COURSE GUIDE

BIO 406
PARASITOLOGY AND IMMUNOLOGY

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Introduction

Parasitology and Immunology (406) is a second semester course. It is a two credit unit elective course which all students offering Bachelor of Science (BSc) in Biology can take.

Parasitology and Immunology is an important area of study for scientists. Immunity is a biological term that describes a state of having sufficient biological defenses to avoid infection, disease, or other unwanted biological invasion. Immunity involves both specific and non-specific components. Since this course parasitology and immunology entails the study of body defence mechanism, we will focus on the types of immunity and their processes, hypersensitivity, interaction of antibody with antigens. Also, immunology of tissue transplantation and infection will explain further.

This course deals with parasitology and immunity with emphasis to different types of immunity, defence mechanisms, processes, functions and interaction of antibody to antigen.

What You Will Learn In This Course

In this course, you have the course units and a course guide. The course guide will tell you briefly what the course is all about. It is a general overview of the course materials you will be using and how to use those materials. It also helps you to allocate the appropriate time to each unit so that you can successfully complete the course within the stipulated time limit.

The course guide also helps you to know how to go about your Tutor-Marked-Assignment which will form part of your overall assessment at the end of the course. Also, there will be tutorial classes that are related to this course, where you can interact with your facilitators and other students. Please I encourage you to attend these tutorial classes.

This course exposes you to parasitology and immunology, a sub-discipline and very interesting field of Biology.

Course Aims

This course aims to enable you to know/understand the different types of immunity, defence mechanisms, processes, functions and interaction of antibody to antigen.

Course Objectives

To achieve the aim set above, there are objectives. Each unit has a set of objectives presented at the beginning of the unit. These objectives will give you what to concentrate and focus on while studying the unit and during your study to check your progress.

The Comprehensive Objectives of the Course are given below. At the end of the course/after going through this course, you should be able to:

- Define immunity
- Describe the theories of immunity
- Have an understanding of types of immunity and their importance to man
- Explain Infections and types
- Prevention and protection from infections
- Explain Immediate hypersensitivity
- Explain Type I, II, III and IV hypersensitivity
- Explain Low-level autoimmunity
- Identify Causes of autoimmunity
- Name and explain Genetic Factors
- Explain Environmental Factors affecting autoimmunity

Working Through the Course

a. To successfully complete this course. You are required to read each study unit, read the textbooks and other materials provided by the National Open University.
b. Reading the reference materials can also be of great assistance.
c. Each unit has self –assessment exercise which you are advised to do. At certain periods during the course you will be required to submit your assignments for the purpose of assessment.
d. There will be a final examination at the end of the course. The course should take you about17 weeks to complete.
e. This course guide provides you with all the components of the course, how to go about studying and how you should allocate your time to each unit so as to finish on time and successfully.

The Course Materials

The main components of the course are:

1 The Study Guide
2 Study Units
3 Reference/ Further Readings

4 Assignments
5 Presentation Schedule

Study Units

The study units in this course are given below:

Module 1 Immunity

Unit 1 Immunity
Unit 2 Infection, immunity and protection
Unit 3 Antigen

Module 2 Hypersensitivity

Unit 1 Hypersensitivity
Unit 2 Autoimmunity
Unit 3 Immunology of Tissue Transplantation

In module one, unit one, two and three extensively explain different types of immunity and protection, infection, and interaction of antibody with antigen.

Module Two is concerned with hypersensitivity; inappropriate responds of the immune system to the presence of antigen, autoimmunity; is the failure of an organism to recognise its own constituent parts as self, which allows an immune response against its own cells and tissues and immunology of tissue transplantation.

Each unit will take a week or two lectures, will include an introduction, objectives, reading materials, self-assessment question(s), conclusion, summary, Tutor-Marked Assignments (TMAs), references and other reading resources.

There are activities related to the lecture in each unit which will help your progress and comprehension of the unit. You are required to work on these exercises which together with the TMAs will enable you to achieve the objective of each unit.

Presentation Schedule

There is a time-table prepared for the early and timely completion and submissions of your TMAs as well as attending the tutorial classes. You are required to submit all your assignments by the stipulated date and time. Avoid falling behind the schedule time.

Assessment

There are three aspects to the assessment of this course.

The first one is the self-assessment exercises. The second is the Tutor-Marked Assignments and the third is the written examination or the examination to be taken at the end of the course.

Do the exercises or activities in the unit applying the information and knowledge you acquired during the course. The Tutor-Marked Assignments must be submitted to your facilitator for formal assessment in accordance with the deadlines stated in the presentation schedule and the assignment file.

The work submitted to your tutor for assessment will account for 30% of your total work.

At the end of this course you have to sit for a final or end of course examination of about a three-hour duration which will account for 70% of your total course mark.

Tutor -Marked Assignment

This is the continuous assessment component of this course and it accounts for 30% of the total score. You will be given four (4) TMAs by your facilitator to answer. Three of which must be answered before you are allowed to sit for the end of the course examination.

These answered assignments must be returned to your facilitator.

You are expected to complete the assignments by using the information and material in your reading references and study units.

Reading and researching into the references will give you a wider view point and give you a deeper understanding of the subject.

Make sure that each assignment reaches your facilitator on or before the deadline given in the presentation schedule and assignment file. If for any reason you are not able to complete your assignment, make sure you contact your facilitator before the assignment is due to discuss the possibility of an extension. Request for extension will not be granted after the due date unless there is an exceptional circumstance.

Make sure you revise the whole course content before sitting for examination. The self-assessment activities and TMAs will be useful for this purposes and if you have any comments please do before the

examination. The end of course examination covers information from all parts of the course.

Course Marking Scheme

Assignment	**Marks**
Assignment 1-4	Four assignments, best three marks of the four count at 10% each - 30% of course marks.
End of course examination	70% of overall course marks
Total	100% of course materials

Facilitators/ Tutors and Tutorials

Sixteen (16) hours are provided for tutorials for this course. You will be notified of the dates, times and location for these tutorial classes.
As soon as you are allocated a tutorial group, the name and phone number of your facilitator will be given to you.

These are the duties of your facilitator:

- He or she will mark and comment on your assignment
- He will monitor your progress and provide any necessary assistance you need.
- He or she will mark your TMAs and return to you as soon as possible.

(You are expected to mail your tutored assignment to your facilitators at least two days before the schedule date).

Do not delay to contact your facilitator by telephone or e-mail for necessary assistance if:

- you do not understand any part of the study in the course material
- you have difficulty with the self-assessment activities
- you have a problem or question with an assignment or with the grading of the assignment.

It is important and necessary you attend the tutorial classes because this is the only chance to have face to face contact with your facilitator and to ask questions which will be answered instantly. It is also a period where you can point out any problem encountered in the course of your study.

Summary

Parasitology and Immunology (406) is a course which explain the body defence mechanism; how level of immunity in the organism can cause infection and response of antibody and antigen to infection.

Also, the how natural or artificial, innate or acquired=adaptive and either active or passive immunity function in organism.

On the completion of this course, you will have an understanding of basic knowledge of different types of immunity, antibody-antigen interaction, infection, immunity and protection, hypersensitivity and autoimmunity. In addition, you will be able to answer the following questions:

- what do you understand by the term Immunity?
- explain innate immunity
- what is acquired immunity
- what is immunity?
- what is an infection?
- what are the types of resistance to infections?
- what are antigens
- differentiate between endogenous and exogenous antigens
- describe the interactions between antibodies and antigens
- state what antigens are composed of chemically.
- list 3 characteristics an antigen must have to be immunogenic
- briefly describe how the body recognises an antigen as foreign.
- what is autoimmunity
- discuss the pathogenesis of autoimmunity
- discuss on the genetic factors affecting autoimmunity
- the list of questions you are expected to answer is not limited to the above list.

I believe you will agree with me that Mycology is a very interesting field of biology.

I wish you success in this course.

MAIN COURSE

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MODULE 1 IMMUNITY

UNIT 1 IMMUNITY

CONTENTS

1.0 INTRODUCTION

Immunity is a biological term that describes a state of having sufficient biological defences to avoid infection, disease, or other unwanted biological invasion. Immunity involves both specific and non-specific components. The non-specific components act either as barriers or as eliminators of a wide range of pathogens irrespective of antigenic specificity. Other components of the immune system adapt themselves to each new disease encountered and are able to generate pathogen- specific immunity.

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- define immunity
- describe the theories of immunity
- explain types of immunity and their importance to man.

3.0 MAIN CONTENT

3.1 Concept of Immunity

The concept of immunity has intrigued mankind for thousands of years. The prehistoric view of disease was that it was caused by supernatural forces, and that illness was a form of theurgic punishment for evilthoughts visited upon the soul by the gods or by one's enemies. Betweenthe time of Hippocrates and the 19th century, when the foundations of the scientific method were laid, diseases were attributed to an alteration or imbalance in one of the four humours. The modern word "immunity" derives from the Latin *immunis*, meaning exemption from military service, tax payments or other public services. The first written descriptions of the concept of immunity may have been made by the Athenian Thucydides who, in 430 BC, described that when the plague hit Athens "the sick and the dying were tended by the pitying care of those who had recovered, because they knew the course of the disease and were themselves free from apprehensions. For no one was ever attacked a second time, or not with a fatal result". The term "immunes", is also found in the epic poem "Pharsalia" written around 60 B.C. by thepoet Marcus Annaeus Lucanus to describe a North African tribe's resistance to snake venom.

The first clinical description of immunity which arose from a specific disease causing organism is probably Kitab fi al-jadari wa-al-hasbah (A Treatise on Smallpox and Measles, translated 1848) written by the Islamic physician Al-Razi in the 9th century. In the treatise, Al Razi describes the clinical presentation of smallpox and measles and goes on to indicate that that exposure to these specific agents confers lasting immunity. However, it was with Louis Pasteur's Germ theory of disease that the fledgling science of immunology began to explain how bacteria caused disease, and how, following infection, the human body gainedthe ability to resist further infections.

The birth of active immunotherapy may have begun with Mithridates VI of Pontus. To induce active immunity for snake venom, he recommended using a method similar to modern toxoid serum therapy, by drinking the blood of animals which fed on venomous snakes. According to Jean de Maleissye, Mithridates assumed that animals feeding on venomous snakes acquired some detoxifying property in theirbodies, and their blood must contain attenuated or transformedcomponents of the snake venom. The action of those components might be strengthening the body to resist the venom instead of exerting toxic effect. Mithridates reasoned that, by drinking the blood of these animals,he could acquire similar resistance to the snake venom as the animals feeding on the snakes. Similarly, he sought to harden himself against

poison, and took daily sub-lethal doses to build tolerance. Mithridates is also said to have fashioned a 'universal antidote' to protect him from all earthly poisons. For nearly 2000 years, poisons were thought to be the proximate cause of disease, and a complicated mixture of ingredients, called Mithridate, was used to cure poisoning during the Renaissance. An updated version of this cure, Theriacum Andromachi, was used well into the 19th century. In 1888 Emile Roux and Alexandre Yersin isolated diphtheria toxin, and following the 1890 discovery by Behring and Kitasato of antitoxin based immunity to diphtheria and tetanus, the antitoxin became the first major success of modern therapeutic Immunology.

In Europe, the induction of active immunity emerged in an attempt to contain smallpox. Immunisation, however, had existed in various forms for at least a thousand years. The earliest use of immunisation is unknown, however, around 1000 A.D. the Chinese began practicing a form of immunisation by drying and inhaling powders derived from the crusts of smallpox lesions. Around the fifteenth century in India, the Ottoman Empire, and east Africa, the practice of variolation (poking the skin with powdered material derived from smallpox crusts) becamequite common. Variolation was introduced to the west in the early 18th century by Lady Mary Wortley Montagu. In 1796, Edward Jenner introduced the far safer method of inoculation with the cowpox virus, a non-fatal virus that also induced immunity to smallpox. The success andgeneral acceptance of Jenner's procedure would later drive the general nature of vaccination developed by Pasteur and others towards the end of the 19th century.

3.2 Passive Immunity

Passive immunity is transmitted by antibodies or lymphocytes preformed in another host. The passive administration of antibody against bacteria makes immediately available excess antitoxin to neutralise the toxins. Likewise, preformed antibodies to certain viruses can be injected during the incubation period to limit viral multiplication. The main advantage of passive immunisation with preformed antibodies is the prompt availability of large amounts of antibody; disadvantages are the short life span of these antibodies and possible sensitivity reactions if antibodies from another species are administered.

Passive immunity is the transfer of active immunity, in the form of readymade antibodies, from one individual to another. Passive immunity can occur naturally, when maternal antibodies are transferred to the foetus through the placenta, and can also be induced artificially, when high levels of human (or horse) antibodies specific for a pathogen or toxin are transferred to non-immune individuals. Passive immunisation is used when there is a high risk of infection and insufficient time for the

body to develop its own immune response, or to reduce the symptoms of ongoing or immunosuppressive diseases. Passive immunity provides immediate protection, but the body does not develop memory, therefore the patient is at risk of being infected by the same pathogen later.

Naturally acquired passive immunity

Maternal passive immunity is a type of naturally acquired passive immunity, and refers to antibody-mediated immunity conveyed to afoetus by its mother during pregnancy. Maternal antibodies (MatAb) are passed through the placenta to the foetus by an FcRn receptor on placental cells. This occurs around the third month of gestation. IgG is the only antibody isotype that can pass through the placenta. Passive immunity is also provided through the transfer of IgA antibodies found in breast milk that are transferred to the gut of the infant, protecting against bacterial infections, until the newborn can synthesise its own antibodies.

Artificially acquired passive immunity

Artificially acquired passive immunity is a short-term immunisation induced by the transfer of antibodies, which can be administered in several forms; as human or animal blood plasma, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, and in the form of monoclonal antibodies (MAb). Passive transfer is used prophylactically in the case of immunodeficiency diseases, such as hypo-gammaglobulinemia. It is also used in the treatment of several types of acute infection, and to treat poisoning. Immunity derived from passive immunisation lasts for only a short period of time, and there is also a potential risk for hypersensitivity reactions, and serum sickness, especially from gamma globulin of non-human origin.

The artificial induction of passive immunity has been used for over a century to treat infectious disease, and prior to the advent of antibiotics, was often the only specific treatment for certain infections. Immunoglobulin therapy continued to be a first line therapy in the treatment of severe respiratory diseases until the 1930’s, even after sulfonamide lot antibiotics were introduced.

Passive transfer of cell-mediated immunity

Passive or "adoptive transfer" of cell-mediated immunity, is conferredby the transfer of "sensitised" or activated T-cells from one individual into another. It is rarely used in humans because it requires histocompatible donors, which are often difficult to find. In unmatched donors this type of transfer carries severe risks of graft versus host disease. It has, however, been used to treat certain diseases including some types of cancer and immunodeficiency. This type of transfer
differs from a bone marrow transplant, in which hematopoietic stem cells are transferred.

IN TEXT QUESTION
What is passive immunity?
Passive immunity is the transfer of active immunity, in the form of readymade antibodies, from one individual to another.

3.3 Active Immunity

Active immunity is induced after contact with foreign antigens. This contact may consist of clinical or subclinical infection, immunisation with live or killed infectious agents or their antigens, exposure to microbial products or transplantation of foreign cells. In all these instances, the host actively produces antibodies and lymphoid cells acquire the ability to respond to the antigens. Advantages of active immunity include long-term resistance –based on memory of prior contact with antigen and the capacity to respond faster and to a greater extent on subsequent contact with the same antigen, disadvantages include the slow onset of resistance and the need for prolonged orrepeated contact with the antigen.

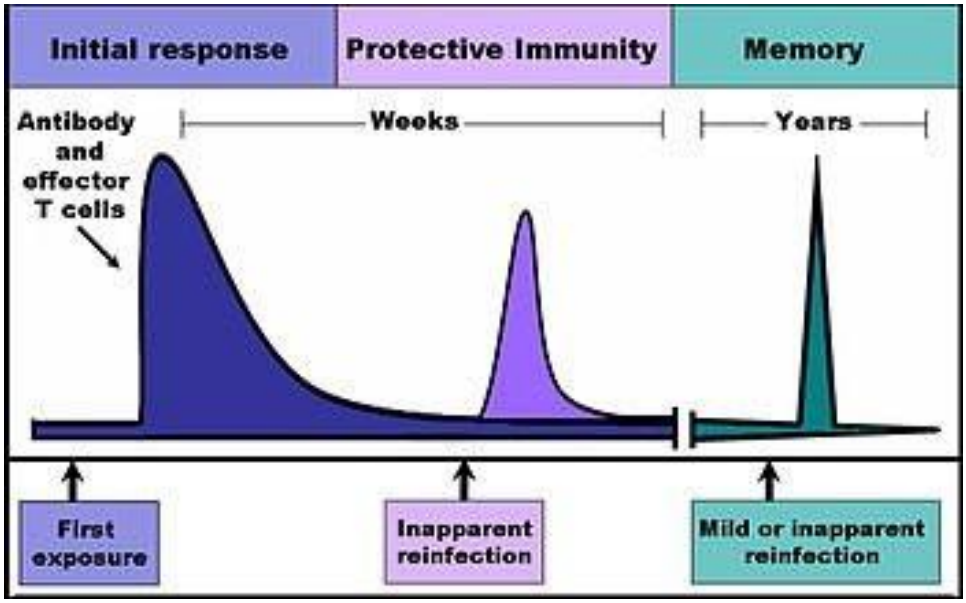


Fig. 1: The Time Course of an Immune Response. Due to the formation of immunological memory, re-infection atlater time points leads to a rapid increase in antibody production and Effector T cell Activity. These laterinfections can be mild or even inapparent.

When B cells and T cells are activated by a pathogen, memory B-cells and T- cells develop. Throughout the lifetime of an animal these memory cells will "remember" each specific pathogen encountered, and are able to mount a strong response if the pathogen is detected again. This type of immunity is both active and adaptive because the body's immune system prepares itself for future challenges. Active immunity often involves both the cell-mediated and humoral aspects of immunity as well as input from the innate immune system. The *innate system* is present from birth and protects an individual from pathogens regardless

of experiences, whereas adaptive immunity arises only after an infection or immunisation and hence is "acquired" during life.

Innate Immunity
Naturally acquired active immunity occurs when a person is exposed to a live pathogen, and develops a primary immune response, which leads to immunological memory. This type of immunity is “natural” because itis not induced by deliberate exposure. Many disorders of immune system function such as immunodeficiency and immuno-suppression can affect the formation of active immunity.

Artificially acquired active immunity
Artificially acquired active immunity can be induced by a vaccine; a substance that contains antigen. A vaccine stimulates a primary response against an antigen without causing symptoms of the disease. The term vaccination was coined by Edward Jenner and adapted by Louis Pasteur for his pioneering work in vaccination. The method Pasteur used entailed treating the infectious agents for those diseases so they lost the ability to cause serious disease. Pasteur adopted the name vaccine as a generic term in honour of Jenner's discovery, which Pasteur's work built upon.

In 1807, the Bavarians became the first group to require that theirmilitary recruits be vaccinated against smallpox, as the spread of smallpox was linked to combat. Subsequently the practice of vaccination would increase with the spread of war.

There are four types of traditional vaccines:

a. Inactivated vaccines are composed of micro-organisms that have been killed with chemicals and/or heat and are no longer infectious. Examples are vaccines against flu, cholera, plague, and hepatitis A. Most vaccines of this type are likely to require booster shots.
b. Live, attenuated vaccines are composed of micro-organisms that have been cultivated under conditions which disable their ability to induce disease. These responses are more durable and do not generally require booster shots. Examples include yellow fever, measles, rubella, and mumps.
c. Toxoids are inactivated toxic compounds from micro-organisms in cases where these (rather than the micro-organism itself) causeillness, used prior to an encounter with the toxin of the micro- organism. Examples of toxoid-based vaccines include tetanus anddiphtheria.
d. Subunit -vaccines are composed of small fragments of disease causing organisms. A characteristic example is the subunit vaccine against Hepatitis B virus.

