	T he quantitative precipitin test,it was developed by	Kendall	Heidelberg	Heidelberg &Kendall	Rodney porter	Heidelberg &Kendall
5	The VDRL test is used to diagnosis	AIDS	Gonorrhea	Genital Herpus	Syphilis	Syphilis
6	The binding of complement to Ag-Ab complex is called	antigen binding	complement fixation	antibody binding	non-complement fixation	complement fixation
7	ELISA technique was first introduced by	Kohlar &Milstein	Engral&Perlma	Dreyer&Burnet	Rodney porter	Engral&Perlma
8	Set of antigens on the surface of all nucleated cells of human bidy	Transplantation ag	human leucocyte ag	Thymus dependent ag	thymus independent ag	human leucocyte ag
9	Hybridoma technology was developed by	Kohlar &Milstein	Engral&Perlman	Dreyer&Burnet	Rodney porter	Kohlar &Milstein

10	A method of measuring Ag or Ab using radiolabelled Ag	ELISA	DIBA	RIA	Immunodiffusion	RIA
11	Well-felix reaction is used to test	typhus	malaria	cholera	small pox	typhus
12	Which test is used for the detection of anti Rh Ab	Widal test	Coomb's test	Rh blood typing	Well-felix reaction	Coomb's test
13	Test used for the diagnosis of typhoid fever	Widal test	Coomb's test	Rh blood typing	Well-felix reaction	Widal test
14	Anti-streptomycin-O test is used to detect	rheumatoid fever	malaria	typhus	cholera	cholera
15	Corticosteroids &cyclosporin are used in prevention of	cancer	graft rejection	typhus	cholera	graft rejection
16	Which are involved in cytotoxicity and destruction of tumor cells	Macrophage	T cells	Phagocytes	NK cells	NK cells
17	……..are used for the treatment of autoimmune disease	Corticosteroids&cyclosporin	chloramphenicol	Quinone	Sulphonamides	Corticosteroids&cyclosporin
18	…….is used for the treatment of lepromatous leprosy	µ interferon	b interferon	¶ interferon	g interferon	g interferon
19	Burkitti lymphoma is caused by	Hepatitis-B virus	Epstein-Barr virus	Herpes virus	Retro virus	Epstein-Barr virus
20	Test which is used to detect both Ag & Ab using labeled anti- human Ab	Solid phase RIA	Single Radial immunodiffusion	Radial immunodiffusion	Single linear immunodiffusion	Solid phase RIA
21	Gastric auto-Ag reacting with auto Ab present in serum of patient suffering from	Pernicious anaemia	Haemolytic anaemia	rheumatoid fever	malaria	Pernicious anaemia
22	Which test is used to detect autoantibodies and antibodies to tissue & cellular antigen	Immunoassay	Complement fixation	Immunofluorescence	Immunoelectrophoresis	Immunofluorescence
23	The complement fixation test detects	Antigen	Antibody	lymphocytes	Rh factor	Antibody
24	Identification of specific protein in complex mixture of proteins can be accomplished by	Northern blotting	Western blotting	Southern blotting	Southern hybridisation	Western blotting

