COURSE GUIDE

MCB 317
IMMUNOLOGY AND IMMUNISATION

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Published by:
National Open University of Nigeria

Printed 2013

ISBN: 978-058-589-3

Printed by:

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INTRODUCTION

This course guide tells you in concrete terms what to expect in the course and also provides you with relevant information including course aims, objectives, assessments and reading lists.

The hand book also gives you a total insight to various issues relating to immunology and immunisation in all ramifications. The course material alongside this course guide will together help you to have better understanding in both the social and scientific contexts as there are limited conventional books on immunology and immunisation except journals, newsletters, newspapers, health articles and the like.

Please keep this book properly as you will definitely be referring to it from time to time because it serve as a good source of knowledge acquisition in the exciting fields of immunology and immunisation. This course is also aimed at sensitising the people, old and young; male and female; poor and rich; literate and illiterate towards demanding their rights to be immunised against preventable diseases with the same passion with which they now demand the right to vote.

WHAT YOU WILL LEARN IN THIS COURSE

This course is entitled 'Immunology and Immunisation' and it essentially embraces issues relating to and affecting the origin and development of immune system as well as the emergence and utilisation of immunisation in all ramifications.

Globally, key development have led to important re-direction and enhanced strategies for the provision of good health services. First, there have been significant advances in biomedical research that make the prospect of a healthy population free of preventable diseases. These new developments in the sciences led to positive prospects towards a healthy population free of many serious diseases. Immunology is a very crucial aspect which also led to the development of effective immunisation programme making it an important component of the National Health Care Policy.

This course covers extensively various aspects of both Immunology and Immunisation. Basically, immunology is the study of immunity which is a state of resistance to infection conferred by the presence of antibodies capable of combining with antigens or antitoxin which neutralise toxins or other chemicals in the body whereas immunisation on the other hand is the artificial means by which immunity is initiated or augmented either through active or passive means.

Immunology is basic biology science, but it is a fact that its important applications in medicine warrant a special effort to encourage its integration in public health programmes. The development of immunology of the last twenty years in both developing and industrialised countries has particularly influenced the evolution of the struggle against infectious diseases. Thus, the body's defense mechanisms against infections are better understood and the microbial antigens able to produced protection against pathogenic agents are better characterised and resulting into new approaches to the preparation of vaccine and rapid improvement may be expected in preventing the infections that are responsible for millions of deaths.

Immunisation is often achieved by using vaccines containing attenuated micro-organisms or inactive micro-organism or bacterial products such as toxins. This results in antibody production and is generally long lasting. Immunisation can also be achieved by injection of antibodies which is generally of short duration and affords only temporary protection.

Immunology and Immunisation are treated together in this course as the two automatically go together as immunology leads to and gives clue to immunisation via vaccines production. This course therefore deals extensively with virtually all aspects of immunology and immunisation such as immunity, antigens and antibodies, immune response to infections; autoimmunity, immunosuppression, immune deficiency, hypersensitivity, vaccines in terms of production, requisition, collection, storage, distribution and administration.

COURSE AIMS

The aim of this course first and foremost is to impart knowledge on learners so as to make them competent individuals in the public health related issues particularly to the various aspects of immunology and immunisation.

The study of a course like this is also expected to improve considerable the effectiveness of serological diagnosis of infectious disease.

Also, allergic reactions in many viral, parasitic or bacterial infections is aimed at changing therapeutic approaches to infections via judicious use of new immunological methods towards the improvement of the health status of population not only here in Nigeria but also all over the world.

The course is also desired to make available to developing countries including Nigeria, the exceptional possibilities offered by progress in immunology obtainable from a course like this.

The course should enable learners to later take on the responsibility for developing the immunological methods required by the health situation of their country and to ensure the preparation of vaccines and serological reagents are of good quality.

COURSE OBJECTIVES

This course is set to achieve the following objectives in conjunction with the earlier mentioned aims.
At the end of this course you should be able to:

- operate in any health setting especially in the aspects of immunology and immunisation
- explain the various practical applications of immunology and immunisation
- demonstrate skills in caseload and patients' management of immunisable and vaccine-preventable diseases
- recognise and appreciate the interplay of immunology and immunisation in all ramifications
- stimulate peoples' interest, particularly learners to have better insight to both social and scientific efforts in immunological studies.

WORKING THROUGH THIS COURSE

It is sincerely hoped that you and other learners will make conscious efforts to carefully read through this course guide alongside the course material as many times as possible, spending quality time on each occasion. I will recommend a minimum of at least two hours per day. You are obviously required to spend as much time as possible to thoroughly peruse the course materials and not mere wading through as you require a good understanding of the basic principles of the course so as to be able to properly master the key issues of the subject matter. I therefore encourage you to take good care of your study materials and read them as often as possible.

The study materials are highly simplified thus quite easy, simple, readable, explicit and self-explanatory. It is also well illustrated with definitions, descriptions and examples which make it not only comprehensive but equally comprehensible. I will further admonish you to please make efforts to attend tutorial sessions with appointed facilitators at the study centres, where you will have the rare

opportunity of direct contact and interpersonal relationship with both instructors and peers. Face-to-face is said to be better than a hundred letter. There is also the other saying that seeing is believing.

Finally, I which to further encourage you to make regular contact with your mate and interact effectively with staff members at the study centre to give you the opportunity to brainstorm, rub minds together, and exchange ideas and share knowledge through e-mails, text messages, phone calls and physical contacts.

COURSE MATERIALS

The main components of the course are:

1. The Course Guide
2. Study Units
3. References/Further Reading
4. Assignments
5. Presentation Schedule

In addition to the aforementioned materials, you will also be given a list of recommended resources such as newsletter, Newspapers, Magazines, Journals, Research reports, websites, text books and other resources for latest information and development on issues related to immunology immunisation.

However, the aforementioned resources and materials are not in any way or under any guise or disguise imposed on you as they are optional which you may or may not use. But you are enjoined, without coercion or force to check them out as additional sources of information for knowledge.

I want to further emphasise to you again that the list of recommend resources is not compulsory but may serve as necessary supplements and complements to the course materials.

STUDY UNITS

The following are the various study units contained in the course:

Module 1 Immunology

Unit 1 Definition and Types of Immunology
Unit 2 How the Immune System Develops
Unit 3 Overview of the Immune System

Module 2 Immunology II

Unit 1 Definition and Types of Immunity
Unit 2 Components of the Immune System
Unit 3 Immunity and Infectious Diseases
Unit 4 Test in Clinical Immunology

Module 3 Immune Response to Infections

Unit 1 Cell-mediated Immune Response
Unit 2 Hypersensitivity Reactions
Unit 3 Immunodeficiency
Unit 4 Autoimmunity

Module 4 Immune System Disorders

Unit 1 Disorders of the T Cells
Unit 2 Other Possible Disorders
Unit 3 Cells involved in Immune Responses

Module 5 Immunisation

Unit 1 Vaccines
Unit 2 Immunisation Overview
Unit 3 The Childhood Killer Disease
Unit 4 The Cold Chain System
Unit 5 Immunisation Schedules and Activities

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Wikipedia, the free encyclopedia in Encarta.

www.google.com

ASSESSMENT

There are three aspects to the assessment of the course. First is self-assessment exercise, second consists of the Tutor-Marked Assignment and third is the written examination/end of course examination.

You are advised to do the exercise. In tackling the assignments, you are expected to apply information, knowledge and techniques you gathered during the course. The assignments must be submitted to your facilitator for formal assessment in accordance with the deadlines stated in the presentation schedule and the assignment file.

TUTOR-MARKED ASSIGNMENT (TMA)

The TMA is the continuous assessment component of the course and it accounts for 30% of the total score. You will have four TMAs to answer three of which will be done prior to the end of course examination without which you might not be allowed to sit for the said end of term or end of course examination. The best three papers of the four TMAs will be used for your assessment. The TMAs will be given to you by your course facilitator. You must return your answers typed and in the prescribed assignment envelop well labelled by the stipulated deadline for submission of such assignments.

FINAL EXAMINATION AND GRADING

This is the examination that concludes the list of assignments for this course and it constitutes 70% of the whole course. You will definitely be informed of the due date(s) for the examination(s). Be also informed that the aforementioned examination dates may or may not coincide with the University Semester examination.

Use the time, between finishing the last unit and sitting for the examination, to revise the whole course. You might find it useful to review your self-test, TMAs and comments on them before the examination. The end of course examination covers information from all parts of the course.

COURSE MARKING SCHEME

Assignment	Marks
Assignments 1-4	Four TMAs, 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.

HOW TO GET THE MOST OUT OF THIS COURSE

Implicit interest and regular culture of reading are of utmost requirements for getting the best out of this course. It is paramount that you should at least purchase one of the textbooks that are recommended for you. More importantly, attending tutorials sessions and completing your assignments on time will certainly assist you to get the best out of this course.

FACILITATORS/TUTORS AND TUTORIALS

There are 16 hours of tutorials provided in support of this course. You will be notified of the dates, times and location of these tutorials as well as the name and phone number of your facilitator, as soon as you are allocated a tutorial group.

Your facilitator will mark and comment on your assignments, keep a close watch on your progress and any difficulties you might face and provide assistance to you during the course. You are expected to mail your Tutor- Marked Assignment to your facilitator before the scheduled date (at least two working days are required). They will be marked by your tutor and returned to you as soon as possible.
Do not delay to contact your facilitator by telephone or e-mail if you need assistance.

The following might be circumstances in which you would find assistance necessary. You would have to contact your facilitator if:
You do not understand any part of the study or the assigned readings.
You have difficulty with the self-tests.
You have a question or problem with assignments or with the grading of assignments.

You should endeavour to attend the tutorials. This is the only chance to have face to face contact with your course facilitator and to ask questions which are answered instantly. You can raise any problem encountered in the course of your study.

To gain much benefit from course tutorials prepare a question list before attending them. You will learn a lot from participating actively in discussions.

SUMMARY

This course intends to provide you and other learners with basic knowledge on immunology and immunisation in all likely and possible ramifications so that at the end of the day, that is at the end of the course, you would have acquired enough knowledge, current information, latest ideas and general awareness about immunology and immunisation in terms of:

- Definition and types of immunology alongside historical examination.
- Current understanding of the immune system, the components clinical observation and complimentary evidence.
- Simplified view of the immune system and body defence.
- Immunity types, actions and tests in clinical immunology.
- Cell-mediated response, hypersensitivity reactions, immunodeficiency and autoimmunity.
- T cells disorders and other disorders as well as cells involved in immune response plus immunotherapy.
- Definition, types, origin, development and the production of vaccines.
- Immunisation and the childhood killer diseases.
- Immunisation schedules and activities.
- The cold chain system.

I wish you the best in this course and that you really enjoy the way the course material is packaged as the subject matter (immunology and immunisation) tends to be a bit tough complex and appears difficult to understand as not many textbooks are available in the market even in the libraries. Most people do not show interest in this field, including scientist though its study is fundamental to disease control and even the eventual eradication of most infections disease. I plead with you to create and develop interest in immunology as you will reap the reward in future. It is futuristic.

GOOD LUCK!

MAIN COURSE

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MODULE 1 IMMUNOLOGY I

UNIT 1 DEFINITION AND TYPES OF IMMUNOLOGY

CONTENTS

1.0 INTRODUCTION

This module deals with certain fundamental issues about immunology particularly the definition and types of immunology, as well as how the immune system develops in line with its origin. There is also going to be a brief overview of the immune system by way of introduction.

2.0 OBJECTIVES

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

- define immunology
- discuss the origin, development and general knowledge including a clear view of immunology.

3.0 MAIN CONTENT

3.1 Definition of Immunology

Immunology: According to Wikipedia, it is a broad branch of biomedical science that covers the study of all aspects of the immune system in all organisms. It deals with, among other things, the physiological functioning of the immune system in states of both health and disease; malfunctions of the immune system in immunological

disorders (autoimmune diseases, hypersensitivities, immune deficiency, transplant rejection); the physical, chemical and physiological characteristics of the components of the immune system in vitro, in situ, and in vivo. Immunology has applications in several disciplines of science, and as such is further divided.

3.2 Histological Examination of the Immune System

Even before the concept of immunity (from *immunise*, Latin for "exempt") was developed, numerous early physicians characterised organs that would later prove to be part of the immune system. They primary lymphoid organs of the immune system are thymus and bone marrow, and secondary lymphatic tissues such as spleen, tonsils, lymph vessels, lymph nodes, adenoids, and skin. When health conditions warrant, immune system organs including the thymus, spleen, portion of bone marrow, lymph nodes and secondary lymphatic tissues can be surgically excised for examination while patients are still alive.

Many components of the immune system are actually cellular in nature and not associated with any specific organ but rather are embedded or circulating in various tissues located throughout the body.

3.3 Types of Immunology

Classical Immunology
Classical immunology ties in with the fields of epidemiology and medicine. It studies the relationship between the body systems, pathogens, and immunity. The earliest written mention of immunity can be traced back to the plaque of Athens in 430 BC. Thucydides noted that people who had recovered from a previous bout of a disease could nurse the sick without contracting the illness a second time. Many other ancient societies have references to this phenomenon, but it was not until the 19th and 20th centuries before the concept developed into scientific theory.

The study of the molecular and cellular components that comprises the immune system, including their function and interaction, is the central science of immunology. The immune system has been divided into a more primitive innate immune system and acquired or adaptive immune system of vertebrates, the later of which is further divided into humoured and cellular components.

The humoral (antibody) response is defined as the interaction between antibodies and antigens. Antibodies are specific proteins released from a certain class of immune cells (B lymphocytes).

Antigens are defined as anything that elicits generation of antibodies, hence they are Antibody Generators. Immunology itself rests on an understanding of the properties of these two biological entities. However, equally important is the cellular response, which can not only kill infected cell in its own right, but is also crucial in controlling the antibody response. Put simply, both systems are highly interdependent.
In the 21st century, immunology has broadened its horizons with much research being performed in the more specialised niches of immunology. This includes the immunology function of cells, organs and systems not normally associated with the immune system, as well as the function of the immune system outside classical models of immunity.

Clinical Immunology
Clinical immunology is the study of diseases causes by disorders of the immune system (failure aberrant action, and malignant growth of the cellular elements of the system). It also involves diseases of other systems, where immune reactions play a part in the pathology and clinical features.

The diseases caused by disorders of the immune system fall into two broad categories: **immunodeficiency,** in which parts of the immune system fail to provided an adequate response (examples include chronic granulomatous disease), and **autoimmunity**, in which the immune system attacks its own host's body (examples include systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's disease and myasthenia gravis). Other immune system disorders include different hypersensitivities, in which the system responds inappropriately to harmless compounds (asthma and other allergies) or responds too intensely.

The most well-know disease that affects the immune system itself is AIDS, caused by HIV. AIDS is an immunodeficiency characterised by lack of CD4+ ("helper") T cells and macrophages, which are destroyed by HIV.

Clinical immunologists also study ways to prevent transplant rejection, in which the immune system attempts to destroy allograft or engrafts.

Developmental Immunology

The body's capability to react to antigen depends according to age (of the person), antigen type, maternal factors and the area where the antigen is presented. Neonates are said to be in a state of physiological immunodeficiency, because both their innate and adaptive immunological responses are greatly suppressed. Once born, a child's immune system responds favourably to protein antigens while not as well to glycoprotein and polysaccharides. In fact, many of the infections acquired by neonates are caused by low virulence organisms like Staphylococcus and Pseudomonas. In neonates, opsonic activity and the ability to activate the complement cascade is very limited. For example, the mean level of C3 in a newborn is approximately 65% of that found in the adult. Phagocytic activity is also greatly impaired in newborns.

This is due to lower opsonic activity, as well as diminished up-regulation of intergrin and seletin receptors, which limit the ability of neutrophils to interact with adhesion molecules in the endothelium. Their monocytes are slow and have a reduced ATP production, which also limits the newborns phagocitic activity. Although, the number of total lymphocytes is significantly higher than in adults, the cellular and humoral immunity is also impaired. Antigen presenting cells in newborns have a reduced capability to activate T cells. Also, T cells of a newborn proliferate poorly and produce very small amounts of cytokines like IL-2, IL-4, IL-4, IL-12, and IFN-g which limits their capacity to activate the humoral response as well as the phagocitic activity of macrophage B cells develop early in gestation but are not fully active.

Diagnostic Immunology

The specificity of the bond between antibody and antigen has made it an excellent tool in the detection of substances in a variety of diagnostic techniques. Antibodies specific for a desired antigen can be conjugated with a radiolabel, fluorescent label, or color-formaing enzyme and are used as a "probe" to detect it. However, the similarity between some antigens can lead to false positives and other errors in such tests by antibodies cross-reacting with antigens that aren't exact matches.

Evolutionary Immunology

Study of the immunity in extant and extinct species is capable of giving us a key understanding of the evolution of species and the immune system.

A development of complexity of the immune system can be seen from simple phagocytotic protection of single celled organisms. From circulating antimicrobial peptides in insects to lymphoid organs in vertebrates, of course, like much of evolutionary observation, these physical properties are often seen from the anthropocentric aspect. It

should be recognised that every organism living today has an immune system absolutely capable of protecting it from most forms of harm; those organisms that did not adapt their immune systems to external threats are no longer around to be observed.

Insects and other arthropods, while not possessing true adaptive immunity, show highly evolved systems of innate immunity, and are additionally protected from external injury (and exposure to pathogens) by their chitinous shells.

Reproductive Immunology
This area of the immunology is devoted to the study of immunological aspects of the reproductive process including fetus acceptance. The term has also been used by fertility clinics to address fertility problems, recurrent miscarriages, premature deliveries, and dangerous complications such as pre-clampsia.

According to the American Academy of Allergy, Asthma, and Immunology (AAAAI), "an immunologist is a research scientist who investigates the immune system, of vertebrates (including the human immune system). Immunologists include research scientists (Ph.D.) who work in laboratories. Immunologists also include physicians who, for example, treat patients with immune system disorders. Some immunologists are physician-scientists who combine laboratory research with patient care."

4.0 CONCLUSION

The definitions of immunology given by different authors and authorities which has been clearly summarised by Wikipedia makes the subject matter very simple for you to understand and the concept of histological examination of the immune system further simplifies it. Alongside the different types of immunology are carefully described with vivid examples.

5.0 SUMMARY

In this unit, we have learnt that:

- immunology is a broad branch of biochemical science that covers the study of all aspects of the immune system in all organisms
- histological examination of the immune system actually helped physicians to correctly characterise the concept of immunity
- types of immunology identified by scientists include the followings among others:
    a) Classical immunology

b) Clinical immunology
c) Developmental immunology
d) Diagnostic immunology
e) Evolutionary immunology

6.0 TUTOR-MARKED ASSIGNMENT

i. What is immunology?
ii. Mention and describe any 6 types of immunology

7.0 REFERENCES/FURTHER READING

Wikipedia, the Free Encyclopaedia in Encarta.

www.google.com

UNIT 2 HOW THE IMMUNE SYSTEM DEVELOPS

CONTENTS

1.0 INTRODUCTION

This unit is a follow up to the foundation unit 1 which serves as the main introductory part. Essentially, unit 2 dwells on how the immune system develops in which basic issues relating to the origin and production of immunity towards establishing the immune system is discussed. Other issues raised and discussed in this unit include clinical observation to immune system development and stem cell existence in relation to immune system development as well as cellular pathways in stem cell differentiation in the production of immunity.

2.0 OBJECTIVES

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

- discuss the basic issue about immune system origin
- identify the clinical observations associated with the system
- explain stem cell existence and cellular pathways in its differentiation.

3.0 MAIN CONTENT

3.1 How the Immune System Develops

Environmental and genetic signals cue cells as they differentiate into the many linkages that recognise foreign antigens and fight off invaders.

The marvelous array of deftly interacting cells that defend the body against microbial and viral invaders arises from a few precursor cells that

first appear about nine weeks after conception. From that point onward, the cells of the immune system go through a continuously repeated cycle of development. The stem cells on which the immune system depends both reproduce themselves and give rise to many specialised lineages—*B* cells, macrophages, killer T cells, helper T cells, inflammatory T cells and others. The cells of the immune system are not isolated in a single space or arrayed in the form of a single organ; instead they exist as potentially mobile entities, unattached to other cells. This characteristic is not only crucial to their function but also confers a boon on researchers, who can isolate immune cells in relatively pure form at every stage of differentiation. Experimenter can thus determine the properties of cells and construct cellular 'family trees,' or lineages.

The information gained in this way serves biologists attempting to understand the general subject of how cells develop and differentiate; a process may starts with a fertilized egg and culminates in the consummate complexity of an adult organism. Even more important in the short run, this knowledge makes possible attempts to treat the many diseases that can arise when immune cells either fail to develop normally in the fetus or deviate from their proper pattern of growth later in life.

3.2 Current Understanding of the Immune System

The current understanding of how the various components of the system develop is almost completely at odds with beliefs that researchers held only three decades ago. We now know that all immune systems are derived from a relatively small number of progenitors in the bone marrow and thymus.

Before the 1960s, immunologists thought all the different kinds of cells required for an immune response were produced locally in lymphoid organs such as the spleen, appendix and lymph nodes, which are distributed throughout the body. That view began to change as a result of animal experiments and clinical observations of immune system dysfunction.

Perhaps the earliest of the pivotal events leading to the modern theories of immune cell origin were the atomic bomb attacks on Hiroshima and Nagasaki. Many people exposed to radiation released by the explosions died 10 to 15 days later from internal bleeding or infection. Animal experiments conducted to explore what happened to such casualties revealed that whole-body radiation kills the generation cells in blood-forming and lymphoid organs. Without the cells responsible for clotting and for fighting invaders, the body dies.

Investigation found that the radiation syndrome could be treated by injecting a small sample of bone marrow cells from a genetically identical donor. Further work with mice demonstrated that the entire blood and immune systems of mice that recovered from radiation were derived from donor cells. A fraction of the newly reconstituted bone marrow from these irradiated mice could in turn save other mice exposed to radiation. Clearly, the bone marrow contained cells capable both of differentiating into all blood cell lineages and of reproducing themselves.

Immunology discovered fairly early that some bone marrow cells can give rise to progeny of several different types – but not necessarily all. Thus parents can be defined by their individual characteristics and by the characteristics of their lineage (all cells arising from one precursor and said to belong to a single clone). A worker can grow cells from many different clones in culture to provide enough cells at each stage of differentiation for analysis.

In 1961, Ernest A. McCulloch and James E. Till of the Ontario Cancer Institute in Toronto found evidence that a single cell of the proper kind could in theory reconstitute an entire blood system. They injected bone marrow cells into irradiated mice and noticed that many of the mice developed bumps on their spleens. Each bump contained several distinct cell types. The two workers and their colleagues showed that all the cells in a bump were derived from a single progenitor. They proposed the existence of a relatively rare population of cells—hematopoietic stem cells—that could both reproduce themselves and also generate all blood cell types.

The establishment of the crucial part played by bone marrow cells was followed by the discovery of a similarly essential role for the thymus. Removal of the thymus from newborn mice compromised the development of lymphocytes elsewhere in the body. (Lymphocytes are white blood cells that attack bacteria and other foreign matter.) The mice from which the thymus had been removed experienced severe lifelong immunodeficiency.

In another important group of experiments, researchers removed a lymphoid organ called the bursa of Fabricius from chicks (the bursa plays the role in chickens that bone marrow does in humans). The operation did not affect the same lymphocyte lineages that the removal of the thymus did; instead it stopped production of cells that matured to become plasma cells, which secrete antibodies. The chicks thus exhibited immunodeficiency of a different kind.

3.3 Clinical Observation as Complementary Evidence

Clinical observations provided complementary evidence for the existence of two lymphoid lineages. In some infants the thymus developed normally, but the bone marrow becomes malfunctioned. These children had lymphocytes in their peripheral tissues but suffered from a congenital deficiency of plasma cells. Conversely, infants born without a thymus but with normal bone marrow produced plasma cells but only a small number of lymphocytes.

Studies of lymphoid malignancies revealed the same developmental pattern. Many kinds of lymphoid tumors in mice were found to originate in the thymus, and early removal of the organ prevented the development of lymphomas elsewhere. Meanwhile a different lymphoma in chickens could be cured by removing the bursa of Fabricius. Apparently, the two lymphoid organs have distinct, essential functions. Each seems responsible for a different class of immune cell.