Most vaccines are given by hypodermic injection as they are not absorbed reliably through the gut. Live attenuated polio and some typhoid and cholera vaccines are given orally in order to produce immunity based in the bowel.

IN TEXT QUESTIONS

How is active immunity acquired?

Answers

Active immunity is induced after contact with foreign antigens.

3.3 Innate Immunity

The innate immunity system is what we are born with and it is nonspecific; all antigens are attacked pretty much equally. It is genetically based and we pass it on to our offspring.

Surface Barriers or Mucosal Immunity

a. The first and, arguably, most important barrier is the skin. The skin cannot be penetrated by most organisms unless it already hasan opening, such as a scratch, or cut.

b. Mechanically, pathogens are expelled from the lungs by ciliary action as the tiny hairs move in an upward motion; coughing and sneezing abruptly eject both living and nonliving things from the respiratory system; the flushing action of tears, saliva, and urine also force out pathogens, as does the sloughing off of skin.

c. Sticky mucus in respiratory and gastrointestinal tracts traps many microorganisms.

d. Acid pH (< 7.0) of skin secretions inhibits bacterial growth. Hair follicles secrete sebum that contains lactic acid and fatty acids both of which inhibit the growth of some pathogenic bacteria and fungi. Areas of the skin not covered with hair, such as the palms and soles of the feet, are most susceptible to fungal infections. Think athlete's foot.

e. Saliva, tears, nasal secretions, and perspiration contain lysozyme, an enzyme that destroys Gram positive bacterial cell walls causing cell lysis. Vaginal secretions are also slightly acidic (after the onset of menses). Spermine and zinc in semen destroy some pathogens. Lactoperoxidase is a powerful enzyme found in mother's milk.

f. The stomach is a formidable obstacle insofar as its mucosa secrete hydrochloric acid (0.9 < pH < 3.0, very acidic) and protein-digesting enzymes that kill many pathogens. The stomachcan even destroy drugs and other chemicals.

Normal flora are the microbes, mostly bacteria, that live in and on our bodies with, usually, no harmful effects to us. We have about 10^{13} cells in our bodies and 10^{14} bacteria, most of which live in the large intestine. There are 10^3–10^4 microbes per cm^2 on the skin (*Staphylococcus aureus*,

Staph. epidermidis, diphtheroids, streptococci, *Candida*, etc.). Various bacteria live in the nose and mouth. Lactobacilli live in the stomach and small intestine. The upper intestine has about 10^4 bacteria per gram; the large bowel has 10^{11} per gram, of which 95–99% are anaerobes (An anaerobe is a microorganism that can live without oxygen, while an aerobe requires oxygen.) or bacteroides. The urogenitary tract is lightly colonized by various bacteria and diphtheroids. After puberty, the vagina is colonized by *Lactobacillus aerophilus* that ferment glycogen to maintain an acidic pH level. Normal flora fill almost all of the available ecological niches in the body and produce bacteriocidins, defensins, cationic proteins, and lactoferrin all of which work to destroy other bacteria that compete for their niche in the body. The resident bacteria can become problematic when they invade spaces in which theyare not meant to be. As examples: (a) staphylococcus living on the skin can gain entry to the body through small cuts. (b) Some antibiotics, in particular clindamycin, kill some of the bacteria in our intestinal tract.

This causes an overgrowth of *Clostridium difficile*, which results in pseudomembranous colitis, a rather painful condition wherein the inner lining of the intestine cracks and bleeds. A phagocyte is a cell that attracts (by chemotaxis), adheres to, engulfs, and ingests foreign bodies. *Promonocytes* are made in the bone marrow, after which they are released into the blood, they are called circulating *monocytes*, which eventually mature into macrophages (meaning "big eaters", see below).

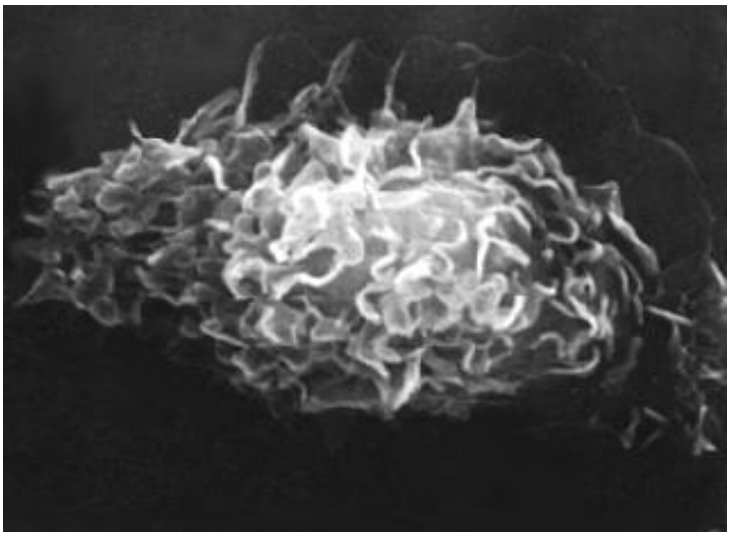


Fig. 2: Some macrophages are concentrated in the lungs, liver (Kupffer cells), lining of the lymph nodes and spleen, brain microglia, kidney mesoangial cells, synovial Acells, and osteoclasts. They are long-lived, depend on mitochondria for energy, and are best at attacking dead cells and pathogens capable of living within cells. Once a macrophage phagocytises a cell, it places some of its proteins, called epitopes, on its surface—much like a fighter plane displaying its hits. These surface markers serve as an alarm to other immune

cells that then infer the form of the invader. All cells that do this are called antigen presenting cells (APCs).

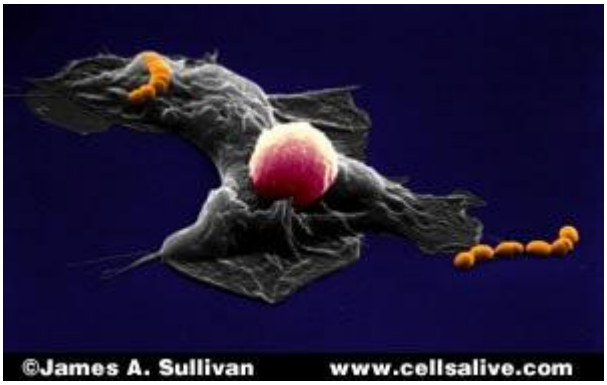


Fig. 3: The non-fixed or *wandering macrophages* roam the blood vessels and can even leave them to go to an infection site where they destroy dead tissue and pathogens. Emigration by squeezing through the capillary walls to the tissue is called diapedesis or extravasation. The presence of histamines at theinfection site attracts the cells to their source.

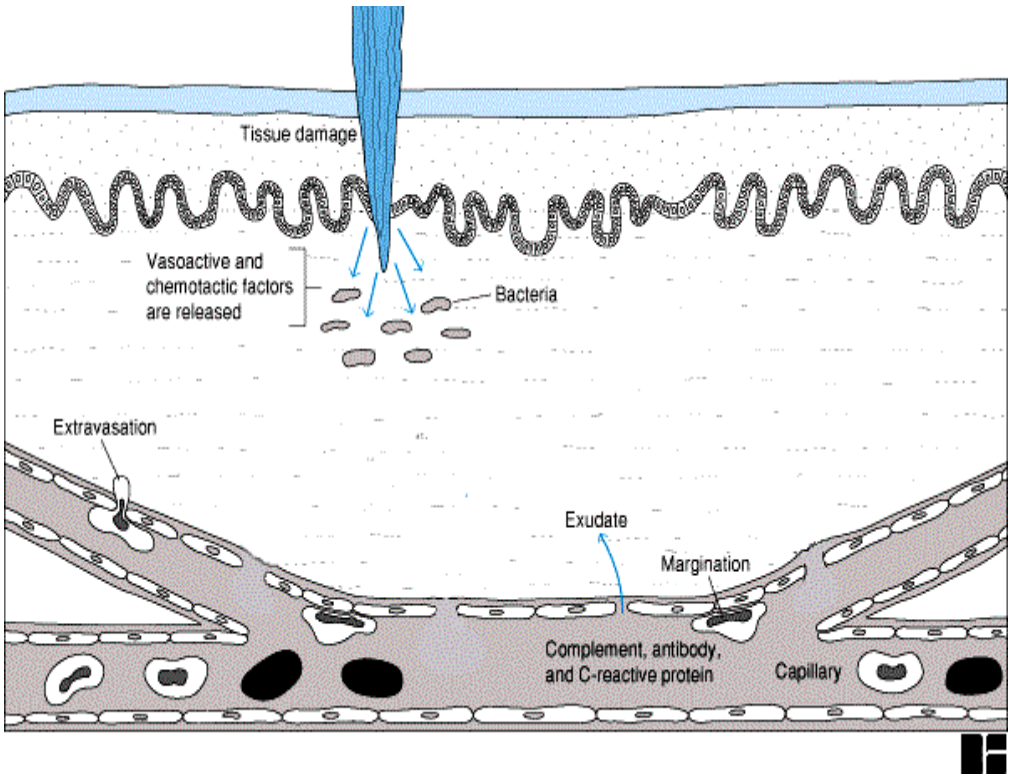


Fig. 4: Natural killer cells move in the blood and lymph to lyse(cause to burst) cancer cells and virus-infected body cells. They are large granular lymphocytes that attach to the glycoproteins on the surfaces of infected cellsand kill them.

Polymorphonuclear neutrophils, also called polys for short, are phagocytes that have no mitochondria and get their energy from stored glycogen. They are nondividing, short-lived (half-life of 6–8 hours, 1–4

day lifespan), and have a segmented nucleus. [The picture below shows the neutrophil phagocytising bacteria, in yellow.] They constitute 50–75% of all leukocytes. The neutrophils provide the major defence against pyogenic (pus-forming) bacteria and are the first on the scene to fight infection. They are followed by the wandering macrophages about three to four hours later.

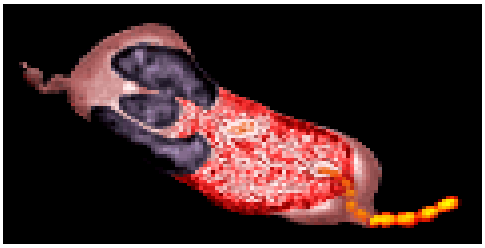


Fig. 5: The complement system is a major triggered enzymeplasma system. It coats microbes with molecules that make them more susceptible to engulfment by phagocytes. Vascular permeability mediators increase the permeability of the capillaries to allow more plasma and complement fluid to flow to the site ofinfection. They also encourage polys to adhere to the walls of capillaries (margination) from which they can squeeze through in a matter of minutes to arrive at a damaged area. Once phagocytes do their job, they die and their "corpses," pockets of damaged tissue, and fluid form pus.

Fig. 6: Eosinophils are attracted to cells coated withcomplement C3B, where they release major basic protein (MBP), cationic protein, perforins, and oxygen metabolites, all of which work together to burn holes incells and helminths (worms). About 13% of the WBCs are eosinophils. Their lifespan is about 8–12 days. Neutrophils, eosinophils, and macrophages are all phagocytes.

Dendritic cells are covered with a maze of membranous processes that look like nerve cell dendrites. Most of them are highly efficient antigen presenting cells. There are four basic types: Langerhans cells, interstitial dendritic cells, interdigitating dendritic cells, and circulating dendritic cells. Our major concern will be Langerhans cells, which are found in the epidermis and mucous membranes, especially in the anal, vaginal, and oral cavities. These cells make a point of attracting antigen and

efficiently presenting it to T helper cells for their activation. [This accounts, in part, for the transmission of HIV via sexual contact.]

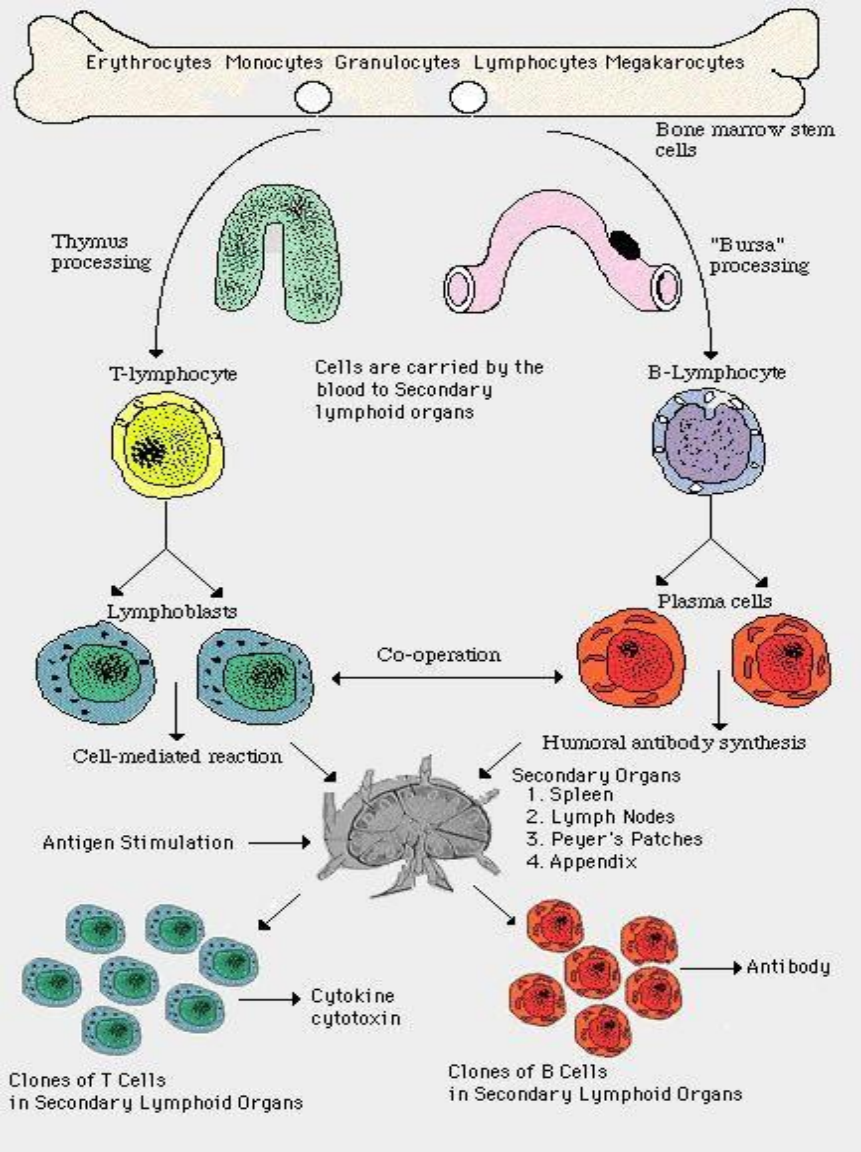


Fig. 7: Each of the cells in the innate immune system bind toantigen using pattern-recognition receptors. Thesereceptors are encoded in the line of each person. This immunity is passed from generation to generation. Over the course of human development these receptors for pathogen-associated molecular patterns have evolved via natural selection to be specific to certain characteristics of broad classes of infectious organisms. There are several hundred of these receptors and they recognise patterns of bacterial lipopolysaccharide, peptidoglycan, bacterial DNA, dsRNA, and othersubstances. Clearly, they are set to target both Gram- negative and Gram-positive bacteria.

3.5 Acquired Immunity

Lymphocytes come in two major types: B cells and T cells. The peripheral blood contains 20–50% of circulating lymphocytes; the rest move in the lymph system. Roughly 80% of them are T cells, 15% B cells and remainder are null or undifferentiated cells. Lymphocytes constitute 20–40% of the body's WBCs. Their total mass is about the same as that of the brain or liver. B cells are produced in the stem cellsof the bone marrow; they produce antibody and oversee humoral immunity. T cells are nonantibody-producing lymphocytes which are also produced in the bone marrow but sensitised in the thymus and constitute the basis of cell-mediated immunity. The production of these cells is diagrammed below. Parts of the immune system are changeable and can adapt to better attack an invading antigen. There are two fundamental adaptive mechanisms: cell-mediated immunity and humoral immunity.

Cell-mediated immunity
Macrophages engulf antigens, process them internally, then display parts of them on their surface together with some of their own proteins. This sensitises the T cells to recognise these antigens. All cells are coated with various substances. CD stands for cluster of differentiation and there are more than one hundred and sixty clusters, each of which is a different chemical molecule that coats the surface. CD8+ is read "CD8 positive." Every T and B cell has about 10^5 = 100,000 molecules on its surface. B cells are coated with CD21, CD35, CD40, and CD45 inaddition to other non-CD molecules. T cells have CD2, CD3, CD4, CD28, CD45R, and other non-CD molecules on their surfaces.

The large number of molecules on the surfaces of lymphocytes allows huge variability in the forms of the receptors. They are produced with random configurations on their surfaces. There are some 10^{18} different structurally different receptors. Essentially, an antigen may find a near-perfect fit with a very small number of lymphocytes, perhaps as few as one.

T cells are primed in the thymus, where they undergo two selection processes. The first *positive* selection process weeds out only those T cells with the correct set of receptors that can recognise the MHC molecules responsible for self-recognition. Then a *negative* selection process begins whereby T cells that can recognize MHC molecules complexed with foreign peptides are allowed to pass out of the thymus. Cytotoxic or killer T cells (CD8+) do their work by releasing lymphotoxins, which cause cell lysis. Helper T cells (CD4+) serve as managers, directing the immune response. They secrete chemicals called lymphokines that stimulate cytotoxic T cells and B cells to grow and divide, attract neutrophils, and enhance the ability of macrophages to

engulf and destroy microbes. Suppressor T cells inhibit the production of cytotoxic T cells once they are unneeded, lest they cause more damage than necessary. Memory T cells are programmed to recognise and respond to a pathogen once it has invaded and been repelled.

Humoral immunity

An immunocompetent but as yet immature B-lymphocyte is stimulated to maturity when an antigen binds to its surface receptors and there is aT helper cell nearby (to release a cytokine). This sensitises or primes theB cell and it undergoes clonal selection, which means it reproduces asexually by mitosis. Most of the family of clones becomes plasma cells. These cells, after an initial lag, produce highly specific antibodies at a rate of as many as 2000 molecules per second for four to five days. The other B cells become long-lived memory cells. Antibodies, also called immunoglobulins or Igs, constitute the *gamma globulin* part ofthe blood proteins. They are soluble proteins secreted by the plasma offspring (clones) of primed B cells. The antibodies inactivate antigens by, (a) complement fixation (proteins attach to antigen surface and causeholes to form, i.e., cell lysis), (b) neutralisation (binding to specific sites to prevent attachment—this is the same as taking up a parking space),
(c) agglutination (clumping), (d) precipitation (forcing insolubility and settling out of solution), and other more arcane methods.

Constituents of gamma globulin are: IgG-76%, IgA-15%, IgM-8%, IgD-1%, and IgE-0.002% (responsible for autoimmune responses, such as allergies and diseases like arthritis, multiple sclerosis, and systemic lupus). IgG is the only antibody that can cross the placental barrier to the foetus and it is responsible for the 3 to 6 month immune protection of newborns that is conferred by the mother.