25	The technique used for the isolation of the antigen of interest for further analysis	Immunoprecipitation	Immunodiffusion	Immunofluorescence	Complement fixation	Immunoprecipitation
26	……is the most widely used organic dye for the immunofluorescence procedure	crystal violet	Azo dyes	bromophenol blue	Fluorescein	Fluorescein
27	……is the injection of Ag into body to produce immunity and protect against disease	Innate immunity	Vaccination	Complement fixation	Passive immunity	Vaccination
28	Vaccines prepared from the toxins and chemicals of microbes	Cellular	sub-cellular	Attenuated	Homologous	sub-cellular
29	Vaccines prepared from the polysaccharide or protein units of bacteria	Cellular	sub-cellular	Toxoid	sub unit	sub unit
30	The immunity transferred from the mother to the child	Natural passive immunization	Active immunization	cell mediated	Humoral	Natural passive immunization
31	Substance,which stimulatespecific immune	Antibody	Antiserum	Immunogen	Allergen	Allergen
32	The immunization of an individual with antigens from within its own species	Alloimmunization	Active immunization	cell mediated	Autoimmunization	Alloimmunization
33	The strength of binding between antigen and antibody is termed	Fixation	Avidity	Atopy	Eczema	Avidity
34	Having the ability to step cell growth	Cytostatic	cytotoxic	cytophilic	cytokines	cytokines
35	Having the ability to kill cells	Cytostatic	cytotoxic	cytophilic	cytokines	cytophilic
36	A large, primitive looking, cell capable of division & differentiation	B cell	T cell	NK cell	Blast cell	B cell
37	The substance, which increase immunity response to an antigen	allergen	alloantigens	adjuvants	aggluitnogens	adjuvants
38	Erythema causes inflammation in redness of ----------	Skin	lung	tissues	liver	Skin
39	Second antibody molecules in the sandwich technique are simply	gloublins	antigens	anti- gloublins	antibody - gloublins	anti- gloublins

40	Ab against immunogloublin,by injecting immunogloubulin intoanimal of other species	Antiserum	antitoxins	antibodies	anti- gloublins	anti- gloublins
41	A local inflammatory reaction due to a type III hypersensitive reaction	Asthma	Arthus reaction	haemolysis	oesnophilia	Arthus reaction
42	An animal that contains cells from two or more genetically different individual	Chimera	genera	non-genera	non-chimera	Chimera
43	Cell surface molecule classified accordingtointernationally accepted	haptens	epitopes	CD molecule	Interferon	CD molecule
44	Which of the following is a quantitative precipitation technique	Gel diffusion	diffusion	immunoelectrophoresis	radial immunodiffusion	radial immunodiffusion
45	Which of these antibody assays is primary binding test	Fluorescent antibody	immunoelectrophoresis	Agglutination	Complement fixation	Fluorescent antibody
46	Serum IgM levels may be measured by means of	RID	direct agglutination	passive agglutination	Active agglutination	passive agglutination
47	The gel diffusion technique is	1^0 binding test	2^0 binding test	3^0 binding test	4^0 binding test	2^0 binding test
48	The most sensitive immunological test in terms of the amount of Ab detectable is	RIA	RID	ELISA	gel-precipitation test	RIA
49	Incomplete antibodies are antibodies that	lack a Fc region	lack a Fab region	cannot bind Ag	cannot agglinate Ag	cannot agglinate Ag
50	The ligand for the small protein avidin is	Ig	biotin	Fluorescein	Ferrilin	Ferrilin
51	Which of these is secondary binding test	ELISA	RIA	Immunoelectrophoresis	mouse protection test	Immunoelectrophoresis
52	Immune complex precipitates are formed in	Ag excess	Ab excess	The zone of equivalence of	Absence of electrolyte	The zone of equivalence of
53	Antiglobulins are	Incomplete Ag	Abs against Ig	Agglutinating Ab	None of these	Abs against Ig
54	The major forces linking Ag&Ab are	hydrogen bonds	Covalent bonds	Ionic bonds	Hydrophobic bonds	Hydrophobic bonds

55	The Ag –combining site of an antibody molecule determines its	Isotype	Idiotype	Allotype	Hypertype	Hypertype
56	One major vaccine component that causes allergic reaction	Egg Ag	Viral Ag	Bacterial Ag	Endotoxin	Viral Ag
57	Deficiency of which minerals is most likely to lead to an immunodeficiency	Calcium	Zinc	Lead	Iron	Zinc
58	The drug that is mainly used to treat AIDS patients is	Azidiothymidine	Tetracyclin	Imuran	Cortisone	Azidiothymidine
59	Which of the following blood group Ags is not determined by carbohydrate epitopes	A	Rhesus	O	B	Rhesus
60	The complement present in higher concentration in the blood is	C_4	C_1	C_3	C_5	C_3