By the late 1960s, it had become clear that stem cells give rise to two broad lineages of lymphocytes (as well as the other blood cells). One consists of the *B* cells, which originate in the bone marrow and produce antibodies that bind to foreign proteins and mark them for attack by other cells. They act against extracellular pathogens such as bacteria. The other, the *T* cells, arises in the thymus. *T* cells handle such intracellular pathogens as viruses in addition to such intracellular parasites as tuberculosis. *T* cells also secrete molecules known as lymphokines, which direct the activity of *B* cells, other *T* cells and other parts of the immune system.

Once formed, cells of both types migrate to the spleen, lymph nodes and intestinal lymphoid tissues. There, they can encounter antigen, the molecular signature of microbial or viral invaders, and be called into action. Lymphocytes continuously circulate through the body's vascular and lymphatic systems, stopping periodically in the lymphoid organs as they patrol for foreign antigens.

3.4 Stem Cell Existence

The existence of the stem cell was first posited in 1961, researchers made little progress in identifying actual examples until the early 1980s. At that time, biologists established specific assays for *B, T* and myeloid precursors. They could then isolate bone marrow cells to determine which surface proteins were present or absent on particular clone-forming cells, in mice, scientists in one of the laboratories (Weissrnan’s) found progenitors for *B, T* and other blood cells in only a small fraction of the total population of bone marrow cells, about one in 2,000. These turned

out to be stem cells. The search for human stem cells required the same kind of techniques that had proved so useful in mice. In the course of this search, Joseph M. McCune and his colleagues at Stanford University developed a technique that turned out to allow the testing of this fraction of bone marrow and lymph nodes into a strain of mice that had no immune system of their own. They succeeded in establishing a functioning human blood-forming and *T* cell-developing system. Since doing this work, McCune has founded a biotechnology company, Systemix (with which Weissman is associated).

Researchers at Systemic injected candidate human stem cells into these mice and showed that they could thereby reconstitute the blood-forming and immune systems. Interestingly, the human-derived thymus cells also proved vulnerable to infection with the human immunodeficiency virus (HIV), which causes AIDS; the infection depleted the same kind of circulating human immune cells which are destroyed in AIDS. Stem cells differentiate into *B* or *T* lineages in response to cues (many of them still unknown) from their environment. This phenomenon can be seen in the embryo, where the distinction between *B and T cells* becomes clear. Early in fetal life, stem cells migrate from the blood-forming organs to the thymus in distinct waves. Once in the thymus, these cohorts of stem cells divide and differentiate. They give rise to successive kinds of *T* cells that populate the lining (epithelium) of the skin, various orifices (such as the mouth and vagina) and the organs that connect with them (the gastrointestinal tract, uterus and so forth) before producing the later generations that circulate to the lymphoid organs. These cells can be distinguished by free molecules (known as TCRs. for *T* cell receptors) they carry on their surface. Moreover, they appear to be produced in a very specific order. Early cells carry receptor whose components consist of so-called gamma and delta chains, whereas later ones carry receptors made of alpha and beta chains. In mice, for example, the first wave of cells appears between the 13th and 15th day of gestation and carries a TCR type known as gamma 3. These cells emigrate to the skin, where they may serve as sentinels that recognise and destroy skin cells that have become infected, cancerous or otherwise damaged.

The next wave, which appears between the 15th and 20th days of gestation, takes up residence mainly in the lining of the reproductive organs in females and in the epithelium of the tongue in both sexes. These cells carry TCR called gamma 4. Subsequently, waves emigrate for the most part to the spleen (gamma) and to the lining of the intestinal tract (gamma 5).

The first and second waves of these cells are made only in the fetal thymus. Later in development and throughout life, the stem cells that settle in the thymus differentiate predominantly into T cell carrying alpha-beta receptors, the so-called helper and killer T cells.

The order in which stem cells generate these waves of progeny matches the order in which DNA encoding the different gamma-chain types appears on the TCR gene. It appears that the stem cells 'read out' a development program that depends on the age of the animal.

Early development of the *B* cell system proceeds along similar but less complex lines. The stem cells proven that enter the *B* cell path do so in the same tissues in which other white blood and red blood cells are formed. Early in embryonic life, they are produced in the liver, but later the stem cells migrate to the bone marrow.

B cell generated in the fetal liver may differ from those formed later in the bone marrow. The earlier cells make antibodies that can bind to a wide variety of antigens but with relatively low affinity. The later cells, in contrast, carry antibodies that react much more strongly but with only one or two antigens. It appears that the mechanisms that *B* cells employ to produce a full range of antibodies come into play only near the time of birth. Each *B* cell in the mature organism bears on its surface a unique antibody receptor complex that it uses to recognise a specific antigen.

Scientists have learned a great deal about how a few stem cells can produce this enormous diversity of *B* cells. To trace the process, experimenters have learned to recognise the many surface proteins that cells express as they divide and progress along the *B* cell path of differentiation. These molecular markers are a primary means by which cells interact with nearby cells; consequently, a *B* lymphocyte will display different proteins as it matures.

The signals that tell a stem cell daughter to enter the *B* cell pathway instead of becoming a red cell or another type of white cell appear to come primarily from other cells in the immediate environment. When the late Cheryl Whitlock and Owen N. Witte of the University of California at Los Angeles first discovered how to raise *B* cells in long-term cultures, they found that stromal cells (large, veil-like cells in the bone marrow) are essential for culturing *B* cells. The stromal cells interact with progenitor B (pro-B) cells by means of surface molecules. They also make soluble protein factors (such as interleukin-7) that bind to receptors on the *pro-B* and pre-5 cells, signaling them to divide and to differentiate.

As they divide, *pro-B* cells begin the process that will culminate in the expression of a unique antibody receptor complex. First, they rearrange the gene fragments that encode the light and heavy immunoglobulin chains that will form an antibody molecule. These genes are actively transcribed as soon as rearrangement is complete. The order in which the gene fragments begin functioning is crucial to the later development of the *B* cell. The genes directing the construction of the heavy chains are

typically shuffled and begin functioning first. (The ceils are then called *pro-B* cells,) The genes encoding light chains are then rearranged and also start functioning. These cells also commence to produce two additional proteins, immunoglobulin's alpha and beta (Ig alpha and beta), which span cell membranes. The immunoglobulin heavy chain and their light-chain partners associate with Ig alpha and Ig beta to form an antigen receptor unit that migrates to the cell surface. There it can interact with antigens and send appropriate signals back to the nucleus. Cells that reach this stage of differentiation are called *B* cells, and they enter the bloodstream en route to peripheral tissues.

The *B* cell population responds to an extremely diverse range of antigens. To guide the manufacture of its light and heavy chains, each cell selects one combination of its gene fragments out of more than a million possibilities. In addition, each developing cell can modify the gene-splicing sites to further increase variability in the DNA encoding the antigen-binding site. And as if that diversity were still insufficient; the cell can even insert new nucleotide sequences at the joint between fragments as it splices them together.

The cell rewrites its genetic code by means of the enzyme terminal deoxynucleotide transferase. This enzyme is expressed only in the nucleus of pro-5 cells, where heavy-chain gene rearrangement usually occurs. Sometimes, however, light-chain genes are rearranged first. Hiromi Kubagawa of the University of Alabama at Birmingham uncovered this fact when he infected early *9* lineage cells with Epstein-Barr virus, creating a self-reproducing culture whose immunoglobulin genes were frozen at that early stage of development. He found pre-5" cells that had rearranged only their light chains; their joints contained new sequences, suggesting that the shuffling had taken place before transferase activity stepped.

Thus far, we have been discussing *B* cell development as if it were a path that all cells follow to the end once they have embarked on it. That is not the case. When Dennis G. Osmond, now at McGill University, counted the number of cells in the pro-B, pre-B and *B* stages in mouse bone marrow, he found that half or more of the cells apparently die during the pre-B stage.

Researchers theorise that pre-B cells die unless they receive a survival signal; some kind of molecular messenger from nearby cells. The 'kiss of life' may bind to a receptor that appears on the surface of late-stage pre-B cells. This receptor is composed of heavy chains paired with a so-called surrogate light-chain complex. The surrogate complex, unlike the antigen receptors produced by mature *B* cells, is encoded by genes that do not require rearrangement for their expression.

When Daisuke Kitamura and his colleagues at the University of Cologne prevented the expression of these receptors, they found that the production of *B* cells fell to less than a tenth its normal level. The *B* cells that survived may have been the ones that rearranged their light-chain genes early, thus producing non-surrogate light chains at an early enough stage to substitute for the missing receptor.

Other *B* cells die, not because they fail to receive a 'kiss of life' but rather because they carry a 'kiss of death'. Some rearrangements of a *B* cell's gene fragments will make antibodies that react to title body's own cells. Lineages carrying these antibodies must be eliminated.

The negative selection process begins when newly formed *B* cells first interact with their environment. Self-reactive cells rapidly encounter large quantities of antigen to which their antibodies can bind molecules on the surfaces of their neighbours. If the binding is strong enough, the antibody receptor will transmit signals into the cell, causing it to commit suicide in what is known as apoptosis (programmed cell death). Immature *B* cells that do not react strongly to self-antigen survive and mature. Later they can respond to antigenic stimulation from oneself molecules. This general principle was first demonstrated in chicks and mice treated with antibodies against the IgM receptors on immature *B* cells: early administration of receptor antibodies aborted *B* cell development, whereas doses given later stimulated it. Early in development, the signal transmitted by the antibody receptors induces apoptosis by activating enzymes that cleave nuclear DNA. Virtually no reactive *B* cells survive to maturity.

Clones that survive the selection process can migrate to the peripheral lymphoid tissues. There they finally begin the working phase of their life history. Eventually, after being stimulated by both antigens and B cells, they may return to the bone marrow to undertake their final maturation into antibody-secreting plasma cells.

The *T* cell pathway is somewhat more complex. Stem cells in the thymus that commit to this line of development may eventually mature into several different kinds of *T* cells, including helper and killer.

Developing *T* cells pass through a number of winnowing points. The first challenge tests their ability to recognise antigens presented to them by other cells; an essential attribute for a functioning immune cell. Molecules of the so-called major histocompatibility complex (MHC) hold fragments of protein antigens for presentation to *T* cells. MHC molecules are divided into two types, class I and class II, developing cells in the thymus scan their environment to determine whether they recognise any self-MHC, If they can, they survive; if not, they die.

Once the maturing *T* cells have survived this challenge, the next step is the destruction of the cells bearing receptors that react too well to the body's own tissues (just as with *B* cells). Ultimately, only *T* cells with receptors that can recognise both foreign peptides and self-MHC survive to leave the thymus and take up residence throughout the body. Immunologists trying to fill in the details of this picture started by tracing the line of descent from stem cell to emigrant *T* cell. To test lineage relationships, researchers used stem cells and progeny bearing cleanly realisable markers. They introduced these cells, at different stages of maturation, into fee thymuses of mice whose cells bore no such markers. By waiting hours or days, the worker could then determine what offspring their transplants had spawned.

Thymus cells transplanted at the earlier stage of development express virtually none of the common *T* cell markers on their surface: little or no CD4 co-receptor protein and neither T cell receptor structures nor the co-receptor protein known as CD8. (CD8 binds to class I MHC, whereas CD4 binds to class II MHC.) A day after transplantation, however, these large cells have reproduced themselves and given rise to other large cells bearing CD8 but no CD4 of TCR (human thymic cells at a similar stage of development express CD4 but not CD8 or TCR). These cells in turn divide into progeny that bear CD4, CD8 and small amounts of TCR. This stage is the first at which a *T* cell progenitor expresses TCR on its surface. The expression of CD4 at these early stages of development may explain why HIV so virulently depletes *T* cells: the virus is believed to bind to CD4 molecules, and so it may attack these primitive thymic progenitors, cutting off the entire line of their progeny while the cell are changing their surface proteins, they are also rearranging their genes to produce *T* cell receptor. In the mouse, for example, assembly and surface expression of TCR chain begin at or before the stage at which they express both CD4 and CD8. These progenitors are poised to interact with MHC-bearing cells in the thymus: Most of those binding to class I MHC molecules will become killer cells. Those binding to class II develop mainly into helper cells, although some also become killer cells (Cells that do not bind to any MHC shrink and die).

Once they have become committed to one path, the intermediate-stage cells shut down production of the receptor type they will no longer use (either CD8 or CD4) and express addition TCR. They also acquire homing receptors' that enable them to leave the bloodstream and enter the peripheral lymphoid organs. Finally, they leave the thymus. Not all potential *T* cell, of course, complete this line of development. Some undergo negative selection, in which signals from other cells (those carrying self-antigen attached to self-MHC) cause apoptosis. Cells in the thymus can supposedly trigger positive or negative selection depending on the layer of primitive fetal tissue from which they derived: endoderm,

mesoderm or ectoderm. The thymus is unusual among lymphoid organs in containing cells from all three sources.

3.5 The Cellular Pathways

Cells derived when particular stem cells began differentiating into *B* or *T* cells come together in the peripheral tissues. Most of the remaining stages in the development of both kinds of cells take place when their receptors have been triggered by or encountered a foreign substance.

Inside the lymphoid organs, *T* and *B* cells that have matured but are not yet engaged in immune responses reside in separate domains. After the immune cells have been stimulated by antigens, the cells that will participate in antibody production undergo a complex set of interactions to form new structures called germinal centres.

Three kinds of cells congregate in these germinal centres at the interface between *T* and *B* domain: activated helper *T* cells, *B* cells and dendritic cells, a type of antigen-presenting cell. A few cells proliferate in response to the antigens; soon their clones make up most of the population in the centres.

While they are proliferating the *B* cell also differentiates and mutate. They modify the DNA in their gene fragments to make antibodies similar to those that bound to the antigen in question (but perhaps even more reactive). Some of the *B* cells interact with helper *T* cells and then give rise to plasma cells which are of several kinds. The antibodies they generate all react to the same antigen but elicit different immune responses. Yet other *B* cells become so-called memory cells. They will not participate immediately in the body’s defense but rather will retain a molecular record of past invaders to speed response in the future.

Although the immune response is orchestrated within the lymphoid organs, lymphocytes do not merely reside there waiting to be called on. James L. Gowans and his colleagues at the University of Oxford demonstrated in 1959 that immune cells circulate between the bloodstream and the lymphoid organs. This traffic provides each lymphoid organ with a rapid sampling of all lymphocytes that might possess receptors for the foreign antigens currently attracting the body's attention.

Circulating lymphocytes pass into lymphoid organs by means of a specialised kind of blood vessel, the HEV (high endothelial venule, named for the blocky surface of its walls). Only lymphocytes can pass through the HEVs; they express homing receptors that match counter receptors on the HEV walls. These receptors appear to come in two

varieties: one that homes in on lymph nodes, and another that matches surface molecules expressed by lymphoid organs in the gastrointestinal tract.

When *T* and *B* cells are activated, they quickly stop producing their usual homing receptor molecules and revert to making another interim mat they produced early in their development. This molecule binds to the vascular-cell adhesion molecule, VCAM-1 (which also appears on stromal cells in the bone marrow and epithelial cells inside the thymus). As a result, these activated cells no longer pass through the walls of normal lymphoid-organ HEVs when they are released into the bloodstream. Instead they home in on blood vessels serving infected, inflamed and antigen-bearing tissues. The vessels in these inflamed areas may express VCAM-I, whereas those elsewhere do not. By returning to a cellular expression of their early development, the cells fulfill their ultimate task.

This simplified version of how the cells of the immune system develop and mature does not tell the entire story. For example, a number of other adhesion molecules are involved in interactions between lymphocytes and endothelial or stromal cells. Indeed, researchers still have much to learn about the means by which cells receive the signals that cause them to undergo programmed death, to continue living or to grow and differentiate. One important question is how stem cells choose between reproducing themselves and producing offspring committed to a particular lineage. This problem is of more than theoretical significance: if stem cells prove useful in the restoration of congenital or acquired immunodeficiencies, methods that increase their numbers either in the test tube or in the body might improve patients' chances for recovery. Stem cells are also an obvious target for gene therapy that might either replace a defective gene or endow the cells' progeny with abilities to survive in a hostile environment, such as a body carrying HIV.

In addition, as researchers understand more fully the path from stem cell to activated-*B* or *T* cells, they will make headway in treating diseases where that development goes dangerously wrong. Inherited or acquired defects in genes essential for the growth and differentiation of immunocompetent cells can result in immunodeficiency or lymphoid malignancies.

Inherited defects can block development of *T*or *B* cells at many different stages, depending on the product of the gene in question. For example, a defect in the gene encoding the enzyme adenosine deaminase (ADA) allows toxic metabolic products to accumulate in the bone marrow and thymus, preventing lymphocytes from synthesising DNA and dividing. Affected infants lack *T* and *B* cells and so cannot defend themselves

against infection (hence the term ‘severe combined immunodeficiency disease or SCID). Armed with an understanding of the function of stem cells, Robert A. Good and his colleagues at the University of Minnesota Medical School showed that SCID could be cured by transplanting compatible bone marrow from a healthy sibling, but unfortunately most patients lack a suitable donor. Michael R. Blaese and his coworkers at the National Cancer Institute, however, have succeeded in inserting a functional ADA gene in deficient *T* lymphocytes, thereby repairing one essential limb of the immune system.

During the first half of this year, researchers found the genes responsible for three other immunodeficiency diseases. All are on the X chromosome and affect boys (who have only one copy of the X's genetic information), but each aborts immune system development at a different level. One, a mutation in a protein kinase gene essential for transmitting signals for pre-5 cell growth and development, causes a gross deficit of mature *B* cells and the antibodies they secrete. Another is the consequence of a mutation in the gene for one of the three chains that make up the receptor for the growth factor interleukin-2. This defect sabotages the development of helper *T* cells, which in turn prevents *B* cells from maturing into plasma cells. The third disorder to be elucidated is caused by a defect in the gene encoding the surface molecules through which *T* and *B* cells interact in boys whom the CD4 molecule or its receptor is malformed and produce only IgM antibodies; they lack the signal that causes *B* cells to divide and make high-affinity antibodies of other classes.

Identification of these genes could lead to gene replacement therapy for these deficiencies. These three gene defects were discovered almost simultaneously by several groups of investigators; knowledge of the development and function of the immune system may have reached a level at which the genetic basis for other immune disorders may soon be found. Consequently, clinical benefits may accrue rapidly.

Although lymphoid malignancies also result from genetic malfunctions, they differ in a number of ways from immunodeficiency diseases. Most important, malignancy requires the accumulation of several mutations, all of which favour excessive cell growth and survival at the expense of maturation and natural death. Complex multicellular organisms have evolved many checkpoints for monitoring cell growth and survival. To overcome this complex defense, the malignant sequence of mutations must usually begin in the stem cells or their immediate clonal progeny to permit the gradual evolution of a malignant clone of cells that can elude all these monitoring mechanisms. Even if a person inherits a gene predisposing to malignancy, the affected cells must acquire additional mutations during their life span to become malignant. Once one mutation favouring growth or survival occurs, however, the odds increase that a cell

will persist long enough to suffer another growth-promoting mutation and thus a third or fourth.

This principle can be seen in follicular lymphoma, an extremely slow growing malignancy of *B* cells in germinal centers. Virtually all follicular lymphomas contain a translocation of a gene called *bcl-2,* which produces a messenger that prevents programmed cell death. The gene is usually turned off when an activated cell fails to recognise antigen or reshuffles its mini-genes so as to make self-reacting antibodies, but in follicular lymphoma cells it resides next to an antibody gene that is turned on in *B* cells and so remains active indefinitely.

The multistep path to malignancy may also explain why *B* cell malignancies are four times as common as those involving *T* cells. Stem cells in the bone marrow produce *B* cells throughout life (and thus have many years over which to accumulate mutations). Most *T* cells, in contrast, are produced early in life; the thymus withers as people age, leaving fewer thymic stem cells and their offspring to mutate.

Once developmental and molecular biologists unravel the signals that guide stem cells and their intricate lines of progeny, they may be able to manipulate the development of the immune system from within. Clinicians will then be able to strengthen responses to invaders, mitigate the damage that immune cells do to self, and correct or eliminate those cell lines that would otherwise propagate families of malignancy.

4.0 CONCLUSION

The study of how immune system develops throws a big light on its origin and manifestations in terms of activities and functions. For you and other learners to be able to have a good grasp of this course, there is an absolute need for a thorough understanding of this Unit as it gives a very good and solid foundation to the study of immunology.

5.0 SUMMARY

In this unit, we have learnt that:

- immune system develops using environmental and genetic signal cue cells as they differentiate into the many lineages that recognise foreign antigens and fight off invaders
- all immune systems derived from a relatively small number of progenitors in the bone marrow and thymus
- clinical observations provided complementary evidence for the existence of lymphoid lineages

- existence of the stem cell was first posited in 1961, researchers made little progress in identifying actual example until the early 1980s when Biologists established specific assays for *B*, *T* and myeloid precursors
- cellular pathways often diverge when particular stem cells began differentiating into *B* or *T* cells come together in the peripheral tissues
- the study of the immune system to the development of gene replacement therapy to correct deficiencies.

6.0 TUTOR-MARKED ASSIGNMENT

Briefly describe how the immune system develops.

7.0 REFERENCES/FURTHER READING

Wikipedia, the free encyclopaedia in Encarta.

www.google.com

UNIT 3 OVERVIEW OF THE IMMUNE SYSTEM

CONTENTS

1.0 INTRODUCTION

This unit directly follows the processes of immune system development so as to ease your understanding of what system and processes are involved in the production of immunity which is essentially about body defence against infectious diseases.

This unit also displays in graphical form the immune system, to enhance better comprehension by learners as the pictorial analysis is well annotated to facilitate a free flow of communication between learners and facilitators during tutorial sessions.

2.0 OBJECTIVES

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

- review the simplified immune system pictorially
- illustrate the immune system in graphical form
- explain the basic principles of the body defence system.

3.0 MAIN CONTENT

3.1 Overview of the Immune System

We are constantly being exposed to infectious agents and yet, in most cases, we are able to resist these infections. It is our immune system that enables us to resist infections. The immune system is composed of two major subdivisions, the innate or non-specific immune system and the adaptive or specific immune system. The innate immune system is our first line of defence against invading organism while the adaptive immune system acts as a second line of defence and also affords

protection against re-exposure to the same pathogen. Each of the major subdivisions of the immune system has both cellular and humoral components by which they carry out their protective function. In addition, the immune system has distinct functions. Although these two arms of the immune system have distinct functions, there is interplay between these systems (i.e., components of the innate immune system influence the adaptive immune system and vice versa) which also has anatomical features that function as barriers to infection.

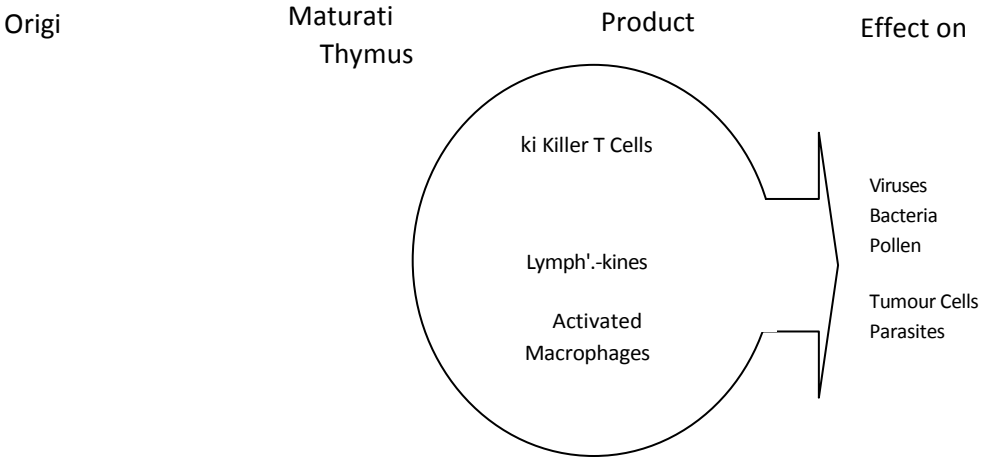
There is interplay between these systems. Although the innate and adaptive immune systems both function to protect against invading organisms, they differ in a number of ways. The adaptive immune systems requires some time to react to an invading organism, whereas the innate immune system includes defences that, for the most part, are constitutively present and ready to be mobilised upon infection. Second, the adaptive immune system is antigen specific and reacts only with the organism that induced the response. In contrast, the innate system is not antigen specific and reacts equally well to a variety of organisms, finally, the adaptive immune system demonstrates immunological memory. It “remembers” that it has encountered an invading organism and reacts more rapidly on subsequent exposure to the organism. In contrast, the innate immune system does not demonstrate immunological memory.