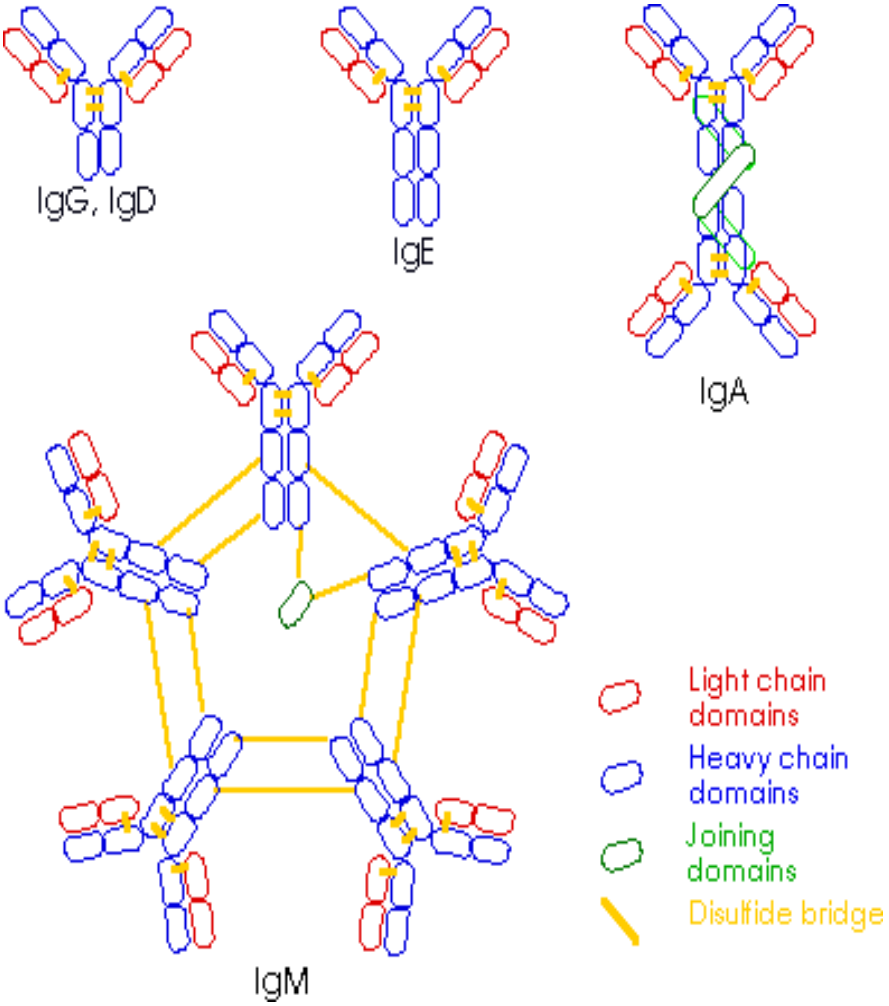


Fig. 8: IgM is the dominant antibody produced in primaryimmune responses, while IgG dominates in secondary immune responses. IgM is physically much larger than the other immunoglobulins.

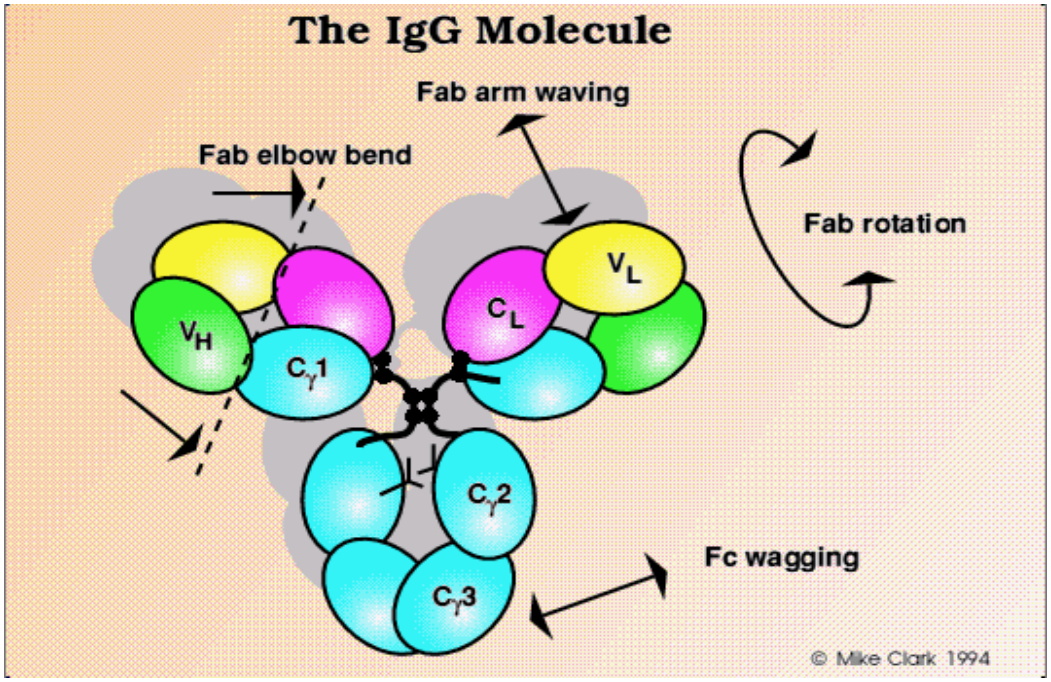
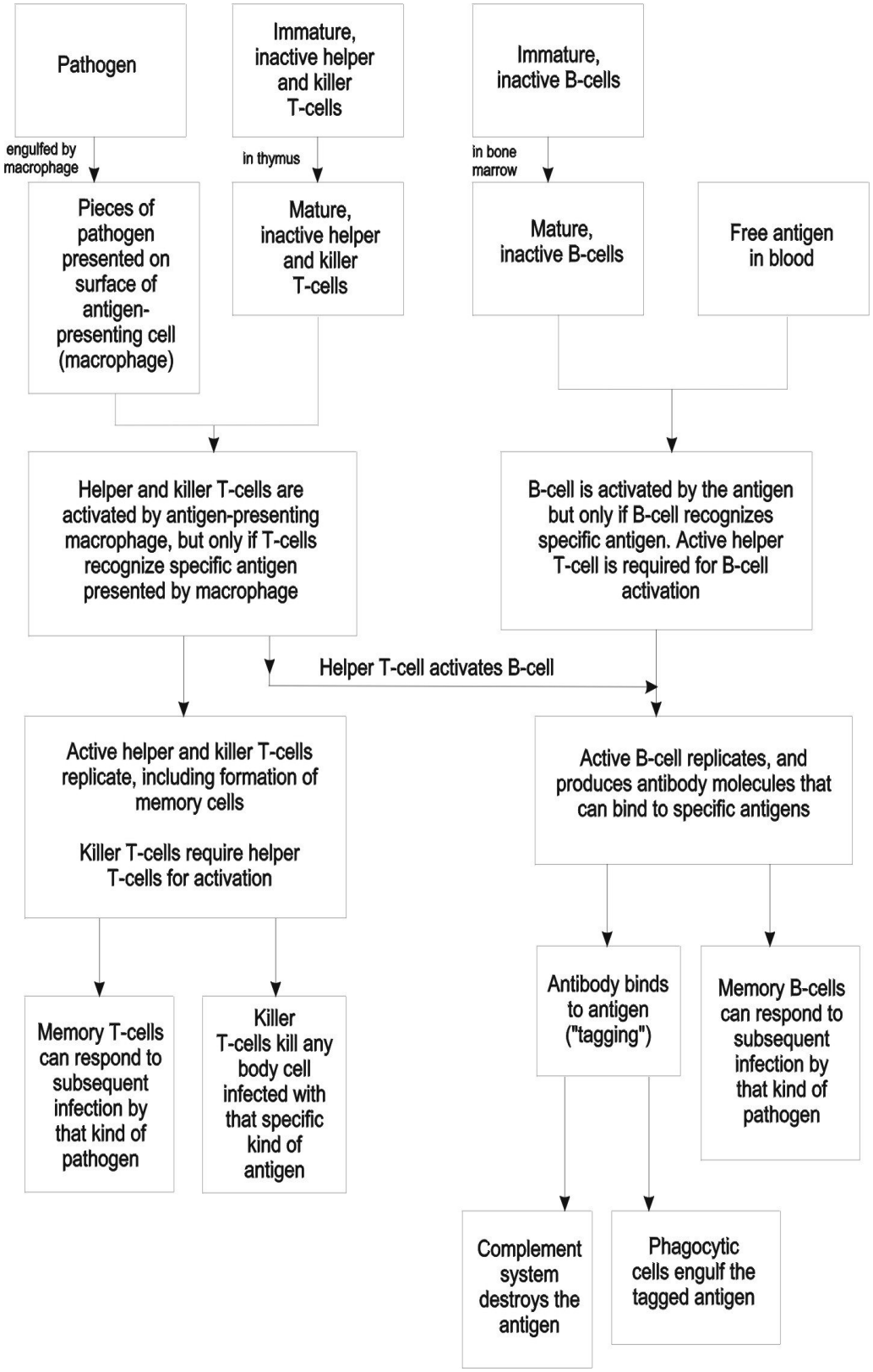


Fig. 9: Notice the many degrees of flexibility of the antibody molecule. This freedom of movement allows it to more easily conform to the nooks and crannies on an antigen. The upper part or Fab (antigen binding) portion of the antibody molecule (physically and not necessarily chemically) attaches to specific proteins [called epitopes] on the antigen. Thus, antibody recognises the epitope and not the entire antigen. The Fc region is crystallisable and is responsible for effector functions, i.e., the end to which immune cells can attach.

Lest you think that these are the only forms of antibody produced, you should realise that the B cells can produce as many as 10^{14} conformationally different forms.

The process by which T cells and B cells interact with antigens is summarised in the diagram below.



In the ABO blood typing system, when an A antigen is present (in a person of blood type A), the body produces an anti-B antibody, and similarly for a B antigen. The blood of someone of type AB, has both antigens, hence has *neither* antibody. Thus that person can be transfused

with any type of blood, since there is no antibody to attack foreign blood antigens. A person of blood type O has neither antigen but both antibodies and cannot receive AB, A, or B type blood, but they can donate blood for use by anybody. If someone with blood type A received blood of type B, the body's anti-B antibodies would attack the new blood cells and death would be imminent.

All of these of these mechanisms hinge on the attachment of antigen and cell receptors. Since there are many, many receptor shapes available, WBCs seek to optimise the degree of confluence between the two receptors. The number of these "best fit" receptors may be quite small, even as few as a single cell. This attests to the specificity of the interaction. Nevertheless, cells can bind to receptors whose fit is less than optimal when required. This is referred to as cross-reactivity. Cross-reactivity has its limits. There are many receptors to which virionscannot possibly bind. Very few viruses can bind to skin cells.

The design of immunising vaccines hinges on the specificity and cross-reactivity of these bonds. The more specific the bond, the more effective and long-lived the vaccine. The smallpox vaccine, which is made from the vaccinia virus that causes cowpox, is a very good match for the smallpox receptors. Hence, that vaccine is 100% effective and provides immunity for about 20 years. Vaccines for cholera have a relatively poor fit so they do not protect against all forms of the disease and protect for less than a year.

The goal of all vaccines is promote a primary immune reaction so that when the organism is again exposed to the antigen, a much stronger secondary immune response will be elicited. Any subsequent immune response to an antigen is called a secondary response and it has

- a shorter lag time
- more rapid buildup
- a higher overall level of response
- a more specific or better "fit" to the invading antigen
- utilises IgG instead of the large multipurpose antibody IgM.

IN TEXT QUESTION
What are the types of lymphocytes?
Answer
Lymphocytes come in two major types: B cells and T cells.

4.0 CONCLUSION

The student should be able to discuss on the following topics:

- Theories of immunity
- Passive and Active Immunity
- Innate and Acquired Immunity.

5.0 SUMMARY

Immunity can be natural or artificial, innate or acquired=adaptive, and either active or passive.

- Active natural (contact with infection): develops slowly, is long term, and antigen specific.
- Active artificial (immunisation): develops slowly, lasts for several years, and is specific to the antigen for which the immunisation was given.
- Passive natural (transplacental -mother to child): develops immediately, is temporary, and affects all antigens to which the mother has immunity.
- Passive artificial (injection of gamma globulin): develops immediately, is temporary, and affects all antigens to which the donor has immunity.

6.0 TUTOR-MARKED ASSIGNMENT

i. What do you understand by the term immunity?
ii. Explain innate immunity.
iii. What is acquired immunity.

7.0 REFERENCES/FURTHER READING

A "al-Razi" (2003). *The Columbia Electronic Encyclopedia.* Sixth Edition. Columbia University Press.

Coico, R., Sunshine, G., & Benjamin, E. (2003). "Immunology: A Short Course." Pg. 48.
Geo. F.B, Janet, S.B.& Stephen, A. M. (2001). *Medical Microbiology*.
Gherardi, E. The Concept of Immunity. History and Applications.
Immunology Course Medical School, University of Pavia.

Janeway, Charles; Paul Travers, Mark Walport, & Mark Shlomchik (2001). *Immunobiology.* Fifth Edition. New York and London: Garland Science. ISBN 0-8153-4101-6.

Keller, Margaret A. & Richard, Stiehm E. (Oct 2000). "Passive Immunity in Prevention and Treatment of Infectious Diseases." *Clinical Microbiology Reviews* 13 (4): 602–614.

Lindquester, Gary J. (2006). Introduction to the History of Disease. *Disease and Immunity*, Rhodes College.
Microbiology and Immunology On-Line Textbook: USC School of Medicine.

Silverstein, Arthur M. (1989). *History of Immunology*. Academic Press.

UNIT 2 INFECTION, IMMUNITY AND PROTECTION

CONTENTS

1.0 INTRODUCTION

In the previous unit you learnt about the different types of immunity. In this unit you will learn more deeply on the immune system. The immune system is the body's defence against infectious organisms and other invaders. Through a series of steps called the immune response, the immune system attacks organisms and substances that invade body systems and cause disease.

The immune system is made up of a network of cells, tissues, and organs that work together to protect the body. The cells involved are white blood cells, or leukocytes, which come in two basic types that combine to seek out and destroy disease-causing organisms or substances.

Leukocytes are produced or stored in many locations in the body, including the thymus, spleen, and bone marrow. For this reason, they are called the lymphoid organs. There are also clumps of lymphoid tissue throughout the body, primarily as lymph nodes, that house the leukocytes.

The leukocytes circulate through the body between the organs and nodes via lymphatic vessels and blood vessels. In this way, the immune system works in a coordinated manner to monitor the body for germs or substances that might cause problems.

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- define the immune system
- define infections and state types of infections and
- specify how to prevent infections.

3.0 MAIN CONTENT

3.1 Infection

An infection is the colonisation of a host organism by parasite species. Infecting parasites seek to use the host's resources to reproduce, often resulting in disease. Colloquially, infections are usually considered to be caused by microscopic organisms or microparasites like viruses, prions, bacteria, and viroids, though larger organisms like macroparasites and fungi can also infect.

Hosts normally fight infections themselves via their immune system. Mammalian hosts react to infections with an innate response, often involving inflammation, followed by an adaptive response. Pharmaceuticals also help fight infections.

Diagnosis of infections can be difficult as specific signs and symptoms are rare. If an infection is suspected, blood, urine and sputum culture tests are usually the first step. Chest x-rays and stool analysis may also aid diagnosis. Spinal fluid can be tested to ensure that there is no brain infection.

In children the presence of cyanosis, rapid breathing, poor peripheral perfusion, or a petechial rash increases the risk of a serious infection by greater than 5 fold. Other important indicators include parental concern, clinical instinct, and temperature greater than 40 °C.

Infections could be as a result of bacteria or a virus. Bacterial and viral infections can both cause symptoms such as malaise, fever, and chills. It can be difficult to distinguish between bacterial and viral infection but it is important to do so, because viral infections cannot be cured by antibiotics.

There is a general chain of events that applies for infections to occur. The chain of events involves several steps which include infectious agent, reservoir, entering a susceptible host, and exit and transmission to new hosts. Each of the links must be present in a chronological order for an infection to develop and understanding these steps helps health care

workers target the infection and prevent it from occurring in the first place.

Infection begins when an organism successfully colonises a host by entering the body, growing and multiplying. Most humans are not easily infected but those who are weak, sick, and malnourished, have cancer or are diabetic have increased susceptibility to chronic or persistent infections. Individuals who have a suppressed immune system are particularly susceptible to opportunistic infections. Invasion of the host generally occurs through the mucosa in orifices like the oral cavity, nose, eyes, genitalia, anus, or open wounds. While a few organisms can grow at the initial site of entry, many migrate and cause systemic infection in different organs. Some pathogens grow within the host cells (intracellular) whereas others grow freely in bodily fluids.

Wound colonisation refers to nonreplicating microorganisms within the wound, while in infected wounds replicating organisms exist and tissue is injured. All multicellular organisms are colonised to some degree by extrinsic organisms, and the vast majority of these exist in either a mutualistic or commensal relationship with the host. An example of the former would be the anaerobic bacteria species which colonise the mammalian colon, and an example of the latter would be the various species of staphylococcus which exist on human skin. Neither of these colonisations would be considered infections. The difference between an infection and a colonisation is often only a matter of circumstance. Organisms which are non-pathogenic can become pathogenic given specific conditions, and even the most virulent organism requires certain circumstances to cause a compromising infection. Some colonising bacteria, such as *Corynebacteria sp.* and *viridans streptococci*, prevent the adhesion and colonisation of pathogenic bacteria and thus have a symbiotic relationship with the host, preventing infection and speeding wound healing.

The variables involved in the outcome of a host becoming inoculated by a pathogen and the ultimate outcome include the:

- route of entry of the pathogen and the access to host regions that it gains
- intrinsic virulence of the particular organism
- quantity or load of the initial inoculant
- immune status of the host being colonised.

As an example, the staphylococcus species present on skin remain harmless on the skin, but, when present in a normally sterile space, such as in the capsule of a joint or the peritoneum, will multiply without resistance and create a huge burden on the host.

Infections result in diseases. Disease can arise if the host's protective immune mechanisms are compromised and the organism inflicts damage on the host. Microrganisms can cause tissue damage by releasing avariety of toxins or destructive enzymes. For example, *Clostridium tetani* releases a toxin which can paralyze muscles, or staphylococcus releases toxins which can produce shock and sepsis. Not all infectious agents cause disease in all hosts. For example less than 5% of individuals infected with polio develop the disease. On the other hand, some infectious agents are highly virulent. The prion causing mad cow disease and Creutzfeldt–Jakob disease kills almost all animals and people that are infected.

Persistent infections occur because the body is unable to clear the organism after the initial infection. Persistent infections are characterised by the continual presence of the infectious organism often as latent infection with occasional recurrent relapses of active infection. There are some viruses that can maintain a persistent infection by infecting different cells of the body. Some viruses once acquired never leave the body. A typical example is the herpes virus which tends tohide in nerves and become reactivated when specific circumstances arise. Persistent infections cause millions of deaths globally each year. Chronic infections by parasites account for high morbidity and mortality in many underdeveloped countries.

In order for infecting organisms to survive and repeat the cycle of infection in other hosts, they (or their progeny) must leave an existing reservoir and cause infection elsewhere. Transmission of infections can take place via many potential routes. Infectious organisms may be transmitted either by direct or indirect contact. Direct contact occurs when an individual comes into contact with the reservoir. This may mean touching infected bodily fluids or drinking contaminated water or being bitten by the deer tick. Direct contact infections can also result from inhalation of infectious organisms found in aerosol particles emitted by sneezing or coughing. Another common means of direct contact transmission involves sexual activity - oral, vaginal, or anal sex. Indirect contact occurs when the organism is able to withstand the harsh environment outside the host for long periods of time and still remain infective when specific opportunity arises. Inanimate objects that are frequently contaminated include toys, furniture, door knobs, tissue wipes or personal care products from an infected individual. Consuming food products and fluid which have been contaminated by contact with an infecting organism is another case of disease transmission by indirect contact.

A common method of transmission in under developed countries isfecal-oral transmission. In such cases, sewage water is used to wash food or is

consumed. This results in food poisoning. Common pathogenswhich are transmitted by the fecal-oral route include *Vibrio cholerae*, *Giardia* species, rotaviruses, *Entameba histolytica*, *Escherichia coli*, and tape worms. Most of these pathogens cause gastroenteritis.

All the above modes are examples of horizontal transmission because the infecting organism is transmitted from person to person in the same generation. There are also a variety of infections transmitted vertically - that is from mother to child during the birthing process or fetal development. Common disorders transmitted this way include AIDs, hepatitis, herpes, and cytomegalovirus

IN TEXT QUESTION
What is infection?
Answer.
An infection is the colonisation of a host organism by parasite species.

3.2 Examples of Infections

Specific bacterial infections
H pylori is associated with inflammation of the stomach and is a common cause of stomach ulcers and gastritis. At least 10 percent of individuals infected with h pylori develop an ulcer. Moreover, there isan increased risk of stomach cancer after an infection with this organism.

Methicillin-resistant staphylococcus aureus predominantly affects theskin and is considered to be a super bug as it is very resistant to antibiotics. This bacterium is known to generate a variety of toxic enzymes which can lead to vomiting, diarrhoea, shock and sepsis. MRSA is quite common in hospitals and today there is great cause for concern about its spread.

Chronic ear infections
Chronic ear infections are a common problem in childhood. These infections may be due to bacteria or the common cold virus. The disorder often presents with persistent blockage of the ear, hearing loss, chronic ear drainage, balance problems, deep ear pain, headache, fever, excess sleepiness or confusion. Chronic ear infections usually develop slowly over many years in patients who have had ear problems. The treatment of persistent ear infections is complex and requires a combination of antibiotics, corticosteroids, and/or placement of tubes. When this fails surgery is required to control the infection.

Osteomyelitis
Osteomyelitis is a bone infection caused by various bacteria and can occur in both children and adults. When bone gets infected, there is continuous pain, fever and it is painful to move the extremity. Bone infections are

acquired from infections elsewhere in the body, from trauma or are spread from adjacent infected tissues. The diagnosis of bone infection requires a bone scan, blood cultures and x rays. Sometimes the bone marrow is aspirated to discover the specific organism. Osteomyelitis is a serious infection and carries a high complication rate if not treated promptly. If the infection is diagnosed rapidly, the prognosis is good. However chronic Osteomyelitis can take years to heal and can keep on recurring. Individuals at risk of Osteomyelitis include those who have artificial joints or metal components in their joint.

Lyme disease

Lyme is a tick borne disease that can cause a skin rash, fever, chills, body aches, and joint pain. Some infected individuals develop severe weakness and temporary paralysis. Lyme disease is caused by at least three species of bacteria belonging to the genus *Borrelia,* which are carried by deer ticks. Infections are more common during summer,especially if the host spends time in grassy woodlands where ticksbreed. When the infection is diagnosed promptly, most people do recover fully. However, there are some individuals who keep on having recurring or lingering symptoms long after the infection has been treated. When it becomes chronic, Lyme Disease can present with a variety of symptoms including migrating joint pains, headaches, confusion, excess fatigue, inability to sleep, paralysis of one side of the face, and difficulty concentrating. Even though there are reliable tests available they are not one hundred percent sensitive. While most individuals do respond to a 14 day course of antibiotics, some individuals take considerably longer.

3.3 Prevention as a Means of Protection

Viable treatment and prevention strategies will disrupt the infectioncycle. For example, direct transmission can be diminished by adequate hygiene, maintaining a sanitary environment, and health education.

When infection attacks the body, *anti-infective* drugs can suppress the infection. Four types of *anti-infective* or drugs exist: antibacterial (antibiotic), antiviral, antitubercular, and antifungal. Depending on the severity and the type of infection, the antibiotic may be given by mouth, injection or may be applied topically. Severe infections of the brain are usually treated with intravenous antibiotics. Sometimes, multiple antibiotics are used to decrease the risk of resistance and increase efficacy. Antibiotics only work for bacteria and do not affect viruses. Antibiotics work by slowing down the multiplication of bacteria or by killing the bacteria. The most common classes of antibiotics used in medicine include penicillin, cephalosporins, aminoglycosides, macrolides, quinolones and tetracyclines.

Techniques like hand washing, wearing gowns, and wearing face masks can help prevent infections from being passed from the surgeon to the patient or vice versa. Frequent hand washing remains the most important defence against the spread of unwanted organisms. Nutrition has to be improved and one has to make changes in life style- such as avoiding the use of illicit drugs, using a condom, and entering an exercise programme. Cooking foods well and avoiding eating foods which have been left outside for a long time is also important. Do not take antibiotics for longer than needed. Long term use of antibiotics leads to resistance and chances of developing opportunistic infections like clostridium difficile colitis. Vaccination is another means of preventing infections by facilitating the development of immune resistance in vaccinated hosts.

3.4 Non-Specific Resistance

Innate or non-specific resistance is the mechanism by which the host eliminates most invading micro-organism by non-specific immunological means. There are three major mechanisms of non- specific immunity to infection:

- Surface/ Mechanism barriers
- Action of phagocytic cells
- The role of complement.

Surface/Mechanism Barriers
The skin is the most obvious mechanical barrier preventing micro-organisms from gaining access to the body. Fatty acids and lysozyme contained in sweat lower the pH and render the skin uninhabitable to most bacteria or immobilise the micro-organisms. The mucociliary action of cells lining the respiratory tract is another non-specific mechanical protective mechanism, as is the acid produced in the stomach which renders the gastrointestinal environment hostile to infectious agents. The mucociliary lining of the lungs, tears and saliva all provide some protection against infection.

Action of Phagocytic Cells
Once micro-organisms penetrate surface barriers, it becomes exposed to the action of phagocytic cells. Phagocytosis of micro-organisms and their killing intracellularly by prteolytic and other enzymes is the most primitive of defences against microbes which manage to gain access into the body. Three main cells involved in non specific immune responses to infection include; macrophages, polymorphonuclear neutrophilis (PMN) and eosinophils.

Macrophages are found in abundance in the liver, spleen, lymph, nodes, the lungs and sub-epithelial tissues of the skin. Their main function is to

phagocytose particulate matter including bacteria, viruses and antigen/antibody complexes. The larger the substances, the more readily it is phagocytosed by macrophages and this action is independent of any specific immunological mechanism.

Polymorphs reside in the bone marrow where they are plentiful and although they are normally short-lived, prolonged infection leads to polymorphonuclear leucocytosis in the peripheral blood. Polymorphs may also accumulate in the lymph nodes causing lymphadenopathy. Phagocytic cells are attracted to the site of infection by chemotactic factors, the most powerful of which are the complement breakdown products C3a and C5a. A variety of other serum substances such as prostaglandin E1 and tuftsin produced by the spleen also serve as chemotactic agents and some bacteria possess low molecular weight substances which serve to attract them to the site of infection. Broadly, the same chemotactic factors are responsible for attracting PMN and monocytes to the site of inflammation but in addition to Ca5, immune complexes are active monocyte chemotactic factors. Lymphokines attract macrophages to the site of immune reaction and immobilise them there. The phagocytic cells form pseudopodia around the microbe eventually engulfing it to form a phagosome. The phagosome is lined byits own wall and is therefore effectively extracellular. The cytoplasm of the phagocytic cells contains granules full of powerful bactericidal substances and when these granules fuse with the phagosome, they formthe vaculole, killing the microbes.

3.5 Specific Immune Response to Infection

Specific humoral immunity is based on antibodies directed against the invading micro-organism. There are two main phases in antibody production. After initial contact with the antigen a few days or weeks elapse before antibodies are produced. First IgM then IgG antibodies are produced but the titres of both are low in this phase, known as the primary antibody response. Subsequent exposure to the same antigen evokes a much faster and more sustained antibody production. This secondary response resulting in a persistence of the antibody is responsible for resistance to infection. Antibodies can also directly neutralise the effects of micro-organisms by combining with their toxins, thus preventing the appearance of illness. Antibodies also act in concert with complement to cause bacterial lysis. Antibody-dependent parasite killing is best exemplified by schistosome in a cyotoxic manner that is independent of complement.

Cell –mediated Immunity

This important in those infections where the organisms are intracellular because they are inaccessible to humoral antibody. Specific cell-

mediated immunity to infection is the function mainly of T lymphocytes and macrophages. Contact between antigen, macrophages and lymphocytes leads to the production of lymphokines, memory T lymphocytes and killer cells. Such killer cells attack and destroy infected cells bearing the antigen in question releasing the microbes in them which now become exposed to humoral antibody capable of neutralisingthem or their effects. The lymphocyte killing of the target cell does not require antibody or complement. Lymphokines are soluble factors released by T lymphocytes as a result of contact with antigen. Thelymphokines enhance the phagocytic activity of macrophages. Macrophages are activitated by the lymphokines. Such activated macrophages exhibit greatly enhanced cytotoxicity to infectious agents as well as tumour cells. Macrophage activation is important in controlling infections such as leprosy, tuberculosis and a number of viralinfections.

IN TEXT QUESTION

What is the function of T lymphocytes?

Answer:

Specific cell- mediated immunity to infection is the function mainly of

T lymphocytes and macrophages.

4.0 CONCLUSION

The student has learnt the following:

- Infections
- Immunity
- Prevention of infections.

5.0 SUMMARY

With the huge array of infectious micro-organisms in the environment, the host has to develop the ability to mount appropriate defence mechanisms in order to prevent recurrent infections and survive. Nature has endowed mankind with just that ability. Several different mechanisms have been evolved by living organism including man to counter the effects of invasion by pathogens.

6.0 TUTOR-MARKED ASSIGNMENT

i. What is immunity?
ii. What is an infection?
iii. What are the types of resistance to infections?

7.0 REFERENCE/FURTHER READING

Koh, GCKW, van der Poll T.& Peacock, S.J. (2011). "The Impact of Diabetes on the Pathogenesis of Sepsis". *Eur J Clin Microbiol & Infect*

Dis. doi:10.1007/s10096-011-1337-4.

Nursing Pharmacology Made Incredibly Easy. Lippincott Williams & Wilkins. 2009.p.483.

Prudhomme, S. Bonnaud, B. & Mallet, F. (2005). Endogenous Retroviruses and animal reproduction. *Cytogenet Genome Res,* 110: 353-364.doi:10.1159/000084967.

Salimonu, L.S.(2004). *Basic Immunology for Students of Medicine and Biology*. College Press and Publishers Limited.

UNIT 3 ANTIGEN

CONTENTS

1.0 INTRODUCTION

In this unit, you will learn about antigen. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen thatis recognised by the body as non-self and stimulates an adaptive immuneresponse. For simplicity, both antigens and immunogens are usuallyreferred to as antigens. An antigen is any substance that causes your 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.

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- explain antigens, immunogen and epitope
- mention the characteristics of antigens and what substances may act as antigens
- identify how antigens are recognised as foreign.

3.0 MAIN CONTENT

3.1 Specific Terminology

To be immunogenic, an antigen must possess three characteristics:

- be of high molecular weight
- exhibit chemical complexity, and
- exhibit foreignness (recognised as non-self by the body).

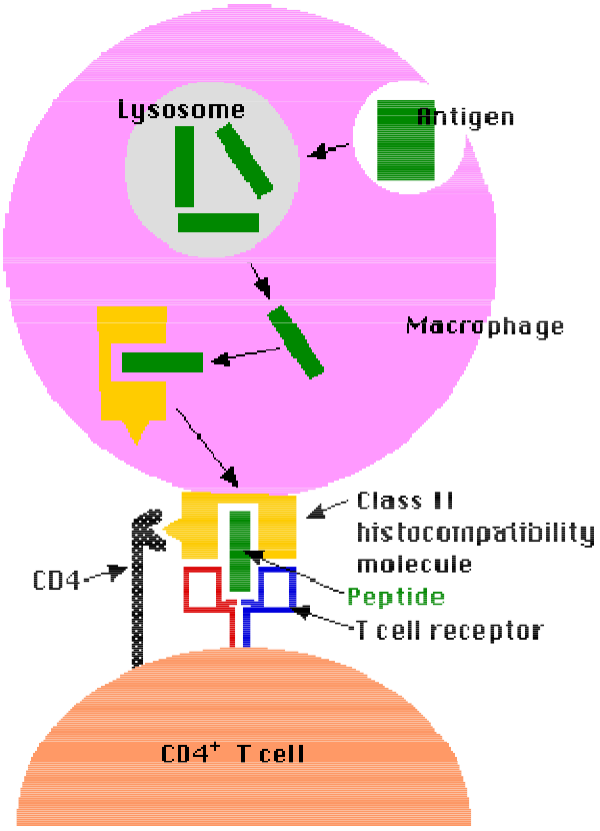
Antigens are macromolecules that elicit an immune response in thebody. Antigens can be proteins, polysaccharides, conjugates of lipids with, proteins (lipoproteins) and polysaccharides (glycolipids).

It will be helpful to distinguish between

- antigens that enter the body from the environment; these would include
- inhaled macromolecules (e.g., proteins on cat hairs thatcan trigger an attack of asthma in susceptible people)
- ingested macromolecules (e.g., shellfish proteins thattrigger an allergic response in susceptible people)
- molecules that are introduced beneath the skin (e.g., on asplinter or in an injected vaccine)
- antigens that are generated within the cells of the body; these would include:
- proteins encoded by the genes of viruses that have infecteda cell
- aberrant proteins that are encoded by mutant genes; suchas mutated genes in cancer cells.

In all cases, however, the initial immune response to any antigen absolutely requires that the antigen be recognised by a T lymphocyte ("T cell"). The truth of this rule is clearly demonstrated in AIDS: the infections (viral or fungal or bacterial) that so often claim the life of AIDS patients do so when the patient has lost virtually all of his or her $CD4^+$ T cells.

The two categories of antigens are processed and presented to T cells by quite different mechanisms.



3.2 Origin of Antigens

Antigens can be classified in order of their class.

Exogenous antigens

Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection. The immune system's response to exogenous antigens is often subclinical. By endocytosis or phagocytosis, exogenous antigens are taken into the antigen-presenting cells (APCs) and processed into fragments. APCs then present the fragments to T helper cells ($CD4^+$) by the use of class II histocompatibility molecules on their surface. Some T cells are specific for the peptide:MHC complex. They become activated and start to secrete cytokines. Cytokines are substances that can activate cytotoxic T lymphocytes (CTL), antibody-secreting B cells, macrophages, and other particles.

Some antigens start out as exogenous antigens, and later become endogenous (for example, intracellular viruses). Intracellular antigens can be released back into circulation upon the destruction of the infectedcell.

Antigen-presenting cells

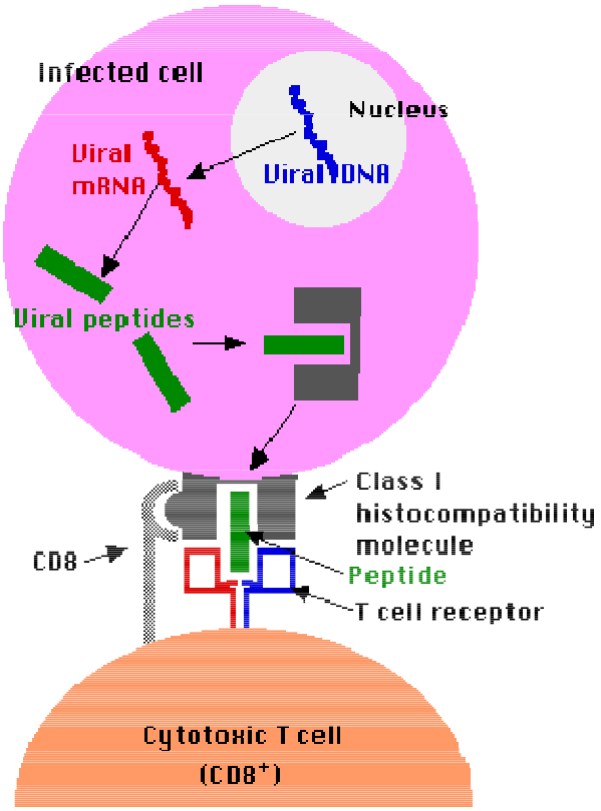
- An antigen–presenting cell engulfs the antigen by endocytosis.
- The endosome fuses with a lysosome where the antigen is degraded into fragments (e.g. short peptides).

- These antigenic peptides are then displayed at the surface of the cell nestled within a class II histocompatibility molecule.
- Here they may be recognised by $CD4^+$ T cells.

Endogenous antigens

Antigens that are generated within a cell (e.g., viral proteins in **any** infected cell) are:

- degraded into fragments (e.g., peptides) within the cell and then
- displayed at the surface of the cell nestled within a class I histocompatibility molecule.
- Here they may be recognised by $CD8^+$ T cells.
- Most $CD8^+$ T cells are cytotoxic and have the machinery to destroy the infected cell (often before it is able to release a fresh crop of viruses to spread the infection).



Endogenous antigens are antigens that have been generated within previously-normal cells as a result of normal cell metabolism, or because of viral or intracellular bacterial infection. The fragments are then presented on the cell surface in the complex with MHC class I molecules and activated cytotoxic $CD8^+$ T cells recognise them. When recognised, the T cells begin to secrete various toxins that cause the lysis or apoptosis of the infected cell. In order to keep the cytotoxic cells from

killing cells just for presenting self-proteins, self-reactive T cells are deleted from the repertoire as a result of tolerance (also known as negative selection). Endogenous antigens include xenogenic (heterologous), autologous and idiotypic or allogenic (homologous) antigens.

Autoantigens
An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognised by the immune system of patients suffering from a specific autoimmune disease. These antigens should, under normal conditions, not be the target of the immune system, but, due to mainly genetic and environmental factors, the normal immunological tolerance for such an antigen has been lost in these patients.

Tumour antigens
Tumour antigens or *neoantigens* are those antigens that are presented by MHC I or MHC II molecules on the surface of tumour cells. These antigens can sometimes be presented by tumour cells and never by the normal ones. In this case, they are called tumour-specific antigens (TSAs) and, in general, result from a tumour-specific mutation. More common are antigens that are presented by tumour cells and normalcells, and they are called tumour-associated antigens (TAAs). Cytotoxic T lymphocytes that recognise these antigens may be able to destroy the tumour cells before they proliferate or metastasize.

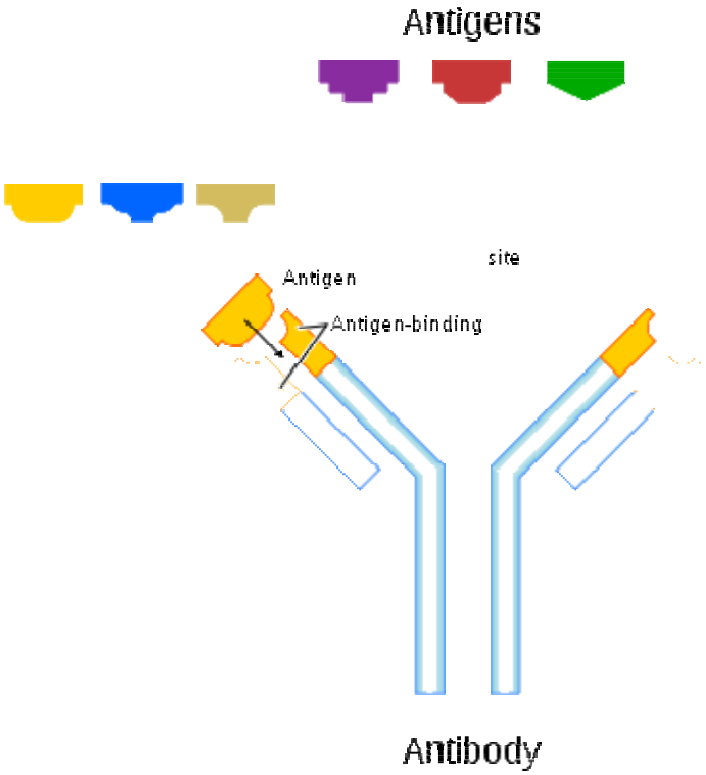
Tumour antigens can also be on the surface of the tumour in the form of, for example, a mutated receptor, in which case they will be recognised by B cells.