All cells of the immune system have their origin in the bone marrow and they include myeloid (neutrophils, basophils, eosinpophils, macrophages and dendritic cell) and lymphoid (*B* lymphocyte, *T* lymphocyte and Natural Killer) cells, which differentiate along distinct pathway. The myeloid progenitor (stem) cell in the bone marrow gives rise to crythrocytes, platelets, neutrophils, neutrophis, monocytes/macrophages and dendritic cells whereas the lymphoid progenitor (stem) cell gives rise to the NK, *T* cells and *B* cells. For *T* cell development the precursor *T* cells must migrate to the thymus where they undergo differentiation into two distinct types of *T* cells; The THI cells, which help the CD8+ pre-cytotoxic cells to differentiate into cytotoxic *T* cells, and TH2 cells, which help *B* cells, differentiate into plasma cells, which secrete antibodies.

The main function of the immune system is self/non-self discrimination. This ability to distinguish between self and non-self is necessary to protect the organism from invading pathogens and to eliminate modified or altered cells (e.g. malignant cells). Since pathogens may replicate intracellularly (viruses and some bacteria and parasites) or extracellularly (most bacteria, fungi and parasites) different components of the immune system have evolved to protect against these different types of pathogens. It is important to remember that infection with an

organism does not necessarily mean diseases, since the immune system in most cases will be able to eliminate the infection before the diseases occurs. Diseases occur only when the bolus of infection is high, when the virulence of the invading organism is great or when immunity is compromised. Although the immune system, for the most part, has beneficial effects, there can be detrimental effects as well. During inflammation, which is the response to an invading organism, there may be local discomfort and collateral damage to healthy tissue as a result of the toxic produced by the immune response. In addition, in some cases the immune response can be directed toward self tissues resulting in autoimmune disease.

3.2 The Immune System-A Simplified View



1. The three main types of white blood cells that participate in the immune response originate in the bone marrow. *T* cells migrate into the thymus, to play a role in cellular immunity, combating fungi and viruses and helping to reject tumours and transplanted organs. Phagocytes or scavengers can ingest and destroy invaders such as the pneumococcus, the commonest cause of bacterial pneumonia. The third type cell is the *B* cell. When *B* cell interacts with antigens such as bacteria, the cells multiply and produce antibodies which either attack the microbes or react with organisms so that they are more easily killed by phagocytes.
2. The first step in developing an allergy is exposure to certain pollens, dusts, moulds and so on. The body reacts or becomes allergic to these substances (allergens) by producing a protein known as IgE antibody, which is responsible for IgE antibodies can attach to the surface of two types of cells: the basophils, found in the blood, and the mast cells, found in tissues such the respiratory tract, the gastrointestinal tract and the skin.

→ IgE Antibody
→ Mast Cell

3. Each IgE antibody will react only with the allergen against which it was made. This means that an IgE antibody made against ragweed pollen will only react with another grain of ragweed pollen; hence the importance of knowing exactly to which substance one is allergic. When an allergic person again encounters this allergen, it binds to the IgE antibodies that are already on the surface of the mast cells or basophils, and histamine is released.

(*Diagrams adapted from P. Young: Asthma and allergies: an optimistic future, US National Institute of Health*).

← Ragweed

← lgE

3.3 Body's Defence System

Immunology, the science which deals with the body's response to antigenic challenge, is a highly complex study and one which is difficult to express in "layman's language." It is a very broad scientific discipline whose relevance to most fields of medicine has become apparent in recent years. Immunological mechanisms are involved in the protection of the body against infectious agent but periodically they can also cause damage. This can be the case in some infectious diseases, such as leprosy, and occurs in the so-called "auto-immune" disorders where the body's reactions harm itself.

Immunology tests are now routinely used in clinical practice, and in some cases they are indispensable for the diagnosis of diseases and the subsequent care of patients. Unfortunately, however, routine use has become so extensive that those tests are often used unnecessarily, resulting in unjustified cost to the health system.

In the past, antisera used for the diagnosis and treatment of some conflictions could only be obtained by immunising animals. The quality of the antiserum obtained as a result depended not only on the antigen injection but on the way in which each individual animal responded to the antigen, which could not be predicted. In any case, the antibody response produced by each animal was very heterogeneous and was directed against many different sites on the antigen. This heterogeneity of antibody response made studies very difficult, such as those aiming at the identification of the antigenic determinant on parasites capable of

stimulating a protective immune response. The introduction of new technology developed only a few years ago and called hybridoma technology (discussed in this issue by Professor Capron), is revolutionising immunology. This technique permits the production of antibodies *in vitro* against *single* antigenic determinants (epitopes). It is now possible to obtain unlimited amounts of very homogeneous and specific antibodies. Already we can use such antibodies for diagnosis and possibly in future, they will be used to treat patients.

Allergic diseases are recognised to be a serious public health problem in industrialised countries. The most common of these conditions, such as hay fever are not life-threatening but sufferers go to the doctor very often and, as a consequence, the economic burden is high, both for the patient and for the community. The social-economic importance of allergic diseases in developing countries has not yet been fully assessed, but epidemiological studies undertaken in some selected countries seem to show a high prevalence of these conditions.

Developing countries are steadily becoming more capable of undertaking research on problems of local importance, in order to achieve self reliance. Research on these disease problems needs well-trained scientists in all fields of medicine. As a contribution to this goal, WHO has set up a training programme in immunology? *At the moment of birth, we all arrived equipped with a natural defence system against disease. Immunology is the science which seeks to strengthen and safeguard that defence system.*

4.0 CONCLUSION

At this point, I am convinced that you would have gotten a good grasp of what immune system is all about after studying all the three units of this module particularly, this unit 3 that deals with the overview of the immune system, simplified view of the system and body defence system. All of which will provide a good template for a better understanding of subsequent modules and units of the course.

5.0 SUMMARY

In this unit, we have learnt that:

- we are constantly being exposed to infectious agents and yet, in most cases, we are able to resist these infections
- although the innate and adaptive immune systems both function to protect the body against invading organisms, yet they differ in a number of ways

- all the cells of the immune system have their origin in the bone marrow and they include myeloid (neutrophils, macrophages, basophis, eosinpophils and dendritic cells) and lymphoid (*B* lymphocyte, *T* lymphocyte and natural killer) cells
- the main function of the immune system is body defence by killing off invaders as they emerge before wrecking any havoc.

6.0 TUTOR-MARKED ASSIGNMENT

Present a simplified view of the body defence system.

7.0 REFERENCES/FURTHER READING

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MODULE 2 IMMUNOLOGY II

UNIT 1 DEFINITION AND TYPES OF IMMUNITY

CONTENTS

1.0 INTRODUCTION

This module is aimed at building on the foundation laid in module 1 with regards to the origin and development of the immune system and in particular it is a continuation of the previous unit (unit 3 of module 1).

2.0 OBJECTIVES

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

- list the basic types of immunity as they occur in immunology
- describe each type of immunity.

3.0 MAIN CONTENT

3.1 Definition of Immunity

According to Brooker (2000), immunity is the state of resistance to infection conferred by the presence of antibodies capable of combining with antigens or antitoxins which neutralise toxins or other chemicals. Immunity is the body's ability to resist infection, afforded by the presence of circulating antibodies and white blood cells.

3.2 Types of Immunity

There are different types of immunity, Booker (2000) categorised immunity into two: natural and artificial:

1. Natural which may be inborn (passive) or acquired by the transfer of maternal antibodies via the placenta to the unborn baby. It could be transfer through the breast milk too. Naturally acquired active immunity occurs when a person produces his own antibodies in response to having the disease or being exposed to the micro – organism over time.
2. Artificial is yet another type of immunity acquired by Immunisation;
3. Martin (2003) classified immunity into four: active, cell – mediated, humoral or passive.
4. Active immunity that arises when the bodies own cells produce and remains able to produce appropriate antibodies following an attack of a disease of deliberate stimulation.
5. Cell – mediated immunity which results from the action of T – lymphocytes.
6. Humoral immunity resulting from the activity of phagocytic cells, natural killer cells and other mechanisms present before exposure to infection.
7. Passive immunity is a temporary immunity that may be provided by injecting ready – made antibodies in antiserum taken from another person or an animal already immune. Babies have passive immunity, conferred by antibodies from the maternal blood and colostrums, to common diseases for several weeks after birth.

4.0 CONCLUSION

This unit appears too simple but it is quite crucial to acquire this knowledge of properly defining what immunity stands for and the different types of it that exist according to the classifications put forward by different authorities.

5.0 SUMMARY

In this unit, we have learnt that:

- there are different definitions of immunity mentioned in the unit which includes those of Brooker (2000), Martin (2003) and other general opinions
- according to Brooker (2000), immunity can be classified into two (1) Natural and (2) Artifitial

- according to Martin (2003) immunity can be of four categories (1) cell – mediated (2) active (3) humoral (4) passive.

6.0 TUTOR-MARKED ASSIGNMENT

Define and classify immunity as much as you can.

7.0 REFERENCES/FURTHER READING

Brooker, C. (2000). *Mosby Nurses Pocket Dictionary*. (31st ed.). London: Harcourt Limited.

Martin, E. A. (2003). *Mini Dictionary for Nurses.* (5th ed.). Oxford: Oxford University Press.

UNIT 2 COMPONENTS OF THE IMMUNE SYSTEM

CONTENTS

1.0 INTRODUCTION

Just as most other matters have components so also the immune system has its own components. These components include macrophages, lymphocytes, Antigen receptors, Antigen presenting cells, monocytes etc. The components play complimentary roles and help the body to build the defense system discussed in unit 3 of module 1. These different components also play different roles as assigned to them by nature in addition to the complimentary roles they involve in with other components.

2.0 OBJECTIVES

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

- explain the existence of the different components of the immune system
- state the roles of the components in defending the body against infections.

3.0 MAIN CONTENT

3.1 Macrophages

White blood cells are the mainstay of the immune system. Some white blood cells, known as macrophages, play a function in innate immunity by surrounding, ingesting, and destroying invading bacteria and other foreign organisms in a process called phagocytosis (literally, “cell eating”), which is part of the inflammatory reaction. Macrophages also

play an important role in adaptive immunity in that it attach to invading antigens and deliver them to be destroyed by other components of the adaptive immune system.

3.2 Lymphocytes

Lymphocytes are specialised white blood cells whose function is to identify and destroy invading antigens. All Lymphocytes begin as "stem cells" in the bone marrow, the soft tissue that fills most bone cavities, but they mature in two different places. Some lymphocytes mature in the bone marrow and are called *B* lymphocytes. *B* Lymphocytes, or *B* cells, make antibodies, which circulate through the blood and other body fluids, binding to antigens and helping to destroy them in humoral immune responses.

Other lymphocytes, called *T* lymphocyte, or Cells, mature in the thymus, a small glandular organ located behind the breastbone. Some *T* lymphocytes, called cytotoxic (cell - poisoning) or killer *T* lymphocytes, generate cell – mediated immune response, destroying cells that have specific antigens on their surface that are recognised by the killer *T* cells. Helper *T* lymphocytes, a second kind of *T* lymphocyte, regulates the immune system by controlling the strength and quality of all immune responses.

Most contact between antigens and lymphocytes occurs in the lymphoid organs the lymphnodes, spleen, and tonsils, as well as specialised areas of the intestine and lungs (see lymphatic system). Mature lymphocytes constantly travel through the blood to the lymphoid organs and then back to the blood again. This recirculation ensures that the body is continuously monitored for invading substances.

3.3 Antigen Receptors

One of the characteristics of adaptive immunity is that it is specific. Each response is tailored to a specific type of invading antigen. Each lymphocytes, as it matures, makes an antigen receptor – that is, a specific structure on this surface that can bind with a matching structure on the antigen like a lock and key. Although lymphocytes can make billions of different kinds of antigen receptors, each individual lymphocyte makes only one kind. When an antigen enters the body, it activates only the lymphocytes whose receptors match up with it.

3.4 Antigen – Presenting Cells

When an antigen enters body cell, certain transport molecules within the cell attach themselves to the antigen and transport it to the surface of the

cell, where they "present" the antigen to *T* lymphocytes. These transport molecules are made by a group of genes called the major histocompatibility complex (MHC) and are therefore known as MHC molecules. Some MHC molecules, called class II MHC molecules, present antigens to helper *T* cells.

3.5 Monocytes

Maternal factor also play a role in the body's immune response. At birth, most of the immunoglobulin is present in maternal IgG. Because IgM, IgD, IgE and IgA don't cross the placenta, they are almost undetectable at birth. Although some IgA are provided in breast milk, these passively acquired antibodies can protect the newborn up to 18 months, but their response is usually short – live and of low affinity, these antibodies can also produce a negative response. If a child is exposed to the antibody for a particular antigen before being exposed to the antigen itself, then the child will produce a dampened response. Passively acquired maternal antibodies can suppress the antibody response to active immunisation. Similarly the response of *T* cells to vaccination differs in children compared to adults, and vaccines that induce Th1 responses in adults do not readily elicit these same responses in neonates. By 6 – 9 months after birth, a child's immune system begins to respond more strongly to glycoproteins. Not until 12 – 24 months of age is there a marked improvement in the body's response to polysaccharides. This can be the reason for the specific time frames found in vaccination schedules.

During adolescence, the human body undergoes several physical, physiological and immunological changes. These changes are started and mediated by different hormones. Depending on the sex, either testosterone or 17 – ß – oestradiol, act on male and female bodies accordingly, start acting at ages of 12 and 10 years. There is evidence that these steroids act directly not only on the primary and secondary sexual characteristics, but also have an effect on the development and regulation of the immune system. There is an increased risk in developing autoimmunity for pubescent and post pubescent females and males. There is also some evidence that cell surface receptors on B cells and macrophages may detect sex hormones in the system. The female sex hormone 17 – ß – oestradiol has been shown to regulate the level of immunological response. Similarly, some male androgens, like testosterone, seem to suppress the stress response to infection; but other androgens like DHEA have the opposite effect, as it increases the immune response instead of down playing it. As in females, the male sex hormones seem to have more control of the immune system during puberty and the time right after than in fully developed adults. Other than hormonal changes, physical changes like the involution of the

thymus during puberty will also affect the immunological response of the subject of patient.

4.0 CONCLUSION

The ability of the immune system to mount a response to diseases is dependent on many complex interactions between the components of the immune system and the antigens on the invading pathogens or disease – causing agents.

5.0 SUMMARY

In this unit, we have learnt that:

- The main components of the immune system are macrophages, lymphocytes, antigen receptors, antigen presenting cells and monocytes.

6.0 TUTOR-MARKED ASSIGNMENT

List the main components of the immune system and write briefly on each of them.

7.0 REFERENCES/FURTHER READING

Wikipedia, the free encyclopaedia in Encarta.

www.google.com

UNIT 3 IMMUNITY AND INFECTIOUS DISEASES

CONTENTS

1.0 INTRODUCTION

This unit discusses immunity and infectious diseases by exposing you to the principle and mechanism through which the body system fights against infections. The unit serves as a follow up to the previous unit 2 by explaining how the components of the immune system fight diseases in the body via immunity actions including phagocytosis, non – specific immunity actions such as the activities of killer cells involving both intracellular killing and nitric oxide – dependent killing.

2.0 OBJECTIVES

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

- recall the principles and mechanism whereby the body fights infections
- discuss the functions of killer cells and phagocytes as well as the processes of phagocytosis and intracellular killing.

3.0 MAIN CONTENT

3.1 Non – Specific Immunity Actions

The elements of the innate (non-specific) immune system include anatomical barriers, secreting molecules and cellular components. Among the mechanical anatomical barriers are the skin and internal epithelial layers, the movement of the intestines and the oscillation of broncho-pulmonary cilia. Associated with these protective surfaces are chemical and biological agents.

A. Anatomical Barriers to Infections

1. Mechanical Factors

The epithelial surfaces form a physical barrier that is very impermeable to most infectious agents. Thus, the skin acts as our first line of defense against invading organisms. The desquamation of skin epithelium also helps remove bacteria and other infectious agents that have adhered to the epithelial surfaces. Movement due to cilia or peristalsis helps to keep air passages and the gastrointestinal tract free from microorganisms. The flushing action of tears and saliva helps prevent infection of the eyes and mouth. The trapping affect of mucus that lines the respiratory and gastrointestinal tract helps protect the lungs and digestive systems from infection.

2. Chemical Factors

Fatty acids in sweat inhibit the growth of bacteria. Lysozvme and phospholipids found in tears, saliva and nasal secretions can breakdown the cell wall of bacteria and destabilise bacterial membranes. The low pH of sweat and gastric secretions prevents growth of bacteria. Defenses (low molecular weight proteins) found in the lung and gastrointestinal tract have antimicrobial activity. Surfactants in the lung act as opsonins (substances that promote phagocytosis of particles by phagocytic cells).

3. Biological Factors

The normal flora of the skin and in the gastrointestinal tract can prevent the colonisation of pathogenic bacteria by secreting toxic substances or by competing with pathogenic bacteria for nutrients or attachment to cell surfaces.

B. Humoral Barriers to Infection

The anatomical barriers are very effective in preventing colonisation of tissues by microorganisms. However, when there is damage to tissues, the anatomical barriers are breached and infection may occur. Once infectious agents have penetrated tissues, another innate defense mechanism comes into play, namely acute inflammation. Humoral factors play an important role in inflammation, which is characterised by edema and the recruitment of phagocytic cells. These humoral factors are found in serum or they are formed at the site of infection.

1. Complement System

The complement system is the major humoral non-specific defense mechanism (see complement chapter). Once activated complement can lead to increased vascular permeability, recruitment of phagocytic cells, and lysis and opsonization of bacteria.

2. Coagulation System

Depending on the severity of the tissue injury, the coagulation system may or may not be activated. Some products of the coagulation system can contribute to the non-specific defenses because of their ability to increase vascular permeability and act as chemotactic agents for phagocytic cells. In addition, some of the products of the coagulation system are directly antimicrobial. For example, beta-lysine, a protein produced by platelets during coagulation can lyses many Gram positive bacteria by acting as a cationic detergent.

3. **Lactoferrin and Transferring**
   By binding iron, an essential nutrient for bacteria, these proteins limit bacterial growth.
4. **Interferons**
   Interferons are proteins that can limit virus replication in cells.
5. **Lysozyme**
   Lysozyme breaks down the cell wall of bacteria.
6. **Interleukin**-1 - 11-1 induces fever and the production of acute phase proteins, some of which are antimicrobial because they can opsonize bacteria

C. Cellular Barriers to Infection

Part of the inflammatory response is the recruitment of polymorphonuclear eosinophiles and macrophages to sites of infection. These cells are the main line of defense in the non-specific immune system.

1. **Neutrophils**
   Polymorphonuclear cells are recruited to the site of infection where they phagocytose invading organisms and kill them intracellularly. In addition, PMNs contribute to collateral tissue damage that occurs during inflammation.
2. **Macrophages**
   Tissue macrophages and newly recruited monocytes which differentiate into macrophages also function in phagocytosis and intracellular killing of microorganisms. In addition, macrophages are capable of extracellular killing of infected or altered self target cells. Furthermore, macrophages contribute to tissue repair and act as antigen-presenting cells, which are required for the induction of specific immune responses.
3. **Natural Killer (NK) and Lymphokine Activated Killer (LAK) Cells**
   NK and LAK cells can nonspecifically kill virus infected and tumor cells. These cells are not part of the inflammatory response but they are important in

nonspecific immunity to viral infections and tumor surveillance.

4. Eosinophils

Eosinophils have proteins in granules that are effective in killing certain Parasites.

3.2 Phagocytosis and Intracellular Killing

A. Phagocytic Cells

1. Neutrophiles/Polymorphonuclear Cells (PMN)

PMNs are motile phagocytic cells that have lobed nuclei. They can be identified by their characteristic nucleus or by an antigen present on the cell surface called CD66. They contain two kinds of granules, the contents of which are involved in the antimicrobial properties of these cells. The primary or azitrophilic granules, which are abundant in young newly formed PMNs, contain cationic proteins and aefensins that can kill bacteria, proteolytic enzymes like elastase, and cathepsin G to breakdown proteins, lysozyme to break down bacterial cell walls, and characteristically, myeloperoxidase, which is involved in the generation of bacteriocidal compounds. The second type of granule found in more mature PMNs is the secondary or specific granule. These contain lysozyme, NADPH oxidase components, which are involved in the generation of toxic oxygen products, and characteristically lactoferrin, an iron chelating protein and B12-binding protein.

2. Monocytes/Macrophages

Macrophages are phagocytic cells that have a characteristic kidney-shaped nucleus. They can be identified morphologically or by the presence of the CD 14 cell surface marker. Unlike PMNs they do not contain granules but they have numerous lysosomes which have contents similar to the PNM granules.

B. Response of Phagocytes to Infection

Circulating PMNs and monocytes respond to danger (SOS) signals generated at the site of an infection. SOS signals include N- formyl - methionine containing peptides released by bacteria, clotting system peptides, complement products and cytokines released from tissue macrophages that have encountered bacteria in tissue. Some of the SOS signals stimulate endothelial cells near the site of the infection to express cell adhesion molecules such as ICAM-1 and selecting which bind to components on the surface of phagocyte cells and cause the phagocytes to adhere to the endothelium. Vasodilators produced at the site of infection cause

the junctions between endothelial cells to loosen and the phagocytes then cross the endothelial barrier by "squeezing" between the endothelial cells in a process called diapedesis. Once in the tissue spaces some of the SOS signals attract phagocytes to the infection site by chemotaxis (movement towards an increasing chemical gradient). The SOS signals also activate the phagocytes, which results in increased phagocytosis and intracellular killing of the invading organisms.

C. Initiation of Phagocytosis

Phagocytic cells have a variety of receptors on their cell membranes through which infectious agents bind to the cells. These include:

1. Fc Receptors

Bacteria with IgG antibody on their surface have the Fc region exposed and this part of the Ig molecule can bind to the receptor on phagocytes. Binding to the Fc receptor requires prior interaction of the antibody with an antigen. Binding of IgG-coated bacteria to Fc receptors results in enhanced phagocytosis and activation of the metabolic activity of phagocytes (respiratory burst).

2. Complement Receptors

Phagocytic cells have a receptor for the 3rd component of complement, C3b. Binding of C3b-coated bacteria to this receptor also results in enhanced phagocytosis and stimulation of the respiratory burst.

3. Scavenger Receptors

Scavenger receptors bind a wide variety of polyanions on bacterial surfaces resulting in phagocytosis of bacteria.

4. Toll-Like Receptors

Phagocytes have a variety of Toll-like receptors (pattern recognition receptors or PRRs) which recognise broad molecular patterns called PAMPs (pathogen associated molecular patterns) on infectious agents. Binding of infectious agents via Toll-like receptors results in phagocytosis and the release of inflammatory cytokines (IL-1,TNF-alpha and IL-6) by the phagocytes.

D. Phagocytosis

After attachment of a bacterium, the phagocyte begins to extend pseudopods around the bacterium. The pseudopods eventually surround the bacterium and engulf it, and the bacterium is enclosed in a phagosome. During phagocytosis, the granules or lysosomes of the phagocyte fuse with the phagosome and empty their contents. The result is a bacterium engulfed in a

phagolysosome which contains the contents of the granules or lysosomes.

E. Respiratory Burst and Intracellular killing

During phagocytosis there is an increase in glucose and oxygen consumption which is referred to as the respiratory burst. The consequence of the respiratory burst is that a number of oxygen-containing compounds are produced which kill the bacteria being phagocytosed. This is referred to as oxygen-dependent intracellular killing. In addition, bacteria can be killed by pre-formed substances released from granules or lysosomes when they fuse with the phagosome. This is referred to as oxygen-independent intracellular killing.

1. Oxygen-Dependent Myeloperoxidase Intracellular Killing

During phagocytosis glucose is metabolised via the pentose monophosphate shunt and NADPH is formed. Cytochrome B which was part of the specific granule combines with the plasma membrane NADPH oxidase and activates it. The activated NADPH oxidase uses oxygen to oxidise the NADPH. The result is the production of superoxide anion. Some of the superoxide anion is converted to H_2O_2 and singlet oxygen by superoxide dismutase. In addition, superoxide anion can react with H_2O_2 resulting in the formation of hydroxyl radical and more singlet oxygen. The result of all of these reactions is the production of the toxic oxygen compounds superoxide anion (O_2-X H_2O_3, singlet oxygen (O_2) and hydroxyl radical (OH-).