Nativity
A native antigen is an antigen that is not yet processed by an APC to smaller parts. T cells cannot bind native antigens, but require that they be processed by APCs, whereas B cells can be activated by native ones.
Antigenic specificity

Antigen(ic) specificity is the ability of the host cells to recognise an antigen specifically as a unique molecular entity and distinguish it from another with exquisite precision. Antigen specificity is due primarily to the side-chain conformations of the antigen. It is a measurement, although the degree of specificity may not be easy to measure, and need not be linear or of the nature of a rate-limited step or equation.

3.3 Interaction of Antibody with Antigens

NATURE OF ANTIGEN-ANTIBODY REACTIONS
Lock and Key Concept



The combining site of an antibody is located in the Fab portion of the molecule and is constructed from the hypervariable regions of the heavy and light chains. X-Ray crystallography studies of antigen-antibody interactions show that the antigenic determinant nestles in a cleft formed by the combining site of the antibody as illustrated above.

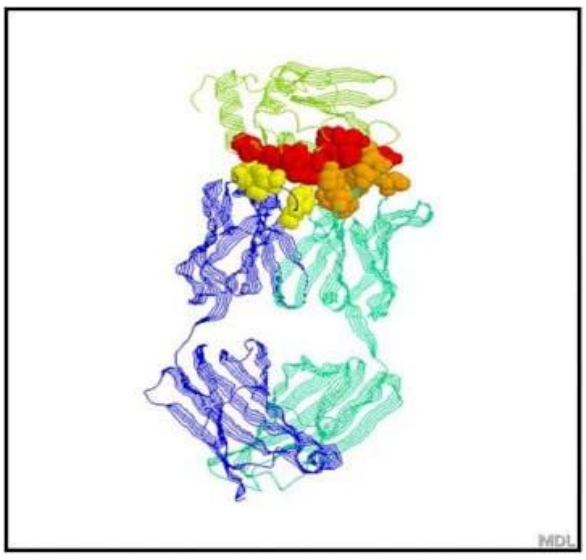


Fig. 1: Mariuzza, R.A., Biochemistry 39, 6296, 2000 Source: Li, Y., Li., Smith-Gill, S.J.

Thus, our concept of antigen-antibody reactions is one of a key (*i.e.*the antigen) which fits into a lock (*i.e.* the antibody).

Non-covalent Bonds
The bonds that hold the antigen to the antibody combining site are all non-covalent in nature. These include hydrogen bonds, electrostatic bonds, Van der Waals forces and hydrophobic bonds. Multiple bonding between the antigen and the antibody ensures that the antigen will be bound tightly to the antibody.

Reversibility
Since antigen-antibody reactions occur via non-covalent bonds, they are by their nature reversible.

AFFINITY AND AVIDITY

Affinity
Antibody affinity is the strength of the reaction between a single antigenic determinant and a single combining site on the antibody. It is the sum of the attractive and repulsive forces operating between the antigenic determinant and the combining site of the antibody as illustrated in Figure 2.

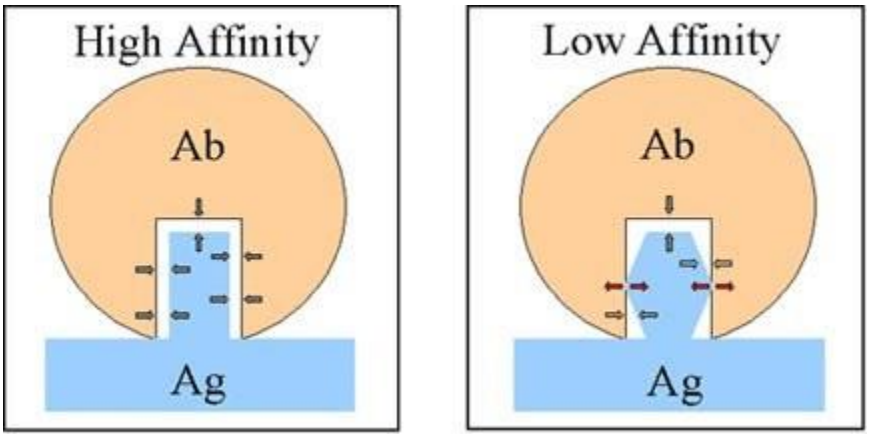


Fig. 2

Affinity is the equilibrium constant that describes the antigen-antibody reaction as illustrated in Figure 3. Most antibodies have a high affinity for their antigens.

$$Ag + Ab \leftrightarrow Ag\text{-}Ab$$

Applying the Law of Mass Action:

$$K_{eq} = \frac{[Ag\text{-}Ab]}{[Ag] \times [Ab]}$$

Fig. 3

Avidity

Avidity is a measure of the overall strength of binding of an antigen with many antigenic determinants and multivalent antibodies. Avidity is influenced by both the valence of the antibody and the valence of the antigen. Avidity is more than the sum of the individual affinities. This is illustrated in Figure 4.

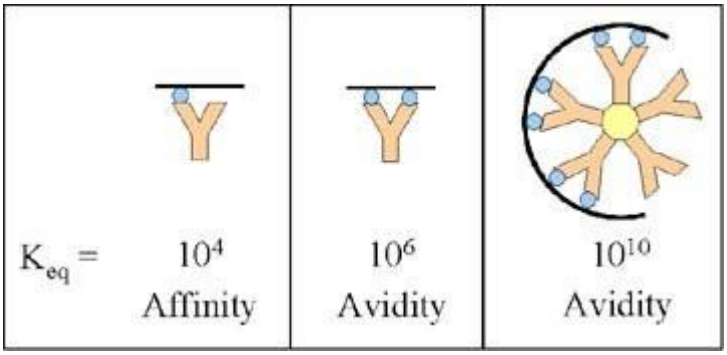


Fig. 4

To repeat, affinity refers to the strength of binding between a single antigenic determinant and an individual antibody combining site whereas avidity refers to the overall strength of binding between multivalent antigens and antibodies.

SPECIFICITY AND CROSS REACTIVITY

Specificity

Specificity refers to the ability of an individual antibody combining site to react with only one antigenic determinant or the ability of a population of antibody molecules to react with only one antigen. In general, there is a high degree of specificity in antigen-antibody reactions. Antibodies can distinguish differences in:

- The primary structure of an antigen
- Isomeric forms of an antigen

- Secondary and tertiary structure of an antigen

Cross reactivity
Cross reactivity refers to the ability of an individual antibody combining site to react with more than one antigenic determinant or the ability of a population of antibody molecules to react with more than one antigen. Figure 5 illustrates how cross reactions can arise. Cross reactions arise because the cross reacting antigen shares an epitope in common with the immunising antigen or because it has an epitope which is structurally similar to one on the immunising antigen (multispecificity).

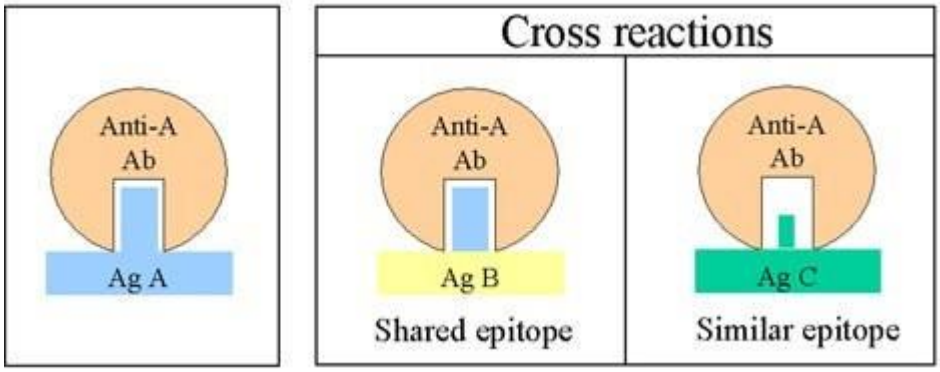


Fig. 5

TESTS FOR ANTIGEN-ANTIBODY REACTIONS

Factors affecting measurement of antigen-antibody reactions
The only way that one knows that an antigen-antibody reaction has occurred is to have some means of directly or indirectly detecting the complexes formed between the antigen and antibody. The ease with which one can detect antigen-antibody reactions will depend on a number of factors.

Affinity
The higher the affinity of the antibody for the antigen, the more stable will be the interaction. Thus, the ease with which one can detect the interaction is enhanced.

Avidity
Reactions between multivalent antigens and multivalent antibodies are more stable and thus easier to detect.

Antigen to antibody ratio
The ratio between the antigen and antibody influences the detection of antigen-antibody complexes because the size of the complexes formed is related to the concentration of the antigen and antibody. This is depicted in Figure 6.

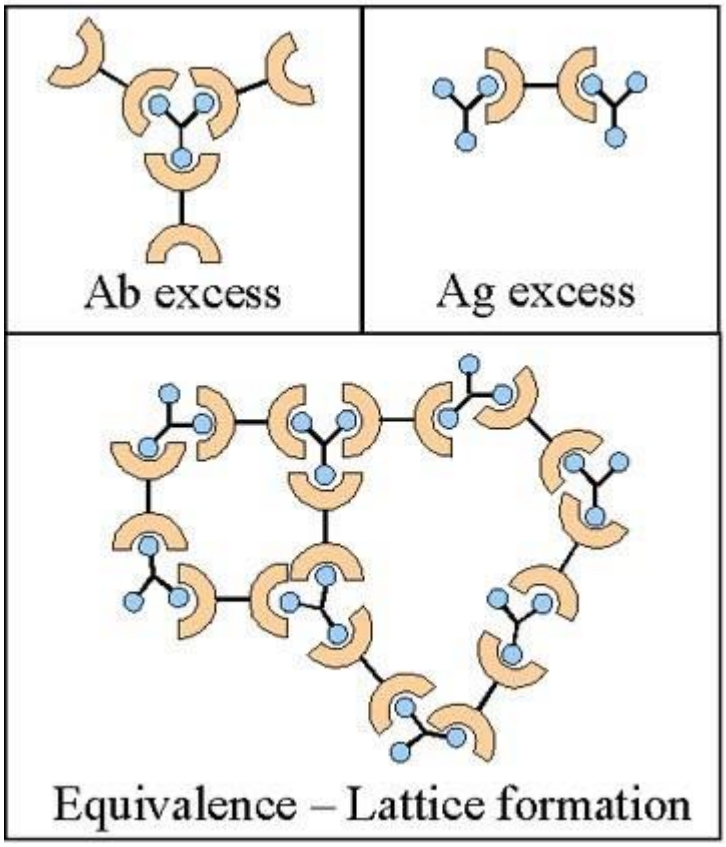


Fig. 6

Physical form of the antigen

The physical form of the antigen influences how one detects its reaction with an antibody. If the antigen is a particulate, one generally looks for agglutination of the antigen by the antibody. If the antigen is soluble one generally looks for the precipitation of the antigen after the production of large insoluble antigen-antibody complexes.

Agglutination Tests Agglutination/Hemagglutination

When the antigen is particulate, the reaction of an antibody with the antigen can be detected by agglutination (clumping) of the antigen. The general term agglutinin is used to describe antibodies that agglutinate particulate antigens. When the antigen is an erythrocyte the term hemagglutination is used. All antibodies can theoretically agglutinate particulate antigens but IgM, due to its high valence, is particularly good agglutinin and one sometimes infers that an antibody may be of the IgM class if it is a good agglutinating antibody.

Qualitative agglutination test

Agglutination tests can be used in a qualitative manner to assay for the presence of an antigen or an antibody. The antibody is mixed with the particulate antigen and a positive test is indicated by the agglutination of the particulate antigen (Figure 7).

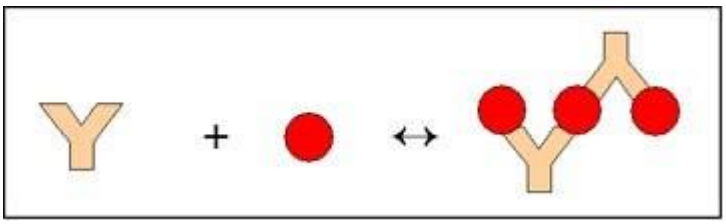


Fig. 7

For example, a patient's red blood cells can be mixed with antibody to a blood group antigen to determine a person's blood type. In a second example, a patient's serum is mixed with red blood cells of a known blood type to assay for the presence of antibodies to that blood type in the patient's serum.

Quantitative agglutination test

Agglutination tests can also be used to measure the level of antibodies to particulate antigens. In this test, serial dilutions are made of a sample to be tested for antibody and then a fixed number of red blood cells or bacteria or other such particulate antigen is added. Then the maximum dilution that gives agglutination is determined. The maximum dilution that gives visible agglutination is called the titer. The results are reported as the reciprocal of the maximal dilution that gives visible agglutination. Figure 8 illustrates a quantitative hemagglutination test.

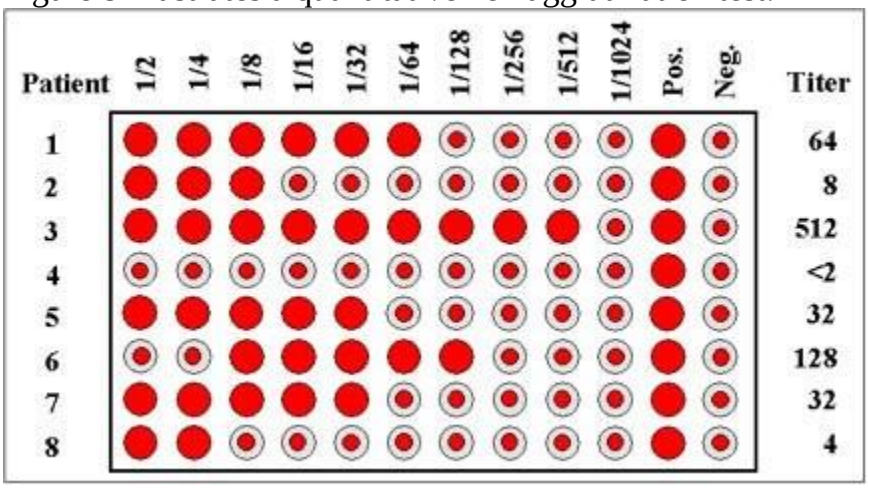


Fig. 8

Prozone effect - Occasionally, it is observed that when the concentration of antibody is high (i.e. lower dilutions), there is no agglutination and then, as the sample is diluted, agglutination occurs. The lack of agglutination at high concentrations of antibodies is called the prozone effect. Lack of agglutination in the prozone is due to antibody excess resulting in very small complexes that do not clump to form visible agglutination.

Applications of agglutination tests

i. Determination of blood types or antibodies to blood group antigens.
ii. To assess bacterial infections
e.g. A rise in titre of an antibody to a particular bacterium indicates an infection with that bacterial type. N.B. a fourfold risein titre is generally taken as a significant rise in antibody titre.

Practical considerations

Although the test is easy to perform, it is only semi-quantitative.

IN TEXT QUESTION
What is agglutination?
Answer
The general term agglutinin is used to describe antibodies that agglutinate particulate antigens.

4.0 CONCLUSION

The student has learnt the following:

- The definition of antigens
- The importance of antigens to man
- Origin of antigens
- Interaction of antibody with antigens

5.0 SUMMARY

An antigen is a foreign molecule that, when introduced into the body, triggers the production of an antibody by the immune system. Theimmune system will then kill or neutralise the antigen that is recognised as a foreign and potentially harmful invader. These invaders can be molecules such as pollen or cells such as bacteria. The term originally came from antibody generator and was a molecule that binds specifically to an antibody, but the term now also refers to any molecule or molecular fragment that can be bound by a major histocompatibility complex (MHC) and presented to a T-cell receptor. "Self" antigens are usually tolerated by the immune system; whereas "Non-self" antigens are identified as invaders and attacked by the immune system.

6.0 TUTOR-MARKED ASSIGNMENT

i. What are antigens?
ii. Differentiate between endogenous and exogenous antigens.
iii. Describe the interactions between antibodies and antigens.
iv. State what antigens are composed of chemically.
v. List 3 characteristics an antigen must have to be immunogenic
vi. Briefly describe how the body recognises an antigen as foreign.

7.0 REFERENCES/FURTHER READING

Antigens. http://biology-pages.info/

Guyton & Hall (2006). *Textbook of Medical Physiology*. 11th Edition. Page 440. Philadelphia: Elsevier, Inc. PA.

Parham, Peter (2009). *The Immune System.* 3rd Edition. pg. G:2, Garland Science, Taylor and Francis Group, LLC.

Parham, Peter (2009). *The Immune System.* 3rd Edition. pg. G:11, Garland Science, Taylor and Francis Group, LLC.

"Kuby Immunology." 6th Edition. Macmillan. 2006, pg. 77 ISBN 1429202114, 9781429202114.

Lindenmann, Jean (1984). "Origin of the Terms 'Antibody' and 'Antigen.'" *Scand. J. Immunol.* 19 (4): 281–5.

MODULE 2 HYPERSENSITIVITY

UNIT 1 HYPERSENSITIVITY

CONTENTS

1.0 INTRODUCTION

The immune system is an integral part of human protection against disease, but the normally protective immune mechanisms can sometimes cause detrimental reactions in the host. Such reactions are known as hypersensitivity reactions, and the study of these is termed immunopathology. The traditional classification for hypersensitivity reactions is that of Gell and Coombs and is currently the most commonly known classification system. It divides the hypersensitivity reactions into the following 4 types:

a. Type I reactions (ie, immediate hypersensitivity reactions)involve immunoglobulin E (IgE)–mediated release of histamine and other mediators from mast cells and basophils.
b. Type II reactions (ie, cytotoxic hypersensitivity reactions)involve immunoglobulin G or immunoglobulin M antibodies bound to cell surface antigens, with subsequent complement fixation.
c. Type III reactions (ie, immune-complex reactions) involve circulating antigen-antibody immune complexes that deposit in postcapillary venules, with subsequent complement fixation.
d. Type IV reactions (ie, delayed hypersensitivity reactions, cell-mediated immunity) are mediated by T cells rather than by antibodies.

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- describe immediate hypersensitivity
- differentiate Types I,II, III and IV hypersensitivity.

3.0 MAIN CONTENT

3.1 Hypersensitivity

Occasionally, the immune system responds inappropriately to the presence of antigen. These responses are referred to as *hypersensitivities*. There are four different types of hypersensitivities that result from different alterations of the immune system. These types are classified as:

a. Type I: Immediate Hypersensitivity
b. Type II: Cytotoxic Hypersensitivity
c. Type III: Immune Complex Hypersensitivity
d. Type IV: Delayed Hypersensitivity

3.2 Type I Hypersensitivity

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may cause a range of symptoms from minor inconvenience to death. The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen, although sometimes it may have a delayed onset (10 - 12 hours).

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

The mechanism of reaction involves preferential production of IgE, in response to certain antigens (often called allergens). The precise mechanism as to why some individuals are more prone to type-I hypersensitivity is not clear. However, it has been shown that such individuals preferentially produce more of TH2 cells that secrete IL-4, IL-5 and IL-13 which in turn favour IgE class switch. IgE has very high affinity for its receptor (Fcε; CD23) on mast cells and basophils.

A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances (figure 1).

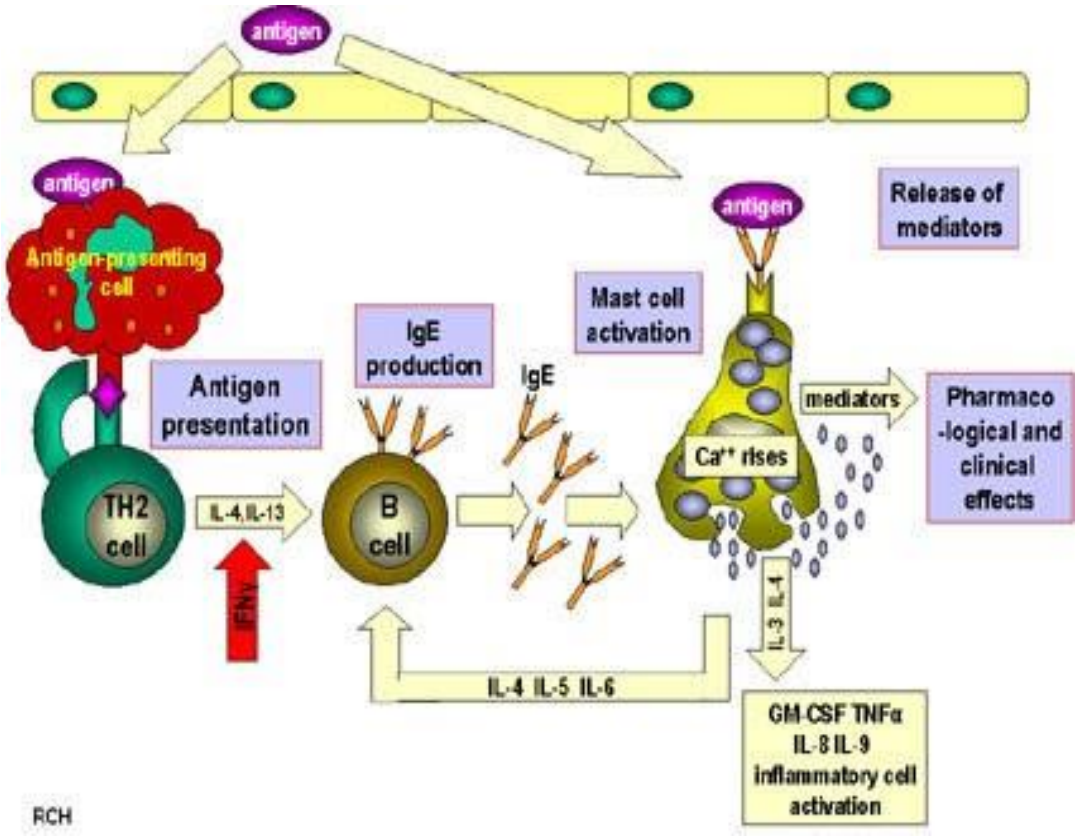


Fig. 1: Induction and Effector Mechanisms in Type 1 Hypersensitivity

Cross-linking of IgE Fc-receptor is important in mast cell triggering. Mast cell degranulation is preceded by increased Ca++ influx, which is a crucial process; ionophores which increase cytoplasmic Ca^{++} also promote degranulation, whereas, agents which deplete cytoplasmic Ca^{++} suppress degranulation.

The agents released from mast cells and their effects are listed in Table 1. Mast cells may be triggered by other stimuli such as exercise, emotional stress, chemicals (*e.g.*, photographic developing medium, calcium ionophores, codeine, *etc.*), anaphylotoxins (*e.g.*, C4a, C3a, C5a, *etc.*). These reactions, mediated by agents without IgE-allergen interaction, are not hypersensitivity reactions, although they produce the same symptoms.

Table 1: Pharmacologic Mediators of Immediate Hypersensitivity

MEDIATOR	
Preformed mediators in granules	
Histamine	bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
Tryptase	Proteolysis
kininogenase	kinins and vasodilatation, vascular permeability, edema
ECF-A (tetrapeptides)	attract eosinophil and neutrophils
Newly formed mediators	
leukotriene B_4	basophil attractant
leukotrieneC_4, D_4	same as histamine but 1000x morepotent
prostaglandinsD_2	edema and pain
PAF	platelet aggregation and heparin release: microthrombi

The reaction is amplified by PAF (platelet activation factor) which causes platelet aggregation and release of histamine, heparin and vasoactive amines. Eosinophil chemotactic factor of anaphylaxis (ECF- A) and neutrophil chemotactic factors attract eosinophils and neutrophils, respectively, which release various hydrolytic enzymes that cause necrosis. Eosinophils may also control the local reaction by releasing arylsulphatase, histaminase, phospholipase-D and prostaglandin-E, although this role of eosinophils is now in question.

Cyclic nucleotides appear to play a significant role in the modulation of immediate hypersensitivity reaction, although their exact function is ill understood. Substances which alter cAMP and cGMP levels significantly alter the allergic symptoms. Thus, substances that increase intracellular

cAMP seem to relieve allergic symptoms, particularly broncho-pulmonary ones, and are used therapeutically (Table 2). Conversely, agents which decrease cAMP or stimulate cGMP aggravate these allergic conditions.

Table 2 : Relationship between Allergic Symptomsand Cyclic-nucleotides

Lowering of cyclic-AMP	**Elevation of cyclic-AMP**
stimulation of α-adrenergicreceptor (nor-epinephrin, phenyl-epinephrin) or blocking of β-adrenergic receptor (propanolol)	stimulation of β-adrenergicreceptor (epinephrine, isoproterenol) blocking of α-adrenergic receptor (phenoxybenzamine) inhibition of phosphodiesterase(theophylline) binding of histamine-2 or PGE to their receptors
elevation of cyclic-GMP	
stimulation of γ-cholinergic receptor (acetyl choline, carbacol)	
WORSENING OF SYMPTOMS	**IMPROVEMENT OF SYMPTOMS**

Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests (fig. 1A), measurement of total IgE and specific IgE antibodies against the suspected allergens.

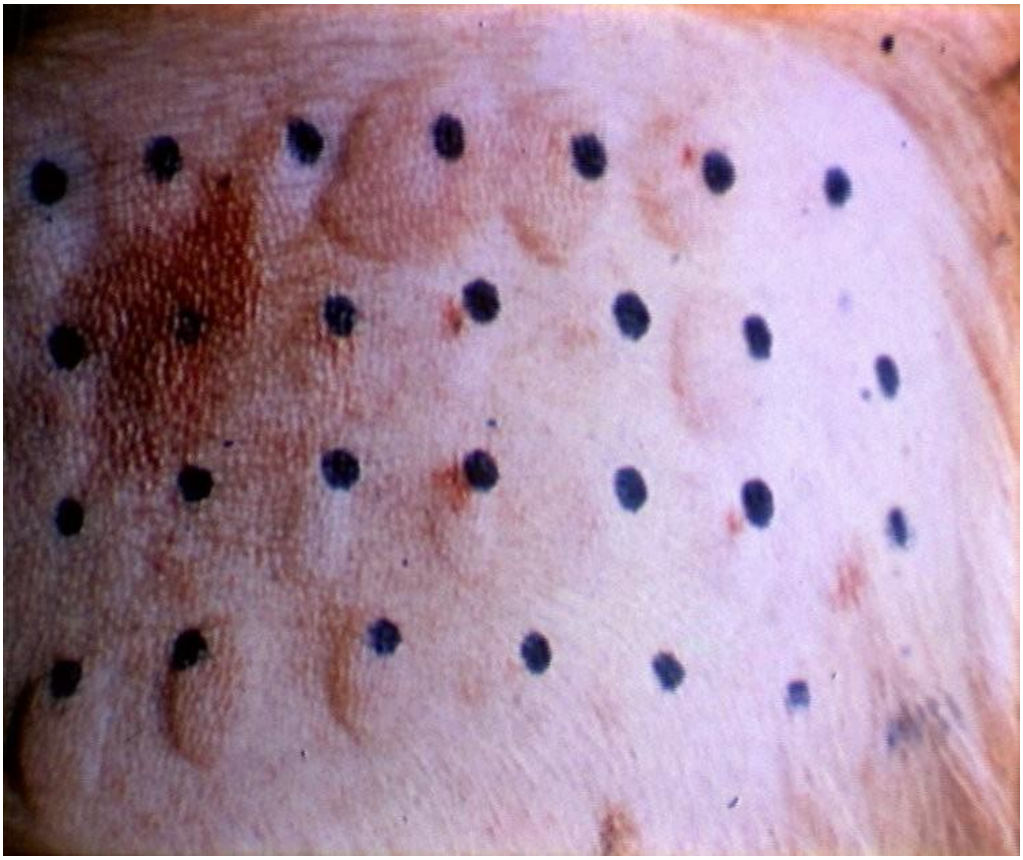


Fig. 1 : A Close-up View of Intradermal Skin Test with Multiple Positive Allergen Responses

Total IgE and specific IgE antibodies are measured by a modification of enzyme immunoassay (ELISA). Increased IgE levels are indicative of an atopic condition, although IgE may be elevated in some non-atopic diseases (*e.g.*, myelomas, helminthic infection, *etc.*).

There appears to be a genetic predisposition for atopic diseases and there is evidence for HLA (A2) association.

Symptomatic treatment is achieved with anti-histamines which block histamine receptors. Chromolyn sodium inhibits mast cell degranulation, probably, by inhibiting Ca^{++} influx. Late onset allergic symptoms, particularly bronchoconstriction which is mediated by leukotrienes, are treated with leukotriene receptor blockers (Singulair, Accolate) or inhibitors of the cyclooxygenase pathway (Zileutoin). Symptomatic, although short term, relief from bronchoconstriction is provided by bronchodilators (inhalants) such as isoproterenol derivatives(Terbutaline, Albuterol). Thophylline elevates cAMP by inhibiting cAMP-phosphodiesterase and inhibits intracellular Ca^{++} release is also used to relieve bronchopulmonary symptoms.
The use of IgG antibodies against the Fc portions of IgE that binds to mast cells has been approved for treatment of certain allergies, as it can block

mast cell sensitisation.

Hyposensitisation (immunotherapy or desensitisation) is another treatment modality which is successful in a number of allergies, particularly to insect venoms and, to some extent, pollens. The mechanism is not clear, but there is a correlation between appearance of IgG (blocking) antibodies and relief from symptoms. Suppressor T cells that specifically inhibit IgE antibodies may play a role.

3.3 Type II Hypersensitivity

Type II hypersensitivity is also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity. Drug- induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples. The reaction time range from minutes to hours. Type II hypersensitivity is primarily mediated by antibodies of the IgM or IgG classes and complement (Figure 2).

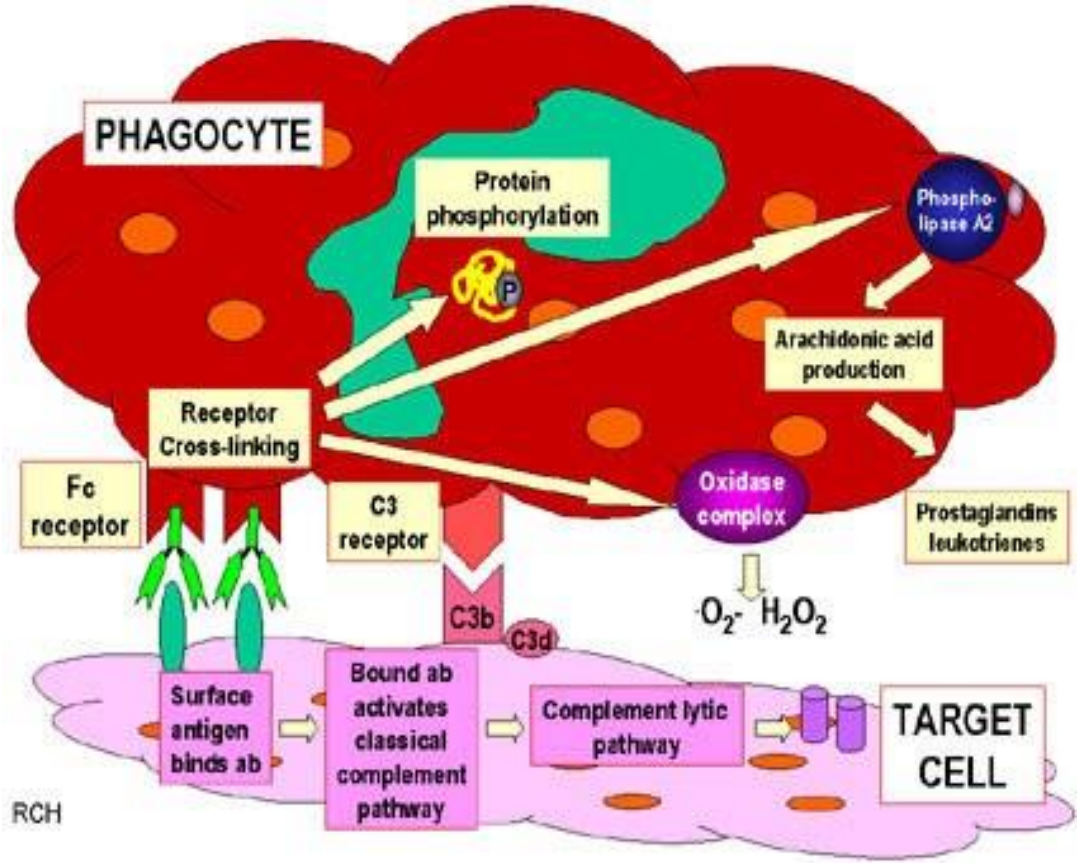


Fig. 2: Type II Cytotoxicity Mechanism
Phagocytes and K cells may also play a role.
The lesion contains antibody, complement and neutrophils. Diagnostic tests include detection of circulating antibody against the tissues involved and the presence of antibody and complement in the lesion (biopsy) by immunofluorescence. The staining pattern is normally smooth and linear,

such as that seen in Goodpasture's nephritis (renaland lung basement membrane) (figure 3A) and pemphigus (skin intercellular protein, desmosome) (figure 3B).

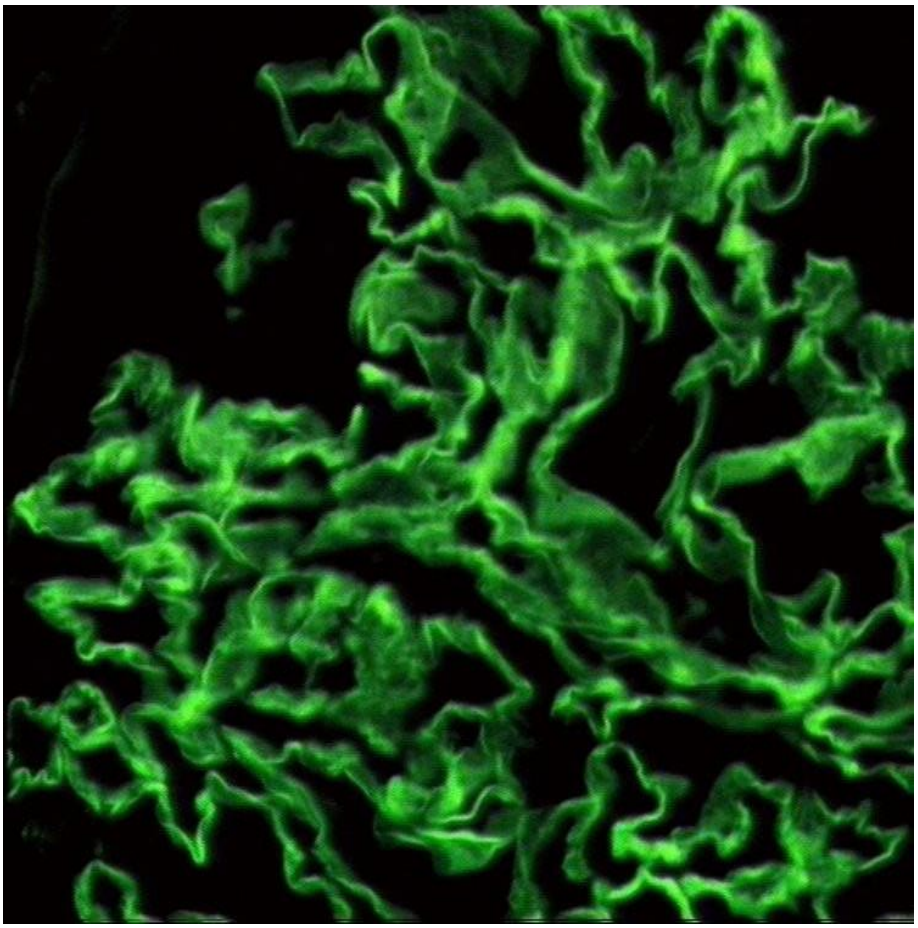


Fig. 3A: Immunofluorescent Stain of Immunoglobulin G (IgG) Showing Linear Pattern in Goodpasture's Syndrome

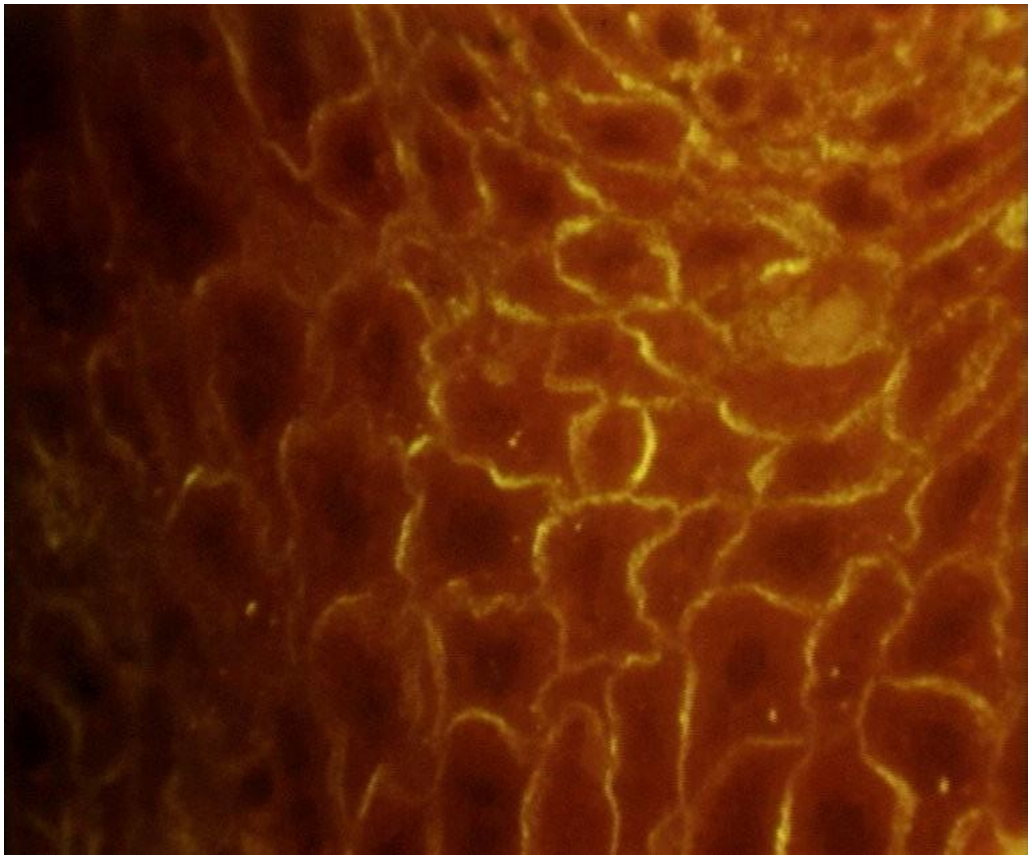


Fig. 3B: ***Pemphigus vulgaris*** **- immunofluorescence**

Treatment involves anti-inflammatory and immunosuppressive agents. In type II hypersensitivity (or cytotoxic hypersensitivity) the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces. The antigens recognised in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen). These cells are recognized bymacrophages or dendritic cells, which act as antigen-presenting cells. This causes a B cell response, wherein antibodies are produced againstthe foreign antigen.