2. Detoxification Reactions

PMNs and macrophages have the means to protect themselves from the toxic oxygen intermediates. These reactions involve the dismutation of superoxide anion to hydrogen peroxide by superoxide dismutase and the conversion of hydrogen peroxide to water by catalase.

3. Oxygen-Independent Intracellular Killing

In addition to the oxygen-dependent mechanisms of killing, there are also oxygen-independent killing mechanisms in phagocytes: cationic proteins (cathepsin) released into the phagolysosome can damage bacterial membranes; lysozyme breaks down bacterial cell walls; lactoferrin chelate iron, which deprives bacteria of this required nutrient hydrolytic enzymes break down bacterial proteins. Thus, even patients who have defects in the oxygen-dependent killing pathways are able to kill bacteria. However, since the oxygen-dependent mechanisms are much more efficient in killing, patients with defects in these pathways are more susceptible and get more serious infections.

3.3 Nitric Oxide-Dependent Killing

Binding of bacteria to macrophages, particularly binding via Toll-like receptors, results in the production of TNF-alpha, which acts in an autocrine manner to induce the expression of the inducible nitric oxide synthetase gene (i-nos), resulting in the production of nitric oxide (NO). If the cell is also exposed to interferon gamma (IFN-gamma), additional nitric oxide will be produced. Nitric oxide released by the cell is toxic and can kill microorganism in the vicinity of the macrophage.

3.4 Non-Specific Killer Cells

Several different cells including NK and LAK cells, K cells, activated macrophages and eosinophils are capable of killing foreign and altered self target cells in a non-specific manner. These cells play an important role in the innate immune system.

A. NK and LAK Cells

Natural killer (NK) cells are also known as large granular lymphocytes (LGL) because they resemble lymphocytes in their morphology, except that they are slightly larger and have numerous granules. NK cells can be identified by the presence of CD56 and CD16 and a lack of CD3 cell surface markers. NK cells are capable of killing virus-infected and malignant target cells but they are relatively inefficient in doing so. However, upon exposure to IL-2 and IFN-gamma, NK cells become lymphokine-activated killer (LAK) cells, which are capable of killing malignant cells. Continued exposure to IL-2 and IFN-gamma enables the LAK cells to kill transformed as well as malignant cells. LAK cell therapy is one approach for the treatment of malignancies.

How do NK and LAK cells distinguish a normal cell from a virus-infected or malignant cell? NK and LAK cells have two kinds of receptors on their surface - a killer activating receptor (KAR) and a killer inhibiting receptor (KIR). When the KAR encounters its ligand, a killer activating ligand (KAL) on the target cell, the NK or LAK cells are capable of killing the target. However, if the KIR also binds to its ligand, then killing is inhibited even if KAR binds to KAL. The ligands for KIR are MHC-class I molecules. Thus, if a target cell expresses class I MHC molecules, it will not be killed by NK or LAK cells even if the target also has a KAL which could bind to KAR. Normal cells constitutively express MHC class I molecules on their surface, however, virus infected and malignant cells down regulate expression of class I MHC. Thus, NK and LAK cells selectively kill virus-infected and malignant cells while sparing normal cells.

B. K Cells

Killer (K) cells are not morphologically distinct type of cell. Rather a K cell is any cell that mediates antibody-dependent cellular cytotoxicity (ADCC). In ADCC antibody acts as a link to bring the K cell and the target cell together to allow killing to occur. K cells have on their surface an Fc receptor for antibody and thus they can recognise, bind and kill target cells coated with antibody. Killer cells which have Fc receptors include NK, LAK, and macrophages which have an Fc receptor for IgG antibodies and eosinophils which have an Fc receptor for IgE antibodies.

All components of the non-specific immune system are modulated by products of the specific immune system, such as interleukins, interferon-gamma, antibody, etc.

4.0 CONCLUSION

Immunity and infections or diseases are jolly friends and they are closely related in their activities. Body immunity via the immune system fights diseases and agents of infection using various methods and mechanisms that have been extensively discussed in this unit.

5.0 SUMMARY

In this unit, we have learnt that:

- diseases or infections stimulate the action of immunity or its production if it is not there already
- the purpose of immunity in the body is to help resist disease or combat infectious agents that gain access to the body
- immunity actions include phagocytosis, intracellular killing by killer cells and nitric oxide- dependent killing.

6.0 TUTOR-MARKED ASSIGNMENT

i. What is immunity?
ii. Explain methods and actions employed by this system to perform its functions.

7.0 REFERENCES/FURTHER READING

Wikipedia, the free encyclopaedia in Encarta.

www.google.com

UNIT 4 TESTS IN CLINICAL IMMUNOLOGY

CONTENTS

1.0 INTRODUCTION

This very unit is the aspect of this course that is concerned with available tests in clinical immunology used to establish and confirm the issue of whether someone has immunity or not. It also helps to probe into the causes or reason for whatever situation is detected using different tests and methods. Different tests and methods employed are also discussed to distinguish or differentiate them from one another. Issues of defective immunity and tissue deposition are also given priority.

2.0 OBJECTIVES

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

- explain why tests are carried out in clinical immunology.
- establish the availability or non – availability of immunity and possible reason(s) for the outcome of each test.

3.0 MAIN CONTENT

3.1 Why Test Patients?

Immunological investigations of patients are largely carried out on the blood, but they may also involve analysis of the cerebrospinal fluid, urine and other tissue fluids. The investigations are directed at answering any of the following sets of questions; which can only be posed after an appropriate, clinical history and examination.

1. Is the patient making specific anti-bodies to any particular infective agent (or a specific antigen derived from it)? If so, it is possible, and in some cases highly probable, that the patient's symptoms are caused by the agent.
2. Is the patient making antibodies to some other substance (non-infective) in the environment, e.g., pollen grains, dust, milk, drugs, etc? If so, are they the sort of antibodies likely to cause allergic symptoms?
3. Is the patient making unusual antibodies to self-constituents and so causing a so-called "auto immune" disease?
4. Is the patient able to make antibodies at all? Are the symptoms due to a failure of the immune system to work properly?
5. Is there direct evidence of microorganisms or their products in the patient's blood or tissues?
6. What is the concentration of the various normal plasma constituents (proteins, peptides, hormones, etc.), which can be measured by immunochemical techniques? Characteristic changes in levels of these constituents are diagnostic in many areas of medicine. For example, the immunological assay of thyroid hormone indicates when there is hypo- or hyper-function of that gland.
7. Are there abnormal proteins or hormones circulating in the plasma or urine? The former are seen in some malignant disorders of cells of the immune system; and the commonly used pregnancy test detects a special hormone present only in the urine of pregnant women.
8. Is there evidence of deposition at the site of tissue damage of immunological proteins, or of infiltration with immunologically active cells?
9. Is the state of cell-mediated immunity normal?
10. Are there special types of abnormal cells (e.g. cancer cells) or their products circulating in the blood?

3.2 Antigen - Antibody Reactions

In providing the answers to these questions, the large majority of the tests employed exploit the antigen-antibody reaction, and the various ways it can be detected. It is only in answers to these questions that some of the tests rely on the special characteristics of living cells (blood lymphocytes, monocytes and polymorphonuclear leucocytes) to respond to specific agents in a particular manner. It is obvious that in employing antigen-antibody reactions for experimental or clinical purposes, one must use either known antigen or a known antibody. For example, to detect the presence of antigen X in the blood or tissues, or to measure the serum concentration of X, one must have

a known and reliable source of anti-X. These reagents are usually prepared in the laboratory or in domestic animals. Conversely, if one wants to know whether the patient is making anti-Y antibodies, one must have a known and reliable source of the antigen Y.

The answers to questions 1-4 above employ known antigens to detect the patient's antibodies in serum, plasma or tissue fluids.

An example of this type of test is the Widal test used in the diagnosis of typhoid fever. This is an *agglutination* reaction, in which the homogeneous opalescent appearance of a suspension of killed typhoid organisms is modified by antibody, which causes agglutination or clumping of the bacilli and disruption of the suspension. The antibodies, which react with surface antigens of the microorganisms, arise as a result of natural infection or immunisation. The strength of most human antibodies is tested by diluting out the serum and noting the highest dilution at which the reaction can be detected.

In the Widal test, an agglutination reaction which is positive only up to a dilution of 1 in 20 is much weaker than one which can still be detected at a serum dilution of 1 in 500. The strength of the reactions against different forms of the typhoid bacillus provides the diagnostic information on whether or not the patient is likely to have the infection. The patient's antibody response may take time to develop, so that a rising titre (concentration) of antibodies to a specific organism during the course of an illness is usually more positively diagnostic than a single estimation.

If the antigen is available in a soluble-form, then the test may exploit the fact that the reactions between solutions of antigen and antibody can result in the formation of an insoluble *precipitate.* Such precipitates are often best visualised in transparent gels, such as agar gel, derived from seaweed. If holes are made in the gel, and the solutions of antigen and antibody are placed in adjacent holes, then the precipitate occurs as a visible line in between the two holes. This reaction is concentration-dependent, and will not be seen if either antigen or antibody is present in excess, or indeed if either is present in quantities less than 1 mg per litre. An example of the clinical use of the precipitation test is to detect antibodies to soluble antigens from birds, which are found in the sera of bird fanciers who get a special type of chronic chest disease.

3.3 Radio-Isotope Tests

Antibodies which are clinically significant are often present in extremely small amounts, and more sensitive methods of detection are needed. For example, the antibodies which are responsible for the acute allergic symptoms of hay fever and asthma belong to a special class of antibodies called immunoglobulin E or IgE. They are present in very small amounts in the serum, indeed all the IgE antibodies together in a normal person's serum seldom total more than one-fifth of a milligramme in a litre. These specific IgE antibodies have to be detected by a test in which the antigen, or some reagent of the test, is labeled with a radioactive isotope, such as Iodine125. The commonly employed test was developed by the Swedish firm Pharmacia, and has been called the Radio Allergo-Sorbent Test (RAST).

In this test, the antigen (or allergen) is chemically coated on to small filter-paper discs. These are mixed with the patient's serum to allow any specific IgE antibodies to that particular antigen to become firmly bound to the disc. The disc is washed and then exposed to a solution of a sheep or goat antiserum to human IgE, in which the antibody molecules have been labelled with Iodine125. This antibody binds to any human IgE which was fixed in the first stage. The level of radio-activity remaining on the disc after further washing indicates the strength of the specific IgE antibodies.

This principle of using a “second antibody” raised in heterologous species against human immunoglubulin is widely used in many procedures to detect human antibodies to known antigens. It is the basis of the *indirect immunofluorescent test*, which is frequently used to detect antibodies to “auto-antigens”. In some instances, the antibodies indicate that a particular organ or tissue is being damaged by an “auto-immune” process, while in others, the antibodies act as diagnostic hallmarks of a particular condition on an empirical basis.

The test uses histological sections of human or animal tissues mounted on microscope slides. The patient's serum is added to the slide, and any anti-tissue antibodies bind to the relevant antigens. Most tissues, of course, consist of a multitude of different structures, and are antigenically very complex. However, this procedure allows the antibodies to “seek out” and bind to only those antigens with which they specifically react.

After washing of the tissue to remove excess serum, the section is exposed to anti-human immunoglobulin, in this instance tagged with fluorescent molecules. These bind to any human antibodies fixed to the tissues in the first stage and allow them to be visualised through

the fluorescent microscope. Some of the commonest antibodies to be detected in this way are the antibodies to the constituents of the nuclei within tissue cells (anti-nuclear antibodies). These are found in the sera of patients with the condition of systemic lupus erythematosus, an auto-immune disease in which the antibodies that develop to nuclear constituents form antigen-antibody complexes and produce damage in many organs, particularly the skin, joints and kidneys. The procedure has also been used to demonstrate anti-bodies to antigens of the thyroid gland in patients with various disorders of that organ. And indeed many types of endocrine gland disorders arise as a result of an "auto-immune" process, and the indirect immunofluorescent test can be used to detect the auto-antibodies which indicate this process.

3.4 Defective Immunity

In patients who experience recurrent infections and seem to have little resistance, it may be necessary to ascertain whether the patient is capable of making antibodies at all. All normal sera contain a certain level of antibodies to commonly occurring micro-organisms, or to such agents as tetanus toxoid with which most individuals are vaccinated as children. Patients who develop a failure to make antibodies usually cease to make any antibody protein (immunoglobulins), and the measurement of their total serum immunoglobulin reveal very low levels (a condition also known as hypo-gammaglobulinaemia).

The measurement of these large molecular weight proteins (and indeed a considerable number of other plasma proteins) is by means of hetero-specific antisera. These provide reagents for the immunochemical *quantitation* of the proteins by some modification or other of the precipitate reaction. If the test serum is added to a constant quantity of a specific antiserum, the amount of precipitate formed is directly proportional to the quantity of antigen present. Direct measurement of the precipitate in agar gel is one of the most frequently used methods for this purpose, but it can also be quantitated with great sensitivity and rapidity by measuring the light scattering of the precipitate in a nephelometer, or its absorbance in a spectrophotometer. These techniques are widely used in clinical biochemistry and immunology departments. The patterns of change in levels of the different plasma proteins are of diagnostic importance in many diseases.

Where the plasma constituent is present in very small amounts, then more sensitive procedures are used. This is the case with many of the *hormones* and small *peplides* of considerable biological significance, such as insulin, thyroid hormones, etc. Some form of nidio-inmiunoassay is usually employed, in which a small amount of the particular substance is tagged with radioactive Iodine. The binding of the radioactive molecules by a specific antiserum is quantitatively inhibited by free unlabelled molecules present in the patient's serum. The same procedures, either precipitation by a specific antiserum or radio-isotope labelling (depending on the quantity involved) can be used to detect substances not normally present in serum. These include substances such as alpha-foeto-protein, a plasma protein present during foetal life which disappears soon after delivery but may occur again in the serum of patients with certain types of liver cancer. Other abnormal proteins are products of microbial infection, such as hepatitis B surface antigen, the product of a hepatitis B infection.

3.5 Tissue Deposition

Deposition of antibodies at abnormal sites, producing immunologic mediated damage, can be detected by direct immunofluorescent examination of tissue biopsies. The sections of the tissue are exposed to fluorescein-labelled anti-human immunoglobulins, and the distribution of fluorescence is noted. This is particularly useful in assisting the microscopic diagnosis of certain skin and kidney diseases.

The same principle, using a conjugated antiserum to specific micro-organisms, can be used to detect the microorganisms in tissues or smears from patients. This permits rapid microbiological diagnosis without the need to culture the organisms, which may take 24 hours or longer.

Tests of cell mediated immunity are less frequently required in clinical immunology at the present time, although they are of great value in research into some of the abnormal mechanisms of disease. Their main use in the clinical field is for the proper diagnosis and management of certain patients, usually children, who show a failure of the immune system to work properly. The tests begin by isolation of the patient’s lymphocytes from the peripheral blood. Lymphocytes are the body cells responsible for initiating the great variety of immune response of which each individual is capable. They have special surface structures referred to as “markers”, and the different types of marker can be detected on the cells by appropriate specific antisera, usually by the technique of fluoresce in – tagging of the antibody molecules. The number and distribution of the markers may indicate whether or not there is a failure

of lymphocyte – dependant immunity. In addition, functional tests of lymphocytes can be done in which the isolated cells are cultured for a number of days in the presence of certain substance called “mitogens “. The most commonly used of these is derived from the jack bean and is called phytohaemaglutinin (PHA). Normal lymphocytes enlarge and divide in the presence of PHA, undergoing a process called “blast transformation“. Functionally defective cells do not do this, and this ability can be correlated with the individual’s ability to develop a proper immune response.

Again, by using antisera to the antigens present on abnormal cells, such as cancer cells, these cells or their products can be detected in the blood and tissues. For instance, certain types of leukaemic cells can now be detected in blood smears and bone marrow, while a material called carcinoembryonic antigen (CEA) can often be found in the plasma of patients with cancer of the bowel. The precise method used depends on the nature and concentration of the antigens concerned, but most of these tests rely on the greater sensitivity of the immunofluorescent or radioimmunoassay procedures.

This has been a brief review of the range of immunological tests employed diagnostically in clinical medicine, a range increasing all the time. Newer techniques have now been developed which employ different substances to label antibody molecules. They include enzymes which are efficient at very low concentrations in acting on special substrates to release coloured products, which can be seen directly or measured by a spectrophotometer. Another group of substances being evaluated as antibody “labels” are lucinogens, capable of generating light energy in the presence of appropriate co – factors. These add to the ways and increase the sensitivity and the ease by which antigen – antibody reactions can be measured. They are likely to be particularly important in circumstances where facilities for radio – active monitoring or immunofluorescence are not available. The methods of producing specific antibodies for diagnostic purposes have been improved, and a unique process called “monoclonal antibody” production has been developed. This provides antibodies of extremely high specificity in potentially unlimited quantities, which are used in clinical laboratory medicine.

It is to be expected that these developments will continue, and it is to be hoped that their judicious use will enable immunology and the immunologist to contribute to the health and well – being of mankind.

4.0 CONCLUSION

Test in clinical immunology began with a consideration of the factors responsible for immunity, to reinfection following a specific infectious disease. It was found that the infection resulted in production and secretion into the circulation of special protein molecules called antibodies. These were able to neutralise the toxins of the germs causing the infections, cause their elimination and assist the body to recover from the infection and prevent reinfection.

5.0 SUMMARY

In this unit, we have learnt the following:

- reasons for instituting clinical immunological tests were examined and ten of such mentioned and discussed
- issue of antigen – antibody reactions as they affect tests in clinical immunology was also examined
- the impact of radio–isotope tests as involved in clinical immunology also looked into
- the aspects of defective immunity as well as tissue deposition were also examined.

6.0 TUTOR-MARKED ASSIGNMENT

Clinical immunology activities, why test patients?

7.0 REFERENCE/FURTHER READING

Thompson, R. A. (1983). Current Test in Clinical Immunology. *Magazine of the World Health Organisation.* Nov. 1983.Geneva.WHO.

MODULE 3 IMMUNE RESPONSE TO INFECTIONS

UNIT 1 CELL-MEDIATED IMMUNE RESPONSE

CONTENTS

1.0 INTRODUCTION

In this unit, discussions are centered on the issue of immune response to diseases through cell-mediated actions. Remember in the earlier modules, particularly in module 2, mention was made of killer cells as well as Antigen presenting cells as being actively involved in phargocytosis, cell-mediated response is a follow up to all those actions.

2.0 OBJECTIVES

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

- explain immune response to infection
- discuss the different ways in which immune response to infection can be carried out.

3.0 MAIN CONTENT

3.1 Central Role of the Th Cells

After Th cells recognise specific antigen presented by an APC, they can initiate several key immune processes. These include:

- selection of appropriate effect or mechanisms (e.g., B cell activation or Tc generation)
- induction of proliferation of appropriate effect or cells and
- enhancement of the functional activities of other cells (e.g., granulocytes, macrophages, NK cells).

There are three subpopulations of Th cells, Th0, Th1 and Th2 cells. When naive Th0 cells encounters antigen in secondary lymphoid tissues, they are capable of differentiating into inflammatory Th1 cells or a helper Th2 cells, which are distinguished by the cytokines they produce. Whether a Th0 cells becomes a Th1 or a Th2 cell depends upon the cytokines in the environment, which is influenced by antigen. For example some antigens stimulate IL-4 production which favours the generation of Th2 cells while other antigens stimulate IL-12 production, which favours the generation of Th1 cells. Th1 and Th2 cells affect different cells and influence the type of an immune response. Cytokines produced by Th1 cells activate macrophages and participate in the generation of Tc cells, resulting in a cell-mediated immune response. In contrast cytokines produced by Th2 cells help to activate *B* cells, resulting in antibody production, in addition, Th2 cytokines also activate granulocytes. Equally important, each subpopulation can exert inhibitory influences on the other. IFN-y produced by Th1 cells inhibits proliferation of Th2 cells and II-10 produced by Th2 cells inhibits production of IFN-y by Th1 cells. In addition, although not shown, IL-4 inhibits production of Th1 cells. Thus, the immune response is directed to the type of response that is required to deal with the pathogen encountered - cell-mediated responses for intracellular pathogens or antibody responses for extracellular pathogens.

3.2 Cell-Cell Interactions in Antibody Responses to Exogenous T-Dependent Antigens

3.2.1 Hapten-Carrier Model

Historically, one of the major findings in immunology was that both T cells and B cells were required for antibody production to a complex protein. A major contribution to our understanding of this process came from studies on the formation of anti-hapten antibodies. Studies with hapten-carrier conjugates established that: 1) Th2 cells recognised the carrier determinants and B cells recognised haptenic determinants; 2) interactions between hapten-specific B cells and carrier-specific Th cells was self MHC restricted; and 3) B cells can function both in antigen recognition and in antigen presentation. B cells occupy a unique position in immune responses because they express immunoglobulin (Ig) and class II MHC molecules on their cell surface. They therefore are capable of producing antibody having the same specificity as that expressed by their immunoglobulin receptor; in addition they can function as an antigen presenting cell. In terms of the hapten-carrier conjugate model, the mechanism is thought to be the following: the hapten is recognised by the Ig receptor, the hapten-carrier is brought into the B cell, processed, and peptide fragments of the carrier protein are presented to a helper T cell. Activation of the T cell results in the production of cytokines that enable the hapten-specific B cell to become activated to produce soluble anti-hapten antibodies.

Note that there are multiple signals delivered to the B cells in this model of Th2 cell-B cell interaction. As was the case for activation of T cells where the signal derived from the TCR recognition of a peptide-MHC molecule was by itself insufficient for T cell activation, so too for the B cell. Binding of an antigen to the immunoglobulin receptor delivers one signal to the B cell, but that is insufficient. Second signals delivered by co-stimulatory molecules are required; the most important of these is CD40L on the T cell.

3.2.2 Primary Antibody Response

B cells are not the best antigen presenting cell in a primary antibody response; dendritic cells or macrophages are more efficient. Nevertheless, with some minor modifications the hapten-carrier model of cell-cell interactions described above also applies to interactions in a primary antibody response.

In a primary response, the Th2 cell first encounters antigen presented by dendritic cells or macrophages. The "primed" Th2 cell can then interact with B cells that have encountered antigen and are presenting antigenic peptides in association with class II MHC molecules. The B cells still requires two signals for activation - one signal is the binding of antigen to the surface Ig and the second signal comes from CD40/CD40 ligand engagement during Th2/B cell-cell interaction. In addition, cytokines produced by the Th2 cell help B cells proliferate and differentiate into antibody secreting plasma cell.

3.2.3 Secondary Antibody Response

As a consequence of a primary response, many memory T and B cells are produced. Memory B cells have a high affinity Ig receptor (due to affinity maturation), which allows them to bind and present antigen at much lower concentrations than that required for macrophages or dendritic cells. In addition, memory T cells are more easily activated than naive T cells. Thus, B/Th cell interactions are sufficient to generate secondary antibody responses. It is not necessary (although it can occur) to “prime” memory Th cells with antigen presented by dendritic cells or macrophages.

3.2.4 Class Switching

Cytokines produced by activated Th2 cells not only stimulate proliferation and differentiation of B cells, they also help regulate the class of antibody produced. Different cytokines influence the switch to different classes of antibodies with different effort functions. In this way the antibody response is tailored to suit the pathogen encountered (e.g. Ig E antibodies for parasitic worm infections).

3.3 Cell-Cell Interactions in Antibody Responses to Exogenous T-Independent Antigens

Antibody responses to T-independent antigens do not require cell-cell interactions. The polymeric nature of these antigens allows for cross-linking of antigen receptors on B cells resulting in activation. No secondary responses, affinity maturation or class switching occurs. Responses to T-independent antigens are due to the activation of a subpopulation of B cells called CD5+B cells (also called B1 cells), which distinguishes them from conventional B cells that are CD5- (also called B2 cells).

CD5+ (Bl) Cells

CD5+ B cells are the first B cells to appear in ontogeny. They express surface IgM but little or no IgD and they produce primarily IgM antibodies from minimally somatically mutated germ line genes. Antibodies produced by these cells are of low affinity and are often polyreactive (bind multiple antigens). Most of the IgM in serum is derived from CD5+ B cells. CD5+ B cells do not give rise to memory cells. An important characteristic of these cells is that they are self-renewing, unlike conventional B cells which must be replaced from the bone marrow. CD5+ B cells are found in peripheral tissues and are the predominant B cell in the peritoneal cavity; B1 cells are a major defense against many bacterial pathogens that characteristically have polysaccharides in their cell walls. The importance of these cells in immunity is illustrated by the fact that many individuals with T cell defects are still able to resist many bacterial pathogens.

3.4 Cell-Cell Interactions in Cell-Mediated Immunity (Generation of Tc Cells in Response to Endogenous Antigens in the Cytosol)

Cytotoxic T lymphocytes are not fully mature when they exit the thymus. They have a functional TCR that recognises antigen, but they cannot lyse a target cell. They must differentiate into fully functional effector Tc cells.

Cytotoxic cells differentiate from a “pre-CTL” in response to two signals:

Specific antigen associated with class I MHC, on a stimulator cell
Cytokines produced by Th1 cells, especially IL-2, and IFN-gamma.

A. Features of CTL-Mediated Lysis

1. CTL killing is antigen-specific. To be killed by a CTL, the target cell must bear the same class I MHC-associated antigen that triggered pre-CTL differentiation.
2. CTL killing requires cell contact. CTL are triggered to kill when they recognise the target antigen associated with a cell surface MHC molecule. Adjacent cells lacking the appropriate target MHC-antigen are not affected.
3. CTLs are not injured when they lyse target cells. Each CTL is capable of killing sequentially numerous target cells.

B. Mechanisms of CTL-Mediated Killing

CTLs utilise several mechanisms to kill target cells, some of which require direct cell-cell contact and others that result from the production of certain cytokines. In all cases, the death of the target cells is a result of apoptosis.

1. Fas- and TNF-Mediated Killing

Once generated CTLs express Fas ligand on their surface, which binds to Fas receptors on target cells. In addition, TNF-a secreted by CTLscan bind to TNF receptors on target cells. The Fas and TNF receptors are a closely related family of receptors, which when they encounter their ligands, for trimers of the receptors. These receptors also contain death domains in the cytoplasmic portion of the receptor, which after tirmerization can activate caspases that induce apoptosis in the target cell.

2. **Granule-Mediated Killing**
   Fully differentiated CTLs have numerous granules that contain perforin and granzymes. Upon contact with target cells, perforin is released and it polymerizes to form channels in the target cell membrane. Granzymes, which are serine proteases, enter the target cell through the channels and activate caspases and nucleases in the target cell resulting in apoptosis.

3.5 Cell-Cell Interactions in Cell-Mediated Immunity (Activation of Macrophages in Response to Endogenous Antigens in Vesicles)

Macrophages play a central role in the immune system, macrophages are involved in:

- initial defense as part of the innate immune system
- antigen presentation to ThI cells
- various effector functions *(e.g.,* cytokine production, bactericidal and tumoricidal activities). Indeed macrophages play an important role not only in immunity but also in reorganisation of tissues. However, because of their potent activities, macrophage can also do damage to tissues.

Many of these macrophage functions can only be performed by activated macrophages. Macrophage activation can be defined as quantitative alterations in the expression of various gene products that enable the activated macrophage to perform some function that cannot be performed by the resting macrophage.

Macrophage activation is an important function of Thl cells. When Thl cells get activated by an APC such as a macrophage, they releases IFN-y, which is one of the two signals required to activate a macrophage. Lipopolysaccharide (LPS) from bacteria or TNF-α produced by macrophages exposed to bacterial products deliver the second signal.

Effects or mechanisms employed by macrophages include the production of:

- TNF-α, which can induce apoptosis
- Nitric oxide and other reactive nitrogen intermediates
- Reactive oxygen intermediates
- Cationic proteins and hydrolytic enzymes; antibody dependent cellular cytotoxicity (ADCC).

Macrophage activation by Thl cells is very important in protection against many different pathogens for example, *Pneumocystis carimii*, an extracellular pathogen, is controlled in normal individuals by activated macrophages; it is, however, a common cause of death in AIDS patients because they are deficient in Th1 cells. Similarly, Mycobacterium tuberculosis, an intracellular pathogen that resides in vesicles, is not efficiently killed by macrophages unless they are activated; hence this infection is a problem in AIDS patients.

3.6 Cell-Cell Interactions in Cell-Mediated Immunity (Activation of NK Cells)

Cytokines produced by activated Th1 cells, particularly II-2 and IFN-y, also activate NK cells to become lymphokine activated killer cells (LAK cells). LAK cells are able to kill virus infected and tumor cells in a non-MHC-restricted manner. Indeed, susceptibility of target cells to killing by NK and LAK cells is inversely proportional to the expression of MHC class1 molecule. The effector mechanisms used by NK and LAK cells to kill target cells is similar to those used by CTLs (e.g., perform and granzymes). NK and LAK cells are also able to kill antibody coated target cells by ADCC.

4.0 CONCLUSION

The cell- mediated immune response involves a complex series of events after antigens enter the body. Helper T cells are required alongside macrophages to bind the presented antigen thereby become activated to divide and secrete interleukin. Cell – mediated immune respond also assist in effective elimination of cells infected in the system in which cells destroyed other cells become active. Cell – mediated immune response resist invaders that reproduce within the body cells, such as viruses and mutated cells as in cancers.

5.0 SUMMARY

In this unit, we have learnt the following:

- Cell – mediated immune response to infection or diseases can be in the following ways or forms which include via: central role of the Th cells and cell – cell interaction.
- Hapten carrier model
- Primary antibody response
- Secondary antibody response
- Class switching.

6.0 TUTOR-MARKED ASSIGNMENT

i. Define and classify immunity as much as you can. What do you understand by immune response to infections?
ii. Explain ways by which immune response to infection can be carried out?

7.0 REFERENCE/FURTHER READING

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UNIT 2 HYPERSENSITIVITY REACTIONS

CONTENTS

1.0 INTRODUCTION

In continuation of the discussion of immune response to infections, this unit is focused on hypersensitivity reaction which according to Martin (2003) is a condition whereby the body system is prone to respond abnormally to the presence of a particular antigen which may cause a variety of tissue reactions ranging from serum sickness to an allergy such as hay fever or, at the severest to anaphylaxis. Types I, II, III and IV of hypersensitivity are also discussed in this unit for ease of understanding of the subject matter.

2.0 OBJECTIVES

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

- explain hypersensitivity reaction in immune response to infections or diseases.

3.0 MAIN CONTENT

3.1 Hypersensitivity Reactions

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.

3.1.1 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 (allergens). IgE has very high affinity for its receptor on mast cells and basophils. A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances. Cross-linking of IgE Fc-receptor is important in mast cell triggering. Mast cell degranulation is preceded by increased Ca++ influx, which is crucial process cytoplasmic Ca++ also promote degranulation, whereas, agents which deplete cytoplasmic Ca++ deqranulation.

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

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 eosinophiis and neutrophils, respectivety, which release various hydrolytic enzymes that cause necrosis. Eosinophils may also control the local reaction by releasing arylsulphatase, histaminases, phospholipase-D and prostaglandin-E, although this role of eosonophils 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. Conversely, agents which decrease cAMP or stimulate cGMP aggravate these allergic conditions.

Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests measurement of total IgE and specific IgE antibodies against the suspected allergens. 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 antihistamines which 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 sensitization.

Hyposensitization (immunotherapy or desensitization) 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 correction between appearance IgG (blocking) antibodies and relief from symptoms. Suppressor T cells that specifically inhibit IgE antibodies may play a role.

3.1.2 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 is minutes to hours. Type II hypersensitivity to primary mediated by antibodies of the IgM or IgG classes and complement. Phagocytes and K cells may also play a role (ADCC).

The lesion contains antibody, complement and neutrophils. Diagnostic tests include detection of circulating antibody against 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 (renal and lung basement membrane) and pemphigus (skin intercellular protein, desmosome) Treatment involves anti-inflammatory and immunosuppressive agents.

3.1.3 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., aspergiHosis), 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. Primary components are soluble immune complexes and complement (C3a, 4a and 5a). The damage is caused by platelets and neutrophils. The lesion contains primarily neutrophils and deposits of immune complexes and complement macrophages infiltrating in later stages may 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 Ig and complement by immunofluorescence. 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 (nephetometry), binding of C1q and Raji cell test are utilised to detect immune complexes. Treatment includes anti-inflammatory agents.

3.1.4 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 which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterised by induration and erythema.

Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison ivy, chemicals, heavy metals, etc.) in which the lesions are more popular. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation.

Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. Cytotoxic T cells (Tc) cause direct damage whereas helper T (TH1) cells secrete cytokines which activate cytotoxic T cells, recruit and activate monocytes

plus macrophages, which cause the bulk of the damage. The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.

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

Diagnostic tests in vivo include delayed cutaneous reaction (e.g. Montoux test) 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.

4.0 CONCLUSION

Hypersensitivity reactions are among the common immune responses to infections, disease or even invaders. The four known types of hypersensitivity reaction can occur at different times or occasion in response to changes happening to the body immune system.

5.0 SUMMARY

In this unit, we have learnt that:

- Hypersensitivity refer 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.
- Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

6.0 TUTOR-MARKED ASSIGNMENT

Explain hypersensitivity reactions in relation to immunity and discuss the four different types of these reactions?

7.0 REFERENCES/FURTHER READING

Brooker, C. (2000). Mosby Nurses Pocket Dictionary (31st ed.). London:Harcourt Limited.

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UNIT 3 IMMUNODEFICIENCY

CONTENTS

1.0 INTRODUCTION

Immunodeficiency is a deficiency in the immune response. And according to Oxford mini dictionary for Nurses, this can be acquired, that is the condition, as in AIDS. There is other means by which one can become immunodeficient which can be as a result of aging or due to immunological changes. Therefore immunodeficiency can be primary or secondary in nature.

2.0 OBJECTIVES

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

- explain clearly that immunodeficiency is not only due to HIV/AIDS infection but can be as a result of aging or even immunological changes.

3.0 MAIN CONTENT

3.1 Immunodeficiencies

Immunodeficiency is the failure of the immune system to protect against disease or malignancy. Primary immunodeficiency is caused by genetic or developmental defects in the immune system. These defects are present at birth but may show up later on in life. Secondary or acquired immunodeficiency is the loss of immune function as a result of exposure to disease agents, environmental factors, immunosuppression, or aging.

3.2 Secondary (Acquired) Immunodeficiencies

Immunodeficiencies Associated with Infections

Bacterial, viral, protozoan, helminthic and fungal infections may lead to B cell, T cell, PMN and macrophage deficiencies. Most prominent among these is acquired immunodeficiency syndrome (AIDS). Secondary immunodeficiencies are also seen in malignancies.

Immunologic Abnormalities in AIDS

All acquired immunodeficiencies have been outdone by AIDS that is caused by Human Immunodeficiency Virus (HIV)-1. This virus was first discovered in 1981 and the patients exhibited fungal infections with opportunistic organisms such as *Pneumocystis carinii* and in other cases, with a skin tumor known as -Kaposi's sarcoma. There are two major types of HIV: HIV-1 and 2, the former being the strain frequently found in North America. HIV is spread through sexual intercourse, infected blood and body fluids as well as from mother to offspring. HIV, which was discovered in 1983, is a retrovirus with RNA that is reverse transcribed to DNA by reverse transciptase (RT) following entry into the cell. The DNA is integrated into the cell genome as a provirus that is replicated along with the cell. HIV-1 does not replicate in most other animals but infects chimpanzees although it does not induce AIDS in them. Severe combined immunodeficient mice (SCID) reconstituted with human lymphocytes can be infected with HIV-1. The HIV-1 virion consists of a viral envelope made up of the outer lipid bilayer of the host cell in which are embedded glycoproteins composed of the transmembrane gp41 along with the associated gp120. The gp120 binds the CD4 expressed on host cells. Within the viral envelope is the viral core or nucleocapsid consisting of a layer of matrix protein composed of p17 and an inner capsid made up of p24. The viral genome consists of two single stranded RNA associated wih RT molecules as well as other enzymes including a protease and an integrase.

Replication Cycle and Targets of Therapy

The virus attaches to the CD4 molecule on Th cells, monocytes and dendritic cells through the gp120 of HIV. For HIV infection, a co-receptor is required. The co-receptor is a chemokine receptor such as CXCR4 or CCR5. CCR5, expressed predominantly on macrophages, and CXCR4 on CD4+T cells serve as co-receptors for HIV infection. After the fusion of HIV envelope and the host membrane, the nucleocapsid enters the cell. The RT synthesises viral DNA which is transported to the nucleus where it integrates with the cell DNA in the form of a provirus. The provirus can remain associated with impaired T-cell functions. Most chemotherapeutic agents used for treatment of malignancies are also immunosuppressive.

Other conditions in which secondary immunodeficiencies occur are sickle cell anemia, diabetes mellitus, protein calorie malnutrition, burns, alcoholic cirrhosis, rheumatoid arthritis, renal malfunction, etc.

Primary immunodeficiencies are inherited defects of the immune system. These defects may be in the specific or non-specific immune mechanisms. They are classified on the basis of the site of lesion in the developmental or differentiation pathway of the immune system.

Individuals with immunodeficiencies are susceptible to a variety of infections and the type of infection depends on the nature of immunodeficiency.

Developmental Defects in Primary Immunodeficiencies

Specific Immune System

There are variety of immunodeficiencies which result from defects in stem cell differentiation and may involve T-cells, B-cells, and/or immunoglobulins of different classes and subclasses.

A defect in the early hematopoiesis which involves stem cells results in reticular dysgenesis that leads to general immune defects and subsequent susceptibility to infections. This condition is often fatal but very rare.

Lymphoid Lineage Immunodeficiency

If the lymphoid progenitor cells are defective, then both the T and B cell lineages are affected and result in the Severe Combined Immunodeficiency (SCID). Infants suffer from recurrent infections especially by opportunistic microorganisms (bacterial, viral, mycotic and protozoan infections).

In about 50% of SCID patients, the immunodeficiency is x-linked whereas in the other half, the deficiency is autosomal. Both are characterised by an absence of T cell and B cell immunity and absence (or very low numbers) of circulating T and B lymphocytes. Thymic shadows are absent on X-rays.

The x-linked severe SCID is due to a defect in the gamma-chain of IL-2 also shared by IL-4, -7, -11 and 15, all of which are involved in lymphocyte proliferation and/or differentiation. The autosomal SCIDs arise primarily from defects in adenosine deaminase (ADA) or purine nucleoside phosphorylase (PNP) genes which results in accumulation of dATP or dGTP, respectively, and cause toxicity to lymphoid stem cells. Other genetic defects leading to SCID include those for RAG1, RAG2 and IL-7-alpha. If suspected of SCID, the patient must not receive live vaccine, as it will result in progressing disease.

Diagnosis is based on enumeration of T and B cells and immunoglobulin measurement. Severe combined immunodeficiency can be treated with a bone marrow transplant. Recently, autosomal SCID patients with ADA deficiency have been treated with a retroviral vector transfected with the gene with some success.

SCID includes Several Disorders

Patients having both T and B cell deficiency lack recombinase activating genes (RAG 1 and 2) that are responsible for the T cell receptor and lg gene rearrangements. These patients are athymic and are diagnosed by examining the T cell receptor (TCR) gene rearrangement. Defects in B cells are not observed in early infant life because of passive antibodies obtained from the mother. NK cells are normal.

In some SCID patients, T cells may be present but functionally defective because of the deficiency in signaling mediated by the CDS chain that is associated with the TCR.

3.3 Immunological Changes

The virus replicates rapidly and within about two weeks the patient may develop fever. The viral load in the blood increases significantly and peaks in two months, after which there is a sudden decline because of the latent virus found in germinal centers of the lymph nodes. CTL develop very early whereas antibodies can be detected between 3 - 8 weeks. The CTL killing of Th cells around 4 - 8 weeks leads to a decrease in CD4+ T cells. When the CD4+ T cell count decreases below 200 per cubic mm, full blown AIDS develops.

There are several barriers to the development of an effective HIV vaccine.

- Attenuated vaccine may induce the disease
- CD4+ T cells may be destroyed by the vaccine
- Antigenic variation of HIV
- Low immunogenicity of the virus by downregulation of MHC molecules
- Lack of animal models
- Lack of in vitro tests

The Following Reagents Have Been Considered in Developing Vaccines

- Immunisation with deletion mutants to reduce pathogenicity
- Vaccination with recombinant proteins
- Gene encoding proteins introduced into virus vectors may be used for vaccination
- Chemokines that compete for the co-receptors
- IL-2 to boost the Th cell

3.4 Immunodeficiencies Associated with Aging

These include a progressive decrease in thymic cortex, hypo-cellularity of and reduction in the size of thymus, a decrease in suppressor cell function and hence an increase in auto-reactivity, a decrease in CD4 cells functions. By contrast B cells functions may be somewhat elevated.

Immunodeficiencies Associated with Malignancies and Other Diseases

B cell deficiencies have been noted in multiple myeloma, Waldenstrom's macnsqiobulinemia, chronic lymphocytic leukemia and well differentiated lymphomas. Hodgkin's disease and advanced solid tumors are Interteukin-2 receptor common gamma chain (IL-2Rvc) may be lacking in patients thereby preventing signaling by IL-2,4,7,9 and 15. These patients are T and NK cell deficient.

Adenosine deaminase (ADA) is responsible for converting adenosine to inosine. ADA deficiency leads to accumulation of adenosine which interferes with DNA synthesis. The patients have defects in T, B and NK cells.

4.0 CONCLUSION

Immunodeficiency can either be primary or secondary/acquired in which the body become vulnerable to all infections including opportunistic ones as it is unable to produce immunity against infections or disease. This situation can be as a result of immunological changes as experienced in HIV/AIDS infection or due to aging or genetic defects in the immune system.

5.0 SUMMARY

In this unit, we have learnt that:

- Immunodeficiency is also referred to as immune deficiency
- It is the failure of the immune system to protect the body against diseases or malignancy
- Immunodeficiency can be primary or secondary
- Primary deficiency is caused by genetic or developmental defects in the immune system
- Secondary immune deficiency is also referred to as acquired deficiency
- Secondary deficiency results from exposure to disease agents, environmental factors, aging or immunosuppression.

6.0 TUTOR-MARKED ASSIGNMENT

Define immunodeficiency and explain the different ways by which it can occur.

7.0 REFERENCES/FURTHER READING

Brooker, C. (2000). Mosby Nurses Pocket Dictionary (31st ed.). London: Harcourt Limited

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UNIT 4 AUTOIMMUNITY

CONTENTS

1.0 INTRODUCTION

This unit handles the issue of Autoimmunity being a very important aspect of immune response. Autoimmunity has to do with immunoglobulin's (autoantibodies) or cell-mediated immunity against somebody components. It is a situation whereby the body cell antigens stimulate an immunological reaction within the body. They include Hashimoto's thyrioditis, rheumatoid arthritis, heamolytic anaemia and Addison's disease.

2.0 OBJECTIVES

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

- demonstrate that autoimmunity is an important aspect of immune response especially in relation to body infection and diseases.

3.0 MAIN CONTENT

3.1 Definition and General Classification

Definition

Autoimmunity can be defined as the breakdown of mechanisms responsible for self tolerance and induction of an immune response against components of the self. Such an immune response may not always be harmful. However, in numerous autoimmune diseases, it is well recognised that products of the immune system cause damage to the self.

Effector Mechanisms in Autoimmune Diseases

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

Genetic Classification

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

Genetic Predisposition for Autoimmunity

Studies in mice and observations in humans suggest a genetic predisposition for autoimmune diseases. Association between certain HLA types and autoimmune diseases has been noted (HLA: B8, B27, DR2, DR3, DR4, DR5 etc.).

3.2 Etiology of Autoimmunity Disease

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

Sequestered antigen

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

Escape of Auto-Reactive Clones

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

Lack of Regulatory T Cells

There are fewer regulatory T-cells in many autoimmune diseases.

Cross Reactive Antigens

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

3.3 Diagnosis and Treatment

Diagnosis

Diagnosis of autoimmune diseases is based on symptoms and detection of antibodies reactive against antigens of tissues and cells involved. Antibodies against cell/tissue associated antigens are detected by immunofluorescence. Antibodies against soluble antigens are normally detected by ELISA or radioimmunoassay. In some cases, a biological /biochemical assay may be used (e.g., Graves diseases, pernicious anemia).

Treatment

The goals of treatment of autoimmune disorders are to reduce symptoms and control the autoimmune response while maintaining the body's ability to fight infections. Treatments vary widely and depend on the specific disease and symptoms: Anti-inflammatory (corticosteroid) and immunosuppressive drug therapy (such as cyclophosphamide, azathioprine, cyclosporine) is the present method of treating autoimmune diseases. Extensive research is being carried out to develop innovative treatments which include: anti-TNF alpha therapy against arthritis, feeding antigen orally to trigger tolerance, anti-idiotype antibodies, antigen peptides, anti-lL2 receptor antibodies, anti-CD4 antibodies, anti-TCR antibodies, etc.

3.4 Model of Autoimmune Diseases

There are a number of experimental and natural animal models for the study of autoimmune diseases. The experimental models include experimental auto-allergic encephalitis, experimental thyroiditis, adjuvant induced arthritis, etc.

Naturally occurring models of autoimmune diseases include hemolytic anemia in NZB mice, systemic lupus erythematosus in NZB/NZW (BW), BXSB and MRL mice and diabetes in obese mice.

4.0 CONCLUSION

Autoimmunity is one of the immune responses of the body to diseases, infections, invaders or to immunological changes. In Autoimmunity, there is a breakdown of mechanism responsible for self tolerance and induction of an immune response against components of the self.

5.0 SUMMARY

In this unit, we have learnt that:

- Autoimmunity is the breakdown of mechanisms responsible for self tolerance and induction of an immune response against components of the self.
- Autoimmune response may not be harmful e.g antibodies.

- However, product of autoimmune response may cause damage to the self unexpectedly.
- Etiology of autoimmunity is not known.
- Autoimmune disease can be diagnosed and treated using models of autoimmune diseases.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss autoimmunity in terms of definition, classification, etiology, diagnosis and treatment.

7.0 REFERENCES/FURTHER READING

Brook, C. (2000). Mosby Nurse's Pocket Dictionary (31st ed.). London: Harcourt Publishers Limited.

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MODULE 4 IMMUNE SYSTEM DISORDERS

UNIT 1 DISORDERS OF THE T- CELLS

CONTENTS

1.0 INTRODUCTION

The module is discussing generally the issue of immune system disorders and possible treatment. The first unit of the module dwells specifically on the disorders of the T cell, and it embraces such aspects as T-cells deficiencies, Di George's Syndrome, disorders of B lymphocytes, non-specific immune system and the disorders of complement system.

2.0 OBJECTIVES

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

- explain the various disorders of the T-cells and
- discuss the various available treatments for your awareness.

3.0 MAIN CONTENT

3.1 Di Georges Syndrome

This is the most clearly defined T-cell immunodeficiency with hyperparathyroidism. The syndrome is associated with hyperparathyroidism, congenital heart disease, low set notched ears and

fish shaped mouth. These defects results from abnormal development of the fetus during the 6th to 10th week gestation when parathyroid, thymus, lips, ears and aortic arch are being formed. No genetic predisposition is clear and not all Di George syndrome babies have thymic aplasia. A thymic graft taken from an early fetus (13-14 weeks of gestation) can be used for treatment. Older grafts may result in GVH reaction. In severely immunodeficient Di George patients, live vaccines may cause progressive infections.

Di George syndrome is autosomal dominant and is caused by a deletion in chromosome 22. The deletions are of variable size but the size does not correlate with severity of the disease. In about 6% of cases, the choromosome 22 microdeletion is inherited but most cases result from de novo deletion which may be caused by environmental factors.

3.2 T- Cell Deficiencies with Variable Degrees of B- Cell Deficiency

a. Ataxia-telangiectasia

Ataxia-telangiectasia is a deficiency of T cells associated with a lack of small blood vessels of the facial area (talengiectasis). T-cell and their functions reduced to various degrees of B (in 70% of the case). There is high incidence of malignancy, particularly leukemia, in these patients; the defects arise from a breakage in chromosome 14 at the site of TCR and lg heavy chain genes.

b. Wiskott-Aldrich Syndrome

This syndrome associated with normal T-cell numbers with reduced functions which get progressively worse. IgM concentration are reduced but igG levels are normal. Both igA and igE levels are elevated.