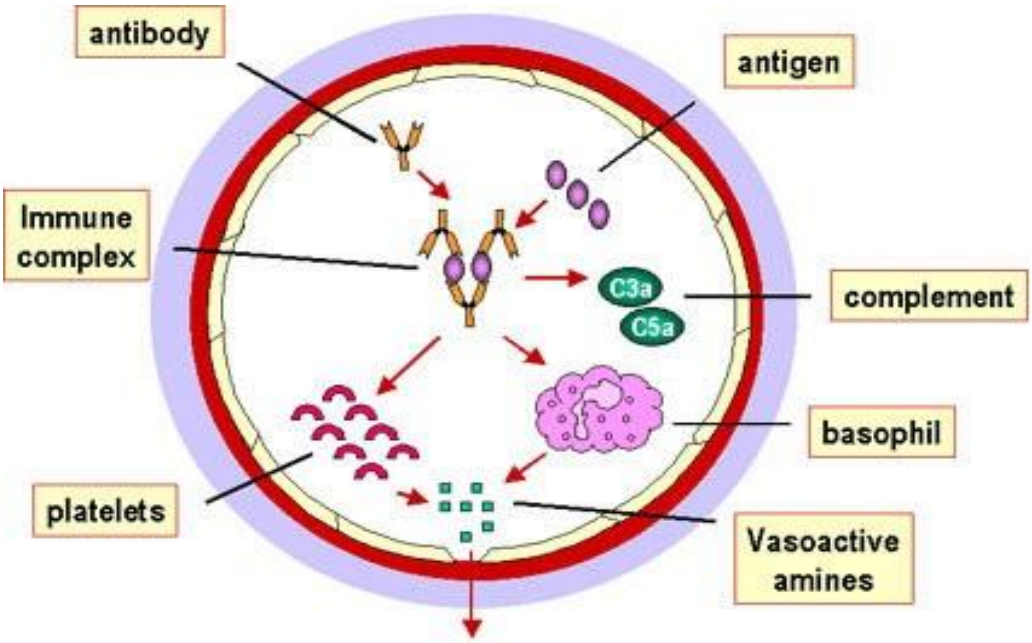
An example of type II hypersensitivity is the reaction to penicillinwherein the drug can bind to red blood cells, causing them to berecognised as different; B cell proliferation will take place andantibodies to the drug are produced. IgG and IgM antibodies bind tothese antigens to form complexes that activate the classical pathway ofcomplement activation to eliminate cells presenting foreign antigens(which are usually, but not in this case, pathogens). That is, mediators ofacute inflammation are generated at the site and membrane attackcomplexes cause cell lysis and death. The reaction takes hours to a day. Another form of type II hypersensitivity is called antibody-dependentcell-mediated cytotoxicity (ADCC). Here, cells exhibiting the foreign

antigen are tagged with antibodies (IgG or IgM). These tagged cells are then recognised by natural killer (NK) cells and macrophages (recognised via IgG bound (via the Fc region) to the effector cell surfacereceptor, CD16 (FcγRIII)), which in turn kill these tagged cells.

3.4 Type III Hypersensitivity

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

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



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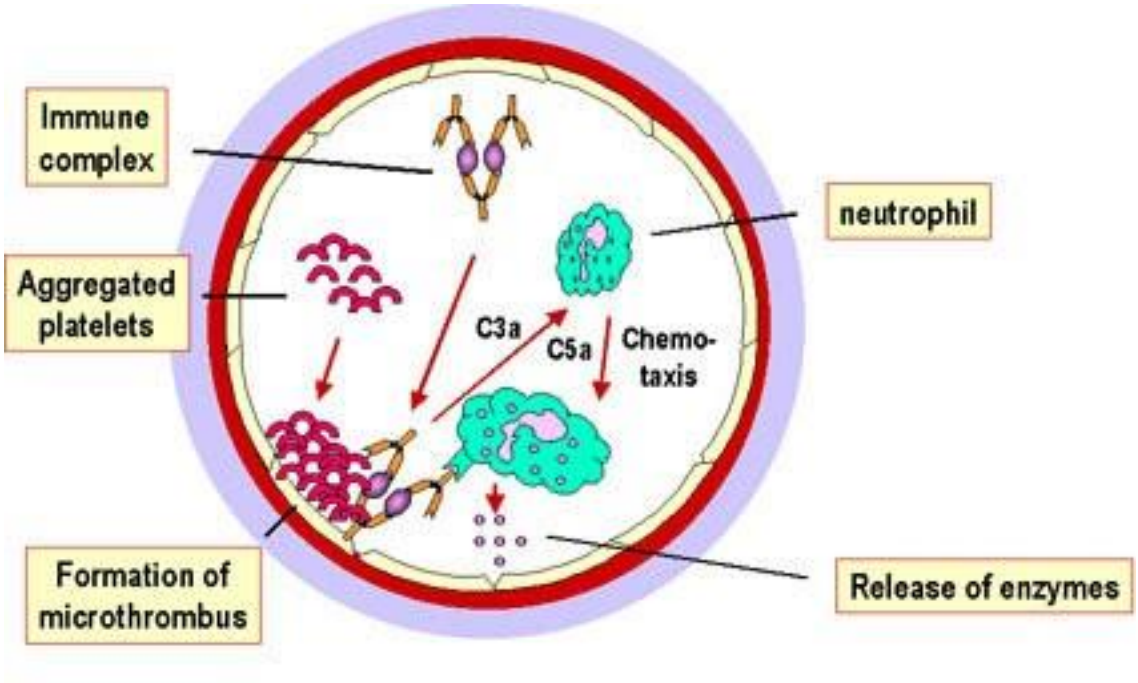

Fig. 4: Mechanism of Damage in Immune Complex Hypersensitivity

The lesion contains primarily neutrophils and deposits of immune complexes and complement. Macrophages infiltrating in later stagesmay be involved in the healing process.

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

3.5 Type IV Hypersensitivity

Type IV hypersensitivity is also known as cell -mediated or delayed type hypersensitivity. The classical example of this hypersensitivity is tuberculin (Montoux) reaction (Figure 5) which peaks 48 hours after the injection of antigen (PPD or old tuberculin).

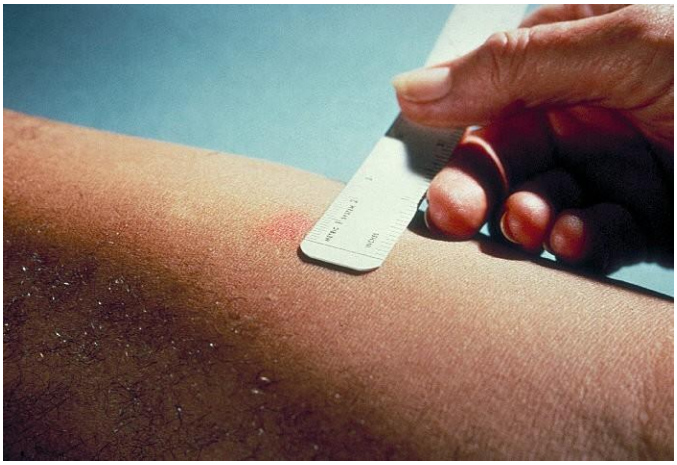

Fig. 5: Mantoux Intradermal Tuberculin Skin Test for Tuberculosis

The lesion is characterised by induration and erythema.

Table 3 : Delayed Hypersensitivity Reactions

Type	Reaction time	Clinical appearance	Histology	Antigen and site
contact	48-72 hr	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, heavy metals, *etc.*)
tuberculin	48-72 hr	local induration	lymphocytes, monocytes, macrophages	intradermal (tuberculin, lepromin, *etc.*)
granuloma	21-28 days	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence (tuberculosis, leprosy, *etc.*)

Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, *etc.*) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison ivy (figure 6), chemicals, heavy metals, *etc.*) in which the lesions are more papular.

Fig. 6: Poison Ivy CDC

Type IV hypersensitivity can be classified into three categoriesdepending on the time of onset and clinical and histological presentation(Table 3).

Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. Cytotoxic T cells (Tc) cause direct damage whereas helper T (TH1) cells secrete cytokines which activate cytotoxic T cells and recruit and activate monocytes and macrophages, which cause the bulk of the damage (figure 4). The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.

Major lymphokines involved in delayed hypersensitivity reactioninclude monocyte chemotactic factor, interleukin-2, interferon-gamma, TNF alpha/beta, *etc.*

Diagnostic tests *in vivo* include delayed cutaneous reaction (*e.g.* Montoux test (figure 5)) and patch test (for contact dermatitis). In vitro tests for delayed hypersensitivity include mitogenic response, lympho-cytotoxicity and IL-2 production.
Corticosteroids and other immunosuppressive agents are used in treatment.

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
responsetime	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 neutrophil s	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

IN TEXT QUESTION

What is Type I hypersensitivity?

Answer

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity.

4.0 CONCLUSION

The student has learnt the following:

- Hypersensitivity
- Types of hypersensitivity
- Examples of each type of hypersensitivity.

5.0 SUMMARY

Hypersensitivity refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitised (immune) state of the host. Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction. It is a series of undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity reactions require a pre-sensitised (immune) state of the host. The four-group classification was expounded by P. H. G. Gell and Robin Coombs in 1963. Hypersensitivity denotes immunologic sensitivity to antigens that manifest itself by tissue reactions that can cause injury. They appear much later. There are 4types of these hypersensitivity states or reactions. Three are immediate and one is delayed. Apart from differences in time intervals, there are also other differences in the mode of transfer of hypersensitivity from a sensitised to a non-sensitised subject.

6.0 TUTOR-MARKED ASSIGNMENT

i. What is hypersensitivity?
ii. Explain immune complex hypersensitivity
iii. What is delayed hypersensitivity?

7.0 REFERENCES/FURTHER READING

Abdul Ghaffar (2010). Microbiology and Immunogy. Hypersensitivity Reactions.

Gell PGH, Coombs RRA, eds. Clinical Aspects of Immunology. 1st ed. Oxford, England: Blackwell; 1963.

Salimonu, L.S. (2004). *Basic Immunology for Students of Medicine and Biology*. College Press and Publishers Limited.

Miriam, K Anand, MD, FAAAAI, FACAAI; Chief Editor: Michael A Kaliner, MD (2012). Immediate Hypersensitivity Reactions . medscape.com

http://www.cehs.siu.edu/fix/medmicro.com (2011). Hypersensitivity

UNIT 2 AUTOIMMUNITY

CONTENTS

1.0 INTRODUCTION

Autoimmunity and autoimmune diseases are consequences of immunological destruction of body's own tissue following loss of recognition by lymphoid organs of the self-cells as self. During differentiation and speciation of lymphoid stem cells in primary organs, most of the cells that are capable of causing autoimmunity are deleted. Yet, the body contains large numbers of lymphocytes that are self-reacting.

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- describe low-level autoimmunity
- name causes of autoimmunity
- explain genetic factors
- list environmental factors affecting autoimmunity.

3.0 MAIN CONTENT

3.1 Causes of Autoimmunity

Controlling factors that restrain the development of autoimmune responses include Ts cells, cytokines and products of macrophages. However, these regulatory mechanisms may be evaded by:

- Release of normally sequestered auto-antigen which is then taken up by antigen presenting cells and hence stimulation of T_H cells.

- Inappropriate expression of MHC class II and inability of auto-reactive T_H cell to recognise potential autoantigens on cells, which do not normally express MHC class II genes.
- Defects in the generation of Ts cells with hyperactivity of T_H. This may overstimulate B-cells for excessive production of antibody that may include auto-reactive ones. In thyroxicosis, antibody to thyroid stimulating hormone TSH receptors combineswith TSH receptors as if it is TSH, therefore autoantibodies to hormone receptors mimic the function of the normal hormone concerned.
- Deletion of self-antigen recognising T- and B-lymphocytes during maturation process. In pernicious anaemia, autoantibody isformed against intrinsic factor. This autoantibody combines with intrinsic factor to disrupt the uptake of Vitamin B12. This is transported across the intestinal mucosa when it combines with intrinsic factor. In systemic lupus erythematosus, immune complexes containg auto-antigens and autoantibodies are deposited in the kidney to cause hypersensitivity, glomerulonephritis and proteinuria.

3.2 Low Level Autoimmunity

While a high level of autoimmunity is unhealthy, a low level of autoimmunity may actually be beneficial. First, low-level autoimmunity might aid in the recognition of neoplastic cells by CD8+ T cells, and thus reduce the incidence of cancer.

Second, autoimmunity may play a role in allowing a rapid immune response in the early stages of an infection when the availability of foreign antigens limits the response (i.e., when there are few pathogens present). In their study, Stefanova et al. (2002) injected an anti-MHC Class II antibody into mice expressing a single type of MHC Class II molecule ($H\text{-}2^b$) to temporarily prevent CD4+ T cell-MHC interaction. Naive CD4+ T cells (those that have not encountered any antigensbefore) recovered from these mice 36 hours post-anti-MHC administration showed decreased responsiveness to the antigen pigeon cytochrome C peptide, as determined by Zap-70 phosphorylation, proliferation, and Interleukin-2 production. Thus Stefanova et al. (2002) demonstrated that self-MHC recognition (which, if too strong may contribute to autoimmune disease) maintains the responsiveness of CD4+ T cells when foreign antigens are absent. This idea ofautoimmunity is conceptually similar to play-fighting. The play-fighting of young cubs (TCR and self-MHC) may result in a few scratches or
scars (low-level-autoimmunity), but is beneficial in the long-term as it primes the young cub for proper fights in the future.

3.3 Immunological Tolerance

Pioneering work by Noel Rose and Witebsky in New York, and Roitt and Doniach at University College London provided clear evidence that,at least in terms of antibody-producing B lymphocytes, diseases such as rheumatoid arthritis and thyrotoxicosis are associated with loss of immunological tolerance, which is the ability of an individual to ignore 'self', while reacting to 'non-self'. This breakage leads to the immune system's mounting an effective and specific immune response against self determinants. The exact genesis of immunological tolerance is still elusive, but several theories have been proposed since the mid-twentieth century to explain its origin.

Three hypotheses have gained widespread attention among immunologists:

a. **Clonal Deletion theory**, proposed by Burnet, according to which self-reactive lymphoid cells are destroyed during the development of the immune system in an individual. For their work Frank M. Burnet and Peter B. Medawar were awarded the 1960 Nobel Prize in Physiology or Medicine "for discovery of acquired immunological tolerance".
b. **Clonal Anergy theory**, proposed by Nossal, in which self-reactive T- or B-cells become inactivated in the normal individualand cannot amplify the immune response.
c. **Idiotype Network theory**, proposed by Jerne, wherein a network of antibodies capable of neutralising self-reactive antibodies exists naturally within the body.

In addition, two other theories are under intense investigation:

- The so-called "Clonal Ignorance" theory, according to which host immune responses are directed to ignore self-antigens
- The "Suppressor population" or "Regulatory T cell" theories, wherein regulatory T-lymphocytes (commonly $CD4^{+}FoxP3^{+}$cells, among others) function to prevent, downregulate, or limit autoaggressive immune responses in the immune system.

Tolerance can also be differentiated into 'Central' and 'Peripheral' tolerance, on whether or not the above-stated checking mechanisms operate in the central lymphoid organs (Thymus and Bone Marrow) or the peripheral lymphoid organs (lymph node, spleen, etc., where self- reactive B-cells may be destroyed). It must be emphasised that these theories are not mutually exclusive, and evidence has been mounting suggesting that all of these mechanisms may actively contribute to vertebrate immunological tolerance.

A puzzling feature of the documented loss of tolerance seen in spontaneous human autoimmunity is that it is almost entirely restricted to the autoantibody responses produced by B lymphocytes. Loss of tolerance by T cells has been extremely hard to demonstrate, and where there is evidence for an abnormal T cell response it is usually not for the antigen recognised by autoantibodies. Thus, in rheumatoid arthritis there are autoantibodies to IgG Fc but apparently no corresponding T cell response. In systemic lupus there are autoantibodies to DNA, which cannot evoke a T cell response, and limited evidence for T cell responses implicates nucleoprotein antigens. In Celiac disease there are autoantibodies to tissue transglutaminase but the T cell response is to the foreign protein gliadin. This disparity has led to the idea that human autoimmune disease is in most cases (with probable exceptions including type I diabetes) based on a loss of B cell tolerance which makes use of normal T cell responses to foreign antigens in a variety of aberrant ways.

3.4 Genetic Factors

Certain individuals are genetically susceptible to developing autoimmune diseases. This susceptibility is associated with multiplegenes plus other risk factors. Genetically predisposed individuals do not always develop autoimmune diseases.

Three main sets of genes are suspected in many autoimmune diseases. These genes are related to:

a. Immunoglobulins
b. T-cell receptors
c. The major histocompatibility complexes (MHC).

The first two, which are involved in the recognition of antigens, are inherently variable and susceptible to recombination. These variations enable the immune system to respond to a very wide variety of invaders, but may also give rise to lymphocytes capable of self-reactivity.

Scientists such as H. McDevitt, G. Nepom, J. Bell and J. Todd have also provided strong evidence to suggest that certain MHC class II allotypes are strongly correlated with:

- HLA DR2 is strongly positively correlated with Systemic Lupus Erythematosus, narcolepsy and multiple sclerosis, and negatively correlated with DM Type 1.
- HLA DR3 is correlated strongly with Sjögren's syndrome, myasthenia gravis, SLE, and DM Type 1.
- HLA DR4 is correlated with the genesis of rheumatoid arthritis, Type 1 diabetes mellitus, and pemphigus vulgaris.

Fewer correlations exist with MHC class I molecules. The most notable and consistent is the association between HLA B27 and ankylosing spondylitis. Correlations may exist between polymorphisms within class II MHC promoters and autoimmune disease.

The contributions of genes outside the MHC complex remain the subject of research, in animal models of disease (Linda Wicker's extensivegenetic studies of diabetes in the NOD mouse), and in patients (Brian Kotzin's linkage analysis of susceptibility to SLE).

Recently, PTPN22 has been associated with multiple autoimmune diseases including Type I diabetes, rheumatoid arthritis, systemic lupus erythematosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, Myasthenia Gravis, vitiligo, systemic sclerosis juvenile idiopathic arthritis, and psoriatic arthritis.

Sex

A person's sex also seems to have some role in the development of autoimmunity, classifying most autoimmune diseases as sex-related diseases. Nearly 75% of the more than 23.5 million Americans who suffer from autoimmune disease are women, although it is less- frequently acknowledged that millions of men also suffer from these diseases. According to the American Autoimmune Related DiseasesAssociation (AARDA), autoimmune diseases that develop in men tendto be more severe. A few autoimmune diseases that men are just as, or more likely to develop as women, include: ankylosing spondylitis, type1 diabetes mellitus, Wegener's granulomatosis, Crohn's disease and psoriasis.

The reasons for the sex role in autoimmunity are unclear. Women appear to generally mount larger inflammatory responses than men when their immune systems are triggered, increasing the risk of autoimmunity. Involvement of sex steroids is indicated by that many autoimmune diseases tend to fluctuate in accordance with hormonal changes, for example, during pregnancy, in the menstrual cycle, or whenusing oral contraception. A history of pregnancy also appears to leave a persistent increased risk for autoimmune disease. It has been suggested that the slight exchange of cells between mothers and their children during pregnancy may induce autoimmunity. This would tip the gender balance in the direction of the female.