Boys with this syndrome develop severe eczema, petechia (due to platelet defect and thrombocytopenia). They respond poorly to polysaccharide antigens and are prone to pyogenic infection. Wiskott-Aldrich syndrome is an X-linked disorder due to defect in a cytoskeletal glycoprotein, CD43.

c. MHC Deficiency (Bare Leukocyte Syndrome)

A number of cases of immunodeficiency have been described in which there is a defect in the MHC class-II transactivator (CIITA) protein gene, which results in a lack of class-II MHC molecule on their APC. Since the positive selection of CD4 cells in the thymus depend on the presence of these MHC molecules, these Patients Associated Protein (PAP) genes hence express the class-I MHC molecules and consequently are deficient in CD8+ T cells.

3.3 Disorders of B Lymphocytes

There are a number of diseases in which T cell numbers functions are normal but immunoglobulin levels are low. These are briefly summarised below:

- **X-linked Infantile Hypogammaglobulinemia**
  X-linked hypogamaglobulinemia, also referred to as Bruton's hypoglobulinemia or agammaglobulinemia, is the most severe hypogammaglobulinemia in which B cell numbers and all immunoglobulin levels are very low. The patients have failure of B-cell maturation associated with a defective B cell tyrosine kinase (btk) gene. Diagnosis is based on enumeration of B cells and immunoglobulin measurement.
- **Transient Hypogammaglobulinemia**
  Children, at birth, have igG levels comparable to that of the mother. Because the half life of igG is about 30 days, its level gradually declines, but by three months of age, normal infants begin to synthesise their own igG. In some infants, however, igG synthesis may not begin until they are 2 or 3 years old. This delay has been attributed to poor T cell help. This results in a transient deficiency of IgG which can be treated with gamma-globulin.
- **Common Variable Hypogammaglobulinemia (Late onset Hypogammaglobulinemia)**
  These individuals have acquired deficiencies of IgG and IgA in the 2nd or 3rd decade of their life and are susceptible to a variety of pyogenic bacteria and intestinal protozoa. They should be treated with specially prepared gamma-globulin for intravenous use.
- **IgA Deficiency**
  IgA deficiency is the commonest of all immunodeficiencies (1/700 of all caucasians). About 20% of individuals with IgA deficiency also have low IgG. IgA-deficient infections. Patients with IgA deficiency have a high incidence of autoimmune diseases (particularly immune complex type) and lymphoid malignancies. Anti-IgA antibodies (IgA) are detected in 30 to 40 percent of patients who should not be treated with Y-globulins. Laboratory diagnosis is based on IgA measurement.
- **Selective IgG Deficiency**
  Deficiencies of different IgG subclasses have been found. These patients are susceptible to pyogenic infections.
- **Hyper-IgM Immunodeficiency**
  Individuals with this type of immunodeficiency have low IgA and IgG concentrations with abnormally high levels of IgM. These patients cannot make a

switch from IgM to other classes which are attributed to a defect in CD40L on their CD4 cells. They are very susceptible to pyogenic infection and should be treated with intravenous gamma-globulins.

3.4 Non-Specific Immune System

Primary immunodeficiencies of the non-specific immune system include defects in phagocytic and NK cells and the complement system.

1. **Defects of the Phagocytic System**
   Defects of phagocytic cells (numbers and/or functions) can lead to increased susceptibility to a variety of infections.
2. **Cyclic Neutropenia**
   This is marked by low numbers of circulating neutrophil approximately every three weeks. The neutropenia lasts about a week during which the patients are susceptible to infection. The defect appears to be due to poor regulation of neutrophil production.
3. **Chronic Granulomatous Disease** (CGD)
   CGD is characterised by marked lymphadenopathy, hepato-splenomegaly and chronic draining lymph nodes. Leukocytes have poor intracellular killing and low respiratory burst in majority of these patients, the deficiency is due to a defect in NADPH oxidase (cytochrome b558: gp91phox, or rarely gp22phox) or other cofactor proteins (gp47phox *gp67phox)* that participate in phagocytic respiratory burst. These patients can be diagnosed on the basis or poor Nitroblue tetrazolium (NBT) reduction which is a measure of respiratory burst. Interferon-gamma therapy has been successful.
4. **Leukocyte Adhesion Deficiency**
   In this disease, leukocytes lack the complement receptor CR3 due to a defect in CD11 or CD18 peptides and consequently they cannot respond to C3b opsonin. Alternatively there may be a defect in integrin molecules, LFA-1 or mac-1 arising from defective CD11a or CD11b peptides, respectively. These molecules are involved in diapedesis and hence defective neutrophils cannot respond effectively to chemotactic signals.
5. **Chediak-Higashi Syndrome**
   Chediak-Hjgasni syndrome is marked by reduced (slower rate) intracellular killing and chemotactic movement accompanied by inability of phagosome and lysosome fusion and proteinase deficiency. Giant lysosomes (intracellular granules) are often seen. The respiratory burst is normal. Accompanying NK cell defects and platelet and neurological disorders are noted.
6. **Disorders of Complement System**
   Complement abnormalities also lead to increased susceptibility to infections. There are genetic deficiencies of various components of complement system, which lead to increased infections. The most serious among these is the C3 deficiency which may arise from taw C3 synthesis or deficiency in factor I or factor H.

4.0 CONCLUSION

The immune system disorders phenomenon is not an unusual thing as the disorders are recorded in different forms such as Di Geore's and like the T-cells; and the form of diseases, and disorders of complement system and of non-specific immune systems. In simple language the immune system disorders are common occurrences.

5.0 SUMMARY

In this unit, we have learnt that:

- Immune system disorders occur as a result of direction from the norm
- T-cell deficiency is one of the disorders while other T-cell disorders include B-cell deficiency, Di-George's, wiskott-Aldrich and other syndromes.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the issue of disorders of the T-cells

7.0 REFERENCE/FURTHER READING

www.goggle.com.

UNIT 2 OTHER POSSIBLE DISORDERS

CONTENTS

1.0 INTRODUCTION

Apart from the disorders of the T-cells discussed in unit 1 of this module, other forms of disorders do exist but they might not be as common as the ones earlier mentioned and they include autoimmune diseases, transplant rejection and allergies: These are likely cases that you will come across in the course of discharging your duties in the field and that is the more reason why you need to familiarise yourself with them all, particularly the allergies and autoimmune diseases. There is also the possibility of transplant rejection.

2.0 OBJECTIVES

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

- explain that there are other disorders of the immune system aside the ones discussed in unit 1 of this module.
- discuss disorders of the immune system ranging from less serious mild allergy, to the life threatening more serious allergy such as transplant rejection, immune deficiencies, and autoimmune diseases.

3.0 MAIN CONTENT

3.1 Allergy

Allergy, sometimes called hypersensitivity, is caused by immune responses to some antigens. Antigens that provoke an allergic response are known as *allergens.* The two major categories of allergic reaction, rapid and delayed, correspond to the two major types of immune responses.

Rapid allergic reactions, such as those to Bee venom, pollen or pets, are caused by humoral immune mechanisms. These immediate hypersensitivity reactions result from the production of IgE antibodies when a person is first exposed to an allergen. The IgE antibodies become attached to *mast cells*— white blood cells containing *histamine,* the chemical that causes the familiar allergic symptoms of runny nose, watery eyes, and sneezing. Mast cells are particularly abundant in the lungs and intestine. If the antigen-binding sites of mast cells become filled with an allergen, the mast cells release histamine.

Allergic reactions that are slow in onset (known as *delayed-type hypersensitivity,* or DTH), such as those to poison Ivy or poison oak, are cell mediated. Extreme examples of DTH occur when macrophages cannot easily destroy invading substances. As a result, T-cells are activated, leading to inflammation of the body tissue. This inflammation continues for as long as the T cells are activated. The bacterium that causes tuberculosis also falls into this category because this bacterium is covered with a waxy coat that macrophages cannot destroy. The resulting DTH leads to the lung and liver damage associated with tuberculosis.

3.2 Transplant Rejection

The immune system recognises and attacks anything different from the substances normally present within an individual, even substances that are only slightly different, such as transplanted tissues and organs.

When an organ is transplanted, the MHC of the donor organ is recognised as foreign and attacked by the recipient's immune system. To minimise the chances of transplant rejection, physicians seek transplant donors who share as many MHC genes as possible with the transplant recipient. Even then, most transplant recipients are given drugs to suppress their immune response and prevent rejection of the transplant.

If the transplanted tissue contains T lymphocytes from the donor, as in bone marrow transplants, these donor T lymphocytes may recognize the recipient's tissues as foreign and attack them. Physicians can reduce or prevent this potentially fatal *graft-versus-host (GVH) reaction* by removing all mature T lymphocytes from the organ or tissue before performing the transplant.

3.3 Immune Deficiency

Deficiencies in immune function may be either inherited or acquired. Inherited immune deficiencies usually reflect the failure of a gene important to the generation or function of immune system components.

Some inherited diseases damage a person's innate immunity by making macrophages incapable of ingesting or breaking down invading organisms. Individuals affected by these diseases are especially susceptible to *opportunistic Infections*—that is, infections by normally harmless organisms that can flourish in a person whose immune system has been weakened.

DiGeorge syndrome is an inherited immune disorder in which a person has no thymus and, therefore, cannot produce mature T lymphocytes. People with this disorder can mount only limited humoral immune responses, and their cell-mediated immune responses are severely limited.

The most extreme example of a hereditary immune deficiency is severe combined immunodeficiency (SCID). Individuals with this disease completely lack both T and B lymphocytes and thus have no adaptive immune responses. People with SCID must live in a completely sterile environment, or else they will quickly die from infections.

Acquired immune deficiencies can be caused by infections and also other agents. For example, radiation therapy *(see* Radiology) and some kinds of drugs used in treating disease reduce lymphocyte production, resulting in damaged immune function. People undergoing such therapies must be carefully monitored for lowered immune function and susceptibility to infections. Environmental and lifestyle factors, such as poor nutrition or stress, can also affect the immune system's general status.

An infectious agent resulting in fatal immune deficiency is the human immunodeficiency virus (HIV). This virus causes acquired immunodeficiency syndrome (AIDS) by infecting and eventually destroying helper T cells. Because helper T cells regulate all immune responses, their loss results in an inability to make adaptive Immune

responses. This complete lack of immune function makes individuals with AIDS highly susceptible to all infectious agents.

3.4 Autoimmune Diseases

Autoimmunity is the immune response of the body turned against its own cells and tissues. Autoimmune diseases may involve either cell-mediated responses, humoral responses, or both. For example, in Type 1 diabetes, the body makes an immune response against its insulin-producing cells and destroys them, with the result that the body cannot use sugars, in myasthenia gravis; the immune system makes antibodies against the normal molecules that control neuromuscular activity, causing weakness and paralysis. In rheumatic fever, the immune system makes antibodies that bind to the heart's valves, leading to permanent heart damage. In systemic lupus erythematosus, commonly known as lupus, the body makes antibodies against many different body tissues, resulting in widespread symptoms.

The mechanisms of autoimmune diseases are poorly understood, and thus the basis for autoimmunity is unclear. Much research focuses on trying to understand these mechanisms and should eventually result in cures.

4.0 CONCLUSION

It is crystal clear that disorders are normal occurrence in the immune system and apart from the common ones, other forms of disorders include Allergy, Transplant rejection, Autoimmune diseases and immudeficiency.

5.0 SUMMARY

In this unit, we have learnt that apart from T-cells disorder, other disorders can also occur in the immune system. These other possible disorders include:

- Immune deficiency
- Allergy
- Transplant rejection
- Autoimmune diseases.

6.0 TUTOR-MARKED ASSIGNMENT

List and discuss other possible disorders in the immune system apart from T-cell disorders.

7.0 REFERENCES/FURTHER READING

Patterson, R. & Ricketti, A. (1983). Allergy World Health Organisation Magazine Nov, 1983 WHO Geneva:

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www.google.com

UNIT 3 CELLS INVOLVED IN IMMUNE RESPONSES

CONTENTS

1.0 INTRODUCTION

This unit discusses the various cells that are involved in the activities of the immune system as well as the specificity of adaptive immune response alongside lymphocyte recirculation. This unit further explains and complement facts and opinions discussed in the introductory part of this module in relation to the disorders of the T-cells.

This unit is also set to give clarifications on many aspects of the other disorders mentioned in unit 2 of this same module 4.

2.0 OBJECTIVES

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

- identify some areas of doubt in the previous units of this module and
- explain the subject matter in this unit.

3.0 MAIN CONTENT

3.1 Overview

The immune system has developed to protect the host from pathogens and other foreign substances. Self/non-self discrimination is one of the hallmarks of the immune system. There are two main sites where pathogens may reside: extracellularly in tissue spaces or intracellularly within a host cell and the immune system has different ways of dealing with pathogens at these sites.

A. Extracellular Pathogens

Antibodies are the primary defense against extracellular pathogens and they function in three major ways:

1. Neutralisation

By binding to the pathogen or foreign substance, antibodies can block the association of the pathogen with their targets. For example, antibodies to bacterial toxins can prevent the binding of the toxin to host cells thereby rendering the toxin ineffective. Similarly, antibody binding to a virus or bacterial pathogen can block the attachment of the pathogen to its target cell thereby preventing infection or colonisation.

2. Opsonization

Antibody binding to a pathogen or foreign substance can opsonize the material and facilitate its uptake and destruction by phagocytic cells. The Fc region of the antibody interacts with Fc receptors on phagocytic cells rendering the pathogen more readily phagocytosed.

3. Complement Activation

Activation of the complement cascade by `antibody can result in lysis of certain bacteria and viruses. In addition, some components of the complement cascade (e.g. C3b) opsonize pathogens and facilitate their uptake via complement receptors on phagocytic cells.

Antibodies binding to and neutralising a bacterial toxin, preventing it from interacting with host cells and causing pathology. Unbound toxin can react with receptors on the host cell, whereas the toxin antibody complex cannot. Antibodies also neutralise complete virus particles and bacterial cells by binding to them and inactivating them. The antigen:antibody complex is eventually scavenged and degraded by rnacrophages. Antibodies coating an antigen render it recognisable as foreign by phagocytes (macrophages and polymorphonuctear leukocytes), which then ingest and destroy it; this is called opsonization.

Activation of the complement system by antibodies coating a bacterial cell. Bound antibodies form a receptor for the first protein of the complement system, which eventually forms a protein complex on the surface of the bacterium that in some cases, can kill the bacterium directly but more generally favours its uptake and destruction by phagocytes. Thus, antibodies target pathogens and their products for disposal by phagocytes.

B. Intracellular Pathogens

Because antibodies do not get into host cells, they are ineffective against intracellular pathogens. The immune system uses a different approach to deal with these kinds of pathogens. Cell-mediated responses are the primary defense against intracellular pathogens and the approach is different depending upon where the pathogen resides in the host cell (i.e. in the cytosol or within vesicles). For example, most viruses' bacteria reside in the

cytoplasm of the host cell, however, some bacteria can actually live within endosomes in the infected host cell. The primary defense pathogens in the cytosol is the cytotoxic T lymphocyte (Tc or CTL). In contrast, the primary defense against a pathogen within vesicles is a subset of helper T lymphocytes (Thl).

1. **Cytotoxic T Lymphocytes**
   CTLs are a subset of T lymphocytes that express a unique antigen on their surface called CDS. These cells recognise antigens from the pathogen that are displayed on the surface of the infected cell and kill the cell thereby preventing the spread of the infection to neighboring cells. CTLs kill by inducing apoptosis in the infected cell.
2. **Th 1 Helper T Cells**
   Th cells are a subset of T cells that express a unique antigen on their surface called CD4. A subpopulation of Th cells, Th1 cells, is the primary defense against intracellular pathogens that live within vesicles. Th1 cells recognise antigen from the pathogen that are expressed on the surface of infected cells and release cytokines that activate the infected cell. Once activated, the infected cell can then kill the pathogen. For example, *Mycobacterium tuberculosis,* the causative agent of tuberculosis, infects macrophages but is not killed because it blocks the fusion of lysosomes with the endosomes in which it resides. Th1 cells that recognise *M. tuberculosis* antigens on the surface of an infected macrophage can secrete cytokines that activate macrophages. Once activated, the lysosomes fuse with endosomes and the *M tuberculosis* bacteria are killed.

Although immune responses are tailored to the pathogen and to where the pathogen resides, pathogens can elicit both an antibody and a cell-mediated response, both of which may contribute to ridding the host of the pathogen. However, for any particular pathogen, an antibody or a cell-mediated response may be more important for defense against the pathogen.

3.2 Cells of the Immune System

All cells of the immune system originate from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages, a myeloid progenitor cell and a lymphoid progenitor cell. These two progenitors give rise to the myeloid cells (monocytes, macrophages, dendritic cells, meagakaryocytes and granulocytes) and lymphoid cells (T cells, B cells and natural kiUey (NK) cells), respectively. These cells make up the cellular components of the innate (non-specific) and adaptive (specific) immune systems.

Cells of the Innate Immune System

Cells of the innate immune system include phagocytic cells (monocyte/macrophages and PMNs), NK cells, basephils, mast cells, eosinophiles and platelets. The roles of these cells have been discussed previously (see non-specific immunity). The receptors of these cells are pattern recognition receptors (PRRs) that recognise broad molecular patterns found on pathogens (pathogen associated molecular patterns, PAMPS).

Cells that Link the Innate and Adaptive Immune System

A specialised subset of cells called antigen presenting cells (APCs) are a heterogenous population of leukocytes that play an important role in innate immunity and also act as a link to the adaptive immune system by participating in the activation of helper T cells (Th cells). These include dentritic cells and macrophages. A characteristic feature of APCs is the expression of a cell surface molecule encoded by genes in the major histocompatibility complex, referred to as class II MHC molecules. B lymphocytes also express class Il MHC molecules and they also function as APCs, although they are not considered as part of the innate immune system. In addition, certain other cells (e.g., thymic epithelial cells) can express class II MHC molecules and can function as APCs.

C. Cells of the Adaptive Immune System

Cells that make up the adaptive (specific) immune system include the B and T lymphocytes. After exposure to antigen, B cells differentiate into plasma cells whose primary function is the production of antibodies. Similarly, T cells can differentiate into either T cytotoxic (Tc) orT helper (Th) cells of which there are two types Th1 and Th2 cells.

There are a number of cell surface markers that are used in clinical laboratories to distinguish B cells, T cells and their subpopulations.

Specificity of the Adaptive Immune Response

Specificity on the adaptive immune response resides in the antigen receptors on T and B cells, the TCR and BCR, respectively. The TCR and BCR are similar in that each receptor is specific for one antigenic determinant but they differ in that CRs are divalent while TCRs are monovalent. A consequence of this difference is that while B cells can have their antigen receptors cross-linked by antigen, TCRs cannot. This has implications as to how B and T cells can become activated.

Each B and T cells has a receptor that is unique for a particular antigenic determinant and there are a vast array of different antigen receptors on both B and T cells. The question of how these receptors are generated was the major focus of immunologists for many years. Two basic hypotheses

were proposed to explain the generation of the receptors: the instructionist (template) hypothesis and the clonal selection hypothesis.

1. **Instructionist Hypothesis**
   The instructionist hypothesis states that there is only one common receptor encoded in the germline and that different receptors are generated, using the antigen as a template would cause the one common receptor to be folded to fit the antigen. While this hypothesis seems simple and very appealing, it was not consistent with what was known about protein folding as dictated by the sequence of amino acids in the protein. In addition, the hypothesis did not account for self/non-self discrimination in the immune system. It could not explain why the one common receptor did not fold around self antigens.
2. **Clonal Selection Hypothesis**
   The clonally selection hypothesis states that the germ line encodes many different antigen receptors - one for each antigenic determinant to which an individual will be capable of mounting an immune response. Antigen selects those clones of cells that have the appropriate receptor. The four basic principles of the clonally selection hypothesis are:

   a. Each lymphocyte bears a *single* type of receptor with a unique specificity.
   b. Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with a high affinity leads to lymphocyte activation.
   c. The differentiated effectors cells derived from an activated lymphocyte will bear receptors of an identical specificity to those of the parental cell from which that lymphocyte was derived.
   d. Lymphocytes bearing receptors for self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes.

The clonal selection hypothesis is now generally accepted as the correct hypothesis to explain how the adaptive immune system operates. It explains many of the features of the immune response: 1) the specificity of the response; 2) the signal required for activation of the response (i.e. antigen); 3) the lag in the adaptive immune response (time is required to activate cells and to expand the clones of cells); and 4) self/non-self discrimination.

3.4 Lymphocyte Recirculation

Since there are relatively few T or B lymphocytes with a receptor for any particular antigen (1/10,000 - 1/100,000), the chances for a successful encounter between an antigen and the appropriate lymphocyte are slim. However, the chances for a successful encounter are greatly enhanced by the recirculation of lymphocytes through the secondary lymphoid organs. Lymphocytes in the blood enter the lymph nodes and percolate through the lymph nodes. If they do not encounter an antigen in the lymph node, they leave via the lymphatics and return to the blood via the thoracic duct. It is estimated that 1-2% of lymphocytes recirculate every hour. If the lymphocytes in the lymph nodes encounter an antigen, which has been transported to the lymph node via the lymphatics, the cells become activated, divide and differentiate to become a plasma cell, Th or Tc cell. After several days, the effector cells can leave the lymph nodes via the lymphatics and return to the blood via the thoracic duct and then make their way to the infected tissue site.

Naive (virgin) lymphocytes enter the lymph nodes from the blood via High Endothelial Venules (HEVs). Homing receptors on the lymphocytes direct the cells to the HEVs. In the lymph nodes, lymphocytes with the appropriate antigen receptor encounter antigen, which has been transported to the lymph nodes by dendritic cells or macrophages. After activation. the lymphocytes express new receptors that allow the cells to leave the lymph node and re-enter the circulation. Receptors on lymphocytes recognise cell adhesion molecules expressed on endothelial cells near the site of an infection and chemokines produced at the infection site help attract the activated cells.

4.0 CONCLUSION

It is a well established fact that certain cells of the body are involved in the activities of the immune system, particularly immune responses through specific processes and methods which include neutralisation, opsonization, complement activation, lymphocyte reirculation etc. The chief of the cells involved in immune responses are the T and B cell as well as the helper Th cells (Th 1 and The 2)

5.0 SUMMARY

In this unit, we have learnt that:

- Certain body cells are involved in immune responses
- Cells involve in immune responses include T and B cells as well as helper Th cells which comprise of Th 1 and Th2 cells.

- Processes of immune response include neutralisation, Opsonization, complement activation, lymphocyte recirculation etc.

6.0 TUTOR-MARKED ASSIGNMENT

i. What do you understand by immune responses?
ii. Discuss processes and methods involved in immune response
iii. Mention the 4 cells involve in the processes

7.0 REFERENCE/FURTHER READING

www.google.com.

MODULE 5 IMMUNISATION

UNIT 1 VACCINES

CONTENTS

1.0 INTRODUCTION

Broker (2000) describes vaccines as an extract prepared from attenuated organisms where as Martin (2003) says it is a special preparation of antigenic material that can be used to stimulate the production of antibodies and thus confer active immunity against a specific disease or a number of diseases. Many vaccines are produced by culturing bacteria or viruses. Other vaccines consist of specially treated toxins or of dead bacteria. The processed organisms losses its virulence but retains its antigenic nature.

2.0 OBJECTIVES

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

- define vaccines and
- explain how they are produced in the laboratory by scientists.

3.0 MAIN CONTENT

3.1 Definitions and Types of Vaccine

Definitions
According to Coventry (1999) vaccines is a substance used to stimulate production of antibodies to give immunity against a disease by causing a mild form of it. Broker (2000) sees vaccines as an extract prepared from attenuated organisms e.g. BCG, rubella bacteria toxins e.g. tetanus and inactivated virus e.g. typhoid. The antigenicity of the organisms is retained but the pathogenicity is reduced. Martin (2003) says vaccine is a special preparation of antigenic materials that can be used to stimulate the development of antibodies and thus confer active immunity against a specific disease or a number of diseases. It is usually given by injection but may be introduced into the skin through light scratches for some diseases e.g. Polio. Many vaccines are produced by culturing bacteria or viruses under conditions that lead to a loss of their virulence but not of their antigenic nature. Others consist of specially treated toxins (toxoids) or dead bacteria that are still antigenic.

Types of Vaccine
1. Live attenuated vaccines contain bacteria or viruses that have been altered so they can't cause disease.
2. Killed vaccines contain killed bacteria or inactivated viruses.
3. Toxoid vaccines contain toxins (or posions) produced by the germ that have been made harmless.
4. Component vaccines contain parts of the whole bacteria or viruses.

Live Attenuated Vaccines
Live attenuated vaccines usually produced from the naturally occurring germ itself. The germs used in these vaccines still can infect people, but they rarely cause serious disease. Viruses are weakened or (or attenuatted) by growing them over and over again in a laboratory under nourishing conditions called cell culture. The process of growing a virus repeatedly-also known as passing-serves to lessen the disease-causing ability of the virus. Vaccines are made from viruses whose disease-causing ability has deteriaorated from multiple passages e.g:

1. Mumps vaccine (MMR vaccine)
2. Rubella (German measles vaccine)
3. Oral polio vaccine (OPV)
4. Varicella (chickenpox vaccine)

Inactivated (killed) vaccines: cannot cause an infection, but they still can stimulate a protective immune response. Viruses are inactivated with chemicals such as formaldehyde.

Examples of inactivated (killed) vaccines

1. Inactivated polio vaccine (IPV), which is the shot form of the polio vaccine
2. Inactivated influenza vaccine

Toxoid Vaccines

Toxoid vaccines are made by treating toxins (or poisions) produced by germs with heat or chemicals, such as formalin, to destroy their ablity to cause illness. Even though toxoids do not cause disease, they stimulate the body to produce protective immunity just like the germs' natural toxins.

Examples of toxoid vaccines:

1. Diphtheria toxoid vaccine (may be given alone or as one of the component in the DTP, DT aP, or dT vaccines)
2. Tetanus toxoid vaccines (may be given alone or as part of DTP, DT aP, or dT)

Component Vaccines

Some vaccines are made by using only parts of the viruses or bacteria. These vaccines cannot cause disease, but they can stimulate the body to produce an immune respone that protects against infection with the whole germ. Four of the newest vaccines are made this way.

Examples of component vaccines:

1. Haemophilus influenzea type b (Hib) vaccine
2. Hepatitis B (Hep B) vaccine
3. Hepatitis A (Hep A) vaccine
4. Pneumococcal conjugated vaccine

3.2 Vaccines For Use In Immunisation

The following are included in the National Programme on Immunisation (NPI)

1. Bacilli Calomette Guerin (BCG) (anti-tuberculous vaccine)
2. Oral Poliomyelitis Vaccine (OPV)
3. Diphtheria, Pertussis, Tetanus (DPT) vaccines
4. Measles Vaccine
5. Tetanus Toxoid (TT)
6. Yellow fever vaccine
7. Hepatitis B
8. Cerebro-Spinal Meningitis (CSM)

3.2.1 Bacille Calmette Guerin (BCG) (anti-tuberculous vaccine)

BCG vaccine contains a live attenuated from of mycobacterium bovis. It is one of the most widely used vaccines in the world, but its efficacy is still the subject of scientific discussion. Uncertainty about the effectiveness of BCG is in part the consequence of a lack on uniformity in polices for the use of the vaccines. Nigeria's policy on BCG immunisation is based on:

1. Operational Considerations

Tuberculosis is a major health problem in Nigeria. Because of the high prevalence of the disease and the high risk of tuberculosis infection in infancy, Nigeria's policy is to immunise infants with BCG as early as possible. The efficacy of BCG vaccine is controversial. Efficacy may vary from one country to another because of differences in the protocols used to administer the vaccine and as a consequence of differences in the epidemiology of tuberculosis in diverse populations.

In Nigeria, BCG is given in the neonatal period when the risk of infection is still low, so as to provide protection against military (disseminated) tuberculosis and tuberculous meningitis-two forms of the disease that are often fatal in children hood.

The global AIDS epidemic is another reason for recommending that infants be given BCG at birth or soon after. By reducing the number of people at risk for infection, the spread of multi-drug resistant organisms can be slowed. Immunisation should be supported by community control efforts with an emphasis on case finding and treatment.

3.2.2 Oral Poliomyelitis Vaccine (OPV)

Oral poliomyelitis vaccine (OPV) is included in the Nigeria Expanded Programme on Immunisation (EPI) because it effectively confers intestinal immunity, is low cost and easy to administer. The vaccine contains three different types of attenuated live virus (types 1, 2 and 3). As the vaccine contains live viruses, it has the potential to cause secondary infections in household and communities. This effect is beneficial and helps in maintaining protective levels of antibodies in those secondarily infected.

Seroconversion rates following the recommended two doses of OPV have been lower in many developing countries than in industrialised countries. The reason for this is not fully understood but may be related to infections with other viruses that interfere with the poliovirus. Low seroconversion can be overcome by administering additional doses of OPV.

In Nigeria, the first dose of OPV should be given at birth and this is followed by three doses during the first life.

The efficacy of three doses of OPV in developing countries is between 72% and 98%. This means that some cases will occur even in fully immunised persons, particularly in polio endemic countries with only three doses of OPV in their routine schedule. For this reason, Nigeria provides four doses per child to assure 100% efficacy, as recommended by WHO.

In many areas, routine immunisation alone may not be sufficient to eradicate wild poliovirus. Supplementary activities may be necessary. Strategies for use in Nigeria include:

- Using OPV in state and LGA immunisation campaigns with the goal of giving two doses of OPV one month apart to all children under 2 years of age regardless of previous immunisation status.
- After campaign, care must be taken to assure that each child receives the full number of doses (four doses) required for immunisation. These additional doses can be given later at state facilitie.
- “Mop up” immunisation programme in high risk areas with health personnel going from house-to-house to ensure total coverage.
- Attention to outbreaks with extensive immunisation activities where suspected cases are detected.

3.2.3 Diphtheria Pertussis Tetanus (DPT) Vaccine

Diphtheria and tetanus toxoid have change very little over the years. They are known to be excellent antigens that have low reatogenicity and are appropriate for preventing these diseases in Nigeria.

The diphtheria and tetanus toxoid are supplied as monovalent vaccines or as components of combined vaccines such as DPT, DT and TT. The Nigeria programme uses DPT to immunise children and the monovalent TT for women in their reproductive years and for older children and adults at risk for tetanus.

Pertussis vaccine is a component of the combined DPT vaccine. There is a very high morbidity and mortality rate caused by pertussis in the first six months of life and because of this, every effort should be made to complete the primary immunisation series with DPT vaccines as early as possible.

Community-based studies in Nigeria have shown that mean age of incidence of pertussis is very low and the case fatality rate high. Three doses of DPT vaccine are required to produce significant immunity against pertussis.

In special populations such as health care providers and school age children, supplemental doses of DPT may be given where there in a need to reduce the risk of exposure to pertussis by newborns, unimmunised children at home and other high risk patients.

The currently available pertussis vaccine contains whole pertussis bacteria killed by chemicals or heat. The vaccine is safe but is the most reatogenic of the EPI vaccines. The reactions are generally limited but without proper counseling they can cause alarm and anxiety for parents and thus contribute to high dropout rates for EPI. Current evidence does not support a causal link between DPT immunisation and severe neurologic conditions but this concern has been highly publicised.

In very rare instances, DPT immunisation may precipitate acute encephalopathy with hypotonic, hyporesponsive episodes. Trials are underway to serve more years. When it does become available, it is likely to be very expensive.

3.2.4 Measles Vaccine

Measles is a highly infectious viral disease and it is the biggest killer among the EPI target diseases. In the absence of vaccination, nearly everyone contracts measles and in Nigeria most unvaccinated children will contact measles before their fifth birthday. The median age of infection is less than 24 months.

There are several different types of live - attenuated measles virus strains available for use in vaccines (Schwarz, Edmonston-Zagreb, AIK-C, CAM-70, L-16 and Moraten strains). These vaccines are very effective and have successfully reduced the occurrence of measles throughout the world. Measles vaccination is generally considered to be the most cost-effective public health intervention in use today. In Nigeria, however, poor quality vaccines, improper handling by health officials during vaccination and break in the cold chain contribute to poor Serocoversion rates among children vaccinated.

In Nigeria, especially in the urban areas, a significant number of measles cases occur, often in children below nine months of age. Because case fatality rates are very high in the first year of life, children should be immunised as soon as 9 months of age.

In certain high risk populations early immunisation at 6 month of age may be indicated. Children given early doses of measles vaccine must be re-immunised as soon after 9 months of age as possible. In communities where high coverage of 9 to 23 months old infants has been achieved, improved vaccination of older children with catch-up vaccination of older unvaccinated children may further reduce the likeliood of exposure of infants.

3.2.5 Tetanus Toxoid

Tetanus toxiod is available alone or combined with diphtheria toxoid and pertussis vaccine, absorbed, as DPT and DT. Tetanus toxoid is one of the most effective immunobiologic agents. One of the most serious health problems confronting Nigeria is neonatal tetanus (NNT).

Tetanus toxoid (TT) should be offered to all women of child bearing age, including pregnant women. Obviously unimmunised women should received five doses of tetanus toxoid. The TT immunisation schedule should include a first dose given at the first contact, a second dose at least 4 weeks after the first dose, and a third dose given 6-12 months after the second dose. The third dose includes high and durable immunity. It should be rein enforced by additional two booster doses. A

woman who has received all five doses of TT will be immune against tetanus for the rest of her childbearing life.

Due to the serious consequences of tetanus infection, every effort should be made to identify and immunise eligible women when they bring children for immunisation or when they attend antenatal clinics. A child receiving 3 dose of DPT, confirmed by card, will count as 2 doses of TT,. Then the child will receives the 3rd, 4th and 5th doses of TT for life time protection. School age children or women in childbearing age must receive the five doses of TT if no previous DPT immunisation record is available.

3.2.6 Yellow Fever Vaccine

The yellow fever vaccine contains a live virus (17D) that has been attenuated. Yellow fever was added to the WHO list of recommended EPI vaccines in 1990 for yellow fever endemic area but had been used in Nigeria before then. The vaccine can be safely administered to infants at 6 months of age and is often combined with measles vaccine at the 9-month immunisation.

3.2.7 Hepatitis B Vaccine

There are two types of inactivated hepatitis vaccines (HB) available. One is manufactured from the plasma of persons who are carriers of HB surface antigen (BHs Ag) and the second is made using recombinant DNA technology. Both vaccines work well to produce immunity in infants and have a low frequency of adverse effects. They are effective even when administered at birth because the antibody an infant receives from its mother (maternal anti-HBs antibody) does not interfere with the development of an immunologic response to the vaccine.

Hepatitis B vaccine is compatible with the other infant vaccines. Immunisation schedules should allow for the first dose to be given as early as possible in high risk populations. The age for the first dose may vary depending on the epidemiological characteristics of the population. Where perinatal transmission of HB is common, the first dose can be given at birth. Three doses are considered a full course.

3.2.8 Cerebro-Spinal Meningitis (CSM) Vaccine

CSM is a recurrent epidemic disease in Nigeria, particularly in the northern states, lying in the meningitis belt, epidemics of CSM have occurred in Nigeria in 1977 and 1986/87 giving rise to high morbidity and morality and neurological disabilities such as mental retardation,

hearing loss, learning disability and seizures. Effective treatment and vaccines against sero groups A, C, Y and W-135 are available.

However, there is the lack of an effective vaccine that can be included in the national EPI. At present outbreak response is slow and ineffective due to lack of emergency preparedness and prompt action. Existing surveillance systems are insensitive to early case detection and quick identification of sero groups. The strategy is to prevent epidemics and reduce morbidity and mortality through surveillance and vaccination and proper treatment of cases. When vaccines are used in epidemic situation, efforts must be made to reach 100% coverage. Several studies have shown that even in situations where 80% have been immunised, the unimmunised remain at considerable risk of the disease.

High molecular weight polysaccharide antigens from organisms of serogroups A,C Y and W -135 are effective in containing outbreaks of CSM. Single antigen and quadric valent vaccines are available for use in control or prevention of outbreaks. Routine immunisation is recommended only for particular high risk groups. An effective group B vaccine is not yet developed.

4.0 CONCLUSION

Vaccines are used to stimulate the production of antibodies and thus confer active immunity against a specific disease or a number of diseases. Vaccines are produced by culturing bacteria or viruses or by the use of specifically treated toxins which offer protection for the body against infections and diseases.

5.0 SUMMARY

In this unit, we have learnt that:

- Vaccines are processed organisms without virulence but with antigenic nature.
- Vaccines stimulate production of antibodies that confer immunity against diseases and infections.
- Many vaccines are produced by culturing bacteria or viruses.
- Specially treated toxins or dead bacteria are also used to produce vaccines.
- There are different types of vaccines which include DTP, OPV, TT, BCG, CSM, Measles, Hepatitis e.t.c.

6.0 TUTOR-MARKED ASSIGNMENT

i. How do you define vaccine?
ii. List different ways of vaccine production
iii. Mention 6 types of vaccine and their use

7.0 REFERENCES/FURTHER READING

Hartvelt, F. (1993). The Children's Vaccines Initiative. World Health Organisation Magazine Mar-Apr 1993 Pp 4-6 Geneva: WHO.

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UNIT 2 IMMUNISATION OVERVIEW

CONTENTS

1.0 INTRODUCTION

Immunisation, according to Brooker (2000) is the artificial means by which immunity is initiated or augmented and can be active or passive in operation. Nicholas (1986) opined that immunisation is one of the most powerful and cost effective health interventions. Nicholas, while commenting on the Expanded Programme on Immunization further stated that effective immunisation programme have major additional advantages in advancing primary health care. In this course, immunisation is also treated as being very important in the health care setting. A portion of this unit is also dedicated to the activities of scientists who contributed to immunisation activities in different ways and forms. Immunisation is no doubt very crucial to the survival of children.

2.0 OBJECTIVES

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

- discuss the crucial role of vaccines and immunisation as a child survival strategy
- identify great scientists who were and still involved in immunisation activities.

3.0 MAIN CONTENT

3.1 Definitions and Types of Immunisation

When the body is first exposed to an antigen, several days will pass before the adaptive immune response becomes active. Immune activity then rises, levels off, and falls. During following exposures to the same antigen, the immune system responds much more quickly and reaches higher levels. Because the first, or primary, immune response is slow, it cannot prevent disease, although it may help in recovery. In contrast, subsequent, or secondary, immune responses usually can prevent disease because the pathogen is detected, attacked, and destroyed before symptoms appear. This complete resistance to disease is called immunity and may be achieved through either active or passive immunisation.

Active Immunisation
Active immunisation occurs when a person's own immune system is activated and generates a primary immune response. Active immunisation can be triggered in two ways, either by natural immunity or by vaccination.

In natural immunisation, the body contracts a disease and recovers. Because a primary immune response occurs during the illness, the immune system will mount a disease-preventing secondary response every time it is subsequently exposed to the disease. Natural immunity is developed during childhood diseases, such as chicken pox. Once exposed to the diseases, a person is no longer susceptible to it.

Vaccination is intentional immunisation against a particular disease by the use of vaccines, substances that are structurally similar to the actual disease-producing agents but that do not produce disease themselves. Most vaccines take one of two forms. The first type of vaccine, such as the vaccines for tetanus and whooping cough, contains chemically killed bacteria or other pathogenic organisms. The other type, such as the oral polio vaccine, contains weakened forms of living organisms that have been genetically selected so they do not produce disease.

Passive Immunisation
Another way to provide immunity is by means of passive immunisation. Passive immunisation does not engage the person's own immune system. Instead, the individual receives antibodies that were created in another person or animal. Such antibodies can be lifesaving when a disease progresses too rapidly for natural immunity to occur. For example, if a person who has not been immunised against tetanus bacteria is exposed to tetanus, the toxin produced by these bacteria would reach a deadly level before a primary immune response could begin. Administering

antibodies against tetanus toxin quickly neutralises the toxin and prevents death.

Passive immunisation has two drawbacks: First, the person does not mount an active immune response, so the immunising effect is temporary and the person is not immune after recovery. Secondly, if passive immunisation is used repeatedly, it occasionally produces side effects.

3.2 Immunisation Milestones

Louis Pasteur (1822-1895) showed how mankind can be protected against rabies. A contemporary portrait and a drawing of his laboratory.

1721 Variolation (deliberate inoculation with smallpox virus), practiced for centuries in Africa, China, India, and the Middle East, is introduced to Europe by Lady Mary Wortley Montagu, wife of the English ambassador in Turkey. In America, the Reverend Cotton Mather learns of variolation from his African slaves and introduces it in Boston.

1796 Edward Jenner, an English medical student, observes that milk-mai2s who have recovered from cow-pox are protected against smallpox. He practises his first inoculation on an 8-year-old boy on 14 May 1796 and announces his findings two years later. The word vaccination (from the Latin word for cow: vacca) replaces the term variolation.

1803 Dr Jenner's pamphlet on vaccination lias been translated into five languages. More than 100,000 persons have been vaccinated in England. Jenner predicts the eventual "annihilation of the smallpox." 1870 Combatants in the Franco-Prussian war meet a common enemy: a smallpox epidemic. The French sustain 23,400 fatalities; the Germans lose only 278. The reason? Tiic German army lias been vaccinated.

1880 German scientist Robert Koch discovers the tubercle bacillus and begins work on a tuberculosis vaccine.

1885 Louis Pasteur of France introduces the rabies vaccine. Previously, a bite from a rabies-infect^3 animal usually resulted in "hydrophobia", which was inevitably f.-.tal. By 1890, rabies vaccination centres exist in major cities throughout the world.

Robert Koch (1843-1910) won the Nobel Prize for physiology and medicine in 1905 with his work on TB nnd ether dis-

1890 The united efforts of bacteriologists Emil A. vort Ben ring of Germany and Shibasaburo Kit sate of Japan 'vv$_L$:lt in the discovery of toxin/antitoxin immunisation for diprT-theria and tetanus. They receive the Nobel Prize for their work in 1902.

Edward Jenner (1749-1823) discovered vaccination and became “the father of immunology,” A doll distracts s child from the brief scratch of the needle.

Paul Ehrlich (1854-1915), another Nobel prizewinner, was a pioneer in diphtheria vaccine.

1897 Paul Ehrlich evaluates the effectiveness of diphtheria antiserum in Germany and receives the Nobel Prize for further work in immunology in 1903.

1906 Albert Calrnette and Camilla Guerin of France produce an attenuated tuberculosis vaccine (bacillus Cal-mette-Guerin)., now called the BCG vaccine.

Following the discovery of the pertussis bacillus by the Belgian scientist Jules Bordet, several types of pertussis vaccines are developed. His work earns him the Nobel Prize in 1919.

1940 After perfecting and testing a safer pertussis vaccine$_l$ American Pearl Kendrick begins trials of a combined diphtheria toxoid and pertussis vac-cine.

1954 Work by John Enders, Thomas Weller, and Thomas Peebles of Harvard University (USA) leads the way to the development of a safe measles - vaccine.

American virologist and physician Jonas Salk produces the inactivated poliomyelitis vaccine (IPV) which is injectable.

1957 Albert Sabin of the United States brings out the live poliomyelitis vaccine. Taken orally, it is designated as OPV.

1958 During the Eleventh World Health Assembly, the Soviet Union points out that the funds devoted to smallpox vaccination probably exceed the cost of wiping out the disease. WHA votes to step up efforts to eradicate smallpox.

All Maow Maalin, the world's List victim of smallpox.

1963 Mass immunisation campaigns using newly developed, safer measles vaccines begin in the United States and Kurope. The United States reported 482,000 cases of measles in 1962; by 1968, the incidence had dropped to 22,000 cases.

1967 The World Health Organisation (wii-j) "t..-ins the campaign to eliminate smallpox from the planet.

1974 WHO'S Expanded Piogramme on Immunisation (KPi) is established.

1977 HP! sets its target: by 1990 to immunise all the world's children againsc the six childhood diseases: measles, pertussis, diphtheria, tuber-culosis, poliomyelitis, and tetanus (including neonatal tetanus).

1977 Mradicavntinent by continent, smallpox makes its uist stand in Somalia, East Africa. The last case, AH Maow Maalin, makes a complete recovery.

1980 The Thirty-third World Health Assembly officially declares smallpox completely eradicated from the planet. By now, safe and effective vaccines exist for about 20 infectious diseases.

1987 World Health Day (April 7) 1987 focuses on EPl, giving added Immunisation programmes worldwide in their attempts to reach the 1990 goal.

1990 Target date for EPl, when children worldwide will have access to immunisation services and will have the possibility of being fully protected against the six vaccine-pre-vent able diseases.

4.0 CONCLUSION

Immunisation is the artificial means by which immunity is initiated or augmented and can be either active or passive in operation. Passive immunity may be conferred by the injection of antisera but the production of active immunity calls for the use of a vaccine. Active immunisation occurs when a person's own immune system is activated and regenerates a primary immune response. Active immunisation can be triggered in two ways, either by natural immunisation or by vaccination. On the other hand passive immunisation is temporary and when used repeatedly may produce side effects.

5.0 SUMMARY

In this unit, we have learnt that:

- Immunisation is the artificial means by which immunity is initiated or augmented.
- Immunisation can be active or passive.
- Active immunisation can triggered in two ways either by natural immunisation or by vaccination.
- Passive immunisation is temporary and when used repeatedly may produce side effects.

6.0 TUTOR-MARKED ASSIGNMENT

i. What do you think immunisation is?
ii. Mention and describe two types of immunisation
iii. What are the benefits or otherwise of the two types?

7.0 REFERENCES/FURTHER READING

Wicket, J.F. (1987). Smallpox Showed the World the Way. World Health Organisation Magazine. Jan-Feb. 1987Geneva: WHO.

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UNIT 3 SIX KILLERS OF CHILDREN

CONTENTS

1.0 INTRODUCTION

The six killers of children are the six childhood immunisable diseases which are also called or referred to as the Target Diseases. Whatever title or name is ascribed to these disease, what is of paramount importance is that they affect and kill children aged 0-5 years who are not immunised against the diseases which include measles, diphtheria, pertussis, tetanus, poliomyelitis and tuberculosis. The six deadly diseases are all immunisable and the vaccines are always available at no cost to children.

2.0 OBJECTIVES

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

- explain the fight by international Agencies like WHO, Unicef etc to wipe out immunisable diseases, particularly poliomyelitis from the surface of the earth as it was done to small pox.

3.0 MAIN CONTENT

3.1 Measles

Every 15 seconds a child dies from **measles**: two million children die each year. Virtually every unprotected child will contract the disease, which may be fatal for those already 'weakened by malnutrition or chronic diarrhea. Complications occur in about 30 per cent of cases, and include ear infections, diarrhea, blindness, and encephalitis.

3.2 Diphtheria

Diphtheria kills between 10 and 15 per cent of its victims. It causes membranes to develop in the throat, and death may follow from asphyxiation. Diphtheria bacilli in the throat also produce a toxin which, in the bloodstream, may attack the heart or nervous system with fatal results.

3.3 Pertusis

Some 51 million children contract **pertussis** (whooping cough) every year; over 600,000 of them die from it. The disease got its common name from the "whoop" children make while desperately trying to inhale after coughing spasms. Complications include: malnutrition (due to excessive vomiting after coughing), permanent brain carnage end pneumonia.

3.4 Neonatal Tetanus

Neonatal **tetanus** is estimated to cause 800,000 deaths a year. Nearly 100 per cent of newborn babies who get it will die. It is caused by unsterile methods of cutting the umbilical cord or by applying germ-laden substances to the stump. immunisation of the mother will give protection to the baby.

3.5 Poliomyelitis

Annually, about 275,000 children are affected by **poliomyelitis.** It is the major cause of lameness in the Third World, where nearly all children get polio before they are three. Although only one out of every 200 infected children develops typical symptoms, among those with recognised polio, one in ten will die.

3.6 Tuberculosis

Tuberculosis attacks as many as ten million victims a year, and is particularly lethal for infants. In the lungs, TB can trigger a rapidly fatal pneumonia or a slow wasting disease, in the bone, it can lead to severe deformities. When TB occurs in the brain, the results are usually fatal.

4.0 CONCLUSION

The six killer diseases of children also known as immunisable childhood diseases or target diseases affect and kill children aged 0-5 years. The inclusion of this unit in this module will further improve the skill of

learners and that of immunisation coverage towards effective control of the diseases and their eventual eradication.

5.0 SUMMARY

In this unit, we have learnt that:

- Six killers of children are also known as the childhood immunisable diseases also referred to as the target diseases.
- The six killer diseases include measles, diphtheria, pertussis, Tetanus, poliomyelitis and tuberculosis.
- The six killer diseases affect mainly children aged 0-5 years.
- Vaccines for the childhood diseases are readily available at no cost to children.