Another theory suggests the females high tendency to get autoimmunity is due to an imbalanced X chromosome inactivation. The X-inactivation skew theory, proposed by Princeton University's Jeff Stewart, has recently been confirmed experimentally in scleroderma and autoimmune thyroiditis. Other complex X-linked genetic susceptibility mechanisms are proposed and under investigation.

3.5 Environmental Factors

An interesting inverse relationship exists between infectious diseases and autoimmune diseases. In areas where multiple infectious diseases are endemic, autoimmune diseases are quite rarely seen. The reverse, to some extent, seems to hold true. The hygiene hypothesis attributes these correlations to the immune manipulating strategies of pathogens. Whilst such an observation has been variously termed as spurious and ineffective, according to some studies, parasite infection is associated with reduced activity of autoimmune disease.

The putative mechanism is that the parasite attenuates the host immune response in order to protect itself. This may provide a serendipitous benefit to a host that also suffers from autoimmune disease. The details of parasite immune modulation are not yet known, but may include secretion of anti-inflammatory agents or interference with the host immune signalling mechanism.

A paradoxical observation has been the strong association of certain microbial organisms with autoimmune diseases. For example, *Klebsiella pneumoniae* and coxsackievirus B have been strongly correlated with ankylosing spondylitis and diabetes mellitus type 1, respectively. This has been explained by the tendency of the infecting organism to produce super-antigens that are capable of polyclonal activation of B-lymphocytes, and production of large amounts of antibodies of varying specificities, some of which may be self-reactive.

Certain chemical agents and drugs can also be associated with the genesis of autoimmune conditions, or conditions that simulate autoimmune diseases. The most striking of these is the drug-induced lupus erythematosus. Usually, withdrawal of the offending drug cures the symptoms in a patient.

Cigarette smoking is now established as a major risk factor for both incidence and severity of rheumatoid arthritis. This may relate to abnormal citrullination of proteins, since the effects of smoking correlate with the presence of antibodies to citrullinated peptides.

3.6 Pathogenesis of Autoimmunity

Several mechanisms are thought to be operative in the pathogenesis of autoimmune diseases, against a backdrop of genetic predisposition and environmental modulation. It is beyond the scope of this article to discuss each of these mechanisms exhaustively, but a summary of some of the important mechanisms have been described:

- T-Cell Bypass - A normal immune system requires the activation of B-cells by T-cells before the former can produce antibodies in large quantities. This requirement of a T-cell can be bypassed in rare instances, such as infection by organisms producing super- antigens, which are capable of initiating polyclonal activation of B-cells, or even of T-cells, by directly binding to the β-subunit of T-cell receptors in a non-specific fashion.
- T-Cell-B-Cell discordance - A normal immune response is assumed to involve B and T cell responses to the same antigen, even if we know that B cells and T cells recognise very different things: conformations on the surface of a molecule for B cells andpre-processed peptide fragments of proteins for T cells. However,there is nothing as far as we know that requires this. All that is required is that a B cell recognising antigen X endocytoses and processes a protein Y (normally =X) and presents it to a T cell. Roosnek and Lanzavecchia showed that B cells recognising IgGFc could get help from any T cell responding to an antigen co-endocytosed with IgG by the B cell as part of an immune complex. In coeliac disease it seems likely that B cellsrecognising tissue transglutamine are helped by T cells recognising gliadin.
- Aberrant B cell receptor-mediated feedback - A feature of human autoimmune disease is that it is largely restricted to a small group of antigens, several of which have known signaling roles in the immune response (DNA, C1q, IgGFc, Ro, Con. A receptor, Peanut agglutinin receptor (PNAR)). This fact gave rise to the idea that spontaneous autoimmunity may result when the binding of antibody to certain antigens leads to aberrant signals being fed back to parent B cells through membrane bound ligands. These ligands include B cell receptor (for antigen), IgG Fc receptors, CD21, which binds complement C3d, Toll-like receptors 9 and 7 (which can bind DNA and nucleoproteins) and PNAR. Moreindirect aberrant activation of B cells can also be envisaged with autoantibodies to acetyl choline receptor (on thymic myoid cells) and hormone and hormone binding proteins. Together with the concept of T-cell-B-cell discordance this idea forms the basis of the hypothesis of self-perpetuating autoreactive B cells. Autoreactive B cells in spontaneous autoimmunity are seen as surviving because of subversion both of the T cell help pathway and of the feedback signal through B cell receptor, thereby overcoming the negative signals responsible for B cell self- tolerance without necessarily requiring loss of T cell self- tolerance.
- Molecular Mimicry - An exogenous antigen may share structural similarities with certain host antigens; thus, any antibody produced against this antigen (which mimics the self-antigens) can also, in theory, bind to the host antigens, and amplify the immune response. The idea of molecular mimicry arose in the context of Rheumatic Fever, which follows infection with Group A beta-haemolytic streptococci. Although rheumatic fever has been attributed to molecular mimicry for half a century no antigen has been formally identified (if anything too many

have been proposed). Moreover, the complex tissue distribution of the disease (heart, joint, skin, basal ganglia) argues against a cardiac specific antigen. It remains entirely possible that the disease isdue to e.g. an unusual interaction between immune complexes, complement components and endothelium.

- Idiotype Cross-Reaction - Idiotypes are antigenic epitopes found in the antigen-binding portion (Fab) of the immunoglobulin molecule. Plotz and Oldstone presented evidence that autoimmunity can arise as a result of a cross-reaction between theidiotype on an antiviral antibody and a host cell receptor for the virus in question. In this case, the host-cell receptor is envisioned as an internal image of the virus, and the anti-idiotype antibodies can react with the host cells.
- Cytokine Dysregulation - Cytokines have been recently divided into two groups according to the population of cells whose functions they promote: Helper T-cells type 1 or type 2. The second category of cytokines, which include IL-4, IL-10 andTGF-β (to name a few), seem to have a role in prevention of exaggeration of pro-inflammatory immune responses.
- Dendritic cell apoptosis - immune system cells called dendritic cells present antigens to active lymphocytes. Dendritic cells that are defective in apoptosis can lead to inappropriate systemic lymphocyte activation and consequent decline in self-tolerance.
- Epitope spreading or epitope drift - when the immune reaction changes from targeting the primary epitope to also targeting other epitopes. In contrast to molecular mimicry, the other epitopes need not be structurally similar to the primary one.
- Epitope modification or Cryptic epitope exposure – this mechanism of autoimmune disease is unique in that it does not result from a defect in the hematopoietic system. Instead, disease results from the exposure of cryptic N-glycan (polysaccharide) linkages common to lower eukaryotes and prokaryotes on the glycoproteins of mammalian non-hematopoietic cells and organs. This exposure of phylogenically primitive glycans activates one or more mammalian innate immune cell receptors to induce a chronic sterile inflammatory state. In the presence of chronic and inflammatory cell damage, the adaptive immune system is recruited and self–tolerance is lost with increased autoantibody production. In this form of the disease, the absence of lymphocytes can accelerate organ damage, and intravenous IgG administration can be therapeutic. Although this route to autoimmune disease may underlie various degenerative disease states, no diagnostics for this disease mechanism exist at present, and thus its role in human autoimmunity is currently unknown.

4.0 CONCLUSION

The student has learnt the following:

- Autoimmunity
- Causes of autoimmunity
- Genetic factors affecting autoimmunity
- The pathogenesis of autoimmunity.

5.0 SUMMARY

Autoimmunity is the failure of an organism to recognise its own constituent parts as self, which allows an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Autoimmunity is often caused by a lack of germ development of a target body and as such the immune response acts against its own cells and tissues. Prominent examples include Coeliac disease, diabetes mellitus type 1 (IDDM), systemic lupus erythematosus (SLE), Sjögren's syndrome, Churg- Strauss Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, rheumatoid arthritis (RA), lupus and allergies. Autoimmune diseases are very often treated with steroids.

6.0 TUTOR-MARKED ASSIGNMENT

i. What is autoimmunity?
ii. Discuss the pathogenesis of autoimmnity.
iii. Discuss on the genetic factors affecting autoimmunity.

7.0 REFERENCE/FURTHER READING

Ainsworth, Claire (Nov. 15, 2003). The Stranger Within. *New Scientist* (subscription).

Edwards, J.C., Cambridge, G. (2006). "B-cell Targeting in Rheumatoid Arthritis and other Autoimmune Diseases." *Nature Reviews Immunology*, 6 (5): 394–403. doi:10.1038/nri1838.
PMID 16622478.

Edwards, J.C., Cambridge, G.& Abrahams, V.M. (1999). "Do self Perpetuating B Lymphocytes Drive Human Autoimmune Disease?". *Immunology*, 97: 1868–1876.

Everyday Health > Women and Autoimmune Disorders By Krisha McCoy. Medically Reviewed by Lindsey Marcellin, MD, MPH. Last Updated: 12/02/2009

Green, R.S.*et al* 2007). "Mammalian N-glycan Branching Protects against Innate Immune Self-recognition and Inflammation in Autoimmune Disease Pathogenesis" Immunity 27: 308-320.

Induction of Autoantibodies against Tyrosinase-Related proteins following DNA Vaccination: Unexpected Reactivity to a Protein Paralogue Roopa Srinivasan, Alan N. Houghton, & Jedd D. Wolchok.

Jerne, N. (1974). "Towards a Network Theory of the Immune System". *Ann Immunol (Paris)* 125**C** (1–2): 373–89. PMID 4142565.

Klein, J. Sato, A. (September 2000). "The HLA System. Second of two Parts". *N. Engl. J. Med.* 343 (11): 782–6. doi:10.1056/NEJM200009143431106. PMID 10984567.

Kubach, J. & *et al* (2005). "Dendritic Cells: Sentinels of Immunity and Tolerance". *Int J Hematol.* 81 (3): 197–203. doi:10.1532/IJH97.04165. PMID 15814330.

Pike, B. Boyd, A. & Nossal, G. (1982). "Clonal Anergy: the Universally Anergic B lymphocyte". *Proc Natl Acad Sci USA,* 79 (6): 2013–7. doi:10.1073/pnas.79.6.2013. PMC 346112. PMID 6804951.

Salimonu, L.S.(2004). *Basic Immunology for Students of Medicine And Biology*. College Press and Publishers Limited.
Stefanova I., Dorfman J. R. & Germain, R. N. (2002). "Self-Recognition Promotes the Foreign Antigen Sensitivity of Naive T Lymphocytes." *Nature,* 420 (6914): 429–434. doi:10.1038/nature01146. PMID 12459785.

Theory: High autoimmunity in Females due to Imbalanced X Chromosome Inactivation: Tolerance and Autoimmunity

UNIT 3 IMMUNOLOGY OF TISSUE TRANSPLANTATION

CONTENTS

1.0 INTRODUCTION

Organ transplantation is the moving of an organ from one body toanother or from a donor site on the patient's own body, for the purpose of replacing the recipient's damaged or absent organ. The emerging fieldof regenerative medicine is allowing scientists and engineers to create organs to be re-grown from the patient's own cells (stem cells, or cells extracted from the failing organs). Organs and/or tissues that are transplanted within the same person's body are called autografts. Transplants that are performed between two subjects of the same species are called allografts. Allografts can either be from a living or cadaveric source. Replacement of diseased organs by transplants of healthy tissues has long been an objective in science. This has been frustrated by the uncooperative attempts by the body to reject grafts from other individuals.

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- identify types of transplants
- describe mechanism of graft rejection
- evanluate immunology of graft rejection
- mention how to recognise prevention of graft rejection

3.0 MAIN CONTENT

3.1 Types of Transplant

Autograft
Autograft is the transplant of tissue to the same person. Sometimes this

is done with surplus tissue, or tissue that can regenerate, or tissues more desperately needed elsewhere (examples include skin grafts, vein extraction for CABG, etc.) Sometimes an autograft is done to remove the tissue and then treat it or the person, before returning it (examples include stem cell autograft and storing blood in advance of surgery). In a rotationplasty a distal joint is used to replace a more proximal one, typically a foot and ankle joint is used to replace a knee joint. The patient's foot is severed and reversed, the knee removed, and the tibia joined with the femur.

Allograft and allotransplantation

An allograft is a transplant of an organ or tissue between two genetically non-identical members of the same species. Most human tissue andorgan transplants are allografts. Due to the genetic difference between the organ and the recipient, the recipient's immune system will identify the organ as foreign and attempt to destroy it, causing transplant rejection.

A subset of allografts is the case in which organs or tissues are transplanted from a donor to a genetically identical recipient (such as an identical twin). Isografts are differentiated from other types of transplants because while they are anatomically identical to allografts, they do not trigger an immune response.

Xenograft and xenotransplantation

A transplant of organs or tissue from one species to another is called a xenograft. An example is porcine heart valve transplants, which is quite common and successful. Another example is attempted piscine-primate (fish to non-human primate) transplant of islet (i.e. pancreatic or insular tissue) tissue. The latter research study was intended to pave the way for potential human use, if successful. Xenotransplantion however is often an extremely dangerous type of transplant because of the increased risk of non-compatibility, rejection, and disease carried in the tissue of the donor and transplanted to the recipient.

Split transplants

Sometimes a deceased-donor organ, usually a liver, may be divided between two recipients, especially an adult and a child. This is not usually a preferred option because the transplantation of a whole organ is more successful.

Domino transplants

This operation is performed on patients with cystic fibrosis because both lungs need to be replaced and it is a technically easier operation to replace the heart and lungs at the same time. As the recipient's native heart is usually healthy, it can be transplanted into someone else needinga heart transplant. This term is also used for a special form of liver transplant in

which the recipient suffers from familial amyloidotic polyneuropathy, a disease where the liver slowly produces a protein that damages other organs. This patient's liver can be transplanted into an older patient who is likely to die from other causes before a problem arises.

This term also refers to a series of living donor transplants in which one donor donates to the highest recipient on the waiting list and the transplant centre utilises that donation to facilitate multiple transplants. These other transplants are otherwise impossible due to blood type or antibody barriers to transplantation. The "Good Samaritan" kidney is transplanted into one of the other recipients, whose donor in turn donates his or her kidney to an unrelated recipient. Depending on the patients on the waiting list, this may sometimes be repeated for up to six pairs, with the final donor donating to the patient at the top of the list.

This method allows all organ recipients to get a transplant even if their living donor is not a match to them. This further benefits patients below any of the recipients on waiting lists, as they move closer to the top of the list for a deceased-donor organ. Johns Hopkins Medical Centre in Baltimore and Northwestern University's Northwestern Memorial Hospital have received significant attention for pioneering transplants of this kind.

3.2 Evidence that Graft Rejection is Immunological

First and Second Set Reactions

Usually the second contact with an antigen represents a more explosive event than the first contact. Rejection of a second graft from the same donor is also more accelerated than the first. Initial vascularisation is poor and may not occur. There is rapid invasion by polymorphs and lymphoid cells including plasma cells. Thrombosis and acute destruction can be seen by 3 – 4 days.

Role of the Lymphocyte

Neonatally, the thymectomised organism finds it difficult to reject skin grafts. This difficulty can be removed by injection of lymphocytes from syngenic normal donors. Recipient of T cells from a donor who already rejected will give accelerated rejection of a further graft of the same type.

Production of Antibodies

After rejection, humoral substances with specificity for graft donor antigens may be recognised. An example in man is lymphocytotoxin. The specificity of the antigens involved in graft rejection is under genetic control. Genetically identical individuals such as uniovular twins have identical transplantation antigens and grafts can be freely exchanged between them.

3.3 Mechanism of Graft Rejection

Lymphocyte – mediated Rejection
Whereas passive transfer of serum from an animal which has rejected a skin allograft cannot usually accelerate the rejection of a similar graft on the recipient animal, injection of lymphoid cells shorten graft survival. A primary role of lymphoid cells in first set rejection is consistent with the histology of the early reaction which shows infiltration by mononuclear cells with very few polymorphs. Neonatal thymectomy prolongs the survival of skin transplants. Also, there is a long survival of grafts on children with thymic deficiencies. T cells are implicated in these regions.

The role of antibody
While earlier experience with skin and solid tumour grafts suggest that they were not readily susceptibile to cytotoxic antibodies, it is not true for all organ transplants. For example although acute early rejection of kidney allograft occurring up to 10days or so after transplantation is characterised by a dense cellular infiltration likely to be cell-mediated immunity, hyperacute rejection occurs within minutes of transplantation in individuals with pre-existing antibodies. Such antibodies arise from blood group incompatibility or pre-sensitisation to class 1 MHC molecules through blood transfusion. The complexity of action and interaction of cellular and humoral factors in graft rejection is considerable. Circumstances exist when grafts are protected from destruction by antibodies, ie., enhancement.

Prevention of Graft RejectionTissue Typing
Since MHC differences provoke the most vicious rejection of grafts, these antigen specificities are being defined in an attempt to minimise rejection by matching graft and recipient in a similar way individuals arecross-matched for blood transfusion where ABO groups provide strong transplantation antigens. Alleles at the three class I loci are identified by C' dependent cytotoxic reactions using monospecific sera. Typing is done by setting up lymphocytes against a panel of such sera in the presence of complement. Class II locus (HLA-D) is defined by the
mixed lymphocyte reaction (MLR) using homozygous stimulating cells for typing. Failure to respond to a given typing cell means that the lymphocytes bear that specificity. HLA alleles are now defined by their gene sequences employing the polymerase chain reaction (PCR) technique. Different HLA antigens are arbitrarily assigned numerical specificities.

Use of Immunosuppressants
The use of agents producing general immunosuppressants can prevent graft rejection. However, because they are non-specific, patients on immunosuppressive therapy tend to be susceptible to infections and are

more prone to develop lymphoreticular cancers, particularly of viral aetiology. Lymphoid cell abltion can be produced through injections of anti-lymphocyte globulin or of monoclonal anti-CD3. For total lymphoid irradiation, fractional irradiation is focused on lymphoid tissues while shielding the bone marrow, lungs and other vital non- lymphoid tissues. Many immunosuppressive drugs now in use were first employed in cancer chemotherapy because of their toxicity to dividing cells. These anti-mitotic drugs are especially toxic for cells of the bone marrow and small intestine and must be used with great care.

IN TEXT QUESTION

What is an allograft?
Answer
An allograft is a transplant of an organ or tissue between two genetically non-identical members of the same species.

4.0 CONCLUSION

The student has learnt the following:

1. Types of transplants
2. Mechanisms of graft rejection

5.0 SUMMARY

The importance of pathology and immunology in transplantation is increasing with the widespread use of organ and tissue transplantation for the treatment of end-stage diseases. Recently, the end points for clinical trials in organ transplantation have been based on pathology, not graft failure. Organ and tissue transplantation has advanced from an experimental procedure used only in life-threatening, emergency procedures to the treatment of choice for a wide range of clinical conditions. Organs are transplanted to rectify an irreversible functional deficit but, unless donor and recipient are genetically identical, graft antigens will trigger a rejection response by the recipient. In the early part of this century, experiments on transplantation of tumours showed that there were strict limitations on the ability of tumour grafts to survive.

6.0 TUTOR-MARKED ASSIGNMENT

i. What do you understand by the term autograft?
ii. What evidence is there to show that graft rejection isimmunological?

7.0 REFERENCES/FURTHER READING

Frohn, C, Fricke, L., Puchta, J.C., Kirchner, H. (February 2001). "The effect of HLA-C matching on acute renal transplant rejection". *Nephrol. Dial. Transplant,* 16 (2): 355–60.

Salimonu, L.S.(2004*). Basic Immunology for Students of Medicine and Biology*. College Press and Publishers Limited.

See WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation, Annexed to World Health Organisation, 2008.