6.0 TUTOR-MARKED ASSIGNMENT

List the six killer diseases of children and discuss them. What other terms are used to identify the diseases?

7.0 REFERENCES/FURTHER READING

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UNIT 4 THE COLD CHAIN SYSTEM

CONTENTS

1.0 INTRODUCTION

According to WHO immunisation standard, the cold chain ensures that vaccines are kept cool and therefore potent all the way from the manufacturer up to the end receives. And unless the cold chain is maintained all through, the vaccine risks having no effect.

Therefore, in line with Nicholas (1986), effective vaccine storage requires the operation of a cold chain at all stages of delivery. For long storage at central or regional stores, live virus vaccines such as measles and oral polio, require temperatures of minus 200c, while diphtheria, pertussis and tetanus (DPT) and tetanus toxoid (TT) and BCG should be stored in the range of +20c to +80c and should never be frozen. However, refrigeration below 80c is necessary for all vaccines to maintain potency.

2.0 OBJECTIVES

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

- justify the need to maintain effective cold chain system as to retain the potency of vaccines else all immunisation will amount to nothing.

3.0 MAIN CONTENT

3.1 Vaccine Storage and Recommended Temperature

The table below shows the recommended storage temperature and maximum time for each vaccine at each link in the cold chain.

Type of Vaccine	Primary store MAX 6 Months	Provincial Store MAX 3 Months	District Store MAX 1 Month	Service level MAX 1 Month
OPV	-150C to --250C	-150C to -250C	+20C to 80C	+20C to 80C
BCG, Measles, MR, MMR, YF, Hib FD CSM	Storing freeze-dried vaccine at -200C is not harmful but it unnecessary. WHO no longer recommends them to be stored at -200C. Instead, these vaccines should be kept in refrigeration and transported at +20 to +80C		+20C to 80C	+20C to 80C
Hep B, DTP-HepB Hib liquid DTP, DT TT, Td	+20C to 80C	+20C to 80C	+20C to 80C	+20C to 80C

3.2 Cold-Chain

- This is a scientific method or system for keeping vaccines cold from the manufacturer to the point of vaccination.
- Vaccines are very sensitive to heat. To maintain their potency, all vaccines used in the National Immunisation Programme are usually stored and distributed under the WHO standards.
- Vaccines are often packed inside insulated container(s), cold boxes and vaccine carriers with enough ice-packs, Cold chain monitors shall be inserted between vaccine packs to monitor the temperature of the vaccine during transportation
- To maintain the cold chain, containers of cold boxes vaccines, are marked VACCINE RUSH, DO NOT OPEN from the manufacturer through all levels of their transportation within the country.
- Federal Government shall instruct port officials and clearing agents not to, under any circumstances, endanger the life of vaccines by delaying their clearing or opening their containers.
- Vaccines shall not be transported in open vehicles of any type.
- Government shall provide boots, jackets and hand gloves for officers working in cold stores.
- Government officials at all levels shall pack vaccines in dry cold conditions, not wet, to prevent peeling off of the labels from the vaccines packets or vials.
- Government shall provide cold chain equipment such as vehicles, generators, motor cycles, books, refrigerators, bicycles, cold boxes, vaccine carriers, ice-packs, etc. for use.

- To encourage private sector participation in provision of immunisation services, government shall assist whenever possible with cold chain equipment such as cold; boxes, ice packs and vaccine carriers to enable then collect vaccines from government cold stores.
- Trained cold chain officers shall have the sole responsibility for vaccine collection, storage and distribution to all levels including private health facilities.
- In the cold rooms where freezers and refrigerators are used, monitoring charts, thermometers, etc. shall be inside the units to allow for twice-daily recording of temperatures. The temperature charts shall be prominently displayed in the cold rooms and record of temperature shall be faithfully kept without any bias for cold chain assessment.
- Refrigerators, freezers, cold boxes and vaccine carriers are to be used only for vaccine storage. No other items of any type shall be found inside these units.

Note that all vaccine imported and produced locally should undergo regular potency testing.

Logistics

Considering the reported misuse of EPI vehicles and equipment at state and LGA levels, government shall not hesitate to take appropriate steps to discourage such acts.

- EPI Managers at all levels shall control appropriate utilisation of EPI vehicles.
- For logistic reasons and for effective programme supervision, EPI vehicles shall not be part of the common vehicle pool.
- Repairs and running costs of EPI vehicles and equipment shall be regarded as State /LGA input into the programme, not as favours.
- EPI Managers must, ensure that EPI vehicle' and equipment are used only for their intended purposes.
- Where these guidelines are not strictly followed, the FMOH &SS shall withdraw the vehicle immediately.
- EPI managers shall ensure proper keeping of log books of EPI vehicles.

3.3 Monitoring of the Cold Chain

When next you visit a large super-market, consider the food cold chain, from which the word vaccine cold chain was developed in the mid-1970s. In order to maintain its quality, fresh food is refrigerated or frozen from the time when it is first stored, through the stages of processing, transport and distribution to the shops. The quality of the

food depends on the continuity of cooling and on the period of time which the distribution process has taken.

We appreciate the quality, but how has it been achieved? Is the cold chain just a network of cooling equipment? Is it just a team of workers trained to order and distribute? Is it simply the technology of processing and packaging? The cold chain is all of these things, bound together in a managerial system whose objectives and whose procedures are clues to everyone involved.

Our experience of the vaccine cold chain enables us to consider some of the root causes of success and failure which we must face in applying the concept.

Things will go wrong!

When you drive your car into a sharp bend, do you imagine meeting a vehicle on your side of the road and check your position on the road and reduce your speed? If so, you are a good driver, because you anticipate the possibility of an emergency and you prepare for it. In the design of the vaccine cold chain we anticipate failure and prepare for it in a number of ways. Here are some examples:

- Electricity fails frequently in most tropical developing countries, and even when the failures are few, the voltage varies widely according to the time of day. The design of refrigeration equipment for vaccine storage in this condition differs from that used in industrialised countries with temperate climates, it is designed to protect vaccine when the power fails or is inadequate. In the latest equipment modified for the cold chain, the cooling energy is stored in the icepack bank which maintains vaccine storage temperatures when the refrigerator receives no power. Ordinary domestic refrigerators have thin insulation and no mass in which to store energy when the power is cut, so the temperature rises quickly in tropical conditions and can easily damage vaccine. This is a common cause of failures in the cold chain.

When equipment fails, when vaccine fails to arrive, when staff becomes sick, the cold chain must continue to function. These emergency procedures are included in training, they are planned drug supervision and they are pasted on walls in the health centre. Who is responsible for the vaccine refrigerator when the responsible person is sick? Where is the vaccine to be placed when the refrigerator stops working? What reserve vaccine stock is needed to allow for delays in vaccine delivery? What vaccines can continue to be given when the icepacks have melted? Where is the technician who can be called when equipment fails?

Unless emergencies are anticipated, they have a habit of expanding out of control, if only one problem occurs and is dealt with promptly, the cold chain is preserved and immunisation continues uninterrupted. We call this ability of the system to survive in spite of mishaps, the robustness of the cold chain design. The cold chain is improved by analysing failures when they occur and taking measures to prevent a recurrence.

Inspect: don't expect?

Dr Fakhry Assaad, Director of WHO's Division of Communicable Diseases up to 1986, frequently offered the advice: "You get what you inspect; not what you expect." This advice precisely describes the cold chain. Inspection begins, in the EPI cold chain, with the handling of vaccine and with the maintenance of equipment.

Every refrigerator in the cold chain contains a thermometer which must be checked twice each day. There is always the danger of the vaccine being exp osed to high daytime temperatures or low nighttime temperatures. Only by inspecting the temperatures regularly can one be confident about the storage conditions of the vaccine and therefore be sure of the effectiveness of immunisation.

This and other cold chain procedures are standardised nationally and internationally in the EPI. So the quality of vaccine handling, the accuracy of stock control and most activities in the cold chain can be followed easily and supervised effectively.

Chemical indicators are also used to check the adequacy of the cold chain. One such cold chain monitor travels with every 3,000 doses of vaccine from the manufacturer to where they are received in the user countries. The monitors are also widely used in national cold chain studies.

Inspection of equipment is as important as inspection of vaccine. Maintenance begins with the users of the equipment who can prevent faults from developing if they understand the equipment and know the maintenance procedures by heart. Practical training, particularly at the time of installation of the equipment, is the best way to turn knowledge of maintenance into a habit. Caring for equipment requires discipline but, most important, the users must be motivated.

Motivation is not always sufficient to prevent a breakdown. At that time, a repair technician is the most needed person. But how do you know who to call? How do you know that he will be able to solve the problem on the spot? How will he know what spares to bring? Again, the answer is: inspection. In successful cold chain systems, the repair technicians visit

the health centres, they keep an inventory of equipment models and where they are located, and they are trained and /quipped with the help of WHO to carry out repairs on the spot.

4.0 CONCLUSION

As effective as vaccines are in the protection of people particularly children 0-5 years and women of childbearing age, it is only the maintenance of a good cold chain system that will eventually lead to success. There is therefore need to maintain the cold chain system from the point of vaccine production to the various location of vaccine usage at the regulated temperature to achieve vaccine's potency.

5.0 SUMMARY

In this unit, we have learnt that:

- The cold chain ensures that vaccines are kept at the recommended temperature to make them potent from manufacturer to users.
- Refrigeration below 80C is necessary for all vaccines to maintain potency.
- Measles and oral polio vaccines require -200C temperature while DPT, TT, BCG should be stored between +20C to +80C
- There is also the need for proper monitoring of the cold chain system and its equipments.

6.0 TUTOR-MARKED ASSIGNMENT

How do you maintain an effective cold chain system?

7.0 REFERENCES/FURTHER READING

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UNIT 5 IMMUNISATION SCHEDULES AND ACTIVITIES

CONTENTS

1.0 INTRODUCTION

This unit deals with preparations for immunisations and the arrangements to be put in place for a successful immunisation schedule at all levels – local, state and national.

Topics that are discussed in this unit include immunisation procedures, vaccine distribution strategies as well as guidelines to determine immunisation needs.

It is noteworthy to mention that immunisation schedule and activities must embrace effective maintenance of the cold chain so as to ensure that vaccine potency is not at risk under whatever circumstances that prevail.

2.0 OBJECTIVES

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

- explain the conditions that are required to achieve a successful immunisation schedule and activities.

3.0 MAIN CONTENT

3.1 Immunisable Schedule

Recommended Schedule for Children with HIV-Infection/AIDS

Vaccine	Asymptomatic HIV Infection	Symptomatic HIV Infection	Optimal Timing of Immunisation
BCG	YES	NO	At birth
DPT	YES	YES	6, 10, 14 weeks
OPV*	YES	YES	0, 6, 10, 1 4 weeks
MEASLES	YES	YES	9 months
HEPATITIS B	YES	YES	As in uninfected children
YELLOW FEVER	YES	NO	
TETANUS TOXOID	YES	YES	5 doses as in infected children women

TT Immunisation Schedule For Women of Childbearing Age

Doses	When to Give	Expected Duration of Protection
TT1	At first contract or as early as possible in pregnancy	None
TT2	At least 4 weeks after TT1	1-3 years
TT3	At least 4 weeks after TT2	5 years
TT4	At least 6 months after TT3 or during subsequent pregnancy	10 years
TT5	At least 1 year after TT4 or during subsequent pregnancy	All the childbearing years

An immunisation schedule contain, information to which health workers may wish to refer when deciding which immunisation types to administer to a child, women of childbearing age and pregnant women. There is no limit to the interval, even if a year passes between the administrations of successive doses of a vaccine, administer the next dose as if the minimum time interval has passed.

Immunisation Schedule for Children under One Year

CONTACT	Minimum target age of child	Type of Vaccine	Dosage	Route of administration	Site
1ST	At birth	HBV 1	0.5ml	ultra muscular	upper arm
		BCG	0.05ml	intra dermal	RT. upper arm
		*OPVO	2 drops	oral	mouth
2ND	6 weeks of age	DPT1	0.5ml	intra muscular	upper outer quadrant of buttock
		OPV1	3 drops	Oral	Mouth
3RD	10 weeks of age	DPT 2	0.5ml	intra muscular	upper outer quadrant of buttock
		OPV2	2 drops	intra muscular	Mouth
		HBV2	0.5ml	intra muscular	upper arm
4TH	14 weeks of age	DPT3	0.5ML	intra muscular	upper outer quadrant of buttock
		OPV3	3 drops	Oral	Mouth
5TH	9-11 months	Measles	0.5ML	Subcutaneous	Left upper Arm
		Yellow Fever	0.5ML	Subcutaneous	Left Upper Arm
		HBV3	0.5ML	intra muscular	upper arm

**** OPV0 must be given before the age of two weeks***

3.2 Immunisation Procedures

In recognition of national interests and priorities the government will continue to provide vaccines and immunisation services free through the public sector. Government shall ensure the provision of vaccines and the use of a national immunisation schedule in order to attain optimal immunologic protection against EPI target disease and other vaccine preventable diseases for:

i. All children as early as possible
ii. Women of childbearing age
iii. Other Kt-risk groups, including HIV positives.

No eligible person shall be denied immunisation unless there are medical contraindications.

Techniques for Vaccine Administration

The recommended site for the administration of each EPI vaccine is shown in the Appendix 1. Vaccines that contain aluminum adjuvant (such as Hepatitis B and DPT) should be injected intramuscularly. The preferred site for infants and small children is the upper front (anterolateral) part of the thigh because this is where there is a lot of muscle mass. In older children, the deltoid muscle may be large enough for these vaccines. In adult women, the deltoid is the recommended site for vaccine administration.

Many Nigerian mothers may ask to have immunisations given in the buttock. This is not recommended for routine immunisations of children or adults because of the risk of injury to the sciatic nerve. In addition, in many adults, the layer of fatty tissue in the buttocks may be deeper than the length of the vaccine needle and the vaccine dose may be deposited in fat instead of muscle. As vaccines are not absorbed well from fatty tissue, the immune response will often be impaired.

Giving several vaccines at the same time, simplifies routine childhood immunisations and reduces the number of times mothers and children have to visit the heath facility. All of the NPI vaccines (BCG, DPT, OPV, measles, yellow fever, hepatitis B and CSM) may be given at one immunisation session but injections should be given in different muscle sites.

Mixing different vaccines in one syringe for injection or using a fluid vaccine to reconstitute a freeze-dried vaccine is not recommended. Such practices can result in lower potency or inactivation of vaccines.

BCG Immunisation

- Make certain that you have adequate supplies for the immunisation session. These should include sterile syringes and needles, cotton wool, vaccines and diluent.
- BCG vaccine is administered by intra-dermal injection. Select the left forearm for older children and adults.
- Clean skin with a cotton swab moistened with sterile water or methylated spirit and let it dry.
- Hold the middle of the child's upper arm firmly with your hand, Your fingers should be at the side of the child's body, your thumb towards you.

- Hold the syringe by the barrel with the milliliter scale upwards and the needle pointing in the direction of the child's shoulder. ***DO NOT TOUCH THE* PLUNGER**.
- Point the needle against the skin, bevel turned up, about 3 cm above your thumb. Gently insert its tip into the upper layer of the skin. Make sure that the needle is in and not under the skin.
- If the needle goes under the skin, take it out and insert it again. If you bend the needle replace it.
- Hold the barrel with your index and middle finger, put your thumb on the plunger.
- Hold the syringe flat (that is, parallel with the surface of the skin), inject the vaccine.
- For children older than one year, inject 0.1 ml.
- For children younger than one year, inject 0.05 ml

If the vaccine is injected correctly into the skin, a flat wheal, with the surface pitted like an orange peel, will appear at the injection site.

Note: If it becomes apparent after the full dose has been injected that the vaccine went under the skin, ask the mother to return with the child in six weeks for examination. If at that time there is no local reaction, re-immunise.

OPV Immunisation

1. Use the dropper or devices supplied with the vaccine
2. If the baby will not open its mouth, gently squeeze its cheeks to open the mouth.
3. Deposit drops of vaccine on the baby's tongue (The dropper should not touch the baby's mouth). If the dropper becomes contaminated, discard it and use a new vaccine vial.
4. At the end of the session, destroy the unused vaccine in any opened vaccine vial. Discard the vial.

DPT Immunisation

1. Make certain that you have adequate supplies for the immunisation session. These should include sterile syringes and needles, cotton wool, vaccine and diluent.
2. Inject the vaccine into the middle of the big muscle in the front of the thigh because of the danger of injuring the sciatic nerve and possibly causing paralysis.
3. Ask the mother to hold the child across her knees so that the front of the thigh is facing upwards. Ask her to hold its legs to prevent moving.
4. Clean the skin with a cotton swab moistened with water or methylated spirit and let it dry.
5. Place your thumb and index finger on each side of the place you intend to inject. Stretch the skin slightly.

6. Put the point of the needle against the skin between your thumb and finger.
7. Quickly push the needle deeply into the muscle (intramuscular).
8. Pull the plunger back. If there is blood in the syringe, discard the vaccine. DO NOT use the syringe and needle again until they have been sterilised. Put the used syringe and needle in a container with disinfectant solution to await cleaning and sterilization. Take a sterile syringe and needle and new vaccine. Repeat the process starting at step 4.
9. When no blood appears in the syringe, inject 0.5 ml vaccine.
10. Withdraw the needle.
11. Rub the injection spot quickly with the swab you used to clean the skin.
12. Use another needle and syringe to immunise the next child.

Measles Immunisation

- Make certain that you have adequate supplies for the immunisation session. These should include sterile syringes, needles, cotton wool, vaccine and diluent.
- Use sterile syringe and needle to reconstitute the measles vaccine using the sterile diluent according to the instructions on the vial.
- Load the sterile syringe with a 0.5 ml dose of the reconstituted measles vaccine.
- Ask the mother to expose the child's upper right arm.
- Clean the skin with a cotton swab moistened with water or methylated spirit and let it dry.
- With the fingers of one hand, pinch up the skin on the outer side of the upper arm.
- Hold the syringe at an angle to the child's arm.
- Do not touch the needle but push it subcutaneously into the pinched-up space.
- To avoid injecting vaccine into a vein, pull the plunger back slightly before pressing it to make the injection. If blood is drawn into the syringe, discard the vaccine. DO NOT use the syringe and needle again until they have been sterilised. Put the syringe and needle in a container with disinfectant solution to await cleaning and sterilization. Obtain a sterile syringe and needle and new vaccine. Repeat the process starting from step 3.
- DO NOT use the syringe and needle again until they have been re-sterilised. Take another sterile syringe and needle with vaccine,
- Press the plunger gently; inject 0.5 ml of vaccine
- Withdraw the needle. If blood appears, wipe it off with a cotton swab.
- Use another sterile needle and syringe to immunise each child.
- Discard all unused vaccines in opened vials at the end of the session.

3.3 Vaccine Distribution Strategies

There are three basic vaccine delivery strategies

1. Fixed Strategy .
2. Outreach Strategy
3. Mobile Strategy

Fixed Strategy
A fixed strategy is used when a health facility immunises people-at the facility. The facility is able to provide immunisation services without assistance or equipment from the L.G.A store. A sufficient number of health workers are assigned to the facility to immunise people. The cold chain equipment and vaccines are at the health facility. A fixed immunisation service is usually the least expensive over the long run because it utilises resources already at the facility and minimises transportation costs.

In this case, the LGA store sends vaccines, cold chain equipment and additional health workers to health facilities that are unable to do immunisation sessions without LGA assistance. The health facility and LGA combine personnel and equipment to be able to do immunisation sessions at the health facility.

Health-Facility Based (Outreach Strategy)
Health workers, vaccines and cold chain equipment go from a health facility to a dispensary, immunisation site or village, Outreach immunisation strategy is more expensive than a fixed immunisation strategy due to the added cost to the health system for transportation and cold storage equipment. It is also the most common type because it adapts to various types of geographical areas and to states and LGAs which have a shortage of resources to adequately staff and equip health facilities.

To help increase access to immunisation services without incurring the additional cost of transport of a health facility outreach strategy, an outreach strategy assisted by the community is being tried in some states. In a community-assisted outreach approach, health workers mobilise the community to pool its resources to cover the cost of transporting the health workers and supplies to and from the community. By eliminating the need for each mother to individually spend time and money in transit to and from the health facility, a community-assisted outreach strategy can save the community's time and money in an area where only a fixed strategy is operating. The approach depends on effective community mobilisation efforts.

Mobile Strategy

This strategy uses a group of health workers who travel to areas where outreaches cannot get to and where no health facility is available. These health workers are not assigned to any facility but usually operate from the state's epidemiology unit. The mobile strategy is the most expensive due to the cost of additional personnel, transportation and equipment.

Selecting an Immunisation Strategy

The decision to be use in vaccine distribution strategy will be influenced by the anticipated involvement of the community and a good knowledge of the resources available for providing immunisation services in the area. The underlisted should always be considered:

1. The physical accessibility of health facilities.
2. Distribution of the target population in relation to those health facilities which are adequately prepared to provide immunisation services.
3. Are there any reasons to exclude a particular facility? This may be based on records or on data provided by LGA or health facility staff.
4. The type and amount of resources available for providing immunisation services in the LGA such as:
   - Cold chain equipment
   - Vaccines and related supplies
   - Allowances for vaccinators, mobile teams and outreaches
   - Vehicles
   - Vehicle spare parts
   - Fuel
   - Prompt and reliable -maintenance of vehicles.

3.4 Guidelines for Determining Immunisation Needs

Vaccination Activities

i. Determine vaccine (s) needed
ii. Review EPI card, ask mother
iii. Administer appropriate vaccines

Do follow-up Activities

a Give health education to mothers.
b Record types and quantities of vaccines used.
c Return opened vaccines to the state EPI store to be destroyed.
d Prepare and submit monthly records.
e Check to be sure that each child has received all the immunisations he is supposed to receive.

f Emphasize the safety of the immunisations.

g Ensure that the mothers know that reactions to vaccines do occur, What they are and what to do if they occur? Explain that if a child has a reaction after the shots, this indicates that the vaccine is working and is developing in the child's body protection against the disease. Emphasize that the reactions are much milder than the disease.

i Ensure that the mothers know when to bring their children for the next immunisation.

j. Ask each mother if she knows when to return. If a mother cannot tell you when she is supposed to return or tells you the wrong date, repeat the correct date to her and remind her that it is very important that she brings her child back on that date.

k. If the Child Health Card recommends nutritional follow-up or treatment for disease or injury, either direct the mother to the proper person or place, or give her instructions on what to do.

Destroy Opened Vaccine and Record Types and Quantities Used

i Return open vials of vaccines to the State EPI store to be destroyed

ii Once a container of vaccines has been opened it must be used. If it cannot be used during the vaccination session, it must be destroyed.

iii Record use

iv. Return empty vials to LGA store

v Never keep opened ampoules of vaccine

vi Record carefully and accurately the amount of each type of vaccine used on the Daily Immunisation Tally Sheet

vii Promptly return unopened vaccine ampoules to the health center refrigerator or freezer

viii Prepare and submit monthly records of immunisation.

4.0 CONCLUSION

The schedule for immunisation showing days and times of immunisation sessions should be made available. It is important that the mothers be informed of this schedule so that all children in the area who are expected to have access to the health facility or immunisation site can receive their first set of immunisation as soon as possible after reaching the recommended age.

In addition, children needs to receive their second and their third doses of DPT and polio vaccines as soon as possible after the minimum one-month interval have passed. In order to ensure that all children in an area are immunised at the earliest acceptable age, immunisation sessions for each health facility or immunisation site should be held either daily or at regularly-scheduled days and times.

The number of immunisation sessions to be scheduled depends on the number of children you expect to immunise in the area who have access to the health facility or immunisation site. This is called target population with access. The target population with access consists of children in the area, less than 2 year old. These children make up about 8% of the total population in Nigeria.

5.0 SUMMARY

In this unit, we have learnt that:

- To have a successful immunisation schedule and activities all tiers of government (Federal, state and local) and all people should play their parts.
- Immunisation schedules in this unit cover children under one year, children with HIV/AIDS and women of childbearing age.
- Immunisation procedures cover vaccines administration.
- Vaccines distribution, strategies discussed include fixed strategy, outreach strategy and mobile strategy.
- Guidelines for determining immunisation needs are also fully attended to.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss in details your understanding of vaccines distribution strategy.

7.0 REFERENCES/FURTHER READING

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